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Association of combined left and right handgrip strength with new-onset chronic kidney disease in middle-aged and older adults: a nationwide multicenter cohort study

Yu Cao[1†], Mengda Tang[1†], Jinghong Zhao[1*] and Liangyu Yin[1*]

Abstract

Background The role of multi-site muscle strength in the incidence of chronic kidney disease (CKD) remains largely unknown. This study aims to investigate the association of combined left and right handgrip strength (CHS) with new-onset CKD in middle-aged and older adults.

Methods This observational multicenter study included 4618 community-dwelling adults without CKD at baseline in 2011. CHS (kg) was assessed at baseline and participants were followed in 2013, 2015, and 2018 to track CKD incidents. Sex-specific thresholds for low CHS were determined using receiver operating characteristic (ROC) analysis. Restricted cubic spline analysis, survival analysis and multivariable-adjusted Cox regression models were used to analyze the association between CHS and new-onset CKD.

Results The study included 2526 women and 2092 men (median age = 58.87 years). During the seven-year follow-up, 503 (10.89%) new CKD cases occurred. CHS was associated with new-onset CKD in both men ($P = 0.021$) and women ($P = 0.009$) in a linear-like manner (both P nonlinearity > 0.05). The optimal thresholds for CHS to predict CKD incidents were 96.15 kg for men and 57.90 kg for women. Kaplan-Meier curves demonstrated that prolonged CHS were positively associated with new-onset CKD in both men ($P < 0.001$) and women ($P = 0.001$). Low CHS, defined using the optimal thresholds, was independently associated with an increased risk of CKD (HR = 1.824, 95% CI = 1.379 to 2.413). This relationship was strengthened in participants with a BMI classification of normal (HR = 2.878, 95% CI = 1.732 to 4.782, P interaction = 0.032) at baseline, as well as those without diabetes (HR = 2.048, 95% CI = 1.514 to 2.771, P interaction = 0.019).

Conclusions This study demonstrated a longitudinal association between CHS and new-onset CKD in middle-aged and older Chinese adults. These findings highlight the potential of early-life multi-site muscle strength interventions for the prevention of CKD.

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Keywords Combined handgrip strength, Chronic kidney disease, CHARLS, Nationwide multicenter cohort study

Introduction

Chronic kidney disease (CKD) has become a significant public health challenge globally over the past few decades. The global all-age prevalence of CKD has increased by 29.3%, accompanied by a corresponding 41.5% increase in the global all-age mortality rate [1]. In China, the prevalence of CKD is approximately 10.8%, which translates to an estimated 119.5 million individuals affected by the disease [2]. Despite optimal treatment, CKD often progresses to end-stage renal disease and is strongly associated with an increased risk of cardiovascular diseases, other health complications, and elevated mortality rates [3, 4]. Alarmingly, CKD is estimated to become the fifth leading cause of death worldwide by 2040 [5]. Therefore, identifying the risk factors and underlying causes of CKD, especially modifiable ones, is essential for developing optimal management and is recommended by current international guidelines [6].

Handgrip strength (HGS) is a simple and effective measure of skeletal muscle strength, which has been linked to various health outcomes in a wide spectrum of diseases [7–9], such as cancer [10, 11], diabetes [12], respiratory diseases [13] and cardio-metabolic diseases [14]. In the context of nephrology, current clinical nutrition guidelines for CKD highlight HGS as an important indicator for assessing both nutritional and functional status [15]. HGS has also been identified as an independent predictor of renal outcomes in CKD patients [16], with low HGS being closely associated with an increased risk of all-cause mortality in those undergoing dialysis [17–21]. Additionally, studies conducted in European [22] and Korean [23] populations have shown a significant negative correlation between HGS and CKD events, further emphasizing the importance of assessing HGS in both clinical and public health settings.

However, current research mainly focuses on individuals who have already developed CKD, and evidence from Chinese community-dwelling middle-aged and older adults remains insufficient. Another knowledge gap is that most previous study only assessed grip strength in only one hand (usually the dominant hand), and research on the association between the combined grip strength of both hands and CKD risk is scarce. Several large cohort studies including both-hand HGS measurements in their protocols [10, 11, 24, 25]. Therefore, clarifying the health impact of combined HGS may provide valuable insights for designing future research and improving the clinical diagnosis of HGS-related diseases in CKD patients. In this large-scale multicenter cohort study, we investigated the association between combined HGS and new-onset CKD using data from the China Health and Retirement Longitudinal Study (CHARLS) project. Our goal is to support decision-making for public health and clinical experts in screening and surveillance of individuals at risk, ultimately helping to reduce the disease burden of CKD.

Methods

Study design and population

This study is an observational cohort study. Participants were derived from the China Health and Retirement Longitudinal Study (CHARLS), a nationally representative longitudinal survey in China [24]. CHARLS uses a structured survey instrument to collect comprehensive data through in-person interviews with a cross-section of Chinese individuals aged 45 and older. The survey includes standardized measures of sociodemographic factors, lifestyle variables, and health-related information. In 2011, the CHARLS enrolled subjects from 10,257 households across 150 counties, districts, and 450 towns in 28 Chinese provinces. Follow-up assessments were conducted biennially. The data were weighted to ensure that the sample accurately represented the national population. More detailed information on the CHARLS methodology was previously reported [25].

In this study, we conducted a retrospective analysis using data from CHARLS waves 2011, 2013, 2015, and 2018. The inclusion criteria were as follows: (1) participants aged 45 years and older at baseline; (2) participants with available data on HGS and other variables relevant to the diagnosis of CKD; and (3) participants without a clinically diagnosed CKD at baseline. The exclusion criteria were: (1) participants with missing data on key study variables or CKD outcomes; (2) participants with CKD at baseline; and (3) participants with outlier values. Based on the population included in the 2011 cross-sectional study, we further excluded participants with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. The eGFR was calculated using the CKD-EPI (Scr-CysC) equation [26]. A flowchart illustrating the inclusion of participants is shown in Fig. 1. The study protocol was approved by the Ethics Review Board of Peking University (approval number: IRB00001052-11015), and all participants provided written informed consent. The study methods involving human subjects complied with the ethical guidelines outlined in the 1964 Declaration of Helsinki and its later revisions. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

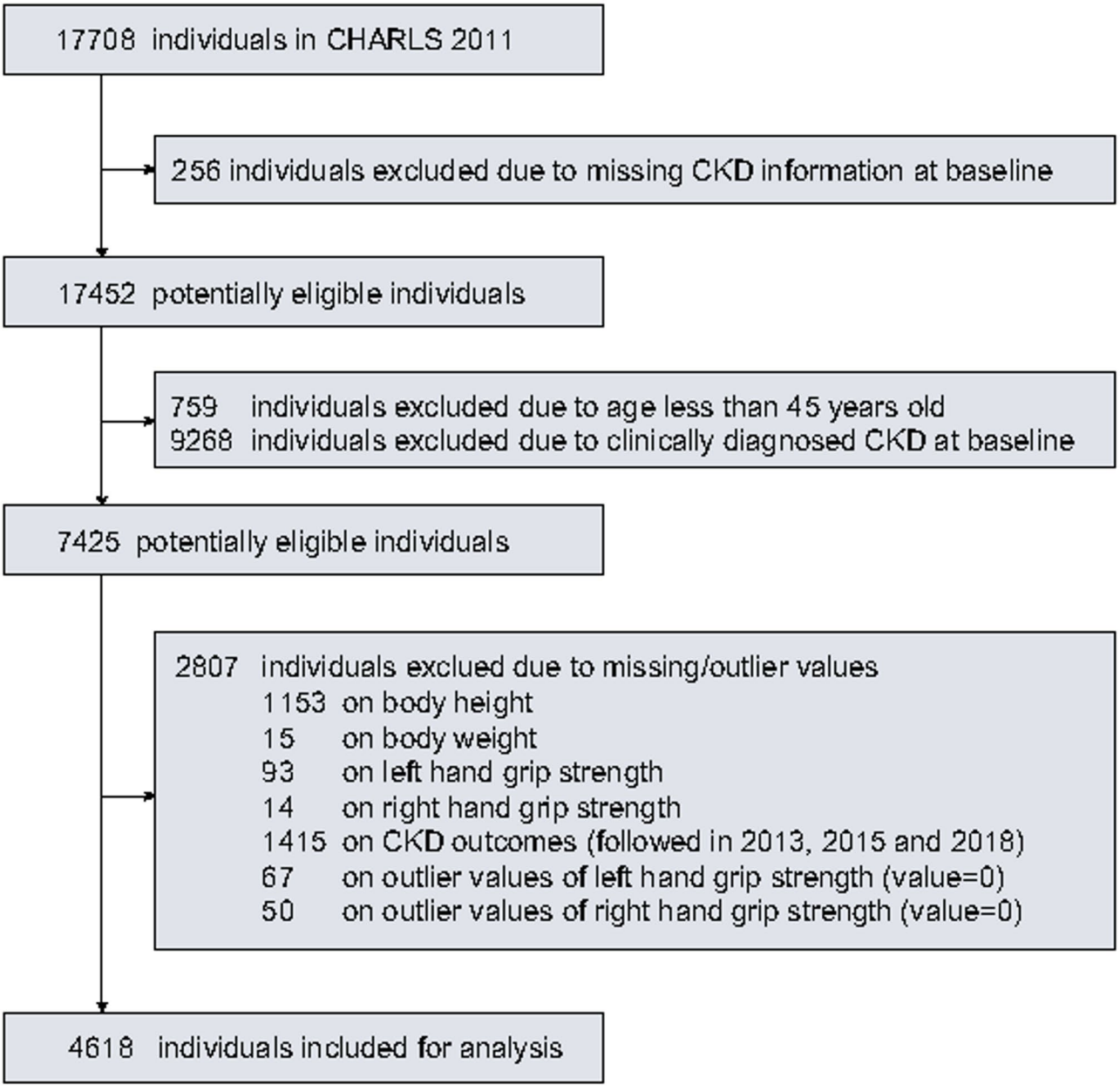

Fig. 1 A flowchart of the subject inclusion

Exposure: combined left and right handgrip strength

HGS was assessed at baseline by project-trained researcher using a dynamometer (Yuejian WL-1000, Nantong, China). Participants were instructed to stand with their arms hanging naturally at their sides and squeeze the handle as hard as possible until the pointer stopped rising. Each hand was measured twice, and the average grip strength of each hand was recorded to obtain the maximum grip strength values for both hands. Combined maximum handgrip strength (CHS) values of the left and right hands were defined as the exposure variable.

Outcome: new-onset chronic kidney disease

Data collected during the follow-up years of 2013, 2015, and 2018, after the initial enrollment in 2011, were analyzed. The primary endpoint of this study was new-onset CKD over the observation period from 2011 to 2018. CKD incidence was determined by asking participants: "Have you been informed by a doctor that you have been diagnosed with kidney disease?" Individuals who answered 'yes' to this question were classified as having CKD, as the question indicated that the kidney disease had been clinically diagnosed and confirmed by a physician. Time-to-event was calculated as the year of

follow-up minus the year of the baseline survey. Previous study showed that self-report of chronic diseases was reliable [27], and many CHARLS-based studies used this approach to define events of chronic diseases [28, 29].

Covariates

The baseline characteristics of the study population were collected by trained researchers using a structured questionnaire, which covered socio-demographic and health-related factors. Socio-demographic factors included age, sex, marital status (married vs. others), residency (rural vs. urban) and educational level (elementary school or below, middle school, and college or above). Health-related factors included body height (cm), body weight (kg), body mass index (BMI, kg/m^2), smoking (yes vs. no), alcohol consumption (yes vs. no), blood pressure (systolic and diastolic, mmHg), activities of daily living (ADL) score (six items, including dressing, bathing, eating, getting in and out of bed, using the toilet, and controlling urination and defecation), comorbidities (hypertension, diabetes, and heart disease), medication use (anti-hypertensive, anti-diabetic, and lipid-lowering drugs), blood urea nitrogen (mg/dL), creatinine (mg/dL), uric acid (mg/dL), and cystatin C (mg/dL). BMI was also categorized as underweight (< 18.5), normal (18.5 to < 24), overweight (24 to < 28), or obese (≥ 28), in accordance with the Chinese recommendations [30].

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and compared using a test. Categorical variables are expressed as number (percentage) and compared using a Chi-squared test. Restricted cubic splines (RCS) were used to analyze the potential nonlinear relationship between CHS and new-onset CKD. Receiver operating characteristic (ROC) curves were used to determine the optimal cutoff value for CHS in predicting new-onset. Kaplan-Meier curves were used for univariate survival analysis. Multivariate Cox regression models were applied to further assess the association between CHS and CKD. Incremental models were developed with an increasing number of covariates: Model 1 was the unadjusted crude model; Model 2 adjusted for baseline age, sex, marital status, place of residence, smoking and drinking status, and BMI; Model 3 adjusted for the variables in Model 2 plus education level, hypertension, diabetes, and heart disease; and Model 4 was the fully adjusted model, which included all variables in Model 3, plus blood urea nitrogen, creatinine, cystatin C, uric acid and the ADL score.

Sensitivity analyses were conducted to assess the time-dependent robustness of the Cox regression models by evaluating the incidence of chronic kidney disease (CKD) at either the first wave of follow-up (baseline in 2011, follow-up in 2013) or the first two waves of follow-up (baseline in 2011, follow-ups in 2013 and 2015). Subgroup analyses were performed within different strata of the adjusted variables to evaluate the modification of the associations observed in the overall population and to assess the generalizability of the observed relationship across various subgroups. The subgroup analyses were stratified by age (≤ 60 vs. > 60 years), sex (female vs. male), marital status (married vs. other), residence (rural vs. urban), drinking status (yes vs. no), smoking status (yes vs. no), BMI categories (underweight, normal, overweight, and obese), educational level (elementary school or below vs. other), hypertension (yes vs. no), diabetes (yes vs. no), heart disease (yes vs. no), use of hypertension medications (yes vs. no), use of diabetes medications (yes vs. no), use of lipid-lowering medications (yes vs. no), blood urea nitrogen (< median vs. ≥ median), creatinine (< median vs. ≥ median), cystatin C (< median vs. ≥ median), uric acid (< median vs. ≥ median) and ADL score (≥ 1 vs. 0). Multiplicative interactions were tested by adjusting for the cross-product terms of CHS and other covariates. Covariates showing statistically significant multiplicative interactions ($P < 0.05$) were considered potential effect modifiers. All analyses were performed using R (version 4.3.1, Foundation for Statistical Computing, Vienna, Austria).

Results

Subjects inclusion and exclusion

A flowchart of the subject inclusion is shown in Fig. 1. Of the 17,708 baseline subjects assessed, 256 were excluded due to missing CKD information, 9268 were excluded because they had clinically confirmed CKD or an eGFR less than 60 ml/min/1.73m^2 at baseline, 759 were excluded due to age less than 45 years old，and an additional 2807 were excluded for lacking key study variables. This left a total of 4618 subjects for the formal analysis. The cohort consisted of 2526 women and 2092 men, with a median age of 58.87 years. Over a seven-year follow-up period, 503 CKD events were recorded (with 83, 272, and 503 events identified in 2013, 2015, and 2018, respectively). Detailed baseline characteristics of the study population, stratified by sex, are shown in Table 1.

Restricted cubic spine analysis

The sex-specific RCS analysis is shown in Fig. 2. A negative, linear-like dose-dependent relationship between CHS and new-onset CKD was observed in men ($P = 0.021$, P for nonlinearity = 0.623, Fig. 2A). Similar result was found in women (Fig. 2B), a significant negative correlation between CHS and CKD risk was observed ($P = 0.009$), with a linear-like manner (P for nonlinearity = 0.974).

Table 1 Baseline characteristics of the study population stratified by sex

Characteristics	Overall (*n* = 4618)	Women (*n* = 2526)	Men (*n* = 2092)
Age, years	58.87 ± 8.92[a]	58.34 ± 8.95	59.52 ± 8.83
Marital status, married (vs. others)	3921 (84.91)[b]	2052 (81.24)	1869 (89.34)
Residency, rural area (vs. urban)	3112 (67.39)	1683 (66.63)	1429 (68.31)
Drinking	1488 (32.22)	299 (11.84)	1189 (56.84)
Smoking	1374 (29.81)	134 (5.31)	1240 (59.50)
Education level, n (%)			
Elementary school or below	4185 (90.62)	2382 (94.30)	1803 (86.19)
Secondary school	386 (8.36)	131 (5.19)	255 (12.19)
College and above	47 (1.02)	13 (0.51)	34 (1.63)
Body height, cm	1.58 ± 0.09	1.53 ± 0.07	1.64 ± 0.07
Body weight, kg	58.94 ± 11.47	56.26 ± 10.77	62.17 ± 11.46
BMI, kg/m^2	24.33 ± 37.18	25.22 ± 49.28	23.26 ± 10.90
Waist circumference, cm	84.64 ± 12.43	84.81 ± 12.92	84.05 ± 11.81
CHS, kg	62.29 ± 19.96	51.21 ± 13.80	75.67 ± 17.94
Blood pressure, mm Hg			
Systolic	128.91 ± 21.12	129.46 ± 22.09	128.26 ± 19.87
Diastolic	74.93 ± 12.04	74.74 ± 11.77	75.16 ± 12.35
Comorbidities, n (%)			
Hypertension	1178 (25.60)	705 (27.99)	473 (22.71)
Diabetes	274 (5.98)	175 (6.98)	99 (4.78)
Heart disease	524 (11.38)	324 (12.86)	200 (9.59)
Dyslipemia	422 (9.31)	253 (10.21)	169 (8.22)
Hepatic disease	145 (3.16)	72 (2.87)	73 (3.51)
Use of medications, n (%)			
Anti-hypertension	825 (17.93)	498 (19.77)	327 (15.70)
Anti-diabetes	154 (3.36)	99 (3.95)	55 (2.65)
Lipid-lowering	200 (4.42)	125 (5.05)	75 (3.65)
Creatinine, mg/dL	0.76 ± 0.16	0.68 ± 0.12	0.85 ± 0.15
Uric acid, mg/dL	4.35 ± 1.18	3.92 ± 1.00	4.87 ± 1.17
Cystatin C, mg/L	0.97 ± 0.18	0.93 ± 0.17	1.02 ± 0.18
eGFR, ml/min/1.73m^2	91.74 ± 15.21	93.01 ± 15.42	90.02 ± 14.80
Blood urea nitrogen, mg/dL	15.54 ± 4.25	14.90 ± 4.04	16.31 ± 4.36
ADL, continuous	0.252 ± 0.757	0.301 ± 0.828	0.192 ± 0.657
CKD onset during 2011–2018	503 (10.89)	237 (9.38)	266 (12.72)

Abbreviations: ADL, activities of daily living; BMI, body mass index; CHS, combined left and right handgrip strength; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

[a] Mean ± standard deviation, all such values

[b] Number (percentage), all such values

Cutoff values of combined left and right handgrip strength by sex

Sex-specific cutoff values for CHS to predict new-onset CKD were determined using ROC curves (Fig. 3). For men (Fig. 3A), the optimal cutoff value for CHS was 96.15 kg (sensitivity = 94.4%, specificity = 13.1%), while for women (Fig. 3B), the cutoff was 57.90 kg (sensitivity = 78.5%, specificity = 32.1%). Based on these optimal cutoff values, CHS were categorized as low and normal groups for future analysis (men, low < 96.15 kg and normal ≥ 96.15 kg; women, low < 57.90 kg and normal ≥ 57.90 kg).

Combined handgrip strength groups and clinical characteristics

Baseline characteristics of the study population, stratified by the CHS groups, are shown in Table 2. Compared to the normal CHS, the low CHS group had higher values/rates for age, rural residency, drinking, smoking, systolic blood pressure, use of anti-hypertension medications, cystatin C, uric acid, blood urea nitrogen, ADL score and new-onset CKD (all $P < 0.005$). In contrast, the low CHS group had lower values/rates for female sex, married individuals, body weight, waist circumference, diastolic blood pressure and eGFR (all $P < 0.005$). In addition, the education level was also different between the two CHS groups ($P < 0.001$).

Univariate and multivariate survival analysis

The results of the Kaplan-Meier analysis are shown in Fig. 4. Compared to the normal CHS group, the low CHS group was associated with an increased risk of CKD in both men ($P < 0.001$, Fig. 4A) and women ($P = 0.001$, Fig. 4B). Multivariate Cox regression models were further created (Table 3). CHS was analyzed both as a continuous variable and as a binary variable (low vs. normal). In the fully adjusted model (Model 4), continuous CHS was negatively associated with the risk of CKD in both men (HR = 0.991, 95% CI = 0.983 to 0.999) and women (HR = 0.987, 95% CI = 0.977 to 0.998). Similarly, when CHS was analyzed as a binary variable, individuals with low CHS had a higher risk of developing CKD (HR = 1.824, 95% CI = 1.379 to 2.413).

Sensitivity analysis

Sensitivity analysis was conducted to only examine CKD incidents occurring within the first two years (Model 5) and within the first four years (Model 6) to explore the impact of the time elapsed. In Model 5, no significant correlation was found between CHS and CKD incidence, regardless of whether the analysis was performed using a continuous or binary format, and this was true for both men and women. In Model 6, no statistically significant associations were observed in both men and women when CHS was treated as a continuous variable. However, when CHS was analyzed as a binary variable, the relationship was maintained in the overall population. (HR = 1.445, 95% CI = 1.010 to 2.067).

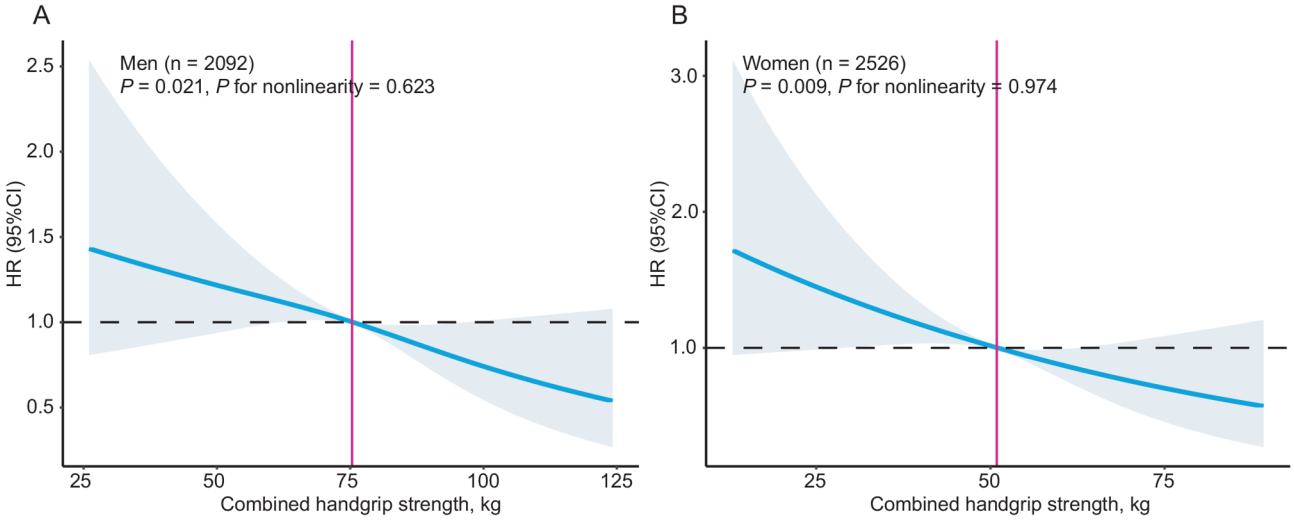

Fig. 2 Restricted cubic spine (RCS) analyses on the association between combined handgrip strength and new-onset chronic kidney disease. (**A**) RCS analysis in men. (**B**) RCS analysis in women

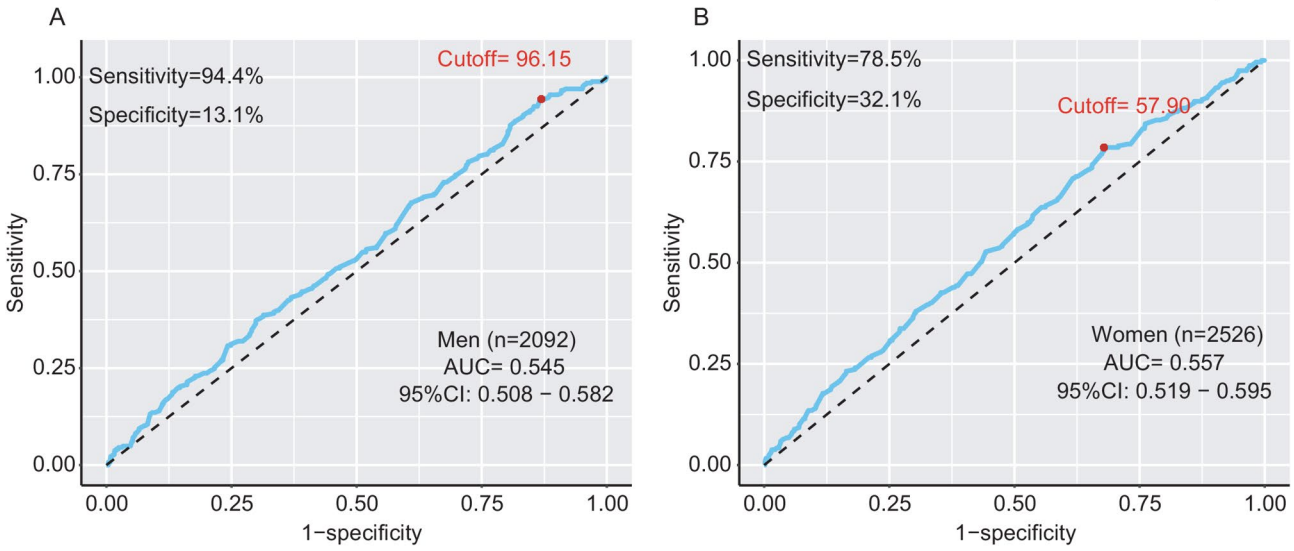

Fig. 3 Receiver operating characteristic (ROC) analyses on the association between combined handgrip strength and new-onset chronic kidney disease. AUC, area under the curve. (**A**) ROC analysis in men. (**B**) ROC analysis in women

Subgroup and interaction analysis

The fully adjusted model was reanalyzed across different covariate subgroups to explore potential effect modifications, and all covariates were statistically tested for interactive effects (Fig. 5). The positive association between CHS and CKD risk appeared to be attenuated in individuals with other marital status (HR = 1.514, 95% CI = 0.740 to 3.097), smoking history (HR = 1.502, 95% CI = 0.832 to 2.713), low body weight (HR = 2.582, 95% CI = 0.315 to 21.149), diabetes (HR = 0.855, 95% CI = 0.384 to 1.902), anti-diabetes medications (HR = 0.488, 95% CI = 0.142 to 1.674). Among them, the interaction between BMI ($P = 0.031$) and the diabetes ($P = 0.019$) group is statistically significant. Overall, the positive association between low CHS and new-onset CKD is robust across different covariate subgroups.

Discussion

This multicenter cohort study included 4618 adults from a nationally-representative cohort of China. The primary goal of this study was to explore the longitudinal association between CHS and new-onset CKD. To the best of our knowledge, this is one of the first large-scale studies to investigate this relationship in a middle-aged and older Chinese population. Our main finding was that low CHS was independently and significantly associated with an increased risk of new-onset CKD. This result is consistent with a previous UK Biobank study, which also

Table 2 Baseline characteristics of the study population by combined handgrip strength

Characteristics	Overall ($n=4618$)	Normal CHS ($n=1039$)[a]	Low CHS ($n=3579$)[a]	*P*
Age, years	58.87 ± 8.92[b]	53.94 ± 7.19	60.29 ± 8.87	< 0.001
Sex, women	2526 (54.70)[c]	785 (75.55)	1741 (48.64)	< 0.001
Marital status, married (vs. others)	3921 (84.91)	909 (87.49)	3012 (84.16)	0.008
Residency, rural area (vs. urban)	3112 (67.39)	1430 (63.84)	2441 (68.20)	0.028
Drinking	1488 (32.22)	255 (24.54)	1233 (34.45)	< 0.001
Smoking	1374 (29.81)	177 (17.04)	1197 (33.53)	< 0.001
Education level, n (%)				< 0.001
Elementary school or below	4185 (90.62)	900 (86.62)	3285 (91.79)	
Secondary school	386 (8.36)	124 (11.93)	262 (7.32)	
College and above	47 (1.02)	15 (1.44)	32 (0.89)	
Body height, m	1.58 ± 0.09	1.58 ± 0.08	1.58 ± 0.10	< 0.001
Body weight, kg	58.94 ± 11.47	62.60 ± 11.19	57.87 ± 11.33	< 0.001
BMI, kg/m^2	24.33 ± 37.18	24.87 ± 3.82	24.18 ± 42.19	0.595
Waist circumference, cm	84.46 ± 12.43	86.52 ± 12.40	83.86 ± 12.38	< 0.001
Blood pressure, mm Hg				
Systolic	128.91 ± 21.12	126.97 ± 19.67	129.48 ± 21.50	< 0.001
Diastolic	74.93 ± 12.04	75.78 ± 11.76	74.68 ± 12.11	0.010
Comorbidities, n (%)				
Hypertension	1178 (25.60)	263 (25.36)	915 (25.67)	0.843
Diabetes	274 (5.98)	58 (5.61)	216 (6.09)	0.565
Heart disease	524 (11.38)	128 (12.34)	396 (11.10)	0.268
Dyslipemia	422 (9.31)	101 (9.82)	321 (9.16)	0.519
Hepatic disease	145 (3.16)	31 (2.99)	114 (3.20)	0.732
Use of medications, n (%)				
Anti-hypertension	825 (17.93)	160 (15.43)	665 (18.65)	0.017
Anti-diabetes	154 (3.36)	27 (2.61)	127 (3.58)	0.127
Lipid-lowering	200 (4.42)	36 (3.51)	164 (4.68)	0.107
Creatinine, mg/dL	0.76 ± 0.16	0.73 ± 0.15	0.76 ± 0.16	< 0.001
Uric acid, mg/dL	4.35 ± 1.18	4.22 ± 1.15	4.39 ± 1.19	< 0.001
Cystatin C, mg/L	0.97 ± 0.18	0.92 ± 0.16	0.98 ± 0.18	< 0.001
eGFR, ml/min/1.73m^2	91.74 ± 15.21	95.73 ± 14.80	90.58 ± 15.13	< 0.001
Blood urea nitrogen, mg/dL	15.54 ± 4.25	15.03 ± 4.19	15.69 ± 4.25	< 0.001
ADL, continuous	0.252 ± 0.757	0.119 ± 0.458	0.290 ± 0.820	< 0.001
CKD onset during 2011–2018	503 (10.89)	66 (6.35)	437 (12.21)	< 0.001

Abbreviations: ADL, activities of daily living; CHS, combined handgrip strength; BMI, body mass index; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

[a] Cutoff value for combined handgrip strength: women (low, < 57.90 kg, normal, ≥ 57.90 kg) and men (low, < 96.15 kg, normal, ≥ 96.15 kg)

[b] Mean ± standard deviation, all such values

[c] Number (percentage), all such values

reported a negative correlation between grip strength and CKD events [22]. This evidence suggests that the association observed in Asian populations may also apply to Caucasian populations. However, most previous studies, including the UK Biobank study, focused only on single-hand grip strength. To date, the association between CHS and CKD events in a nationwide population without CKD remains unclear. Our study addresses this gap, suggesting that CHS can serve as an alternative indicator for assessing physical performance. Given the simplicity of grip strength measurement and its potential as a modifiable risk factor, our findings could support decision-making in both public health and clinical settings. Specifically, they may guide screening and surveillance strategies for individuals at risk, ultimately informing management approaches to reduce the disease burden of CKD.

In the present study, we found that 503 participants (10.89% of the cohort) experienced CKD events during a 7-year follow-up. This proportion was higher than the 2.7% reported in the UK Biobank study [22] and the 4% observed in a study conducted in South Korea [23]. This discrepancy may be attributed to the older age of our study population, which consisted of middle-aged and older adults over 45 years old [25]. Another possible explanation could be differences in prevalence due

Figure 4

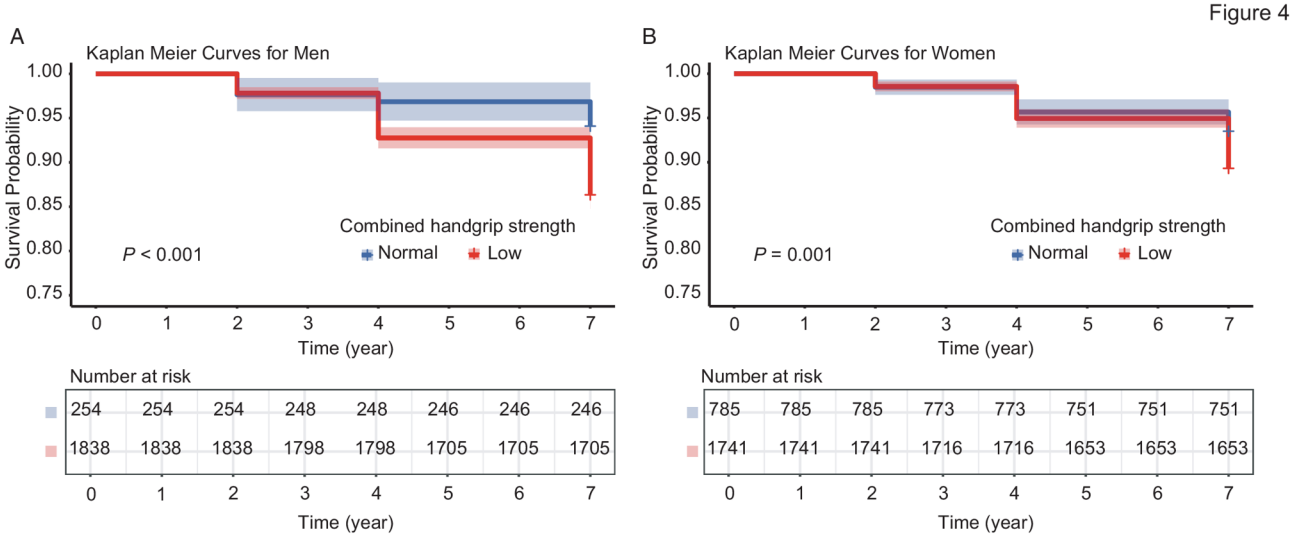

Fig. 4 Kaplan-Meier (KM) curves on the association between combined left and right handgrip strength and new-onset chronic kidney disease. (**A**) KM curves in men. (**B**) KM curves in women

Table 3 Multivariable models of the relationship between combined handgrip strength and new-onset chronic kidney disease

Model	HR (95%CI)					Sensitivity analysis, HR (95%CI)			
	n/events	Model 1	Model 2	Model 3	Model 4	*n*/events	Model 5	*n*/events	Model 6
CHS, continuous									
Men	2092/266	0.991(0.984–0.997)	0.991 (0.983–0.999)	0.992 (0.984–1.000)	0.991 (0.983–0.999)	2092/46	0.993 (0.975–1.013)	2866/147	0.991 (0.980–1.001)
Women	2526/237	0.986 (0.977–0.995)	0.985 (0.975–0.996)	0.987 (0.977–0.998)	0.987 (0.977–0.998)	2526/37	1.003 (0.977–1.030)	2526/125	0.990 (0.976–1.004)
CHS group									
Normal	1039/66	Reference	Reference	Reference	Reference	1039/18	Reference	1039/42	Reference
Low	3579/437	1.944 (1.500–2.518)	1.878 (1.421–2.480)	1.804 (1.364–2.386)	1.824 (1.379–2.413)	3579/65	0.818 (0.456–1.468)	3579/230	1.445 (1.010–2.067)

Abbreviations: HR (95%CI), Hazard ratio (95% confidence interval); CHS, combined handgrip strength

Model 1 is the unadjusted crude model

Model 2 is adjusted for the age at baseline, sex, marital status, residence, drinking status, smoking status, body mass index, educational level

Model 3 is adjusted for the age at baseline, sex, marital status, residence, drinking status, smoking status, body mass index, educational level, hypertension, diabetes, heart disease, use of hypertension medications, use of diabetes medications and use of lipid-lowering medications

Model 4 is adjusted for all variables in Model 3, plus activities of daily living score, blood urea nitrogen, creatinine, cystatin C and uric acid

Model 5 is adjusted for all variables in Model 4, but only assessed the onset of chronic kidney disease at the first wave of follow-up (baseline in 2011, first wave of follow-up in 2013)

Model 6 is adjusted for all variables in Model 4, but only assessed the onset of chronic kidney disease at the first two waves of follow-up (baseline in 2011, second wave of follow-up in 2013 and 2015)

to variations in economic factors, geographic regions, or ethnicity. We also observed that the incidence of CKD in our study was similar to that of a previous study, which reported a CKD prevalence rate of 10.8% in China [20]. Notably, if participants who had already developed CKD at baseline were included, the overall prevalence in our cohort would likely exceed 10%. The most likely reason for this finding is that the CHARLS cohort includes middle-aged and elderly individuals, and CKD incidence is positively correlated with age. These results highlight the importance of early intervention in individuals at younger ages. Future randomized controlled trials are needed to confirm whether early physical exercise can reduce the onset of CKD.

The optimal cut-off values of combined handgrip strength (CHS) for predicting new-onset CKD were 96.15 kg for men and 57.90 kg for women. These cut-offs were higher than those recommended by the Asian Working Group for Sarcopenia (AWGS) 2019 framework [31], which defines the threshold for single-hand grip

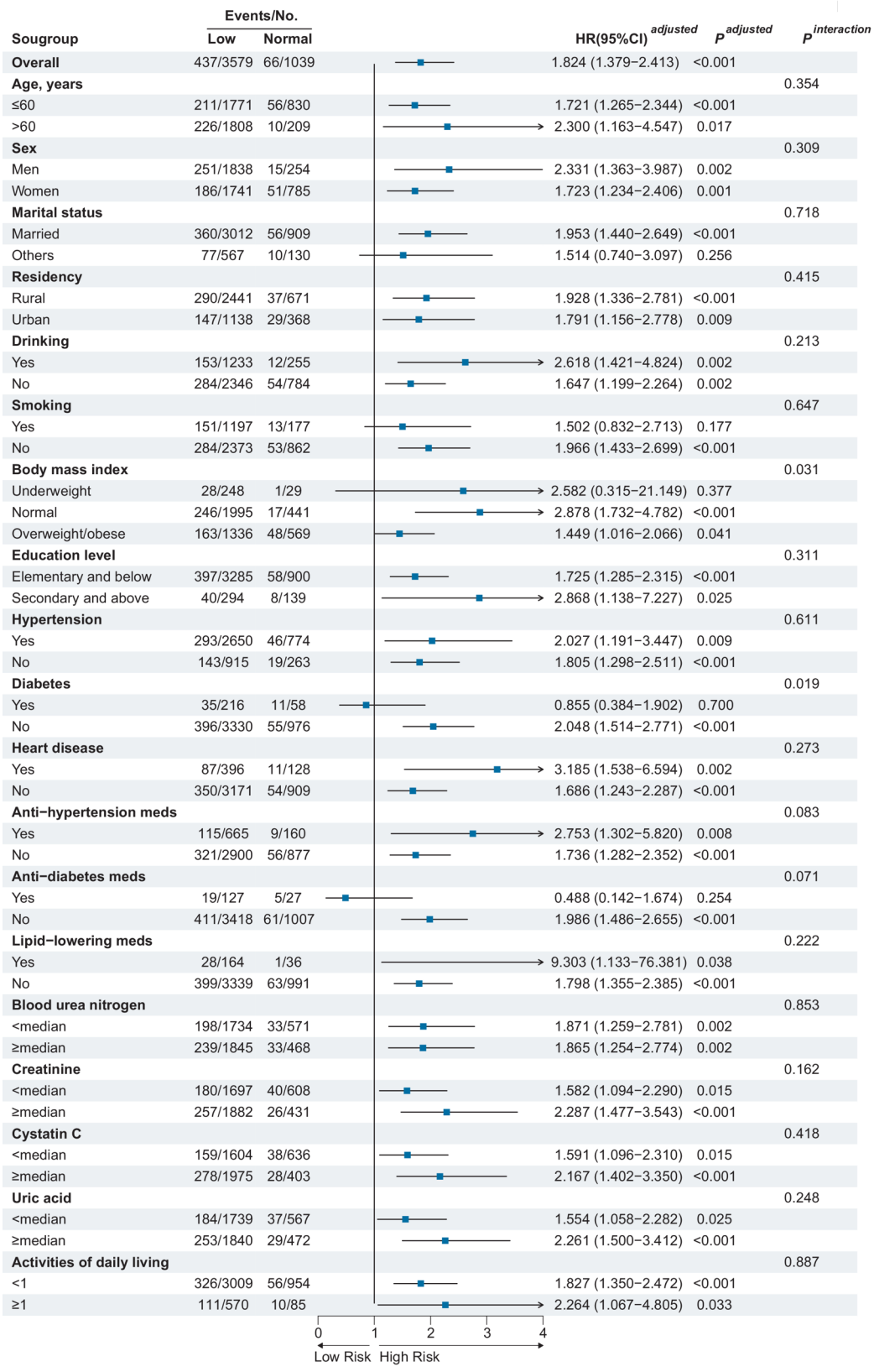

Fig. 5 Subgroup and interaction analysis on the association of combined handgrip strength and new-onset chronic kidney disease. HR, Hazard ratio; CI, confidence interval

strength as 28 kg for men and 18 kg for women. A possible explanation for this difference may be related to the different purposes and methodologies used for calculating the cutoffs. We used ROC analysis with CKD as the binary outcome to determine handgrip strength cutoffs. In contrast, the AWGS cutoffs were derived from large population data and were intended for diagnosing age-related sarcopenia. Moreover, the AWGS cutoffs were originally based on a study involving adults aged ≥ 65 years [32]. As grip strength declines with age, the significant age differences between the populations in the two studies could be an important factor contributing to the different cutoff values. Indeed, our study included a larger proportion of younger adults, which likely explains why the cutoffs (when CHS was divided by two) were higher than those recommended by the AWGS. In an exploratory analysis (data not shown), neither the low CHS (when multiplying the AWGS threshold by two) nor the single-hand grip strength (as defined by the AWGS 2019 criteria), were associated with new-onset CKD. This further supports the idea that HGS cutoffs should be tailored to specific populations or research objectives. Future studies using similar designs to ours, but with more diverse populations, will be valuable for confirming this hypothesis.

The mechanism underlying the results of this study is worth commenting. Grip strength is a key indicator for diagnosing sarcopenia [33], and its decline typically signals impaired skeletal muscle function. Skeletal muscles are widely distributed throughout the body, where they not only play a direct role in maintaining various important physiological functions but also contribute significantly to metabolic processes. As the primary storage site for proteins and a central hub for glucose processing, muscles are crucial in systemic protein metabolism [34]. Studies have shown an inverse relationship between muscle mass and insulin resistance, suggesting that a reduction in muscle mass due to sarcopenia may impair the muscle's ability to uptake glucose, thereby increasing the risk of insulin resistance [34–36]. Insulin resistance, whether systemic or podocyte-specific, is considered a key factor in the development of kidney dysfunction [37]. In addition, research suggests that endothelial dysfunction may be an additional mechanism contributing to sarcopenia [38]. A study by Leung and colleagues has demonstrated that renal microvascular disease is initiated by damage to endothelial cells [39]. In skeletal muscles, physical activity promotes the upregulation of antioxidant defense systems [40], and skeletal muscles also have anti-inflammatory properties [41]. These findings suggest that sarcopenia may be linked to an increase in systemic inflammatory responses, which are known to drive the progression of CKD [42]. Aging may represent another mechanism underlying our findings. Previous research has shown that, even in the absence of age-related complications, the aging process is closely associated with significant changes in kidney structure and function [43]. Moreover, studies suggest that HGS is related to the epigenetic clock, a biomarker used to estimate biological age based on DNA methylation patterns [44]. Individuals with greater grip strength tend to experience a slower rate of epigenetic aging, implying that grip strength may serve as a potential predictor of kidney function decline.

This study has several limitations that should be noted. First, the study's follow-up period was relatively short, and the exact timing of new-onset CKD was not recorded. Although our approach to handling survival data has been suggested as feasible in previous CHARLS-based studies [45, 46], future research that incorporates exact time-to-event or interval-censoring data is needed to replicate our results. Second, CKD events were communicated to the patients by doctors and ultimately self-reported by the participants, which may be subject to recall bias and underestimation. However, previous studies have shown that self-reporting of chronic diseases is reliable [27], and many previous CHARLS studies have used this approach to identify chronic diseases [28, 29]. Even if some underestimation of disease occurred, our reported results would likely be attenuated in magnitude rather than changed in direction. Nevertheless, studies with information on serum index-confirmed CKD events and disease stages are needed to replicate our findings. Third, due to the scope and design limitations of the original CHARLS project, data on the types and dosages of medications used by the participants are not available. Different classes of antihypertensive or antidiabetic medications, such as renin-angiotensin system (RAS) inhibitors or sodium-glucose cotransporter-2 (SGLT2) inhibitors, could impact the progression and development of CKD. Additionally, blood phosphate is suggested to play an important role in the progression of CKD [47], while phosphate data were not included in CHARLS. Future studies should investigate whether these factors modify the associations we observed. Finally, while we have adjusted for many potential confounders, there may still be unaccounted factors that could affect the results. Future study needs to address these concerns.

Conclusions

This study demonstrated a longitudinal association between CHS and new-onset CKD in middle-aged and older Chinese adults. Sex-specific thresholds were calculated to define low CHS. These findings highlight the potential of early-life multi-site muscle strength interventions for the prevention of CKD.

Abbreviations

ADL Activities of daily living
AWGS Asian Working Group for Sarcopenia

BMI	Body mass index
CHARLS	China Health and Retirement Longitudinal Study
CHS	Combined left and right handgrip strength
CI	Confidence intervals
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
HR	Hazard Ratio
RCS	Restricted cubic spline
ROC	Receiver operating characteristic
SD	Standard deviation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

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Author contributions
L.Y. contributed to the conception and design of the research; Y.C. and M.T. contributed to the acquisition and analysis of the data; Y.C., M.T., L.Y. and J.Z. contributed to the interpretation of the data; Y.C. drafted the manuscript; L.Y. critically revised the manuscript; all authors agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Data availability
The data are available from the CHARLS website (https://charls.charlsdata.com/).

Declarations

Ethics approval and consent to participate
All methods were performed in accordance with the Declaration of Helsinki. This work was fully compliant with Ethical Standards and approved by the Ethics Review Committee of Peking University (IRB 00001052–11015). Written informed consent for each participant was obtained prior to sample collection.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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