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Association of sarcopenia index, based on serum creatinine and cystatin C, with incident diabetes mellitus

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Abstract

Background Sarcopenia, characterized by loss of muscle mass and strength, has been linked to various health outcomes, including diabetes mellitus. This study aims to investigate the association of sarcopenia index, based on serum creatinine and cystatin C levels, with incident diabetes mellitus in middle-aged and older adults in China.

Methods This study extracted data from 2015 to 2020 China Health and Retirement Longitudinal Study (CHARLS), including age ≥ 45-year adults without diabetes mellitus at baseline. Sarcopenia index was calculated based on serum creatinine and cystatin C levels, and incident diabetes mellitus was assessed through follow-up surveys. Cox proportional hazards regression models were used to analyze the association between sarcopenia index and incident diabetes mellitus, adjusting for potential confounders, with hazard ratio (HR) with 95% confidence interval (95% CI) reported.

Results During a mean follow-up period of 5.0 years, a total of 501 new cases of diabetes were recorded. A total of 7718 participants were included in the analysis. The median age was 60 years, and 46.2% were male. During a mean follow-up period of 5.0 years, 501 cases of incident diabetes mellitus were identified. After adjusting for covariates, Compared with participants in the lowest quartile, the corresponding diabetes HRs (95% CIs) for participants in the second, third, and fourth quartiles were 0.930 (95% CI 0.724–1.193; $P=0.567$); 0.892 (95% CI 0.685–1.162; $P=0.398$), 0.869 (95% CI 0.657–1.150; $P=0.327$). Restricted cubic spline curves revealed that incident rate decreased with increase in sarcopenia index.

Conclusions This study provides national longitudinal evidence in China on the association of sarcopenia index, based on serum creatinine and cystatin C levels, with incident diabetes mellitus in middle-aged and older adults. Our findings suggest that sarcopenia index may be a useful biomarker for predicting the risk of diabetes mellitus in this population.

Keywords Sarcopenia index, Diabetes mellitus, Cohort study, Incident

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Introduction

Diabetes mellitus is a serious metabolic disease whose incidence and prevalence are increasing globally and has become a major challenge in public health [1]. In recent years, researchers have increasingly focused on the impact of muscle mass and function on the risk of diabetes. Muscle is a major glucose metabolizing organ, and a decrease in its mass and function (i.e., sarcopenia) may increase the risk of developing diabetes [2].

Sarcopenia is a common muscle degeneration syndrome in the elderly, which is mainly characterized by a decrease in muscle mass and strength [3]. Studies have shown that sarcopenia is not only associated with decreased glucose metabolism, but also may lead to insulin resistance and chronic inflammation, which may increase the risk of diabetes mellitus [4, 5]. However, the relationship between sarcopenia and the development of diabetes mellitus is inconsistent and controversial [6, 7].

In recent years, the sarcopenia index based on serum creatinine and cystatin C has been proposed for the assessment of muscle mass and function. This index has the advantages of simple measurement and reproducibility, and has been widely used for sarcopenia screening in various populations [8]. However, the relationship between this novel index and diabetes risk remains largely unexplored. Given the potential clinical utility of this easily accessible biomarker, preliminary evidence from longitudinal studies is needed to establish its value in diabetes risk assessment. Such evidence would provide a foundation for future validation studies and potentially inform diabetes prevention strategies.

Therefore, based on the data from the China Health and Retirement Longitudinal Study (CHARLS), the present study was designed to conduct an initial exploration of the potential predictive role of the sarcopenia index in diabetes risk. This preliminary investigation aims to generate hypotheses for future research and provide early evidence for the possible application of this novel marker in diabetes prevention and management.

Methods

Study population

The data used in this study were obtained from the CHARLS, a large-scale, nationally representative population-based survey on Chinese adults aged 45 years and older [9]. This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies (Table S1). The studies involving human participants were reviewed and approved by the Biomedical Ethical Review Committee of Peking University (IRB00001052-11015). The participants provided their written informed consent to participate in this study. The privacy rights of participants were observed.

All participants of the 2015–2020 CHARLS survey, aged 45 years and older, were included in this study. Participants with a previous diagnosis of diabetes, missing information on key variables, or incomplete follow-up were excluded. A total of 7718 participants were ultimately included for analysis. Figure 1 illustrates the screening process for the study population.

Assessment of sarcopenia index

The sarcopenia index was calculated based on serum creatinine and cystatin C levels with the formula: sarcopenia index = serum creatinine (mg/dL)/serum cystatin C (mg/dL) * 100 [10, 11]. At the baseline (2015) examination, venous blood samples were collected from all participants and serum creatinine and cystatin C concentrations were measured.

Ascertainment of incident diabetes mellitus events

The CHARLS survey assessed participants for a detailed chronic medical history, including asking about any previous physician-diagnosed diabetes. Participants' fasting blood glucose was also measured at

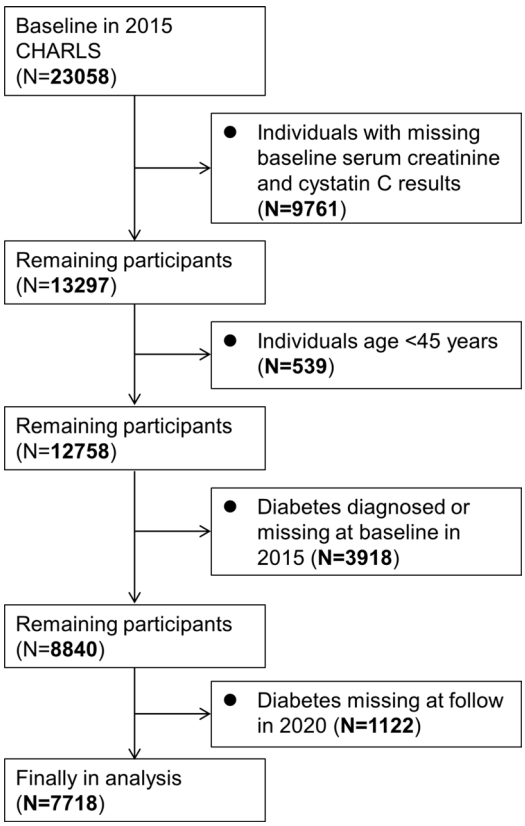

Fig. 1 Flow chart of sample selection and the exclusion criteria

baseline and follow-up examinations. Fasting blood glucose ≥ 7.0 mmol/L or previous physician-diagnosed diabetes was defined as a diabetic event according to the diagnostic criteria of the American Diabetes Association [12]. The outcome event in this study was new-onset diabetes mellitus that developed during the follow-up period.

Covariates

During the baseline survey, general demographic information of the participants, including age, gender, place of residence, marital status, education level, etc., was collected through a standardized questionnaire. Height and weight were also measured and body mass index was calculated. Past medical history information included hypertension, kidney disease, and self-reported health. Lifestyle-related factors such as smoking status, alcohol consumption, and sleep duration were also collected. The percentage of missingness for each covariate is shown in Table S2.

Statistical analysis

Considering that the missing proportion of each covariate is less than 5%, we use the mode to impute it. We compared demographic characteristics, clinical indicators, and lifestyle variables among the different sarcopenia index groups. Continuous variables were analyzed by analysis of variance or Kruskal–Wallis test, and categorical variables by chi-square test. To investigate the relationship between sarcopenia index and the risk of developing diabetes, we constructed Cox proportional risk models for analysis, and the results were presented as hazard ratio (HR) with 95% confidence interval (95% CI). We developed four model: model 1 was unadjusted; model 2 was based on model 1 and adjusted for demographic characteristics, such as age, gender, residence, marital status, and education level; model 3 was based on model 2 and adjusted for lifestyle factors, including smoking and alcohol consumption; model 4 was based on model 3 and adjusted for disease-related variables, including hypertension, kidney disease, Activity of Daily Living, and body mass index. In addition, the sarcopenia index was included as a continuous variable for analysis, and the effect of each increase of 1 unit or 1 standard deviation of sarcopenia index on the risk of diabetes mellitus was estimated. In addition, we reanalyzed the original data (i.e., unimputed) to assess the robustness of the imputed data set. All statistical analyses were performed using Stata 16.0 and *R* software, and the significance level was set at two-sided $P < 0.05$.

Results

Baseline characteristic

A total of 7718 adult participants aged 45 years and older were included for analysis. Participants were categorized into 4 groups according to the distribution of the sarcopenia index: quartile 1 (Q1, sarcopenia index < 81.75, n = 1929), quartile 2 (Q2, 81.75 ≤ sarcopenia index ≤ 93.28, n = 1930), quartile 3 (Q3, 93.29 ≤ sarcopenia index ≤ 106.91, n = 1929) and quartile 4 (Q4, sarcopenia index > 106.91, n = 1930). There were significant differences among the four groups of participants in terms of baseline characteristics, such as age, gender, residence, marital status, and education level (all $P < 0.001$). Compared with Q4, Q1 participants were more likely to smoke ($P < 0.001$) and drink alcohol ($P < 0.001$). In addition, participants in the Q1 group were more likely to have a history of comorbid illnesses, such as hypertension ($P < 0.001$) and depressive symptoms ($P < 0.001$) (Table 1).

Association between sarcopenia index and incident diabetes mellitus events

During a mean follow-up period of 5.0 years, a total of 501 new cases of diabetes were recorded. The incidence rate of diabetes mellitus was 13.75 per 1000 person-years among Q1 group, 13.02 per 1000 person-years among Q2 group, 12.61 per 1000 person-years among Q3 group, and 12.40 per 1000 person-years among Q4 participants.

In the Cox proportional risk models analysis, model 1 (unadjusted) showed that the risk of developing diabetes was reduced by 5.6% (HR = 0.944; 95% CI 0.733–1.215, $P = 0.656$), 8.8% (HR = 0.912; 95% CI 0.707–1.176; $P = 0.479$), and 10.4% (HR = 0.896; 95% CI 0.693–1.156; $P = 0.398$) for the Q2, Q3, and Q4 groups, respectively, as compared with that for the Q1 group (Table 2). This result was validated in model 2 (adjusting for demographic characteristics), model 3 (additional adjustment for lifestyle factors), and model 4 (further adjustment for disease-related variables). When the sarcopenia index was included as a continuous variable in the multivariate adjustment model, the risk of diabetes incidence was reduced by 0.3% for every 1-unit increase in the sarcopenia index (HR = 0.997; 95% CI 0.993–1.001, $P = 0.140$), whereas the risk of diabetes incidence was reduced by 7.6% for every 1-standard deviation increase in the sarcopenia index (HR = 0.924; 95% CI 0.832–1.026, $P = 0.140$) (Table 2). The imputed data set is essentially the same as the original data set result (Table S3).

Data were presented as HR (95% CI).

Model 1: unadjusted.

Model 2: adjusted for age, gender, marry, residence, and education.

Table 1 Participants demographics and baseline characteristics

Characteristic	Sarcopenia index quartile					*P* value
	Overall (N = 7718)	Q1 N = 1929	Q2 N = 1930[1]	Q3 N = 1929	Q4 N = 1930	
Distribution		< 81.75	81.75–93.28	93.29–106.91	> 106.91	
Sarcopenia index	93 (82, 107)	74 (68, 78)	88 (85, 90)	100 (96, 103)	119 (112, 129)	< 0.001[2]
Serum creatinine (mg/dL)	0.76 (0.66, 0.89)	0.66 (0.59, 0.74)	0.73 (0.65, 0.83)	0.80 (0.71, 0.92)	0.90 (0.78, 1.04)	< 0.001[2]
Serum cystatin C (mg/dL)	0.83 (0.72, 0.94)	0.91 (0.81, 1.00)	0.84 (0.74, 0.95)	0.81 (0.71, 0.92)	0.73 (0.64, 0.84)	< 0.001[2]
Age, years (continuous)	60 (53, 67)	63 (57, 70)	61 (53, 67)	60 (53, 66)	58 (51, 64)	< 0.001[2]
Age, years (category)						
< 60	3563 (46.2%)	668 (34.6%)	866 (44.9%)	938 (48.6%)	1091 (56.5%)	< 0.001[3]
≥ 60	4155 (53.8%)	1261 (65.4%)	1064 (55.1%)	991 (51.4%)	839 (43.5%)	
Gender						
Female	4154 (53.8%)	1586 (82.2%)	1226 (63.5%)	815 (42.2%)	527 (27.3%)	< 0.001[3]
Male	3564 (46.2%)	343 (17.8%)	704 (36.5%)	1,114 (57.8%)	1403 (72.7%)	
Marry						
Other	958 (12.4%)	338 (17.5%)	251 (13.0%)	204 (10.6%)	165 (8.5%)	< 0.001[3]
Marry	6760 (87.6%)	1591 (82.5%)	1679 (87.0%)	1725 (89.4%)	1765 (91.5%)	
Residence						
Rural	5052 (65.5%)	1321 (68.5%)	1276 (66.1%)	1266 (65.6%)	1189 (61.6%)	< 0.001[3]
Urban	2666 (34.5%)	608 (31.5%)	654 (33.9%)	663 (34.4%)	741 (38.4%)	
Education						
Non-former education	3450 (44.7%)	1171 (60.7%)	905 (46.9%)	751 (38.9%)	623 (32.3%)	< 0.001[3]
Primary school	1757 (22.8%)	366 (19.0%)	437 (22.6%)	464 (24.1%)	490 (25.4%)	
Secondary school	1699 (22.0%)	267 (13.8%)	416 (21.6%)	461 (23.9%)	555 (28.8%)	
High school and above	812 (10.5%)	125 (6.5%)	172 (8.9%)	253 (13.1%)	262 (13.6%)	
Former drinking						
No	4168 (54.0%)	1368 (70.9%)	1156 (59.9%)	902 (46.8%)	742 (38.4%)	< 0.001[3]
Yes	3550 (46.0%)	561 (29.1%)	774 (40.1%)	1027 (53.2%)	1188 (61.6%)	
Current drinking						
No	4955 (64.2%)	1526 (79.1%)	1353 (70.1%)	1131 (58.6%)	945 (49.0%)	< 0.001[3]
Yes	2763 (35.8%)	403 (20.9%)	577 (29.9%)	798 (41.4%)	985 (51.0%)	
Former smoking						
No	4412 (57.2%)	1476 (76.5%)	1229 (63.7%)	917 (47.5%)	790 (40.9%)	< 0.001[3]
Yes	3306 (42.8%)	453 (23.5%)	701 (36.3%)	1012 (52.5%)	1140 (59.1%)	
Current smoking						
No	5570 (72.2%)	1636 (84.8%)	1460 (75.6%)	1269 (65.8%)	1205 (62.4%)	< 0.001[3]
Yes	2148 (27.8%)	293 (15.2%)	470 (24.4%)	660 (34.2%)	725 (37.6%)	
BMI, kg/m^2						
≤ 18.4	425 (5.5%)	124 (6.4%)	108 (5.6%)	116 (6.0%)	77 (4.0%)	< 0.001[3]
18.4–23.9	3942 (51.1%)	899 (46.6%)	956 (49.5%)	984 (51.0%)	1103 (57.2%)	
> 23.9	3,351 (43.4%)	906 (47.0%)	866 (44.9%)	829 (43.0%)	750 (38.9%)	
CESD[4]						
Normal	5209 (67.5%)	1191 (61.7%)	1268 (65.7%)	1345 (69.7%)	1405 (72.8%)	< 0.001[3]
Depressive symptoms	2509 (32.5%)	738 (38.3%)	662 (34.3%)	584 (30.3%)	525 (27.2%)	
Kidney disease						
No	7045 (91.3%)	1771 (91.8%)	1780 (92.2%)	1754 (90.9%)	1740 (90.2%)	0.101[3]
Yes	673 (8.7%)	158 (8.2%)	150 (7.8%)	175 (9.1%)	190 (9.8%)	
Hypertension						
No	4040 (52.3%)	852 (44.2%)	1046 (54.2%)	1021 (52.9%)	1121 (58.1%)	< 0.001[2]
Yes	3678 (46.7%)	1077 (55.8%)	884 (45.8%)	908 (47.1%)	809 (41.9%)	

Table 1 (continued)

Characteristic	Sarcopenia index quartile					*P* value
	Overall (N = 7718)	Q1 N = 1929	Q2 N = 1930[1]	Q3 N = 1929	Q4 N = 1930	
ADL						
None	6287 (81.5%)	1446 (75.0%)	1573 (81.5%)	1622 (84.1%)	1646 (85.3%)	< 0.001[3]
Impaired	1431 (18.5%)	483 (25.0%)	357 (18.5%)	307 (15.9%)	284 (14.7%)	

[1] Data were presented as Median (IQR) or n (%)

[2] Kruskal–Wallis rank sum test

[3] Pearson's Chi-squared test

[4] Assessed by Center for Epidemiologic Studies Depression Scale, with ≥ 10 was deemed as depressive symptoms

Q quartile, *BMI* body mass index, *CESD* Center for Epidemiologic Studies Depression Scale, *ADL* activity of daily living

Table 2 Association between sarcopenia index and incident diabetes mellitus events among all the participants

Characteristic	Case/total	Incidence rate, per 1000 person-year	Model 1	Model 2	Model 3	Model 4
Sarcopenia index (continuous)	501/7718	12.94	0.998 (0.994, 1.001), 0.246	0.996 (0.992, 1.000), 0.073	0.996 (0.992, 1.000), 0.057	0.997 (0.993, 1.001), 0.140
Sarcopenia index (standardized)	501/7718	12.94	0.944 (0.853, 1.037), 0.246	0.906 (0.813, 1.009), 0.073	0.899 (0.807, 1.003), 0.057	0.924 (0.832, 1.026), 0.140
Sarcopenia index						
Q1	133/1930	13.75	Reference	Reference	Reference	Reference
Q2	126/1929	13.02	0.944 (0.733, 1.215), 0.656	0.888 (0.693, 1.138), 0.348	0.876 (0.684, 1.122), 0.295	0.930 (0.724, 1.193), 0.567
Q3	122/1929	12.61	0.912 (0.707, 1.176), 0.479	0.836 (0.644, 1.086), 0.179	0.825 (0.636, 1.072), 0.15	0.892 (0.685, 1.162), 0.398
Q4	120/1930	12.40	0.896 (0.693, 1.156), 0.398	0.796 (0.604, 1.049), 0.105	0.781 (0.592, 1.029), 0.079	0.869 (0.657, 1.150), 0.327

Model 3: adjusted for Model 2 + former drinking, current drinking, former smoking, current smoking.

Model 4: adjusted for Model 3 + BMI, CESD, hypertension.

A linear and negative association between the sarcopenia index and risk of incident diabetes mellitus events using restricted cubic spline regression was also found (*P* for nonlinearity = 0.489) (Fig. 2).

Discussion

Principal findings

In this study, we investigated for the first time the association between the sarcopenia index and the risk of diabetes mellitus based on the CHARLS nationally representative cohort data. We found that a higher sarcopenia index was associated with a lower risk of diabetes mellitus in middle-aged and elderly population. In addition, we found that a 1 standard deviation increase in sarcopenia index was associated with a 7.6% reduction in the risk of diabetes mellitus. These findings provide new clues for the prevention and management of diabetes.

Comparison with previous studies

This result is in general agreement with previous findings. Several cross-sectional and prospective studies have found that sarcopenia or decreased muscle mass/function is significantly associated with the risk of diabetes [2, 6, 13]. A meta-analysis including seven prospective studies showed that the risk of diabetes mellitus in patients with sarcopenia was 1.55 times higher than that in those without sarcopenia [14]. This study further confirms this association and provides the first evidence-based evidence based on a large, national population sample.

It is worth noting that while previous studies have used dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA) to assess muscle mass, the present study utilized a sarcopenia index based on serum creatinine and cystatin C. Compared with DXA and BIA, this index is simple to measure, reproducible, and highly correlated with muscle mass and functional indices [10, 11]. A cohort study that recruited 2615 middle-aged and older adults found that participants in the lowest sarcopenia index quartile group had a 42% increased risk of cognitive impairment relative to those in the highest

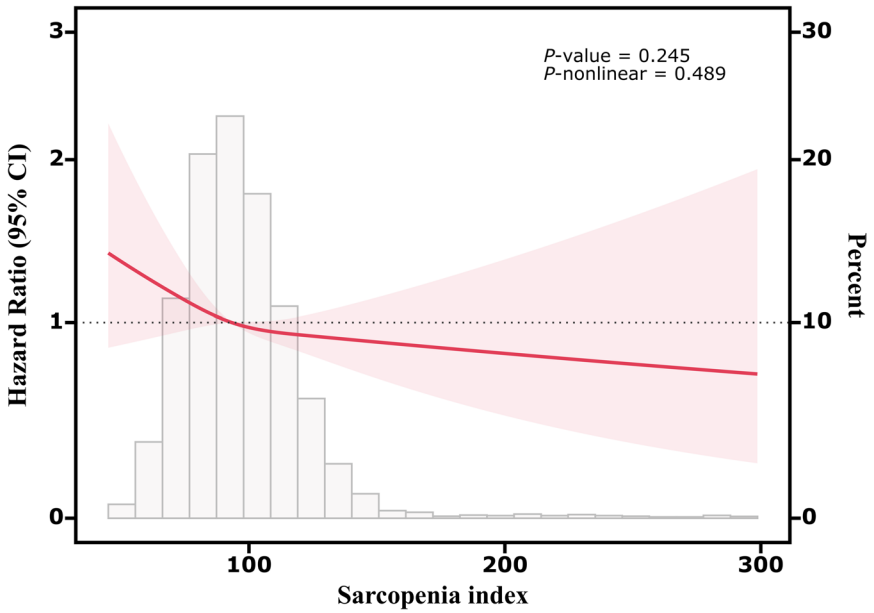

Fig. 2 Spline models of the association between the sarcopenia index and incidence diabetes mellitus. The HR from the multivariate Cox proportional risk models were adjusted for the variables of model 4 in Table 2. The duck red lines indicate the adjusted hazard ratio, and light red shade indicate the 95% confidence interval

sarcopenia index quartile group at 3-month follow-up (odd ratio = 0.58; 95% CI 0.37–0.90) [15]. In addition, another CHARLS-based analysis showed that participants in the sarcopenia index Q1 quartile group had a higher odds of frailty compared to participants in the Q4 quartile group (Q1 vs. Q4: odd ratio = 1.880, 95% CI 1.126–3.139, $P = 0.016$) [16]. This suggests that sarcopenia may be a simple and effective screening tool for sarcopenia, which could be useful for widespread use in clinical practice and large-scale epidemiologic studies.

Potential mechanism

The negative correlation between sarcopenia index and the risk of diabetes mellitus that we observed may stem from several potential mechanisms: first, muscle is the main glucose metabolizing organ, and the decrease in its mass and function may lead to insulin resistance, which may increase the risk of diabetes mellitus [17, 18]. Low sarcopenia index reflects a decrease in muscle mass and strength, which may interfere with glucose metabolism and ultimately lead to diabetes mellitus. Second, sarcopenia is associated with a chronic inflammatory state, which may increase the development of diabetes through mechanisms that promote insulin resistance, apoptosis and oxidative stress [19, 20]. It has been found that patients with sarcopenia are often associated with a high prevalence of metabolic and cardiovascular diseases, which are themselves associated with chronic inflammation [21, 22]. In addition, sarcopenia may affect the body's utilization of nutrients, leading to related metabolic disorders. It has been shown that deficiencies in nutrients such as protein and vitamin D are associated with decreased muscle mass and function and may increase the risk of diabetes [23, 24].

Strength and limitation

The strength of this study lies in the use of data from the CHARLS nationally representative cohort, which has a large sample size, a wide population, and a high degree of external validity. Moreover, the covariates were adjusted to improve the reliability of the results, and the causal relationship between the sarcopenia index and the risk of diabetes mellitus could be better explored.

However, there are some limitations of this study. A major limitation of this study is that we only measured the sarcopenia index at baseline, which cannot capture the dynamic changes during the follow-up period. Although serum creatinine and cystatin C are relatively stable biomarkers in healthy adults [25], they may be influenced by various factors, such as dietary habits, infections, and physical activity levels [26, 27]. Previous studies have shown that both muscle mass and function can change over time, particularly in older adults [28]. Leenders et al. demonstrated that patients with type 2 diabetes showed a greater decline in muscle mass and strength with aging compared to non-diabetic controls [7]. In addition, sarcopenic status could be modified by various lifestyle factors including diet and physical

activity patterns [29]. Therefore, repeated measurements of the sarcopenia index during follow-up would provide more comprehensive information about the temporal relationship between changes in muscle mass and diabetes risk. Future studies incorporating multiple assessments of the sarcopenia index are needed to better understand this dynamic relationship.

Second, although we adjusted for confounding factors as much as possible, there are still some residual confounders that may arise from unmeasured factors, such as dietary habits, which can significantly influence both muscle mass and diabetes risk [30–32], were not measured in CHARLS cohort. In addition, physical activity variables were not included in this study due to their high number of missing variables. These unmeasured confounding factors may have affected the observed association between sarcopenia index and diabetes risk. Third, this study was conducted only in the Chinese population, and further research is needed to verify whether it can be generalized to other regions or ethnic groups. Fourth, although the sarcopenia index is correlated with muscle mass and functional indices, there is no consensus on its diagnostic threshold in this population, and further studies are needed.

Future direction

Several important directions should be considered for future research. First, longitudinal studies with repeated measurements of sarcopenia index are needed to better understand the dynamic relationship between changes in muscle mass and diabetes risk. Such studies would help clarify whether the rate of muscle mass decline, rather than a single baseline measurement, better predicts diabetes development. Second, more comprehensive assessment of potential confounding factors, including detailed dietary patterns, physical activity levels, and inflammatory markers, would provide deeper insights into the underlying mechanisms. Third, studies investigating the optimal cutoff points of sarcopenia index for different populations are warranted, as diagnostic thresholds may vary by age, gender, and ethnicity. Fourth, intervention studies are needed to determine whether strategies targeting muscle mass preservation through exercise programs or nutritional supplementation could effectively prevent diabetes in high-risk populations. Fifth, future research should explore the potential interaction between sarcopenia index and other established risk factors for diabetes, such as obesity, metabolic syndrome, and genetic predisposition. Finally, studies incorporating both sarcopenia index and traditional muscle mass measurement methods (e.g., DXA or BIA) would help validate this simple biomarker's utility in large-scale diabetes risk screening and prevention programs.

Conclusion

In conclusion, this large prospective study provides preliminary evidence that sarcopenia index, based on serum creatinine and cystatin C levels, may be associated with incident diabetes risk in middle-aged and older Chinese adults. While our findings suggest potential utility of this easily accessible marker for diabetes risk assessment, future studies with repeated measurements are needed to validate these results and better understand the temporal relationship between changes in sarcopenia index and diabetes development.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02405-w.

Additional file 1

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Author contributions
FZ, XYW, YB and HFQ conceptualised and designed the study, drafted the initial manuscript, coordinated and supervised data collection, analysed the data and reviewed and revised the manuscript. FZ and HFQ revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability
The data sets for this study are available on https://charls.pku.edu.cn/.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The studies involving human participants were reviewed and approved by the Biomedical Ethical Review Committee of Peking University (IRB00001052-11015). The participants provided their written informed consent to participate in this study. The privacy rights of participants were observed.

Competing interests
The authors declare no competing interests.

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