Research Square

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Association of coexisting osteoporosis risk and low muscle mass with incident cognitive impairment in Chinese middle-aged and older adults: A prospective CHARLS cohort study

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Research Article

Keywords: Osteoporosis Risk, Low Muscle Mass, Cognitive Impairment, Cohort Study, Interaction, Mediation

Posted Date: November 25th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11392759/v1

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Additional Declarations: No competing interests reported.

Abstract

Background There are few studies on the association between osteoporosis risk or low muscle mass and cognitive impairment, especially long-term cohort studies. This study aims to explore the effects of osteoporosis risk, low muscle mass and their interaction on the risk of cognitive impairment in middle-aged and elderly Chinese population.

Methods Data were drawn from the China Health and Retirement Longitudinal Study (CHARLS). Using four waves of visits in 2011, 2013, 2015 and 2018, cognitive impairment was defined by the CHARLS-adapted cognitive scale (total score 0–31) as a harmonized total score < 11; To ensure longitudinal comparability with the 2011–2015 waves, 2018 wave episodic memory scores were harmonized onto the 2015 measurement metric using the Wu et al. (2024)[54] weighted equipercentile equating algorithm. Osteoporosis risk was assessed using the Osteoporosis Self-Assessment Tool for Asians (OSTA). Appendicular skeletal muscle mass (ASM) was estimated by an anthropometric equation validated in Chinese populations, and low muscle mass was defined by ASM/Ht². The primary analysis included 1,708 participants with normal baseline cognition and complete four-wave cognitive follow-up; Sensitivity analysis included 2,765 participants with normal baseline cognition and complete exposure assessment but with missing cognitive data in the subsequent three waves. Participants were divided into four groups: “reference group (no osteoporosis risk and no low muscle mass)”, “only low muscle mass group”, “only osteoporosis risk group” and “both-conditions group”. Cox proportional hazard regression models were used. Multiplicative and additive interactions were tested. Subgroup analysis, sensitivity analysis and mediation analysis were further conducted. Weight and CESD score were considered potential mediators rather than conventional covariates.

Results The overall incidence of cognitive impairment during follow-up was 4.98 per 100 person-waves. The highest incidence was observed in the both-conditions group (8.94 per 100 person-waves), followed by the osteoporosis risk only group (7.41), the low muscle mass only group (4.23), and the reference group (4.08). In the primary fully adjusted Model 4, compared with the reference group, the both-conditions group had a 39% increased risk of incident cognitive impairment (HR=1.39, 95% CI: 1.01–1.90, P=0.044). No significant differences were observed for the low muscle mass only group (HR=1.09, 95% CI: 0.59–2.02, P=0.781) or the osteoporosis risk only group (HR=1.05, 95% CI: 0.73–1.50, P=0.788). There was no significant multiplicative interaction (LRT P=0.598) or additive interaction (RERI=0.244, 95%CI:-0.683–1.001; AP=0.176, 95%CI: -0.537–0.661; SI=2.723, 95%CI: -14.17–13.887) between low muscle mass and osteoporosis risk on cognitive impairment. Mediation analysis showed that weight and CESD score jointly accounted for 76.60% of the association in the both-conditions group (total effect HR=1.349; direct effect HR=1.073; indirect effect HR=1.257; indirect effect via weight=0.197; via CESD=0.032). Although the specific indirect effect through each mediator individually did not reach conventional significance due to shared variance, the significant total indirect effect suggests that both pathways act in concert. Sensitivity analysis using the expanded dataset (n=2,765) showed that the both-conditions group remained associated with increased risk (HR=1.37, 95% CI: 1.09–1.72, P=0.008). Subgroup analysis showed that the both-conditions group had significantly higher risk in participants aged 60–69 years (HR=1.82) and those with primary school education (HR=2.30).

Conclusions Coexisting osteoporosis risk and low muscle mass, rather than either condition alone, identified a high-risk phenotype for incident cognitive impairment, suggesting that community screening should jointly assess bone and muscle health using simple tools (e.g., OSTA and anthropometric muscle mass estimation). Weight and CESD score jointly accounted for 76.6% of this association, although these mediation findings

remain exploratory. No significant interaction between low muscle mass and osteoporosis risk on cognitive impairment was observed.

Mini-abstract. Bone and muscle weaknesses often coexist in later life, but their combined effect on future mental decline was unclear. Following Chinese adults, having both together raised that risk while neither alone did; lighter weight and low mood partly explained why. Simple body measurements can flag those needing earlier brain-health care.

Introduction

The public health burden of cognitive impairment

Cognitive impairment (CI) is a growing public health challenge as populations age[12][13]. It ranges from mild cognitive impairment (MCI) to dementia. In China, MCI prevalence among middle-aged and older adults is 15.5%–20.1%[1][2][4][5], with higher rates in rural areas and among ethnic minorities[1]. Patients with MCI show subjective and objective cognitive decline and progress to dementia at up to 16% per year[14]. Globally, one person develops dementia every four seconds[15]; dementia cases may reach 139 million by 2050, 70% in low- and middle-income countries[1], and China may have 66.3 million by 2050[3]. Risk factors include sex, age, education, lifestyle, and diet[16]; advanced age, low education, and lower MMSE scores worsen cognitive deterioration[6][7][8][9][10]. Gracner et al[17].quantified the life-course burden: per capita lifetime economic burden was $124,000 and total burden $627 billion (59% ADRD, 41% MCI); early-onset CI burden reached $376,000; CI reduced life expectancy by 3.0 years and QALYs by 2.5 years; early- versus late-onset CI reduced life expectancy by 12.3 versus 10.3 years; and MCI in early-onset CI lasted about 13 years, more than 7 years longer than in late-onset CI. Socially, CI causes labor loss, caregiving burden, and heavy healthcare consumption, with disproportionate burden among non-White and low-education groups.

Research Progress on Osteoporosis and Cognitive Impairment

Osteoporosis is a skeletal disease characterized by reduced bone mineral density (BMD), which increases the risk of fractures. Many studies indicate that individuals with osteoporosis are more likely to develop cognitive impairment, and lower bone mineral density is associated with cognitive decline in middle-aged and older populations[18][19]. Existing evidence suggests that the skeleton can interact with the central nervous system through the actions of secreted proteins, bone-derived cells, and regulators of skeletal development[19]. Secreted proteins synthesized by osteocytes, such as osteocalcin[20] and osteopontin[21][22][23], have been shown to affect central nervous system function, and bone marrow-derived cells can migrate to the central nervous system and influence the brain[24][25].

Research Progress on Low Muscle Mass/Sarcopenia and Cognitive Impairment

Sarcopenia is a progressive skeletal muscle disease causing muscle atrophy, limited mobility, and weakness, and it increases falls, functional decline, frailty, and death[26]. Low muscle mass is its core physiological basis and early indicator. A US cohort found that low muscle mass was significantly associated with cognitive dysfunction and risk of CI[26]. Muscle function predicts long-term cognitive decline, and the two conditions share inflammatory, metabolic, and neurodegenerative pathways. The muscle–brain axis involves

neuromuscular junction damage, PI3K-AKT-mTOR dysregulation, upregulation of MuRF1/Atrogin-1/Trim32, reduced protective myokines such as irisin, mature BDNF, and FGF21, increased pro-inflammatory interleukins and pro-BDNF, central inflammation via NF-κB/JNK, gut dysbiosis, endotoxemia, insulin resistance, oxidative stress, and mitochondrial dysfunction, forming a vicious cycle between muscle atrophy and brain injury[27].

Research Gap: Absence of Studies on the Joint Effects of Osteoporosis and Low Muscle Mass

Osteoporosis and low muscle mass frequently coexist as osteosarcopenia and share chronic low-grade inflammation, inadequate nutrition, hormonal decline, and physical inactivity, suggesting additive or synergistic effects on cognitive health. However, most studies examine one exposure in isolation; few include both in the same analytical framework; existing comorbidity studies are mostly cross-sectional; and interaction analyses are rare. Evidence is mostly from developed countries, with few large prospective cohorts in Chinese middle-aged and older adults[28]. Chinese populations differ in body composition, lifestyle, disease spectrum, and education. DXA is accurate but expensive and complex for community screening. The joint effects of OSTA-assessed osteoporosis risk and anthropometric low muscle mass on CI remain insufficiently validated, hindering early identification and primary-care prevention.

Our Study Overview and Significance

Using four CHARLS waves (2011–2018), we included adults aged ≥ 45 years with normal baseline cognition. Osteoporosis risk was assessed by the Osteoporosis Self-Assessment Tool for Asians (OSTA)[46][47]; low muscle mass was defined by ASM/Ht² estimated from a Chinese-validated anthropometric equation[48][49]. Participants were divided into four groups. Cox proportional hazards models examined independent and joint effects; multiplicative interaction was tested by likelihood ratio test; additive interaction was quantified by RERI, AP, and SI; subgroup, sensitivity, and mediation analyses explored robustness and pathways. Weight and CESD score were treated as potential mediators. This is the first systematic prospective Chinese study of osteoporosis risk and low muscle mass on incident CI, providing evidence for the bone–muscle–brain axis and for community screening covering “bone health–muscle health–cognitive health.”Importantly, this study does not provide specific intervention prescriptions. It does not specify resistance or aerobic exercise frequency, intensity, or duration; protein, calcium, or vitamin D doses or dietary patterns; anti-osteoporosis drugs or hormone therapy; depression treatment or cognitive behavioral therapy; randomized controlled trial evidence that any intervention reduces CI; or implementation pathways, cost-effectiveness estimates, and intervention targets. These remain key gaps for future research.

Methods

Study Design and Participants

Clinical trial number: not applicable. This study was based on four waves of prospective follow-up data from the China Health and Retirement Longitudinal Study (CHARLS) from 2011 to 2018, specifically including 2011 (wave 1), 2013 (wave 2), 2015 (wave 3), and 2018 (wave 4). The 2011 wave was used as the baseline, and participants

with normal cognitive function at baseline were included and followed to observe incident cognitive impairment over the subsequent seven years. CHARLS is a longitudinal study of Chinese adults aged 45 years and older, designed to examine the socioeconomic determinants and consequences of aging. The survey includes extensive information on economic status, physical and mental health, demographic characteristics, and social networks among middle-aged and older adults. CHARLS covers 28 provinces in China, involving residents from 150 counties. Data for this study were extracted from the Harmonized CHARLS dataset, which was created through standardized processing of the original CHARLS questionnaire data by the USC Gateway to Global Aging Data. The Harmonized CHARLS harmonizes variable definitions, coding, and missing value indicators across waves, enabling ready-to-use cross-wave longitudinal analysis[43].

We used the 2011 wave as baseline. Cognitive status was assessed across the four waves according to cognitive assessment methods used in previous studies. A total of 11,868 participants with variables required for cognitive function assessment were selected. After excluding participants with missing values required for calculating exposure indicators (n = 2,083), 9,785 participants were able to complete exposure assessment. We then excluded participants with missing baseline cognitive function variables (n = 878), participants with baseline cognitive impairment (n = 427), and participants with missing covariates (n = 5,715), leaving 2,765 participants with normal baseline cognition and complete exposure assessment. This 2,765-participant dataset was used as the sensitivity analysis dataset. After further excluding participants with missing cognitive follow-up variables across waves (n = 1,057), 1,708 participants with complete cognitive follow-up across all four waves constituted the primary analysis dataset. The detailed flow is shown in Fig. 1.

Exposure Grouping: based on two binary indicators—low muscle mass (yes/no) and osteoporosis risk (present/absent)—participants were divided into four groups: (1) reference group: neither osteoporosis risk nor low muscle mass; (2) low muscle mass only group: low muscle mass without osteoporosis risk; (3) osteoporosis risk only group: osteoporosis risk without low muscle mass; and (4) both-conditions group : both osteoporosis risk and low muscle mass. In the subsequent Cox regression analyses, group (1) served as the reference group, and the other three groups were compared with the reference group separately.

Outcome Definition: (1) In the primary analysis using the 1,708 participants with complete follow-up, the outcome was defined as the first occurrence of cognitive impairment during the subsequent follow-up waves among participants with normal cognitive function at baseline. (2) In the sensitivity analysis using the 2,765 participants with missing follow-up data, loss to follow-up for cognitive assessment was treated as censoring. In this model, outcomes included only “cognitive impairment” and “censored”.

Measurement of Cognitive Function

Cognitive function was assessed using the China Health and Retirement Longitudinal Study (CHARLS)-adapted cognitive scale, which is comparable to the Mini-Mental State Examination (MMSE). This scale consists of two domains: mental status integrity and episodic memory. The mental status integrity sub-domain includes orientation (0–5 points), calculation (0–5 points), and drawing (0–1 point), with a total score ranging from 0 to 11. The episodic memory sub-domain comprises immediate and delayed word recall tests, with a maximum raw score of 20 (10 points for immediate recall and 10 points for delayed recall). The overall total cognitive score ranges from 0 to 31 points[53].

Notably, the word recall test underwent major revisions in the 2018 CHARLS wave (Wave 4): the word stimuli were replaced, the immediate recall test was administered for three trials, and visual presentation of word lists was newly introduced. These procedural changes rendered raw memory scores from Wave 4 non-comparable with those from prior waves (2011, 2013, 2015) in longitudinal analyses. To mitigate measurement bias caused by test-form modification, we applied the weighted equipercentile equating algorithm published by Wu et al. (2024)[54] to convert the first-trial immediate recall and delayed recall raw scores of the 2018 wave into 2015-equivalent harmonized memory scores. The cross-walk lookup table from the original publication was adopted for score conversion. The harmonized total cognitive score was calculated by summing the mental status score and the equated immediate and delayed recall scores. For waves 2011, 2013, and 2015, original immediate and delayed word recall raw scores were used directly, and cognitive impairment was defined as a harmonized total score < 11, consistent with previous CHARLS-based studies[53].

Definition of Osteoporosis Risk

We used the Osteoporosis Self-Assessment Tool for Asians (OSTA), proposed by Koh et al. in 2001, to assess osteoporosis risk in the study population. The OSTA score was calculated as follows: OSTA score = 0.2 × [weight (kg) − age (years)] [46]. Based on the OSTA score, participants were categorized into a high-risk group (OSTA < -4), a medium-risk group (-4 ≤ OSTA ≤ -1), and a low-risk group (OSTA > -1)[46][47]. We then defined individuals in the high-risk and medium-risk groups as having osteoporosis risk, and those in the low-risk group as having no osteoporosis risk.

Muscle Mass Assessment

Muscle mass was estimated by appendicular skeletal muscle mass (ASM) using an anthropometric equation previously validated in Chinese populations: ASM = 0.193 × weight (kg) + 0.107 × height (cm) − 4.157 × sex (male = 1, female = 2) − 0.037 × age − 2.631[48][49][52]. After calculating ASM, height-adjusted muscle mass (ASM/Ht²) was computed by dividing ASM by height in meters squared; this index is also referred to as the appendicular skeletal muscle mass index. The cutoff for low muscle mass was based on the lowest 20th percentile of ASM/Ht² in the study population[48][49]. In our study population, the 20th percentiles of ASM/Ht² were 7.09 kg/m² for men and 5.46 kg/m² for women, and values ≤ these cutoffs were considered low muscle mass.

Covariates

Covariates included age (continuous), gender (male/female), educational level (< primary school / primary school / ≥ secondary school), ever had hypertension (no/yes), ever had diabetes (no/yes), ever had cancer (no/yes), smoking (no/yes), drinking (no/yes), and physical activity (no/yes). These variables were included in Model 4 (the primary analysis model).

Weight and CESD score were not included as conventional covariates in the primary model. In a secondary model (Model 5), they were additionally adjusted for. Because the effect estimate for the both-conditions group attenuated after this adjustment, we conducted an exploratory mediation analysis to examine whether weight

and CESD score could statistically account for part of the association. This analysis was exploratory and data-driven rather than based on a prespecified pathophysiological hypothesis.

Statistical Analysis

All statistical analyses were performed using R software (version 4.5.2), with a two-sided significance level set at $\alpha = 0.05$.

Baseline Descriptive Analysis

Continuous variables (age, weight, cesd score) were first tested for normality using the Shapiro–Wilk test, supplemented by Q-Q plots. Normally distributed continuous variables were expressed as mean ± standard deviation, and between-group comparisons were performed using one-way analysis of variance (ANOVA). Non-normally distributed continuous variables were expressed as median (interquartile range, IQR), and between-group comparisons were performed using the Kruskal–Wallis test. Categorical variables (gender, educational level, hypertension, diabetes, cancer, smoking, alcohol consumption, physical activity, age group) were expressed as frequencies (percentages), and between-group comparisons were performed using the chi-square test (Table 1).

Incidence of Cognitive Impairment

The incidence rate of cognitive impairment per 100 person-waves was calculated for each exposure group (Table S1). “100 person-waves” is a composite unit used in longitudinal cohort studies to measure exposure time and observation frequency. It is similar to “person-years,” but because only four fixed time points (waves) were available and the intervals between waves were not exactly equal (2011–2013–2015–2018), “wave” was used as the observation unit rather than “year.” The incidence rate per 100 person-waves = (number of events) ÷ (total person-waves) × 100.

Survival Analysis and Cox Regression

Kaplan–Meier curves were used to plot cognitive-normal survival curves for the four groups, and between-group comparisons were performed using the log-rank test (Figure S2). Cox proportional hazards regression models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). To control for confounding, five progressively adjusted models were constructed: Model 1 (unadjusted), Model 2 (adjusted for age and gender), Model 3 (additionally adjusted for education, hypertension, diabetes and cancer), Model 4 (additionally adjusted for smoking, drinking and physical activity), this was the primary fully adjusted model, and Model 5 (additionally adjusted for weight and CESD score) (Table 2); because these two variables were considered potential mediators, Model 5 was not used as the primary model but was used to illustrate attenuation after adjustment for mediators. The proportional hazards assumption was tested using Schoenfeld residuals, and model diagnostics were performed using deviance residuals.

Interaction Effect Analysis

Low muscle mass (yes/no) and osteoporosis risk (present/absent) were simultaneously included as a product term in the primary fully adjusted Cox model to test multiplicative interaction, and the likelihood ratio test (LRT) was used to compare the goodness of fit of models with and without the interaction term (Table 3). In addition, based on the primary fully adjusted model with the four-category exposure variable, additive interaction measures were calculated, including the relative excess risk due to interaction (RERI), attributable proportion

(AP), and synergy index (SI) (Table 4). Furthermore, the primary adjusted model was used to predict the probability of normal cognition under different exposure combinations at covariate means, and interaction effect survival curves were plotted (Figure S5).

Subgroup Analysis

Stratified analyses were conducted by gender (male/female), age group (< 60 years / 60–69 years / ≥70 years), and educational level (less than primary school / primary school / secondary school or above). The primary adjusted Cox model was repeated within each subgroup to assess the consistency of exposure effects (Table S2).

Sensitivity Analysis

To assess the impact of incomplete follow-up on the results, one sensitivity analysis was conducted using the expanded dataset of 2,765 participants. The primary analysis included 1,708 participants with complete cognitive data across all four waves, excluding those lost to follow-up, which may introduce “complete follow-up bias” and affect the generalizability of the findings. The sensitivity analysis included all 2,765 participants with normal cognition at baseline, with first occurrence of cognitive impairment as the outcome event (event = 1), and loss to follow-up and no cognitive impairment by the end of follow-up treated as censored (censored = 0). The primary fully adjusted Cox proportional hazards regression model (Model 4) was repeated (Table S3) to verify whether the conclusions of the primary analysis remained robust after expanding the sample and tolerating incomplete follow-up.

Mediation Analysis

Because the effect estimate for the both-conditions group attenuated after additional adjustment for weight and CESD score in Model 5, we conducted an exploratory mediation analysis within the Cox proportional hazards framework. Weight and CESD score were treated as candidate mediators. The exposure was defined as a binary indicator of coexistence (both-conditions group = 1, others = 0). We used the Bootstrap method (repeated sampling 1000 times) to test the mediating effect of body weight and CESD between joint exposure and cognitive impairment. Total effect, direct effect, total indirect effect, indirect effect via weight, indirect effect via CESD, and proportion mediated were estimated. Because weight and CESD score were measured at baseline, the temporal ordering of exposure, mediator, and outcome cannot be fully established; therefore, these mediation results should be interpreted as hypothesis-generating rather than as evidence of a specific causal pathway.

Results

Baseline characteristics

A total of 1,708 participants with normal cognitive function at baseline were included in the primary complete-follow-up analysis set. They were categorised into four exposure groups: reference group (n = 1,272), low muscle mass only (n = 66), osteoporosis risk only (n = 167), and both conditions (n = 203).

Age differed significantly across groups (P < 0.001). The osteoporosis-risk-only group had the oldest median age (65, IQR: 62–69 years), whereas the low-muscle-mass-only group was the youngest (50, IQR: 47–54.75

years). Weight, height and CESD score also differed significantly across groups (all $P < 0.001$ or $P = 0.001$).

Sex distribution was not significantly different across groups ($P = 0.094$). Educational attainment differed significantly ($P < 0.001$); the proportion of participants with less than primary school and primary school education was highest in the both-conditions group and osteoporosis-risk-only group. Hypertension ($P < 0.001$), diabetes ($P = 0.021$), smoking ($P = 0.002$) and age group ($P < 0.001$) were significantly unevenly distributed. Drinking ($P = 0.292$), cancer ($P = 0.057$) and physical activity ($P = 0.790$) did not differ significantly across groups.

Regarding age subgroups, the osteoporosis-risk-only group had the highest proportion of individuals aged ≥ 60 years, while the low-muscle-mass-only group was predominantly aged < 60 years (97.0%).

Table 1
Baseline characteristics of participants by exposure group

Characteristic	Level	Reference group	Low muscle mass only group	Osteoporosis risk only group	Both-conditions group	P	Test
n		1272	66	167	203		
Age median(IQR)		53(48–59)	50 (47-54.75)	65 (62–69)	63 (59–68)	< 0.001	Kruskal-Wallis
Weight,kg median(IQR)		64.65 (58.57–70.83)	50.85 (46.22–54.8)	55 (51.4–58.6)	47 (44-50.85)	< 0.001	Kruskal-Wallis
Height,m median(IQR)		1.61 (1.56–1.67)	1.64 (1.57–1.69)	1.55 (1.50–1.59)	1.56 (1.51–1.61)	< 0.001	Kruskal-Wallis
CESD Score median(IQR)		5 (2–10)	6 (3.25-10)	7 (4–12)	7 (3–12)	0.001	Kruskal-Wallis
Gender n,(%)	Male	668 (52.5)	45 (68.2)	86 (51.5)	107 (52.7)	0.094	Chi-square
	Female	604 (47.5)	21 (31.8)	81 (48.5)	96 (47.3)		
Edu_level n,(%)	Below primary	238 (18.7)	11 (16.7)	53 (31.7)	66 (32.5)	< 0.001	Chi-square
	Primary	315 (24.8)	21 (31.8)	59 (35.3)	66 (32.5)		
	Secondary or above	719 (56.5)	34 (51.5)	55 (33.0)	71 (35.0)		
Ever had hypertension n,(%)	No	959 (75.4)	60 (90.9)	109 (65.3)	176 (86.7)	< 0.001	Chi-square
	Yes	313 (24.6)	6 (9.1)	58 (34.7)	27 (13.3)		
Ever had diabetes n,(%)	No	1190 (93.6)	66 (100.0)	155 (92.8)	198 (97.5)	0.021	Chi-square

Continuous variables that follow a normal distribution are expressed as mean (SD), while those that do not follow a normal distribution are expressed as median (IQR). Categorical variables are expressed as n (%). For between-group comparisons: normally distributed continuous variables use one-way analysis of variance (ANOVA), non-normally distributed continuous variables use the Kruskal-Wallis test, and categorical variables use the chi-square test.

Characteristic	Level	Reference group	Low muscle mass only group	Osteoporosis risk only group	Both-conditions group	P	Test
	Yes	82 (6.4)	0 (0.0)	12 (7.2)	5 (2.5)		
Ever had cancer n,(%)	No	1261 (99.1)	64 (97.0)	167 (100.0)	203 (100.0)	0.057	Chi-square
	Yes	11 (0.9)	2 (3.0)	0 (0.0)	0 (0.0)		
Ever smoking n,(%)	No	787 (61.9)	31 (47.0)	114 (68.3)	107 (52.7)	0.002	Chi-square
	Yes	485 (38.1)	35 (53.0)	53 (31.7)	96 (47.3)		
Ever drinking n,(%)	No	744 (58.5)	31 (47.0)	100 (59.9)	120 (59.1)	0.292	Chi-square
	Yes	528 (41.5)	35 (53.0)	67 (40.1)	83 (40.9)		
Physical_activity n,(%)	No	488 (38.4)	28 (42.4)	64 (38.3)	84 (41.4)	0.790	Chi-square
	Yes	784 (61.6)	38 (57.6)	103 (61.7)	119 (58.6)		
Age_group n,(%)	< 60 years	995(78.2%)	64 (97.0)	26 (15.6)	59 (29.1)	< 0.001	Chi-square
	60–69 years	259(20.4%)	2 (3.0)	103 (61.7)	109 (53.7)		
	≥ 70 years	18 (1.4)	0 (0.0)	38 (22.7)	35 (17.2)		

Continuous variables that follow a normal distribution are expressed as mean (SD), while those that do not follow a normal distribution are expressed as median (IQR). Categorical variables are expressed as n (%). For between-group comparisons: normally distributed continuous variables use one-way analysis of variance (ANOVA), non-normally distributed continuous variables use the Kruskal-Wallis test, and categorical variables use the chi-square test.

Incidence of cognitive impairment in each exposure group The incidence rates of cognitive impairment for each exposure group are detailed in Table S1. Over the four waves of follow-up, corresponding to a total of 6,653 person-waves, 331 out of 1,708 participants developed cognitive impairment, yielding an overall incidence density of 4.98 per 100 person-waves. Among the groups, the both-conditions group exhibited the highest incidence rate (8.94 per 100 person-waves), followed by the osteoporosis risk only group (7.41), the low muscle mass only group (4.23), and the reference group (4.08).

Figure S1 shows that the proportion of individuals with cognitive impairment increased steadily across follow-up waves; by Wave 4, 84.1% of participants remained cognitively normal.

Survival analysis

Figure S2 presents the Kaplan–Meier survival curves, illustrating the probability of maintaining normal cognition during follow-up for the four exposure groups. The both-conditions group consistently exhibited the lowest cognitive-normal survival probability throughout the observation period. Then the normal survival probability of cognitive function in the osteoporosis risk only group was also relatively low. The overall difference in the risk of cognitive impairment among the four groups was statistically significant (log-rank test, $P < 0.0001$).

Figure S3 displays the cumulative incidence curves for cognitive impairment over time across the four groups. The trend observed in the cumulative incidence plots was directionally consistent with the findings from the Kaplan–Meier analysis.

Cox proportional hazards regression model

Univariate analysis

In the unadjusted Model 1, the osteoporosis risk only group (HR = 1.92, 95% CI: 1.40–2.63, $P < 0.001$) and the both-conditions group (HR = 2.38, 95% CI: 1.81–3.12, $P < 0.001$) had significantly higher risk of cognitive impairment, whereas the low muscle mass only group did not (HR = 1.04, 95% CI: 0.57–1.90, $P = 0.908$).

Multivariable Stepwise-Adjusted Models

To control for potential confounding, we constructed five sequentially adjusted Cox proportional hazards regression models (Table 2):

In Model 2, after adjustment for age and gender, the both-conditions group remained significant (HR = 1.46, 95% CI: 1.07–1.99, $P = 0.016$), while the osteoporosis-risk-only group was attenuated (HR = 1.04, 95% CI: 0.73–1.50, $P = 0.812$).

In Model 3, results were similar : both-conditions HR = 1.40 (95% CI: 1.02–1.92, $P = 0.036$); osteoporosis-risk-only HR = 1.05 (95% CI: 0.73–1.49, $P = 0.801$); low-muscle-mass-only HR = 1.10 (95% CI: 0.59–2.03, $P = 0.769$).

In Model 4 (the primary fully adjusted Model), the both-conditions group continued to show a significantly elevated risk of cognitive impairment (HR = 1.39, 95% CI: 1.01–1.90, $P = 0.044$). The low-muscle-mass-only group (HR = 1.09, 95% CI: 0.59–2.02, $P = 0.781$) and the osteoporosis-risk-only group (HR = 1.05, 95% CI: 0.73–1.50, $P = 0.788$) did not show statistically significant differences from the reference group (Also visible in Figure S4).

In Model 5, after additional adjustment for weight and CESD score, the both-conditions group was attenuated to non-significance (HR = 0.91, 95% CI: 0.59–1.41, $P = 0.679$), suggesting that weight and CESD score may mediate this association.

Table 2
Multivariable Cox regression models for cognitive impairment

Exposure	Model1 (Unadjusted)	Model2 (+ Age, Gndr)	Model3 (+ Edu,HTN, DM, CA)	Model4* (+ Smk, Drnk, PA)	Model5 (+ Wt, CESD)
Low muscle mass only					
HR(95% CI)	1.04(0.57–1.90)	1.25(0.68–2.31)	1.10(0.59–2.03)	1.09(0.59–2.02)	0.83(0.44–1.58)
P value	0.908	0.474	0.769	0.781	0.574
Osteoporosis risk only					
HR(95% CI)	1.92(1.40–2.63)	1.04(0.73–1.50)	1.05(0.73–1.49)	1.05(0.73–1.50)	0.79(0.53–1.17)
P value	< 0.001*	0.812	0.801	0.788	0.242
Both-conditions					
HR(95% CI)	2.38(1.81–3.12)	1.46(1.07–1.99)	1.40(1.02–1.92)	1.39(1.01–1.90)	0.91(0.59–1.41)
P value	< 0.001*	0.016*	0.036*	0.044*	0.679

HR: hazard ratio; CI: confidence interval. Model 1: unadjusted. Model 2: adjusted for age and gender. Model 3: additionally adjusted for education, ever had hypertension, diabetes and cancer. Model 4: additionally adjusted for smoking, drinking and physical_activity. Model 5: additionally adjusted for weight and CESD score.

Interaction effect analysis

Multiplicative Interaction

Low muscle mass (yes vs. no) and osteoporosis risk (present vs. absent) were included as a product term in the primary fully adjusted Cox model; the main effect HR for low muscle mass was 1.09 (95% CI: 0.59–2.02, P = 0.781), and the main effect HR for osteoporosis risk was 1.05 (95% CI: 0.73–1.50, P = 0.788). The product interaction term (low muscle mass × osteoporosis risk) yielded HR = 1.21 (95% CI: 0.59–2.47, P = 0.603). The likelihood ratio test comparing models with and without the interaction term yielded P = 0.598, indicating no significant multiplicative interaction (Table 3), indicating that no significant multiplicative interaction was observed between low muscle mass and osteoporosis risk. Figure S5 (interaction survival curves) displays the predicted probability of maintaining normal cognition for the four exposure combinations (low muscle mass: yes/no × osteoporosis risk: present/absent), estimated at the mean values of covariates. As shown in the figure, The probability of maintaining normal cognitive function in individuals with low muscle mass and osteoporosis risk is the lowest than that in individuals with low muscle mass or osteoporosis risk alone. However, if the risk of osteoporosis and low muscle mass go through different pathways (interaction is significant), there should be an explosive synergistic effect when the two coexist (such as HR > 2).

Table 3. Multiplicative interaction effects from Cox model

Term	HR (95% CI)	P
Low muscle mass (Yes vs No)	1.09 (0.59–2.02)	0.781
Osteoporosis risk (Yes vs No)	1.05 (0.73–1.50)	0.788
Low muscle mass × Osteoporosis risk	1.21 (0.59–2.47)	0.603
Interaction P (LRT)	Reference	0.598
HRs are from the model 4 including interaction term. Interaction P is from likelihood ratio test comparing models with and without interaction.		

Additive Interaction

Based on the primary fully adjusted Cox model using the four-category exposure variable, additive interaction measures were further calculated. The results (Table 4) showed a RERI of 0.244 (95% CI: −0.683 to 1.001), an AP of 0.176 (95% CI: −0.537 to 0.661), and an SI of 2.723 (95% CI: −14.17 to 13.887). The confidence intervals for all three measures crossed their respective null values (0 for RERI and AP, 1 for SI), suggesting no significant additive interaction between low muscle mass and osteoporosis risk in relation to the development of cognitive impairment.

It should be noted that the confidence interval for the SI was wide. This is attributable to the mathematical nature of the ratio-based SI measure. In our data, the effect estimates for the ‘osteoporosis risk only’ and ‘low muscle mass only’ groups were close to 1 (HRs ≈ 1.05 and 1.09, respectively), resulting in a near-zero denominator (i.e., the sum of excess risks) in the SI formula. This near-zero denominator is highly sensitive to sampling fluctuations in bootstrap resampling, leading to a wide CI. Nevertheless, the CIs for both RERI and AP also crossed the null (0), and all three measures consistently indicated no significant additive interaction.

Table 4
Additive interaction measures (RERI, AP, SI)

Measure	Estimate	95%CI
RERI	0.244	-0.683-1.001
AP	0.176	-0.537-0.661
SI	2.723	-14.17-13.887
RERI: relative excess risk due to interaction; AP: attributable proportion due to interaction; SI: synergy index.		

Figure S6 presents a heatmap that visually displays the crude incidence rates of cognitive impairment across the four exposure combinations. The deepest colour (indicating the highest incidence rate) was observed in the both-conditions group. This pattern is consistent with the findings from Tables 2 and 3,This further supports that the simple superposition of osteoporosis risk and low muscle mass will increase the risk of cognitive impairment.In summary, no significant multiplicative or additive interaction was observed between low muscle mass and osteoporosis risk for incident cognitive impairment in this study. Although the effect estimates showed a positive interaction between osteoporosis risk and low muscle mass in affecting the risk of cognitive impairment, this trend was not statistically supported.

Subgroup analyses

Subgroup analyses were performed stratified by gender, age group, and education level, repeating the fully adjusted Cox model within each stratum; the results are presented in Table S2.

Stratification by sex: In the male subgroup, HRs were 1.16 (95% CI: 0.56–2.40, P = 0.695) for low muscle mass only, 1.27 (95% CI: 0.78–2.07, P = 0.345) for osteoporosis risk only, and 1.41 (95% CI: 0.90–2.21, P = 0.131) for both conditions. In the female subgroup, HRs were 1.14 (95% CI: 0.35–3.65, P = 0.829), 0.90 (95% CI: 0.53–1.54, P = 0.710), and 1.39 (95% CI: 0.88–2.19, P = 0.160), respectively.

Stratification by age group: In the < 60 years group, HRs were 1.05 (0.56–1.96), 1.30 (0.57–2.98), and 1.20 (0.67–2.16). In the 60–69 years group, the both-conditions group had a significantly increased risk (HR = 1.82, 95% CI: 1.18–2.79, P = 0.007); osteoporosis risk only was HR = 1.13 (0.71–1.81, P = 0.597). In the ≥ 70 years group, HRs were 1.73 (0.58–5.13) for osteoporosis risk only and 2.59 (0.85–7.93) for both conditions, without statistical significance.

Stratification by education level: In the <primary school stratum, HRs were 0.72 (0.22–2.29), 1.26 (0.77–2.06), and 1.13 (0.70–1.82). In the primary school stratum, the both-conditions group had a significantly increased risk (HR = 2.30, 95% CI: 1.38–3.85, P = 0.002); osteoporosis risk only was HR = 0.73 (0.36–1.45, P = 0.364). In the ≥secondary school stratum, no significant associations were observed.

Although the both-conditions group showed significant associations in the 60–69 years and primary school strata, tests for interaction between exposure group and stratifying variables were not statistically significant (P for interaction > 0.05 for gender, age group, and education level). These subgroup findings should therefore be interpreted cautiously and may reflect limited statistical power or multiple testing rather than true effect modification.

Sensitivity analysis

To evaluate the impact of incomplete follow-up, we repeated the fully adjusted Cox model using an extended dataset comprising 2765 participants (including those who were lost to follow-up), treat the loss to follow-up in cognitive function assessment as a censoring event.(Table S3). The low-muscle-mass-only group had HR = 1.11 (95% CI: 0.69–1.80, P = 0.659), the osteoporosis-risk-only group had HR = 1.18 (95% CI: 0.92–1.51, P = 0.200), and the both-conditions group had HR = 1.37 (95% CI: 1.09–1.72, P = 0.008). The direction of the association for the both-conditions group remained consistent with the primary analysis, and the association remained statistically significant.

Mediation analysis

Because weight and CESD score were considered potential mediators, mediation analysis was conducted. As indicated in Table 5. The total effect of the both-conditions group on cognitive impairment was HR = 1.349 (log-scale estimate = 0.299, 95% CI: -0.007–0.606). The direct effect was HR = 1.073 (log-scale estimate = 0.070, 95% CI: -0.291–0.465). The total indirect effect was significant (log-scale estimate = 0.229, 95% CI: 0.019–0.445), with an HR of 1.257. The indirect effect via weight was 0.197 (95% CI: -0.008–0.423), and via CESD was 0.032 (95% CI: -0.007–0.077). The proportion mediated was 76.60%. These findings suggest that weight and

CESD score may statistically account for part of the association, although these mediation findings should be interpreted as exploratory.

Table 5
Mediation Analysis Results (Bootstrap)

Effect	Estimate	95% CI	HR
Total effect (log scale)	0.299	-0.007–0.606	1.349
Direct effect (log scale)	0.070	-0.291–0.465	1.073
Indirect effect (total, log scale)	0.229	0.019–0.445*	1.257
Indirect effect via weight	0.197	-0.008–0.423	
Indirect effect via cesd	0.032	-0.007–0.077	
Proportion mediated(%)	76.60		

Discussion

This prospective cohort study, based on four waves of CHARLS data from 2011 to 2018, examined the independent and joint effects of osteoporosis risk and low muscle mass on incident cognitive impairment. The main findings can be summarized as follows: (1) in the primary fully adjusted model (Model 4), the coexistence of osteoporosis risk and low muscle mass was associated with a significantly increased risk of incident cognitive impairment (HR = 1.39, 95% CI: 1.01–1.90); (2) low muscle mass alone did not significantly increase the risk (HR = 1.09, 95% CI: 0.59–2.02); (3) osteoporosis risk alone was not independently significant in the fully adjusted model (HR = 1.05, 95% CI: 0.73–1.50); (4) no significant multiplicative or additive interaction was observed (LRT P = 0.598; RERI 95% CI included 0); and (5) weight and CESD score mediated 76.60% of the association in the both-conditions group, although these mediation findings should be interpreted as exploratory.

Discussion of the Association Between Osteoporosis Risk and Cognitive Impairment

In this nationally representative cohort, osteoporosis risk alone was associated with cognitive impairment in the unadjusted model, but this association attenuated after full adjustment (HR = 1.05, 95% CI: 0.73–1.50). In contrast, the coexistence of osteoporosis risk and low muscle mass remained significant (HR = 1.39, 95% CI: 1.01–1.90). These findings suggest that osteoporosis risk may not act as an independent risk factor in this population, but may contribute to cognitive decline when it coexists with low muscle mass.

Previous studies using DXA-measured BMD or clinically diagnosed osteoporosis have generally reported positive associations. Zhang et al.[19] found that each 1-SD decrease in BMD was associated with a 15%–22% increased risk of dementia. Wang et al.[29] reported an 80% increased risk of all-cause dementia among individuals with osteoporosis. Chang et al.[30] reported an adjusted HR of 1.46 for dementia. The discrepancy may be explained by the use of OSTA, which identifies risk rather than diagnosis, and by the simultaneous inclusion of low muscle mass. Osteoporosis and low muscle mass frequently coexist and share chronic low-grade inflammation, vitamin D deficiency, declining estrogen levels, physical inactivity, and nutritional

imbalance[35][36][37][38]. When both are present, the combined effect may be more detectable than osteoporosis risk alone, consistent with the concept of osteosarcopenia.

Potential mechanisms include bone-derived endocrine factors such as osteocalcin[20], shared risk factors such as vitamin D deficiency and estrogen decline[19][24][25][29], and chronic inflammatory pathways involving IL-6, TNF-α, and osteopontin[21][22][23][24][29]. The OSTA index requires only age and weight, making it simple, low-cost, and suitable for community screening. Although osteoporosis risk alone was not independently significant, its coexistence with low muscle mass may help identify individuals at high risk for cognitive impairment in primary care.

Discussion of the Negative Finding for Low Muscle Mass and Cognitive Impairment

After full adjustment, low muscle mass alone was not independently associated with incident cognitive impairment (HR = 1.09, 95% CI: 0.59–2.02), but it was significant when combined with osteoporosis risk (HR = 1.39, 95% CI: 1.01–1.90). This null finding differs from some previous studies and may reflect differences in exposure definition, outcome measurement, and age composition.

For exposure definition, this study used an anthropometric equation rather than DXA and did not include muscle strength or physical performance. Lin et al.[31] reported that sarcopenia was associated with lower cognitive function using the same estimation formula. Shi et al.[32] found a significant predictive effect of ASMI on MMSE scores. Wang et al.[26] used DXA and three definitions of low muscle mass and found significant associations with DSST scores. Anthropometric estimation may introduce non-differential misclassification and bias estimates toward the null. The AWGS 2019 criteria also include muscle strength and physical performance[34], which were not available here.

For outcome and age composition, this study used a binary cognitive outcome (< 11), whereas Wang et al.[26] and Lin et al.[31] used continuous cognitive measures. A binary outcome may underestimate early effects. Shi et al.[32] found a lagged effect of muscle mass on cognition, and Oudbier et al.[33] noted that muscle mass declines 3%–8% per decade after age 30, accelerating after 60. In this cohort, about 67% were under 60 years, so low muscle mass alone may not yet have reached a detectable threshold. When combined with osteoporosis risk, the cumulative burden may exceed this threshold. Future studies should use DXA, include muscle function, focus on older populations, and extend follow-up[26][31][32][33].

Discussion of the Interaction Effect Results

This study systematically examined the joint effects of low muscle mass and osteoporosis risk on incident cognitive impairment using both multiplicative and additive interaction frameworks. The cox regression results showed that the low muscle mass alone (HR = 1.09, 95% CI: 0.59–2.02) and osteoporosis risk alone (HR = 1.05, 95% CI: 0.73–1.50) were not independently significant, whereas both-conditions group had a significantly increased risk of cognitive impairment in the main adjusted model 4 (HR = 1.39, 95% CI: 1.01–1.90, P = 0.044). However, formal tests for multiplicative interaction (LRT P = 0.598; product term HR = 1.21, 95% CI: 0.59–2.47, P = 0.603) and additive interaction (RERI = 0.244, 95% CI: -0.683 to 1.001; AP = 0.176, 95% CI: -0.537 to 0.661; SI = 2.723, 95% CI: -14.17 to 13.887) were not statistically significant. These findings suggest that the coexistence of osteoporosis risk and low muscle mass is associated with an elevated risk of cognitive impairment, but the

joint effect appears to be primarily additive rather than synergistic. In other words, the combined effect may be approximately the sum of the individual effects, and the lack of a significant interaction indicates that we cannot conclude that the two exposures amplify each other's effect beyond additivity.

Several explanations can account for the discrepancy between the significant joint effect and the non-significant interaction tests. First, the individual effects of low muscle mass and osteoporosis risk were weak and not statistically significant in the fully adjusted model. When two exposures each have a modest effect, the statistical power to detect a multiplicative or additive interaction is substantially lower than the power to detect a main effect. The sample size of this study, particularly the limited number of events in the low muscle mass only group (n = 66) and osteoporosis risk only group (n = 167), may be insufficient to detect weak to moderate interactions. Second, the OSTA screening tool and the anthropometric equation used to estimate muscle mass are simple and suitable for large-scale community-based research, but they inevitably introduce measurement error compared with DXA-measured BMD and muscle mass. Non-differential misclassification of exposures may attenuate interaction estimates toward the null. Third, the follow-up duration and the binary cognitive outcome may not fully capture the cumulative and potentially lagged effects of bone and muscle health on cognitive decline, making it difficult to detect a synergistic interaction even if one exists.

From a pathophysiological perspective, osteoporosis and low muscle mass share numerous core pathways, including chronic low-grade inflammation[36], vitamin D deficiency, declining estrogen levels[38][39], physical inactivity, and nutritional imbalance[35][37][38]. Research[35] has confirmed that sarcopenia and osteoporosis are mutual risk factors with a positive genetic correlation, sharing a large number of risk genes, circulating proteins (enriched in inflammation/immunity), and metabolites (e.g., omega-3 fatty acids). Chronic inflammation, immune dysregulation, and lipid metabolism disorders may constitute their common pathological basis. Because these two conditions act through overlapping mechanisms, their combined effect may be largely captured by the sum of their individual effects, and the additional synergistic component—if any—may be small and difficult to detect. This is consistent with the concept of osteosarcopenia, in which the coexistence of bone and muscle impairment reflects a shared underlying vulnerability rather than two independent pathological processes that multiply each other's impact.

It should also be noted that the effect estimates for interaction were in the positive direction (RERI = 0.244; product term HR = 1.21), although they did not reach statistical significance. The both-conditions group also had the highest crude incidence rate (8.94 per 100 person-waves), and the coexistence of the two conditions was associated with a significantly increased risk in the primary main fully adjusted model (Model 4). These findings suggest that the joint effect of osteoporosis risk and low muscle mass on cognitive impairment may be additive rather than synergistic, but they do not exclude the possibility of a weak synergistic effect that this study was underpowered to detect. Future studies with larger sample sizes, DXA-measured exposures, repeated assessments of bone and muscle health, and longer follow-up are needed to further examine whether the coexistence of osteoporosis and low muscle mass confers an excess risk beyond the sum of their individual effects.

Discussion of Mediation Analysis Results

Because the effect estimate for the both-conditions group attenuated from HR = 1.39 (95% CI: 1.01–1.90) in Model 4 to HR = 0.91 (95% CI: 0.59–1.41) in Model 5 after additional adjustment for weight and CESD score, we

conducted an exploratory mediation analysis to examine whether these two variables could statistically account for part of the association[55]. The mediation analysis showed that the total effect of the both-conditions group was HR = 1.349 (log-scale estimate = 0.299, 95% CI: -0.007–0.606), the direct effect was HR = 1.073 (log-scale estimate = 0.070, 95% CI: -0.291–0.465), and the total indirect effect was significant (log-scale estimate = 0.229, 95% CI: 0.019–0.445; HR = 1.257). The proportion mediated was 76.60%.

These findings suggest that weight loss and elevated depressive symptoms may serve as complete mediators in the pathway linking the coexistence of osteosarcopenia-related phenotypes to cognitive decline, indicating that the detrimental impact of musculoskeletal comorbidity on cognition is largely exerted through metabolic and psychological pathways rather than direct neurological damage. Although the specific indirect effects through weight (0.197, 95% CI: -0.008–0.423) and CESD (0.032, 95% CI: -0.007–0.077) did not individually reach conventional statistical significance, this pattern does not necessarily indicate the absence of mediation through either pathway[55]. Weight and CESD score are correlated and may share overlapping variance; when both are included in the same model, each mediator competes for shared variance, which can inflate the standard error of the individual indirect effect and yield a confidence interval that crosses zero[55]. The significant total indirect effect indicates that the two mediators jointly transmit a substantial portion of the association, rather than that only one of them is responsible. Therefore, the mediation pathway appears to depend on both lower body weight and higher depressive symptoms acting in concert.

The mediating role of lower body weight, rather than higher body weight, is consistent with the characteristics of the study population. In this cohort, the both-conditions group had the lowest median weight (47 kg) compared with the reference group (64.65 kg), and low body weight is a shared feature of both osteoporosis risk and low muscle mass. The OSTA formula includes weight, with lower weight contributing to a higher osteoporosis risk category, and the ASM estimation equation also includes weight, with lower weight contributing to a lower estimated appendicular skeletal muscle mass. Higher body weight would tend to increase OSTA scores and ASM estimates, thereby reducing the probability of being classified into the osteoporosis-risk or low-muscle-mass groups. Therefore, within this analytical framework, weight primarily captures the low-body-weight component of osteosarcopenia, which may reflect malnutrition, frailty, and sarcopenia, all of which have been linked to cognitive decline[57]. Higher body weight may influence cognitive function through obesity-related inflammation and metabolic dysfunction, but it is not the pathway represented by the joint exposure in this study.

Similarly, higher rather than lower CESD scores were relevant. The both-conditions group had a higher median CESD score (7, IQR: 3–12) than the reference group (5, IQR: 2–10). Depressive symptoms may increase the risk of cognitive impairment through chronic inflammation, hypothalamic–pituitary–adrenal axis dysregulation, reduced physical activity, and impaired hippocampal neurogenesis and synaptic plasticity[56]. The positive indirect effects indicate that the adverse impact of the both-conditions group on cognition was mediated through decreased body weight (mean indirect effect = 0.197) and increased CESD scores (mean indirect effect = 0.032). The directionality aligns with the protective role of higher weight (HR = 0.98) and the detrimental role of higher depressive symptoms (HR = 1.04) observed in the Cox model. Thus, the joint mediating pathway appears to involve both a reduction in body weight and an increase in depressive symptoms, which together may reflect a broader frailty-related vulnerability linking osteosarcopenia to cognitive decline.

These mediation findings should be interpreted as exploratory and hypothesis-generating rather than as evidence of a specific causal pathway. The total effect estimate had a little wide confidence interval that included zero, indicating that the proportion mediated should be regarded as an imprecise point estimate.

Discussion of Subgroup Analysis Results

In subgroup analyses, the both-conditions group had a significantly increased risk in participants aged 60–69 years (HR = 1.82, 95% CI: 1.18–2.79, P = 0.007) and those with primary school education (HR = 2.30, 95% CI: 1.38–3.85, P = 0.002). Other subgroups did not show significant associations. Tests for interaction were not significant (P for interaction: gender = 0.686, age = 0.794, education = 0.061), so these findings should be interpreted as hypothesis-generating.

The marginal interaction with education (P = 0.061) is consistent with the cognitive reserve hypothesis[42]. Individuals with higher education have greater synaptic and compensatory capacity and may offset subclinical bone and muscle pathology. Those with lower education may be more sensitive to neurological damage from osteoporosis and low muscle mass, exceeding the cognitive compensatory threshold[40]. Sex did not modify the association. The age-specific findings were exploratory: the < 60 years group may have low incidence and early muscle decline, while the ≥ 70 years group may be limited by sample size and competing etiologies. Overall, these subgroup results require confirmation in larger studies.

Study Strengths

This study provides prospective, population-based epidemiological evidence on the joint effect of osteoporosis risk and low muscle mass on incident cognitive impairment in Chinese middle-aged and older adults. Using four waves of nationally representative CHARLS data, it establishes a clear temporal sequence and reduces reverse causation, offering stronger evidence than cross-sectional studies. It is the first to simultaneously include both exposures in this population, quantifying independent and joint effects through multiplicative and additive interaction analyses and exploring mediation pathways, thereby filling a gap in Chinese evidence on muscle–bone comorbidity and cognitive health. The OSTA and Chinese-validated anthropometric ASM equation require no precision equipment and are suitable for community screening, making the findings directly translatable to primary-care risk stratification across bone, muscle, and cognitive health. Constructed progressively adjusted Cox proportional hazards regression models Cox models, sensitivity analysis treating missing follow-up as censoring, and harmonized cognitive scoring further ensure robust and comparable estimates. Together, these strengths provide epidemiological evidence that coexisting osteoporosis risk and low muscle mass, rather than either alone, identifies a high-risk phenotype for incident cognitive impairment and supports simple community-based screening.

Limitations

Statistical power was insufficient for some subgroup and interaction analyses. In the low muscle mass only group, which included only 66 participants, the number of events in some subgroups was small, increasing the possibility of false-negative findings. Interaction analyses require larger sample sizes, and this study may have been underpowered to detect weak-to-moderate interactions. These negative findings should be verified in larger cohort studies. As an observational study, this study cannot fully exclude residual confounding. Although major confounders were adjusted for, factors such as dietary intake, detailed physical activity, serum vitamin D,

and sex hormones may still simultaneously affect bone health, muscle mass, and cognitive function; therefore, causality cannot be fully established. Finally, this study cannot directly answer which specific exercise, nutritional, pharmacological, or psychological interventions should be used to reduce cognitive impairment; it provides epidemiological evidence for risk stratification rather than interventional guidance.ConclusionThis prospective CHARLS cohort study provides population-based epidemiological evidence that coexisting osteoporosis risk and low muscle mass, rather than either condition alone, identifies a high-risk phenotype for incident cognitive impairment in Chinese middle-aged and older adults. After full adjustment, the both-conditions group had a 39% higher risk (HR = 1.39, 95% CI 1.01–1.90), whereas either condition alone was not independently significant; no significant multiplicative or additive interaction was observed. Importantly, these findings suggest that simple bone–muscle screening using OSTA plus anthropometric muscle mass assessment may effectively identify and provide early warning for individuals at high risk of cognitive impairment in community settings, supporting integrated bone–muscle–cognitive screening in primary care. Another key finding is that lower body weight and depressive symptoms jointly mediated 76.60% of the association, suggesting an important metabolic–psychological pathway, although this mediation finding remains exploratory and hypothesis-generating. This study does not provide specific exercise, nutritional, pharmacological, or psychological intervention prescriptions. Larger cohorts with repeated assessments and randomized controlled trials are needed.

Conclusion

This prospective CHARLS cohort study provides population-based epidemiological evidence that coexisting osteoporosis risk and low muscle mass, rather than either condition alone, identifies a high-risk phenotype for incident cognitive impairment in Chinese middle-aged and older adults. After full adjustment, the both-conditions group had a 39% higher risk (HR=1.39, 95% CI 1.01–1.90), whereas either condition alone was not independently significant; no significant multiplicative or additive interaction was observed. Importantly, these findings suggest that simple bone–muscle screening using OSTA plus anthropometric muscle mass assessment may effectively identify and provide early warning for individuals at high risk of cognitive impairment in community settings, supporting integrated bone–muscle–cognitive screening in primary care. Another key finding is that lower body weight and depressive symptoms jointly mediated 76.60% of the association, suggesting an important metabolic–psychological pathway, although this mediation finding remains exploratory and hypothesis-generating. This study does not provide specific exercise, nutritional, pharmacological, or psychological intervention prescriptions. Larger cohorts with repeated assessments and randomized controlled trials are needed.

Declarations

Ethics approval and consent to participate

All studies involving human subjects were approved by the Biomedical Ethics Committee of Peking University (IRB00001052-11015). The study was conducted in accordance with the Declaration of Helsinki and local laws, regulations, and institutional requirements. Written informed consent was obtained from all individual participants or their legal guardians/next of kin.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the China Health and Retirement Longitudinal Study (CHARLS) repository, https://charls.pku.edu.cn. The data are publicly available to registered researchers.

Competing interests

Weilin Huang, Boyu Chen, Zixuan Zhu, Hanxiang Zhang, Jiaxin Cai, Ping Zhang, Jindong Ding Petersen, and Wenting Cao declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82560642), the Natural Science Foundation of Hainan Province (Grant No. 821RC583, No. 824RC518 and No. 825RC774), the Academic Enhancement Program of Hainan Medical University (Grant No. XSTS2025130 and No. XSTS2025003), and the Undergraduate Research Innovation Training Program of Hainan Medical University (No. RZ2600001171).

Authors' contributions

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Acknowledgments

We would like to express our sincere gratitude to all participants and researchers of CHARLS.

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Figures

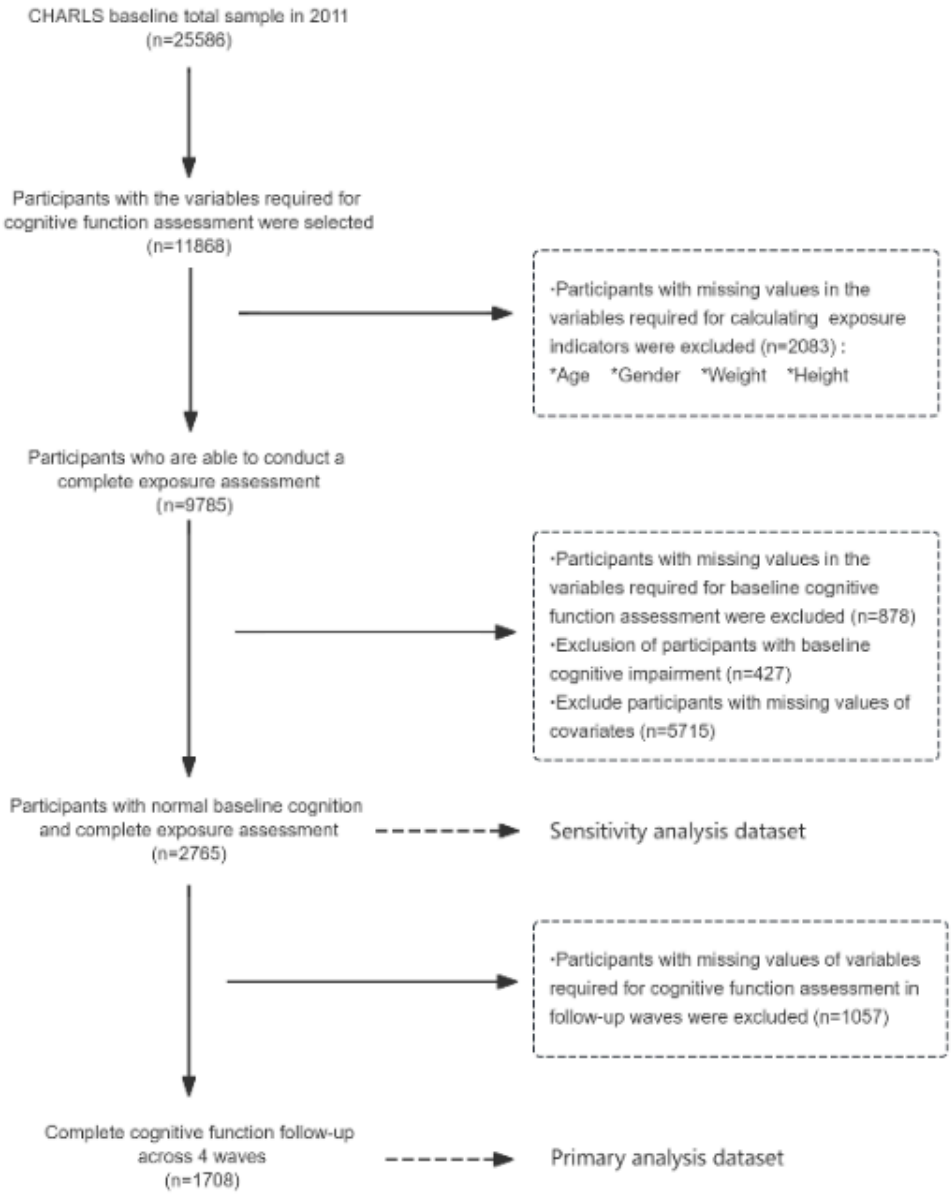

Figure 1

Study flowchart

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