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Sarcopenia and Cardiovascular Diseases in Individuals With Diabetes or Prediabetes

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ABSTRACT

Sarcopenia is a known risk factor for cardiovascular disease (CVD) in individuals with diabetes or prediabetes, but the impact of changes in sarcopenia status on CVD risk remains unclear. This study aimed to examine how changes in sarcopenia status between baseline and the second follow-up survey, conducted 2 years later, influence the risk of developing incident CVD. Incident CVD was identified based on self-reported physician diagnoses of heart disease, such as angina, myocardial infarction, heart failure, or stroke. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for potential confounders. The results showed that participants who progressed from non-sarcopenia to possible sarcopenia or sarcopenia had a higher risk of developing CVD. Their risk was significantly greater compared to those who remained non-sarcopenic (HR 1.37, 95% CI 1.08–1.73). Conversely, individuals who recovered from sarcopenia to non-sarcopenia or possible sarcopenia had a lower risk of CVD. Their risk was lower than those who remained sarcopenic (HR 0.40, 95% CI 0.20–0.82). Among individuals with possible sarcopenia at baseline, those who recovered to non-sarcopenia had a reduced CVD risk. This reduction was significant compared to those who remained in possible sarcopenia (HR 0.62, 95% CI 0.46–0.84). These findings suggest that changes in sarcopenia status have a significant impact on CVD risk, with worsening sarcopenia increasing the likelihood of CVD and recovery lowering the risk in individuals with diabetes or prediabetes.

1 | Introduction

The incidence and mortality rates of cardiovascular disease (CVD) have continued to rise with the aging population, posing a significant public health challenge [1]. In 2019, the global number of CVD cases across 204 countries and regions increased to 523 million, up from 271 million in 1990, with 6.5 million more deaths attributed to CVD during this period [2]. Despite substantial advancements in the treatment of CVDs over the past two decades, CVD remains the leading cause of death worldwide

Abbreviations: ASM, appendicular skeletal muscle mass; ASM/Ht2, height-adjusted muscle mass; AWGS, Asian Working Group for Sarcopenia; BMI, body mass index; CHARLS, China Health and Retirement Longitudinal Study; CI, confidence intervals; CRP, C-reactive protein; CVD, cardiovascular diseases; DXA, dual x-ray absorptiometry; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; PMM, predictive mean matching; SBP, systolic blood pressure; T2DM, type 2 diabetes; TG, triglycerides; UA, uric acid.

Xia Wang and Qingyue Zeng contributed equally to this article as co-first author.

[1]. Type 2 diabetes (T2DM) and prediabetes are prevalent among individuals diagnosed with CVD and are associated with adverse outcomes [3]. Identifying residual risk factors in CVD patients with varying glucose metabolism statuses is crucial for reducing the global burden of CVD.

Sarcopenia, a skeletal muscle disorder prevalent among middle-aged and older adults, is characterized by the progressive loss of muscle strength, mass, and function, often driven by factors such as chronic inflammation, insulin resistance, and mitochondrial dysfunction [4, 5]. Sarcopenia is linked to various adverse clinical outcomes, including a higher risk of falls, fractures, physical disability, frequent hospitalizations, diminished quality of life, and increased mortality [6–8]. Moreover, sarcopenia is closely associated with diabetes, abnormal glucose metabolism, and CVD [9–13]. Understanding the relationship between sarcopenia and CVD in individuals with diabetes or prediabetes may offer new insights into improving the prevention and management of CVD in this high-risk population.

Previous studies have found that possible sarcopenia and sarcopenia increase the risk of new-onset CVD, but these studies primarily focused on sarcopenia status at baseline without considering changes in sarcopenia status during follow-up [14–17]. Investigating changes in sarcopenia status, rather than assessing sarcopenia only at baseline, could reveal a more comprehensive biological link, such as the association between sarcopenia progression and CVD. Importantly, growing evidence suggests that sarcopenia can be reversed with appropriate interventions [18, 19]. Evaluating the risk of new-onset CVD in individuals who recover from sarcopenia could provide critical evidence for incorporating sarcopenia interventions into cardiovascular practice. Thus, it is essential to examine the association between changes in sarcopenia status and the risk of new-onset CVD in individuals with diabetes or prediabetes.

In this study, we utilized prospective cohort data from the China Health and Retirement Longitudinal Study (CHARLS) to explore the association between changes in sarcopenia status and the risk of new-onset CVD in individuals with diabetes or prediabetes. In our statistical analysis, we adjusted for age and sex, and further accounted for sociodemographic factors (marital status, residence location, and education level), lifestyle factors, clinical measures, and comorbidities. This allowed us to isolate the independent effect of sarcopenia on CVD risk, considering the established roles of these factors as key determinants of both sarcopenia and CVD [14, 17]. We hypothesize that the progression of sarcopenia status increases the risk of new-onset CVD, while the recovery from sarcopenia reduces this risk.

2 | Methods

2.1 | Study Design and Population

This study utilized data from the CHARLS, a prospective, nationally representative cohort study conducted in China. The detailed study design is summarized in the methods section of the supporting information. In this study, the first wave of CHARLS (2011) was considered the baseline, and the second wave (2013) served as the follow-up survey (Figure S1). Data from these two waves were used to assess the dynamic changes in sarcopenia status, with subsequent surveys used to track outcomes until the final fifth wave (2020). The study was approved by the Peking University Institutional Review Board, and informed consent was obtained from each participant.

In this study, the classifications of prediabetes and diabetes were primarily based on the American Diabetes Association (ADA) criteria. Prediabetes was defined as a fasting plasma glucose (FPG) of 5.6–6.9 mmol/L or a glycated hemoglobin (HbA1c) level of 5.7%–6.4% (39–47 mmol/mol). Diabetes was defined as an FPG $\geq$ 7.0 mmol/L, HbA1c $\geq$ 6.5% (48 mmol/mol), a self-reported history of diabetes, and/or the use of anti-diabetic medications [20]. Figure 1 illustrates the selection process of the study population. Among the 6687 CHARLS participants with diabetes or prediabetes, 1569 individuals were excluded due to missing sarcopenia status data at baseline (including appendicular skeletal muscle mass [ASM], grip strength, and physical performance). Additionally, 700 participants who had CVD at baseline or were lost to follow-up were also excluded. Ultimately, 4418 eligible participants were included in the baseline sarcopenia status analysis. For the analysis of changes in sarcopenia status, a further 1394 participants were excluded based on similar criteria, leaving 3024 participants in the final analysis.

2.2 | Assessment of Sarcopenia Status

Sarcopenia was assessed according to the 2019 algorithm of the Asian Working Group for Sarcopenia (AWGS), which evaluates three components: muscle strength, ASM, and physical performance [5]. Sarcopenia is diagnosed when low muscle mass is combined with either low muscle strength or poor physical performance.

Muscle strength was measured using a YuejianTM WL-1000 dynamometer, with grip strength tested on both the dominant and non-dominant hands [5]. Low grip strength was defined as <28 kg for men and <18 kg for women.

The ASM was estimated by a validated anthropometric equation in Chinese residents [16]. Several studies have shown that the agreement between the ASM equation model and dual x-ray absorptiometry (DXA) was strong [21]. The cutoff for defining low muscle mass was based on the sex-specific lowest 20% of the height-adjusted muscle mass (ASM/Ht2) among the study population [21, 22]. In our study, body weight and height were measured using a stadiometer and a digital floor scale to the nearest 0.1 cm and 0.1 kg, respectively; the body weight and height were measured in kg and cm, respectively [23]. Finally, the ASM/Ht2 values of <7.01 kg/m^2 in men and <5.31 kg/m^2 in women in 2011, <7.05 kg/m^2 in men and <5.38 kg/m^2 in women in 2013, and <7.07 kg/m^2 in men and <5.39 kg/m^2 in women in 2015.

In terms of physical performance, the gait speed and the chair stand test were performed using the method described by Wu et al. [23]. Further details about the definitions for sarcopenia components in the CHARLS have been described previously [5]. In our study population, only 87 participants (2.0%) were classified as having severe sarcopenia at baseline. Therefore,

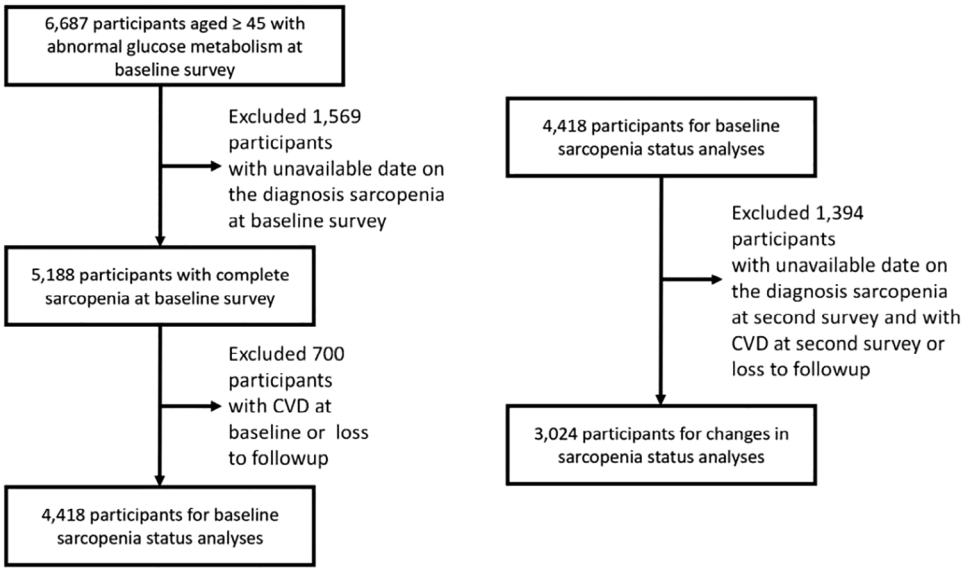

FIGURE 1 | Selection process of the study population. CVD, cardiovascular disease.

participants with severe sarcopenia were merged into the sarcopenia group, resulting in three baseline groups: non-sarcopenia ($n = 2880$), possible sarcopenia ($n = 1148$), and sarcopenia ($n = 390$).

2.3 | Ascertainment of Covariates

The covariates considered in the analysis included age, sex, marital status, education level, residence location, smoking status, drinking status, physical function, body mass index (BMI), systolic blood pressure (SBP), C-reactive protein (CRP), HbA1c, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), uric acid (UA), and common comorbidities such as hypertension. Marital status was categorized as married or other (which included separated, divorced, never married, or widowed). Education level was divided into two categories: junior high school or below, and senior high school or above. The residence location was classified as rural or urban. Smoking status was categorized as never smokers and ever smokers, with the latter including former and current smokers. Similarly, drinking status was divided into never drinkers and ever drinkers. Physical function was evaluated by a six-item activities of daily living (ADL) scale, and individuals reported some difficulty in performing tasks including dressing, bathing, eating, getting in and out of bed, using the toilet, and controlling urination and defecation. The total score ranged from 0 to 6, with a score of 0 indicating no impairment, 1 or more indicating impairment.

2.4 | Assessment of CVD Events

The study outcome was CVD events, including heart disease and stroke. Consistent with previous studies, CVD events were assessed through the following questions: "Have you been told by a doctor that you have been diagnosed with a heart attack, angina, coronary heart disease, heart failure, or other heart problems?" and "Have you been told by a doctor that you have been diagnosed with a stroke?". Participants who reported having heart disease or stroke were classified as having CVD [24, 25].

2.5 | Statistical Analysis

For descriptive statistics, continuous variables were presented as mean (standard deviation) or median (interquartile range), while categorical variables were expressed as count (percentage). To analyze the association between baseline sarcopenia status and the risk of new-onset CVD, hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were calculated using Cox proportional hazards regression models. Four models were estimated: Model 0 was an unadjusted model to estimate crude HRs; Model 1 adjusted for age and sex; Model 2 further adjusted for marital status, residence location, and education level; and Model 3 additionally adjusted for alcohol consumption, smoking status, physical function, BMI, SBP, CRP, HbA1c, TG, HDL-C, and histories of hypertension and dyslipidemia. The missing rates of covariates ranged from 0.15% to 0.74%. Therefore, missing data for covariates were imputed using the predictive mean matching (PMM) method [26]. Similar methods were used to analyze the association with changes in sarcopenia status. The proportional hazards assumption of the Cox regression models was confirmed using Schoenfeld residuals [27].

For the analysis of changes in sarcopenia status, stratified analyses by sex and age (middle-aged: <65 years; older adults: ≥65 years) were also conducted. The statistical significance of interactions was assessed using likelihood ratio tests. Several sensitivity analyses were performed regarding changes in sarcopenia status: (i) to reduce bias from potentially unstable changes in sarcopenia status, sarcopenia status was reassessed at the third survey to ensure stability of the changes (Figure S2); (ii) the primary analysis was repeated with additional adjustments for the use of antihypertensive and antidiabetic medications; (iii) the possible sarcopenia/sarcopenia group was separated from the non-sarcopenia/possible sarcopenia group.

All statistical analyses were conducted using R software (version 4.4.1). All p values were two-sided, with $p < 0.05$ considered statistically significant.

3 | Results

3.1 | Baseline Characteristics of the Study Population

Based on the inclusion and exclusion criteria, a total of 4418 participants (52.4% female, average age 59.1 years) were included in the baseline sarcopenia status analysis. The baseline characteristics of these participants are detailed in Table 1. Compared to those without sarcopenia, participants with sarcopenia were generally older, had a higher proportion of females, were less likely to be married, had lower educational attainment, and were more likely to live in rural areas. Additionally, sarcopenic participants had lower BMI, HbA1c, TG, and UA levels, but higher HDL cholesterol levels.

For the analysis of changes in sarcopenia status, 3024 participants (52.8% female, average age 58.9 years) were included based on the relevant criteria, with their baseline characteristics presented in Table 2.

In the baseline sarcopenia status analysis, the median follow-up period in CHARLS was 9 years, during which 956 participants developed CVD. In the analysis of changes in sarcopenia status, the median follow-up period was 7 years, during which 662 participants developed CVD.

3.2 | Association of Baseline Sarcopenia Status With Incident CVD

The association between baseline sarcopenia status and the risk of new-onset CVD is presented in Table S1. After adjusting for confounding factors, participants with sarcopenia also had a significantly increased risk of developing CVD compared to those without sarcopenia (HR 1.34, 95% CI 1.04–1.72). Furthermore, a clear trend of increasing frailty risk with worsening sarcopenia severity was observed, as indicated by the trend test (p for trend = 0.01). The relationship between baseline sarcopenia status and the risks of heart disease and stroke is also detailed in Table S1.

3.3 | Association of Changes in Sarcopenia Status With Incident CVD

Figure 2 presents the number and percentage of participants whose sarcopenia status changed over the 2-year follow-up period. Among participants without sarcopenia at baseline, 402 (19.5%) progressed to possible sarcopenia or sarcopenia. Conversely, among those with sarcopenia at baseline, 110 (55.0%) recovered to a non-sarcopenia or possible sarcopenia status.

Table 3 shows the association between changes in sarcopenia status and the risk of new-onset CVD. Compared to participants with stable non-sarcopenia status, those who progressed to possible sarcopenia/sarcopenia exhibited a significantly increased risk of new-onset CVD (HR 1.37, 95% CI 1.08–1.73). In contrast, participants with sarcopenia at baseline who recovered to a non-sarcopenia/possible sarcopenia status had a significantly reduced risk of new-onset CVD compared to those with stable sarcopenia status (HR 0.40, 95% CI 0.20–0.82). For participants with possible sarcopenia at baseline, those who recovered to a non-sarcopenia status had a significantly lower risk of new-onset CVD compared to those who remained in the possible sarcopenia status (HR 0.62, 95% CI 0.46–0.84). Additionally, participants with baseline possible sarcopenia who progressed to sarcopenia did not show a statistically significant increase in risk.

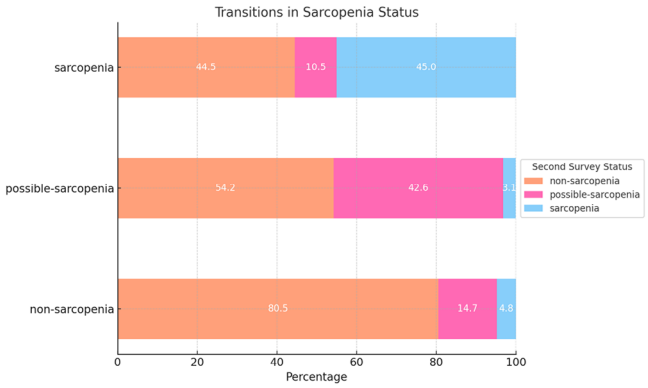

FIGURE 2 | Distribution of sarcopenia status transitions. The text on the left indicates the sarcopenia state at baseline. The time interval between baseline and the second survey was 2 years in the China Health and Retirement Longitudinal Study (CHARLS).

Table S2 provides a detailed description of the association between changes in sarcopenia status and the risk of new-onset heart disease and stroke.

3.4 | Subgroup Analyses and Sensitivity Analyses

In the subgroup analysis, compared to participants with stable non-sarcopenia status, women and participants younger than 65 years who progressed from non-sarcopenia to possible sarcopenia or sarcopenia had a significantly higher risk of developing new-onset CVD (women: HR 1.51, 95% CI 1.14–2.01; <65 years: HR 1.43, 95% CI 1.10–1.85). However, this increased risk was not statistically significant in men or participants aged 65 years and older. Among participants who recovered from sarcopenia to non-sarcopenia or possible sarcopenia, men and those under 65 years showed a reduced risk of new-onset CVD compared to those with stable sarcopenia (men: HR 0.30, 95% CI 0.13–0.71; <65 years: HR 0.24, 95% CI 0.08–0.72). For participants with possible sarcopenia at baseline, recovery to non-sarcopenia was associated with a significantly lower risk of new-onset CVD compared to those who remained in possible sarcopenia across all subgroups, except for those aged 65 and older (women: HR 0.43, 95% CI 0.27–0.68; men: HR 0.68, 95% CI 0.48–0.98; <65 years: HR 0.51, 95% CI 0.36–0.71). Subgroup analysis results related to CVD, heart disease, and stroke are also provided in Tables S3–S5.

When sarcopenia status changes were reassessed using data from the third survey, consistent results were observed, indicating

TABLE 1 | Baseline characteristics of participants for baseline sarcopenia status analyses.

Characteristics	Total ($n = 4418$)	Non-sarcopenia ($n = 2880$)	Possible sarcopenia ($n = 1148$)	Sarcopenia ($n = 390$)	*p* value
Age, mean (SD), years	59.13 ± 8.96	57.04 ± 7.88	61.07 ± 8.96	68.91 ± 8.67	<0.0001
Sex, *n* (%)					<0.0001
Female	2313 (52.35)	1428 (49.58)	662 (57.67)	223 (57.18)	
Male	2105 (47.65)	1452 (50.42)	486 (42.33)	167 (42.82)	
Marital status, *n* (%)					<0.0001
Married	3903 (88.34)	2646 (91.88)	979 (85.28)	278 (71.28)	
Others	515 (11.66)	234 (8.13)	169 (14.72)	112 (28.72)	
Education, *n* (%)					<0.0001
Junior and below	4009 (90.74)	254 3 (88.30)	1083 (94.34)	383 (98.21)	
Senior and above	409 (9.26)	337 (11.70)	65 (5.66)	7 (1.79)	
Residence, *n* (%)					<0.0001
Rural	2875 (65.07)	1802 (62.57)	764 (66.55)	309 (79.23)	
Urban	1543 (34.93)	1078 (37.43)	384 (33.45)	81 (20.77)	
Drinking status, *n* (%)					<0.0001
Ever drinkers	1877 (42.49)	1294 (44.93)	428 (37.28)	155 (39.74)	
Never drinkers	2541 (57.51)	1586 (55.07)	720 (62.72)	235 (60.26)	
Smoking status, *n* (%)					<0.001
Ever smokers	1735 (39.27)	1189 (41.28)	391 (34.06)	155 (39.74)	
Never smokers	2683 (60.73)	1691 (58.72)	757 (65.94)	235 (60.26)	
Physical function					<0.0001
No	3969 (89.84)	2659 (92.33)	999 (87.02)	311 (79.74)	
Yes	449 (10.16)	221 (7.67)	149 (12.98)	79 (20.26)	
BMI, mean (SD) (kg/m^2)	23.86 ± 3.89	24.04 ± 3.82	24.96 ± 3.47	19.25 ± 1.86	<0.0001
SBP, mean (SD) (mm Hg)	132.07 ± 21.26	130.52 ± 20.04	135.15 ± 22.42	134.48 ± 25.06	<0.0001
CRP, mean (SD) (mg/L)	2.91 ± 8.03	2.80 ± 8.33	3.17 ± 7.44	2.90 ± 7.51	0.42
HbA1c, mean (SD), %	5.44 ± 0.96	5.42 ± 0.91	5.53 ± 1.12	5.30 ± 0.81	<0.0001
Triglycerides, mean (SD) (mmol/L)	1.70 ± 1.50	1.75 ± 1.57	1.73 ± 1.49	1.26 ± 0.78	<0.0001
HDL cholesterol, mean (SD) (mmol/L)	1.30 ± 0.41	1.30 ± 0.41	1.25 ± 0.36	1.48 ± 0.42	<0.0001
UA, mean (SD) (mg/dL)	4.53 ± 1.27	4.59 ± 1.28	4.45 ± 1.21	4.36 ± 1.33	<0.001
Hypertension, *n* (%)					<0.0001
No	2543 (57.56)	1768 (61.39)	564 (49.13)	211 (54.10)	
Yes	1875 (42.44)	1112 (38.61)	584 (50.87)	179 (45.90)	
Dyslipidemia, *n* (%)					<0.0001
No	2387 (54.03)	1515 (52.60)	597 (52.00)	275 (70.51)	
Yes	2031 (45.97)	1365 (47.40)	551 (48.00)	115 (29.49)	

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; UA, Uric acid.

that progression to sarcopenia continued to be associated with an increased risk of new-onset CVD, while recovery from sarcopenia was associated with a reduced risk (Tables S6 and S7). These findings remained consistent even after further adjustment for the use of antihypertensive and antidiabetic medications (Tables S8 and S9). Additionally, when analyzing the possible sarcopenia/sarcopenia group separately from the non-sarcopenia/possible sarcopenia group, the results were consistent: participants who progressed from non-sarcopenia to possible sarcopenia or sarcopenia had an increased risk of

TABLE 2 | Baseline characteristics of participants for changes in sarcopenia status analyses.

Characteristics	Total ($n = 3024$)	Non-sarcopenia ($n = 2059$)	Possible sarcopenia ($n = 765$)	Sarcopenia ($n = 200$)	*p* value
Age, mean (SD), years	58.92 ± 8.47	57.33 ± 7.78	60.81 ± 8.43	67.97 ± 8.21	<0.0001
Sex, *n* (%)					<0.001
Female	1596 (52.78)	1034 (50.22)	444 (58.04)	118 (59.00)	
Male	1428 (47.22)	1025 (49.78)	321 (41.96)	82 (41.00)	
Marital status, *n* (%)					<0.0001
Married	2696 (89.15)	1899 (92.23)	652 (85.23)	145 (72.50)	
Others	328 (10.85)	160 (7.77)	113 (14.77)	55 (27.50)	
Education, *n* (%)					<0.0001
Junior and below	2743 (90.71)	1829 (88.83)	718 (93.86)	196 (98.00)	
Senior and above	281 (9.29)	230 (11.17)	47 (6.14)	4 (2.00)	
Residence, *n* (%)					<0.0001
Rural	2026 (67.00)	1332 (64.69)	529 (69.15)	165 (82.50)	
Urban	998 (33.00)	727 (35.31)	236 (30.85)	35 (17.50)	
Drinking status, *n* (%)					<0.01
Ever drinkers	1278 (42.26)	917 (44.54)	286 (37.39)	75 (37.50)	
Never drinkers	1746 (57.74)	1142 (55.46)	479 (62.61)	125 (62.50)	
Smoking status, *n* (%)					0.02
Ever smokers	1171 (38.72)	833 (40.46)	265 (34.64)	73 (36.50)	
Never smokers	1853 (61.28)	1226 (59.54)	500 (65.36)	127 (63.50)	
Physical function					<0.01
No	2753 (91.04)	1898 (92.18)	680 (88.89)	175 (87.50)	
Yes	271 (8.96)	161 (7.82)	85 (11.11)	25 (12.50)	
BMI, mean (SD) (kg/m^2)	23.95 ± 3.85	24.06 ± 3.82	24.85 ± 3.48	19.35 ± 1.74	<0.0001
SBP, mean (SD) (mm Hg)	131.98 ± 21.02	130.63 ± 19.89	134.77 ± 22.50	135.30 ± 24.84	<0.0001
CRP, mean (SD) (mg/L)	2.65 ± 7.55	2.64 ± 8.07	2.76 ± 6.48	2.32 ± 5.53	0.76
HbA1c, mean (SD), %	5.44 ± 0.97	5.43 ± 0.92	5.52 ± 1.11	5.26 ± 0.83	<0.01
Triglycerides, mean (SD) (mmol/L)	1.69 ± 1.53	1.74 ± 1.62	1.69 ± 1.40	1.22 ± 0.75	<0.0001
HDL cholesterol, mean (SD) (mmol/L)	1.30 ± 0.41	1.30 ± 0.41	1.26 ± 0.37	1.49 ± 0.44	<0.0001
UA, mean (SD) (mg/dL)	4.53 ± 1.27	4.58 ± 1.28	4.41 ± 1.24	4.39 ± 1.28	<0.01
Hypertension, *n* (%)					<0.0001
No	1751 (57.90)	1249 (60.66)	392 (51.24)	110 (55.00)	
Yes	1273 (42.10)	810 (39.34)	373 (48.76)	90 (45.00)	
Dyslipidemia, *n* (%)					<0.0001
No	1639 (54.20)	1093 (53.08)	405 (52.94)	141 (70.50)	
Yes	1385 (45.80)	966 (46.92)	360 (47.06)	59 (29.50)	

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; UA, uric acid.

TABLE 3 | Association of changes in sarcopenia status with risks of incident cardiovascular disease.

		Crude model	Model 1	Model 2	Model 3
Character	Events/*n*	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Stable non-sarcopenia	315/1657	Reference	Reference	Reference	Reference
Non-sarcopenia to possible sarcopenia/sarcopenia	104/402	1.42 (1.14, 1.77)	1.32 (1.05, 1.66)	1.34 (1.06, 1.68)	1.37 (1.08, 1.73)
Stable possible sarcopenia	110/326	Reference	Reference	Reference	Reference
Possible sarcopenia to non-sarcopenia	88/415	0.57 (0.43, 0.75)	0.60 (0.45, 0.80)	0.58 (0.43, 0.77)	0.62 (0.46, 0.84)
Possible sarcopenia to sarcopenia	5/24	0.57 (0.23, 1.40)	0.54 (0.22, 1.33)	0.5 (0.20, 1.25)	0.58 (0.23, 1.45)
Stable sarcopenia	26/90	Reference	Reference	Reference	Reference
Sarcopenia to non-sarcopenia/possible sarcopenia	14/110	0.40 (0.21, 0.78)	0.42 (0.21, 0.84)	0.41 (0.20, 0.84)	0.40 (0.20, 0.82)

Notes: Model 1 included adjustments for age and gender; Model 2 further adjusted for marriage, residence, and education level; and Model 3 additionally adjusted for drinking, smoking, physical function, BMI, SBP, CRP, HbA1c, TG, HDL-C, as well as history of hypertension and dyslipidemia.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TG, Triglycerides.

new-onset CVD, while those who recovered from sarcopenia to non-sarcopenia or possible sarcopenia had a reduced risk (Table S10).

4 | Discussion

In this study, we investigated the association between baseline sarcopenia status and changes in sarcopenia status with the risk of new-onset CVD using prospective cohort data in individuals with diabetes or prediabetes. The findings indicate that participants with possible sarcopenia and sarcopenia had a higher risk of developing CVD compared to those without sarcopenia. Additionally, participants who progressed from non-sarcopenia to possible sarcopenia or sarcopenia exhibited a significantly increased risk of CVD. Conversely, participants with possible sarcopenia who recovered to a non-sarcopenia status and those with sarcopenia who recovered to a non-sarcopenia or possible sarcopenia status had a significantly reduced risk of new-onset CVD (Structured Graphical Abstract).

Sarcopenia is becoming increasingly prevalent among the global aging population. Previous research has demonstrated a close relationship between sarcopenia status and cardiovascular health in individuals with diabetes or prediabetes [14–17]. In a prospective cohort study involving 11 974 White European UK Biobank participants with T2DM, it was found that sarcopenia increased the risk of developing CVD, with the onset occurring earlier compared to those without sarcopenia (HR 1.89, 95% CI 1.61–2.21) [17]. Similarly, in a study using DXA to define sarcopenic obesity, 716 Japanese patients were followed for a median of 2.6 years. Sarcopenic obesity was significantly associated with incident CVD even after adjusting for confounding variables (HR 2.63, 95% CI 1.10–6.28) [16]. Our study corroborates these findings, showing a significant increase in CVD risk among participants with possible sarcopenia and sarcopenia in Chinese prospective cohort setting. The biological mechanisms underlying the association between sarcopenia and CVD may involve shared physiological pathways, such as systemic inflammation, oxidative stress, overactivation of the ubiquitin-proteasome system, and impaired glucose tolerance [28–30]. However, our results remained significant even after adjusting for traditional cardiovascular risk factors, further supporting the notion that sarcopenia should be considered an independent risk factor for CVD in individuals with diabetes or prediabetes.

In addition to the baseline sarcopenia status, our study also investigated the associations of changes in sarcopenia status with incident CVD, which were not examined previously. In a previous study comprising 4395 individuals with a total of 10 778 records of sarcopenia state assessment, a total of 60.3% remained possible sarcopenia, 24.5% of individuals with a current state of possible sarcopenia returned to non-sarcopenia, 6.7% progressed to sarcopenia, and 8.5% died by the next follow-up [31]. Our study confirmed previous findings on the dynamic nature of sarcopenia status in the CHARLS cohort. Importantly, compared to participants with stable non-sarcopenia status, those who progressed to possible sarcopenia or sarcopenia exhibited a significantly increased risk of developing CVD. This finding underscores the adverse impact of sarcopenia progression on the incidence of CVD. Conversely, participants who recovered to a non-sarcopenia or possible sarcopenia status from sarcopenia, as well as those who recovered to a non-sarcopenia status from possible sarcopenia, demonstrated a significantly reduced risk of new-onset CVD. These results suggest that reversing sarcopenia has substantial benefits for the prevention of CVD. When sarcopenia status changes were reassessed using data from the third survey, consistent results were observed: progression to sarcopenia remained associated with an increased risk of new-onset CVD, while recovery from sarcopenia was linked to a

decreased risk of CVD. These findings persisted even after further adjustments, highlighting the robustness of the associations. However, these results need to be further replicated and validated in other cohorts to confirm their generalizability.

This study has significant clinical and public health implications. First, integrating sarcopenia assessment into routine cardiovascular practice is crucial, particularly for individuals with diabetes and prediabetes. Individuals with sarcopenia or possible sarcopenia should be prioritized as key target groups for the prevention of adverse cardiovascular events. Additionally, it is important to assess sarcopenia-related risk factors in individuals without sarcopenia to identify those at risk early. By implementing appropriate preventive measures, the progression of sarcopenia can be delayed, thereby reducing the incidence of CVD in these patients. Notably, sarcopenia is a reversible condition, and the study found that individuals who reversed their sarcopenia status had a significantly lower risk of CVD. Therefore, more efforts are needed to implement effective interventions aimed at reversing sarcopenia. Possible sarcopenia might present a better intervention window for CVD prevention than sarcopenia, as individuals with possible sarcopenia are more likely to recover to a non-sarcopenia status (as shown in Table 3). Further research, including real-world data and clinical trials, is needed to explore the best interventions for reversing sarcopenia and to evaluate their effectiveness and safety in cardiovascular practice.

This study has several strengths. To our knowledge, it is the first to investigate the association between changes in sarcopenia status and the risk of new-onset CVD in individuals with diabetes or prediabetes. Additionally, the study included a large, nationally representative sample, enhancing the generalizability of the findings to the middle-aged and older adult population in China. The robustness of the results was also ensured through various sensitivity analyses.

This study has several limitations. First, similar to previous studies, the identification of CVD was based on self-reported physician diagnoses [10, 24, 32]. Due to the absence of medical records in the CHARLS dataset, this approach may introduce classification bias. However, Xie et al. [33] reported that 77.5% of self-reported new-onset coronary heart disease cases were confirmed by medical records in the English Longitudinal Study of Ageing, suggesting reasonable reliability. Nonetheless, our findings should be interpreted with caution. Future research should consider incorporating medical record verification to improve diagnostic accuracy and reduce potential misclassification bias. Second, changes in sarcopenia status were assessed based on two surveys. Although theoretically, using more surveys could provide a more accurate assessment of sarcopenia status changes, our sensitivity analysis, which reassessed sarcopenia status using data from the third survey, yielded consistent results, indicating the reliability of our findings. Nevertheless, future studies should consider integrating more follow-up assessments, if available, to further enhance measurement accuracy. Third, due to the lack of detailed classification of CVD, we were unable to explore the associations between sarcopenia and specific types of heart disease. Fourth, although we adjusted for multiple confounding factors, residual confounding may still exist, such as genetic predisposition and dietary habits. Another limitation of CHARLS is the lack of data on factors potentially linked to the reversal of sarcopenia, such as diet, and the changes in these factors over time. This may limit our understanding of the mechanisms underlying sarcopenia and its relationship with CVD. Although the CHARLS dataset includes a physical activity variable, its broad classification of duration and type limits its accuracy in measuring exercise intensity. Therefore, we did not include it in our models. Future studies should consider more precise and quantitative physical activity assessments to better explore its link with sarcopenia progression and CVD risk. Additionally, the observational design and the dropout rate during follow-up inevitably introducing selection bias should also be taken into account when interpreting and extrapolating our results. Furthermore, the study sample primarily comprises middle-aged and older adults from China, which may limit the generalizability of our findings to other ethnic groups or regions. Given potential differences in genetics, lifestyle, and healthcare systems across populations, future studies should validate these findings in diverse cohorts to improve external applicability. Despite these limitations, this study enhances our understanding of the impact of changes in sarcopenia status on cardiometabolic health in individuals with diabetes or prediabetes.

5 | Conclusion

Changes in sarcopenia status are associated with varying risks of new-onset CVD in individuals with diabetes or prediabetes. Progression of sarcopenia status increases the risk of developing CVD, while recovery from sarcopenia reduces this risk. Future research should focus on developing precise preventive strategies to delay the progression of sarcopenia and implementing targeted interventions to reverse sarcopenia within cardiovascular practice.

Author Contributions

Conceptualization: Q.Z., X.W., and S.L. Data curation: Q.Z. and X.W. Formal analysis: Q.Z. Writing–original draft: Q.Z. and X.W. Writing–review & editing: X.Y. and S.L. Supervision: X.Y. and S.L. All authors actively participated in the research process made substantial contributions to manuscript revisions, and carefully reviewed and approved the final version.

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Ethics Statement

The ethical review board of Peking University meticulously examined and subsequently sanctioned the CHARLS project (IRB 00001052–11014).

Consent

Informed consent was obtained from all subjects prior to their participation in this study.

Conflicts of Interest

No conflicts of interest need to be disclosed.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.