BMC Public Health

RESEARCH

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Bidirectional longitudinal associations between estimated muscle mass and self-reported chronic lung disease in middle-aged and older adults: findings from the China health and retirement longitudinal study

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Abstract

Background The bidirectional relationship between muscle mass and chronic lung diseases (CLD) in middle-aged and older adults remains inadequately explored. This study aims to investigate the bidirectional association between estimated muscle mass and self-reported chronic lung diseases while elucidating the mediating mechanisms underlying this relationship.

Methods This study utilized data from the nationally representative China Health and Retirement Longitudinal Study (2011–2018), focusing on individuals aged 45 years or older. Cox regression was used to investigate the bidirectional relationship between estimated muscle mass and self-reported CLD. Causal mediation analysis was employed to evaluate the role of 16 blood biomarkers as potential mediators. Sensitivity analysis using cross-lagged models was conducted to verify the robustness of the bidirectional association between estimated muscle mass and self-reported CLD.

Results Among 10,591 participants, 1,742 (16%) self-reported CLD during a median follow-up of 4.4 years. Participants with low estimated muscle mass had a 27% higher risk of developing self-reported CLD compared to those with normal muscle mass (HR = 1.27, 95% CI: 1.12–1.44). In a separate analysis of 6,067 participants, 708 (12%) experienced new-onset estimated low muscle mass, with those reporting CLD showing a 26% increased risk of muscle loss during a median follow-up of 2.5 years (HR = 1.26, 95% CI: 1.06–1.49). Notably, individuals with insufficient physical activity exhibited a significantly higher risk of self-reported CLD compared to those who engaged in regular exercise (HR = 1.91; 95% CI: 1.37–2.66). Additionally, the negative impact of low estimated muscle mass was more pronounced in male participants than in females (HR = 1.65; 95% CI: 1.33–2.03) over the same follow-up period. Causal

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mediation analysis suggested that cystatin C may mediate 0.61% of the association between estimated muscle mass and self-reported CLD.

Conclusion There is a bidirectional relationship between self-reported CLD and low estimated muscle mass. Self-reported CLD may cause varying degrees of estimated muscle mass reduction across different population subgroups. Understanding this dynamic and its variations can enhance prevention and treatment strategies for both conditions.

Keywords Muscle mass, Chronic lung disease, Bidirectional association, Causal mediation analysis

Introduction

Population aging is a global challenge, with China facing a particularly severe situation due to its large population base and rapid aging process. According to China's seventh population census, the proportion of China's aging population is increasing, suggesting a sharp rise in the prevalence and mortality of aging-related chronic non-communicable diseases, such as cardiovascular, cerebrovascular, and chronic lung disease (CLD) [1–3]. CLD is the third leading cause of death in China, which is a major cause of disability and death among middle-aged and elderly people in China [4]. Additionally, sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, poses a serious health threat to middle-aged and older adults. Decreased muscle mass can lead to various health issues, including CLD [5]. However, the importance of muscle mass in maintaining body function and metabolic health is often overlooked. Thus, it is crucial to explore the association between CLD and muscle mass in middle-aged and elderly populations to inform public health policy, practice, and clinical interventions, thereby improving health outcomes and reducing socioeconomic burdens.

Preliminary studies have explored the association between CLD and muscle mass, suggesting a potential bidirectional relationship. CLD may exacerbate muscle loss through several mechanisms. First, from a physiological standpoint, respiratory muscle function is crucial for coordinating respiratory and locomotor systems. Dysfunction in these muscles can initiate a vicious cycle: CLD may cause ventilatory limitations that impair respiratory muscle contraction efficiency, while weakened respiratory muscles can further reduce exercise capacity, ultimately leading to systemic muscle mass loss [6]. Second, many CLD, such as chronic obstructive pulmonary disease, are associated with elevated levels of inflammatory cytokines. These cytokines activate enzymes that promote muscle protein catabolism, contributing to muscle mass reduction. Conversely, decreased muscle mass disrupts the balance of myokines secreted by skeletal muscles, potentially facilitating the occurrence of CLD [7, 8]. Existing studies indicate that patients with CLD are three times more likely to develop low muscle mass compared to healthy individuals, while those with low muscle mass face a 70% increased risk of developing incident CLD within five years [9, 10]. Collectively, these findings support the hypothesis of a bidirectional association between estimated muscle mass loss and self-reported CLD.

Beyond establishing this association, research has aimed to identify biological pathways linking CLD and muscle mass. For instance, inflammatory biomarkers such as white blood cell count and C-reactive protein reflect systemic inflammation levels. In patients with self-reported CLD, these biomarkers may promote muscle catabolism by activating relevant enzymes, while inflammatory cytokines could contribute to CLD progression through oxidative stress pathways [11, 12]. Additionally, oxygen transport-related parameters, including hemoglobin and platelet count, may lead to chronic hypoxemia in CLD patients, resulting in anemia or compensatory erythrocytosis. This pathophysiological state may further diminish nutrient supply to muscles and accelerate atrophy [13, 14]. Furthermore, metabolic disturbances commonly observed in CLD patients—such as dyslipidemia and glucose metabolism dysregulation—may exacerbate muscle protein breakdown and reduce muscle mass [13, 14]. Finally, indicators of renal function, such as uric acid levels, warrant consideration. Research by Stenvinkel et al. suggests that chronic hypoxia and sustained inflammation in CLD patients can lead to renal impairment, which may further aggravate muscle wasting through multiple mechanisms [15, 16]. Therefore, it is necessary to investigate these associations to gain a deeper understanding of the mechanisms involved and to identify potential mediators, which could inform early comprehensive preventive measures and individualized clinical treatment. In summary, although a series of studies have been conducted in the past, most previous research has been limited to cross-sectional designs [17, 18]. Even existing longitudinal studies failed to simultaneously examine the bidirectional longitudinal associations between CLD and muscle mass within the same population.

To address these gaps, this study utilized data from the nationally representative China Health and Retirement Longitudinal Study (CHARLS) with two primary objectives: (1) to explore the bidirectional relationship between estimated muscle mass and self-report CLD in Chinese adults aged 45 years and older, and (2) to identify 16 potential mediating biomarkers associated with

this bidirectional linkage. These mediators include white blood cells, hemoglobin, hematocrit, mean corpuscular volume, platelets, C-reactive protein, glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, blood urea nitrogen (BUN), creatinine, glucose, uric acid, and cystatin C. The identification of these mediators aims to reveal potential targets for clinical intervention in the progression of disease.

Methods

Study population

Data were obtained from CHARLS, a nationally representative survey of China's middle-aged and older population aged 45 and over. CHARLS employed a multi-step probability sampling strategy to select 150 representative counties and 450 village/urban communities from 28 provinces across the country. The methodology and core questionnaire of CHARLS have been described in detail in previous studies [19, 20]. The initial national baseline survey of CHARLS was conducted in 2011–2012, with subsequent waves in 2013, 2015, and 2018. All procedures were approved by the Boston University Institutional Review Board (IRB00001052- 11015), and all participants provided informed consent at the time of participation.

In this study, the CHARLS data sets from Waves 1 to 4 ($n = 25586$) were used. First, 8655 participants who were younger than 45 years of age were excluded. To examine the bidirectional relationship between estimated muscle mass and self-reported CLD, this study included two datasets: the new-onset self-reported CLD dataset and the new-onset estimated low muscle mass dataset. In the new-onset self-reported CLD dataset, 1,845 participants diagnosed with self-reported CLD at baseline and 4,495 participants missing a diagnosis of self-reported CLD were excluded, resulting in the inclusion of 10,591 participants. Similarly, in the new-onset estimated low muscle mass dataset, 6,383 participants diagnosed with estimated low muscle mass at baseline and 4,481 participants with missing estimated muscle mass data were excluded, resulting in the inclusion of 6,067 participants (Fig. 1).

Self-reported CLD

Self-reported CLD was assessed through face-to-face interviews conducted by trained researchers. To minimize misclassification, the measurement of CLD included the following questions: (1) "Has a doctor ever diagnosed you with a chronic lung disease such as chronic bronchitis, emphysema, or cor pulmonale, excluding tumors or cancers?" (2) "Do you know if you have CLD?" and (3) "Our records from your last interview show that you have/have not had CLD; is that correct?" If all three questions are answered "yes," the individual is classified as having CLD. In this study, incident self-reported CLD was defined as participants who did not have CLD at

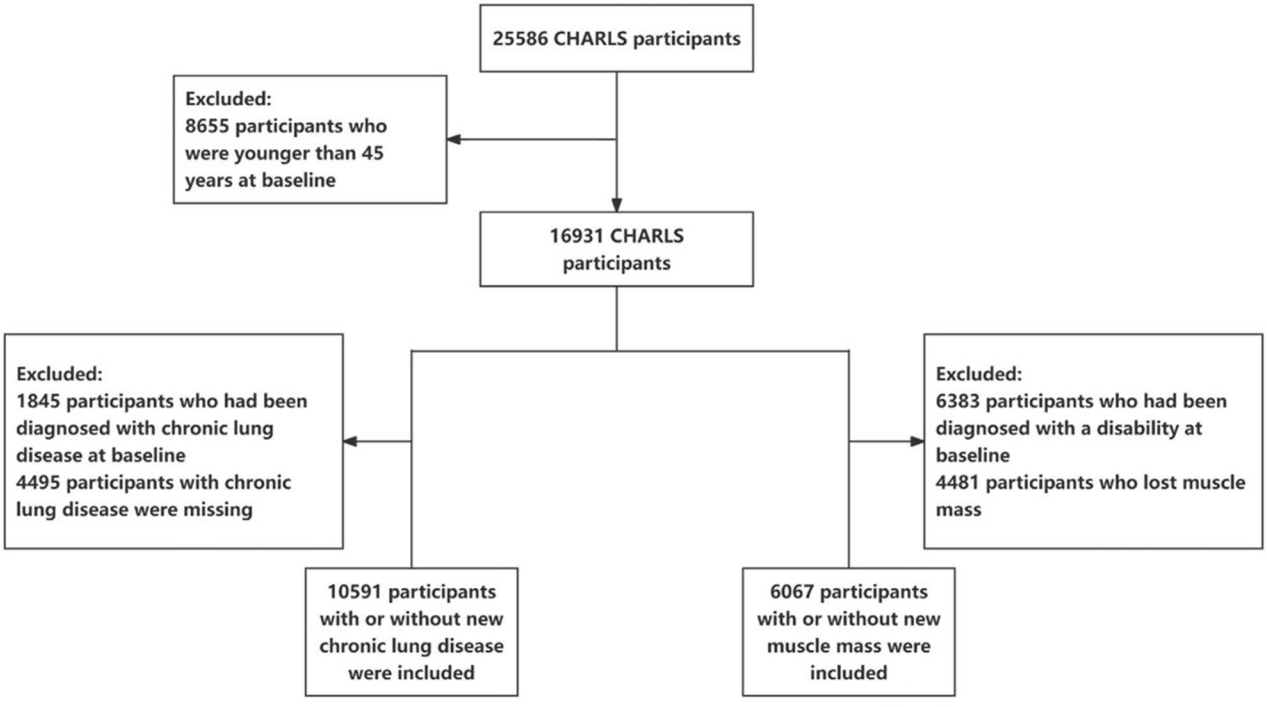

Fig. 1 Flowchart of participants' selection

baseline but reported CLD during Wave 2, 3, or 4 of the survey.

Estimated muscle mass

Estimated muscle mass in the Chinese population was estimated using the validated anthropometric equation:

ASM = 0.193 * body weight + 0.107 * height − 4.157 * sex − 0.037 * age − 2.631.

Height, weight, and age are measured in centimeters, kilograms, and years, respectively. In CHARLS, 1 indicates male, and 2 indicates female. Following the ASM calculation, height-adjusted estimated muscle mass (ASM/Ht2) was calculated by dividing ASM by the square of height in meters. According to prior studies [20, 21], the threshold for identifying estimated low muscle mass was set as the ASM/Ht² corresponding to the lowest 20th percentile of the participants. Estimated low muscle mass in the study was defined if either the second or third wave showed an ASM/Ht² value of < 5.24 kg/m² for females or < 7.00 kg/m² for males, given that height and weight were measured across three waves.

Covariates and mediators

Baseline data were used as covariates [22, 23]: sex (male or female), age (45–59, 60+), marriage (cohabitation or single), education (no formal education, primary, secondary, and above), smoking (yes or no), alcohol consumption (yes or no), physical activity (yes or no), insurance (yes or no), residence (urban or rural), BMI (quantitative variable), disability (yes or no), occupation (agricultural, non-agricultural, unemployed) and number of chronic diseases (quantitative variable). Additionally, 16 indicators from the first wave were selected as potential mediators, after logarithmic transformation. These included white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelets, C-reactive protein, glycated hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood urea nitrogen, creatinine, glucose, uric acid, and cystatin C.

Statistical analysis

Data for quantitative variables were expressed as mean ($\bar{X}$) ± standard deviation (SD), if they conformed to a normal distribution, or as median (M) and interquartile range (IQR) if they did not. Categorical variables were expressed as numbers (N) and percentages (%). Categorical variables were compared using chi-square tests, while quantitative variables were compared using t-tests or nonparametric tests for differences between groups at baseline.

Missing data were addressed using multiple imputations through chained equations, predicting and interpolating missing values from observed values, and performing model estimation and repetitive simulations 50 times to generate a complete dataset [24, 25]. Subsequent analyses were based on the filled dataset. First, to assess the bidirectional association between estimated muscle mass and self-reported CLD, we used Cox regression to calculate hazard ratios (HR) and 95% confidence intervals (CI). The association between estimated muscle mass and self-reported CLD was explored using the time of onset of self-reported CLD as the time of the endpoint, or 2020 if self-reported CLD was not present. Similarly, the association between self-reported CLD and low estimated muscle mass was explored using the time of emergence of low estimated muscle mass as the end time, and 2018 as the end time if low estimated muscle mass was absent.

Second, to more comprehensively elucidate the complex relationship between estimated muscle mass and self-reported CLD, we considered the effects of various dimensions such as physiological differences, lifestyle factors, and social welfare [26–28]. We conducted stratified analyses to develop more effective health intervention strategies tailored to different populations, thereby enhancing the prevention and management of chronic diseases. The stratification variables included gender, age, education, marital status, smoking, alcohol consumption, physical activity, health insurance coverage, residential region, occupation, and disability.

Third, causal mediation analyses were conducted to examine the potential mediating effects within the bidirectional relationship between estimated muscle mass and self-reported CLD. Causal mediation is a statistical method grounded in a counterfactual framework that decomposes the total effect of exposure into direct and indirect effects, thereby elucidating the pathways of influence. This approach necessitates a clear temporal ordering of causal variables and assumes the absence of unobserved confounding factors [29, 30]. The Average Direct Effect (ADE) represents the portion of the total effect that is independent of the mediator, while the Average Causal Mediation Effect (ACME) reflects the portion of the total effect that can be attributed to the mediator. The mediation ratio is calculated by dividing ACME by the sum of ADE and ACME, and then multiplying by 100%. For instance, when analyzing the association between estimated muscle mass and new-onset self-reported CLD, ADE signifies the direct effect of muscle mass on new-onset CLD, excluding any mediation influences, whereas ACME captures the effect of muscle mass on new-onset CLD through the mediator.

Finally, a sensitivity analysis was conducted using the cross-lagged panel model (CLPM) to evaluate the stability and robustness of the bidirectional association between estimated muscle mass and self-reported CLD in Chinese adults aged 45 years and older. The cross-lagged panel

model, a longitudinal analytical framework, enables the examination of predictive relationships between estimated muscle mass and self-reported CLD [23]. This approach characterizes dynamic effects through cross-lagged pathways, establishing autoregressive paths from variables' prior levels to their current states while simultaneously constructing cross-lagged effects connecting one variable's historical levels to another's contemporary status [31]. Model fit was assessed through four key indices: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR) [23]. Conventional cutoff criteria were applied to determine goodness-of-fit, with acceptable thresholds defined as CFI > 0.90, TLI > 0.90, RMSEA < 0.08, and SRMR < 0.08.

All statistical analyses were conducted using R version 4.3.0, employing the "survival", "survminer", "mediation", "lavaan", and "rice" packages. A two-tailed P-value of less than 0.05 was considered indicative of statistical significance.

Results

Descriptive data

The analysis included two data sets (new-onset self-reported CLD and new-onset estimated low muscle mass data sets). Table 1 shows the baseline characteristics of the two datasets. In the new-onset self-reported CLD analysis, 10,591 individuals were included, and 16.4% of participants had new-onset self-reported CLD. Participants with self-reported CLD were more likely to be male, have a secondary or higher level of education, be disabled, be married, smoke, and live in a rural area than participants without self-reported CLD ($P < 0.05$).

In the new-onset estimated low muscle mass analysis, a total of 6,067 individuals were included, and 11.7% of participants had estimated low muscle mass. Compared with participants with estimated normal muscle mass, participants with estimated low muscle mass were more likely to be male, older, have a secondary education or higher, marital status, smoke, have a rural residence, and have a low BMI ($P < 0.05$) (Table 1).

Association between estimated muscle mass and new-onset self-reported CLD

Table 2 presents the association between estimated muscle mass and new-onset self-reported CLD during a median follow-up of 4.4 years. In unadjusted Cox regression models, participants with estimated low muscle mass exhibited a 38% higher risk of self-reported CLD compared to those with normal estimated muscle mass (HR = 1.38, 95% CI: 1.22–1.56). After multivariable adjustment in Model 2, including age, sex, education level, marital status, smoking, alcohol consumption, physical activity, BMI, residential area, number of chronic diseases, insurance status, occupation, and disability, estimated low muscle mass remained significantly associated with a 27% increased self-reported CLD risk (HR = 1.27, 95% CI: 1.12–1.44) (Table 2).

Association between self-reported CLD and new-onset estimated low muscle mass

Table 2 presents the associations between self-reported CLD and new-onset estimated low muscle mass during a median follow-up of 2.5 years. In unadjusted Cox regression models, self-reported CLD participants demonstrated a 39% higher risk of developing low muscle mass compared to those without self-reported CLD (HR = 1.39, 95% CI: 1.18–1.64). After multivariable adjustment in Model 2, including age, sex, education level, marital status, smoking, alcohol consumption, physical activity, BMI, residential area, number of chronic diseases, insurance status, occupation, and disability, self-reported CLD patients still exhibited a 26% increased risk of estimated muscle mass loss (HR = 1.26, 95% CI: 1.06–1.49) (Table 2).

Stratified analysis and interaction analysis

Figure 2 illustrates the association between estimated muscle mass and self-reported CLD, stratified by sex, age, education level, marital status, smoking habits, alcohol consumption, physical activity level, residential area, health insurance coverage, occupational and disability status. The analysis revealed that participants with insufficient physical activity exhibited a significantly elevated risk of self-reported CLD during a median follow-up of 4.4 years (interaction $P < 0.05$). Although no significant interaction effects were observed for other stratification variables, subgroup analyses indicated higher self-reported CLD risks among individuals with secondary education or above compared to those with no formal education or primary education ($P < 0.05$). Similarly, participants with a history of alcohol consumption showed a higher self-reported CLD risk than non-drinkers ($P < 0.05$).

Figure 3 demonstrates the association between self-reported CLD and estimated muscle mass, stratified by the aforementioned variables. Notably, the detrimental effects of low estimated muscle mass appeared more pronounced in male participants during a median follow-up of 2.5 years (interaction $P < 0.05$). While other stratification variables did not show significant interaction effects, subgroup analyses revealed a higher prevalence of estimated low muscle mass among older adults compared to middle-aged individuals ($P < 0.05$). Additionally, unemployed individuals exhibited a higher prevalence of estimated low muscle mass compared to those engaged in agricultural and non-agricultural occupations ($P < 0.05$).

Table 1 Baseline characteristics of the study population

Variables	New-onset Low muscle mass		*P*-Value	New-onset Chronic lung disease		*P*-Value
	No (5359)	Yes (708)		No (8849)	Yes (1742)	
Chronic lung disease (%)						
No	4235 (79.0)	505 (71.3)	< 0.001	-	-	-
Yes	1124 (21.0)	203 (28.7)		-	-	
Low muscle mass (%)						
No	-	-	-	7727 (87.3)	1455 (83.5)	< 0.001
Yes	-	-		637 (12.7)	257 (16.5)	
Disability (%)						
Yes	5048 (94.2)	632 (89.3)	< 0.001	8307 (93.9)	1541 (88.5)	< 0.001
No	311 (5.8)	76 (10.7)		542 (6.1)	201 (11.5)	
Age (%)						
45–59	3424 (63.9)	294 (41.5)	< 0.001	5480 (61.9)	917 (52.6)	< 0.001
60years+	1935 (36.1)	414 (58.5)		3369 (38.1)	825 (47.4)	
Sex (%)						
Male	2437 (45.5)	388 (54.8)	< 0.001	4051 (45.8)	927 (53.2)	< 0.001
Female	2922 (54.5)	320 (45.2)		4798 (54.2)	815 (46.8)	
Education (%)						
No formal education	1368 (25.5)	230 (32.5)	< 0.001	2449 (27.7)	502 (28.8)	< 0.001
Primary school	2211 (41.3)	327 (46.2)		3444 (38.9)	756 (43.4)	
Middle school or above	1780 (33.2)	151 (21.3)		2956 (33.4)	484 (27.8)	
Marriage (%)						
Cohabitation	4878 (91.0)	588 (83.1)	< 0.001	7978 (90.2)	1502 (86.2)	< 0.001
Single	481 (9.0)	120 (16.9)		871 (9.8)	240 (13.8)	
Smoking (%)						
No	3865 (72.1)	419 (59.2)	< 0.001	6309 (71.3)	1121 (64.4)	< 0.001
Yes	1494 (27.9)	289 (40.8)		2540 (28.7)	621 (35.6)	
Alcohol consumption (%)						
No	3608 (67.3)	487 (68.8)	0.461	5889 (66.5)	1137 (65.3)	0.315
Yes	1751 (32.7)	221 (31.2)		2960 (33.5)	605 (34.7)	
Physical activity (%)						
No	457 (8.5)	57 (8.1)	0.722	851 (9.6)	189 (10.8)	0.124
Yes	4902 (91.5)	651 (91.9)		7998 (90.4)	1553 (89.2)	
Insurance (%)						
No	269 (5.0)	33 (4.7)	0.749	493 (5.6)	86 (4.9)	0.314
Yes	5090 (95.0)	675 (95.3)		8356 (94.4)	1656 (95.1)	
Residence (%)						
Urban	1862 (34.7)	212 (29.9)	0.013	3183 (36.0)	572 (32.8)	0.013
Rural	3497 (65.3)	496 (70.1)		5666 (64.0)	1170 (67.2)	
Number of chronic diseases(m(IQR))	1 (0,2)	1 (1,3)	< 0.001	1 (0,2)	1 (0,2)	< 0.001
BMI (mean (SD))	24.93 (7.35)	22.50 (17.96)	< 0.001	23.96 (20.50)	23.55 (13.85)	0.421
Occupation (%)						
Agricultural	2473 (46.1)	324 (45.8)	< 0.001	3722 (42.1)	737 (42.3)	< 0.001
Non-agricultural	1296 (24.2)	116 (16.4)		2369 (26.8)	381 (21.9)	
Unemployed	1590 (29.7)	268 (37.9)		2758 (31.2)	624 (35.8)	

Note: Educational attainment is categorized as having no formal low education (junior high school and below), secondary education (senior high school), and tertiary education and above (bachelor's degree and above)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters)

Mediation analysis

In the mediation analysis of new-onset self-report CLD, 16 biomarkers, including white blood cell count, hemoglobin, and C-reactive protein, were found not to mediate the association between estimated muscle mass and self-report CLD. However, cystatin C mediated 0.61% of the effect of estimated muscle mass on self-report CLD (Fig. 4). Similarly, in the mediation analysis for new-onset estimated low muscle mass, none of the 16 biomarkers, including cystatin C, mediated the relationship between self-reported CLD and estimated muscle mass loss (Fig. 5).

Table 2 Bidirectional association between muscle mass and chronic lung disease among Chinese adults aged 45 or above

	Chronic lung disease		Low muscle mass	
	HR (95%CI)	P-Value	HR (95%CI)	P-Value
Model 1				
	1.38 (1.22–1.56)	< 0.001	1.39 (1.18–1.64)	< 0.001
Model 2				
	1.27 (1.12–1.44)	< 0.001	1.26 (1.06–1.49)	0.008

Note: Model 1 unadjusted; Model 2 adjusted for age, sex, education, marriage, smoking, alcohol consumption, physical activity, BMI, residence, number of chronic diseases, insurance, occupation, and disability

Abbreviations: HR, risk ratio; 95% CI, 95% confidence interval

Sensitivity analysis

Figure 6 presents the results of cross-lagged panel models examining the bidirectional associations between self-reported CLD and estimated muscle mass across three-time points (2011, 2013, and 2015). The models were adjusted for covariates including age, sex, and et al., with all coefficients standardized and model fit indices indicating excellent fit: CFI = 0.999, TLI = 0.999, RMSEA = 0.068, and SRMR = 0.001. The results demonstrated relative stability in both self-reported CLD and estimated muscle mass over time. Notably, the incidence of self-reported CLD in 2011 and 2013 was associated with accelerated subsequent estimated muscle mass decline ($\beta = 0.164$, $p < 0.001$; $\beta = 0.564$, $p < 0.001$, respectively). Conversely, improved estimated muscle mass in 2013 predicted a reduced risk of self-reported CLD onset (β = -0.494, $p < 0.001$). However, estimated muscle mass measured in 2011 did not significantly predict self-reported CLD incidence at the subsequent time point.

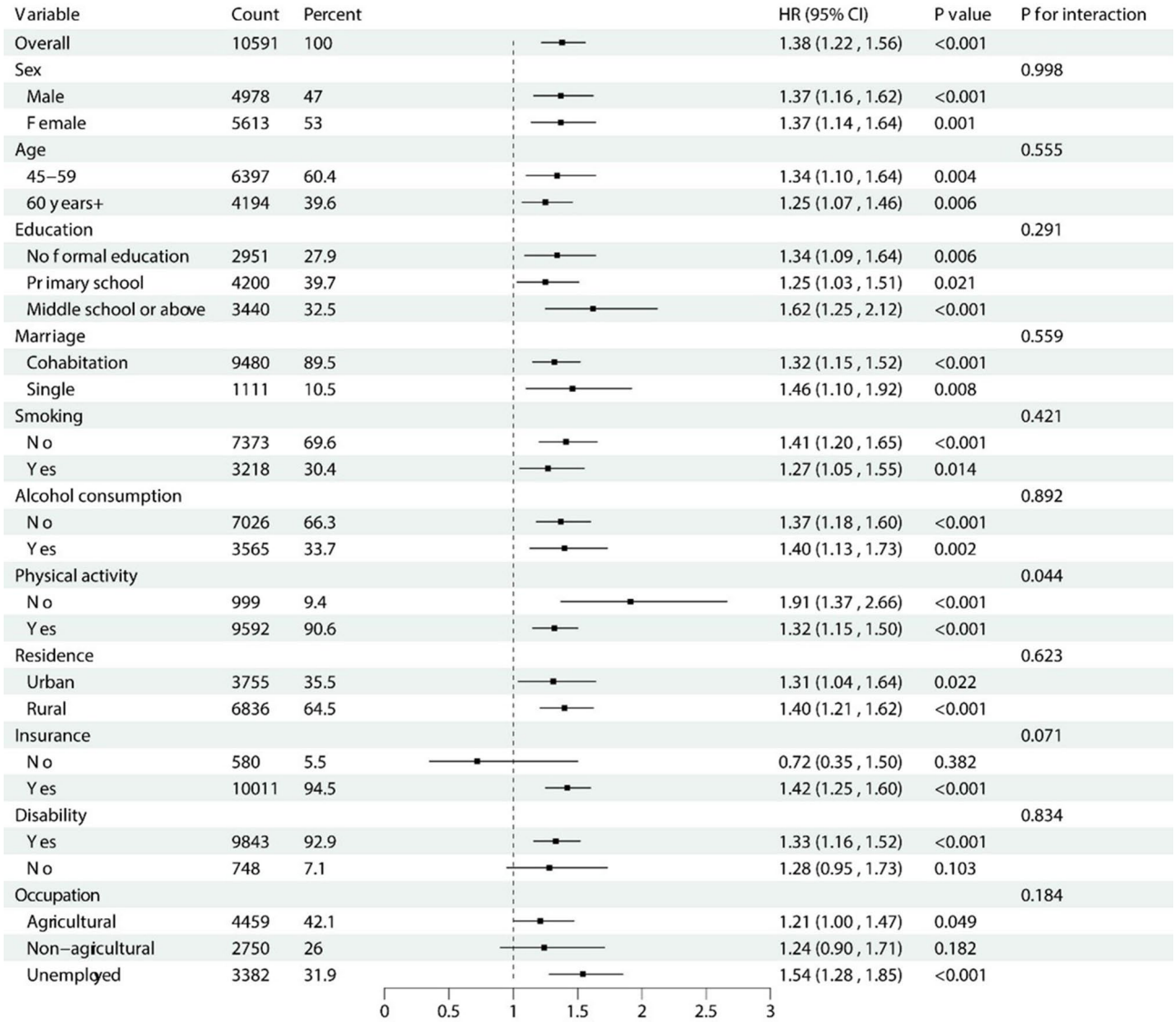

Fig. 2 Stratified analysis of the association between muscle mass and new-onset chronic lung disease among Chinese adults aged 45 or above

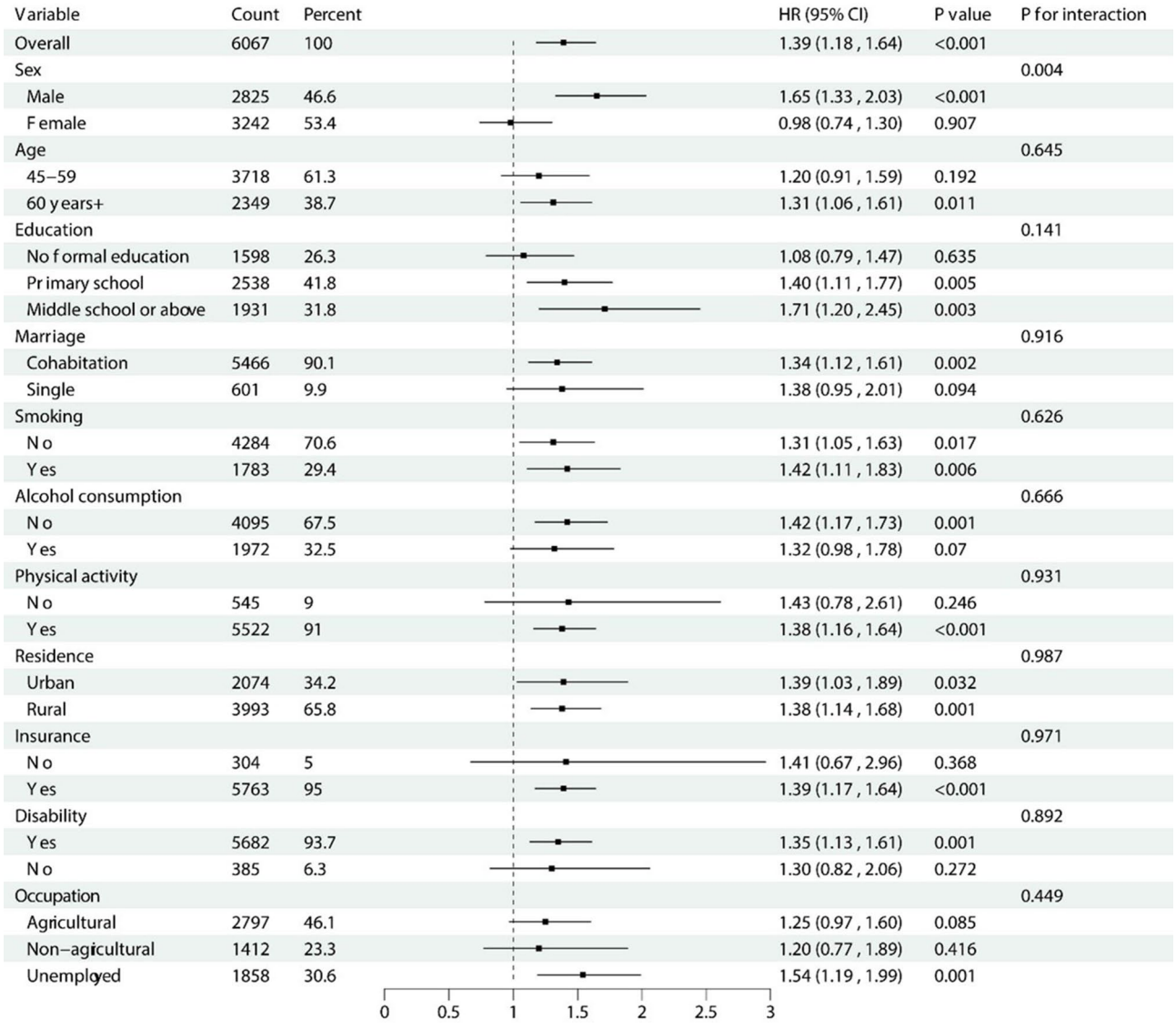

Fig. 3 Stratified analysis of chronic lung disease and new-onset muscle mass association among Chinese adults aged 45 or above

Discussion

In this study, the bidirectional associations between estimated muscle mass and self-reported CLD and potential mediations were explored using a nationally representative cohort of middle-aged and older Chinese adults (age ≥ 45). Results showed that low muscle mass increased the risk of developing CLD. Conversely, CLD reported in baseline also increases the risk of developing estimated low muscle mass. Causal mediation analysis revealed that estimated low muscle mass may influence the development of CLD through cystatin C.

One of the main findings of this study was that low muscle mass may increase the risk of developing CLD, consistent with previous analyses. A longitudinal study from a large Chinese cohort identified low muscle mass as a risk factor for future CLD compared to normal muscle mass [22]. This may be due to low muscle mass leading to a lower metabolic rate and decreased immune function, making the body more susceptible to infections and inflammation, thus increasing the likelihood of CLD [6, 32]. Additionally, older adults were more likely to have low muscle mass, possibly due to the reduced strength of respiratory muscles, affecting lung ventilation and oxygen exchange, thus increasing the risk of CLD [33]. Overall, evidence suggests that low muscle mass may negatively impact CLD. Therefore, it is important to monitor the muscle mass of middle-aged and elderly individuals, enhance their immune function early, and prevent muscle mass decline through dietary and physical activity interventions, such as increasing vitamin D intake [34, 35].

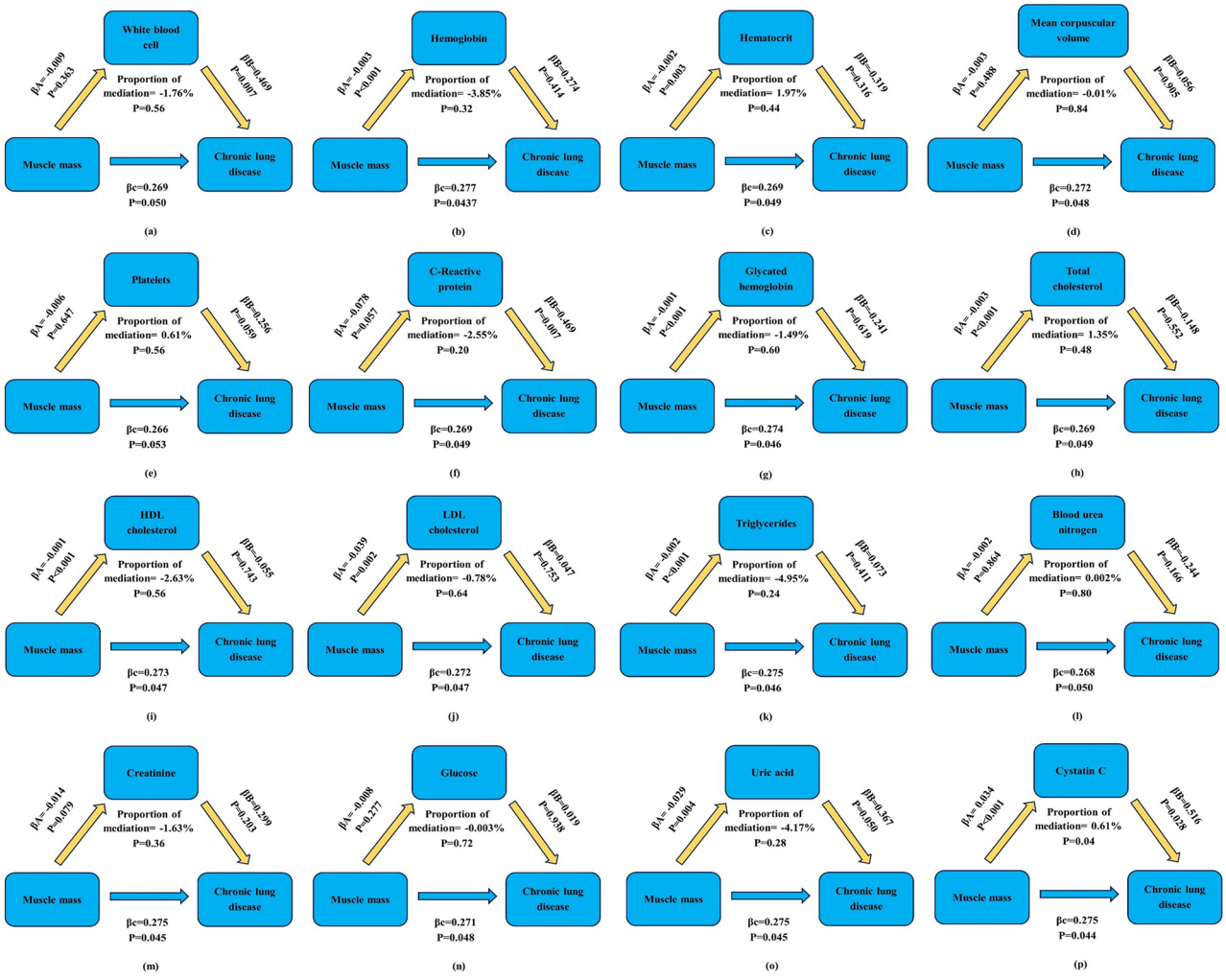

Fig. 4 Association between muscle mass, mediator variables, and chronic lung disease among Chinese adults aged 45 and above. (**a**)-(**p**): Using white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelets, C-reactive protein, glycated hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood urea nitrogen, creatinine, glucose, uric acid, and cystatin C as mediator separately, and the models were all adjusted for age, sex, marriage, education, smoking, alcohol consumption, BMI, disability, insurance, occupation, and residence. β_A represents the effect of baseline muscle mass on the mediator; β_B represents the effect of the mediator on chronic lung disease; and β_C represents the effect of baseline muscle mass on chronic lung disease. The average causal mediation effect (ACME) represents the effect of baseline muscle mass on chronic lung disease via the mediator. The mediation proportion (Prop) was calculated using the formula $ACME?(ADE + ACME) \times 100\%$. In causal mediation analysis, a linear regression model was used to estimate the relationship between the independent variable, the dependent variable, and the mediator, and a logistic regression model was used to estimate the relationship between the independent variable and the dependent variable. A p-value < 0.05 is considered significant

The second major finding of this study is that participants with self-reported CLD were more likely to develop low muscle mass during follow-up. A multicenter study demonstrated a significant decrease in whole-body muscle function in patients with COPD [36]. This result may be related to mechanisms involving protein, inflammation, and other factors. First, CLD can lead to inadequate oxygenation, affecting muscle metabolic function and inhibiting protein synthesis, leading to muscle atrophy [37]. Second, CLD is often associated with systemic inflammation, which can promote muscle proteolysis and inhibit synthesis [38]. Third, reduced physical activity due to dyspnea and a lack of weight-bearing exercise also contributes to reduced muscle mass [6, 39]. Fourth, patients with self-reported CLD often experience decreased appetite and nutrient malabsorption, leading to insufficient energy and protein intake, further reducing estimated muscle mass [40]. Therefore, middle-aged and elderly individuals should pay attention to the emergence of CLDs and undergo regular health assessments. If respiratory discomfort is experienced, timely examination and intervention, such as endurance exercise training (e.g., bicycling, walking) for 20 to 60 min three to five

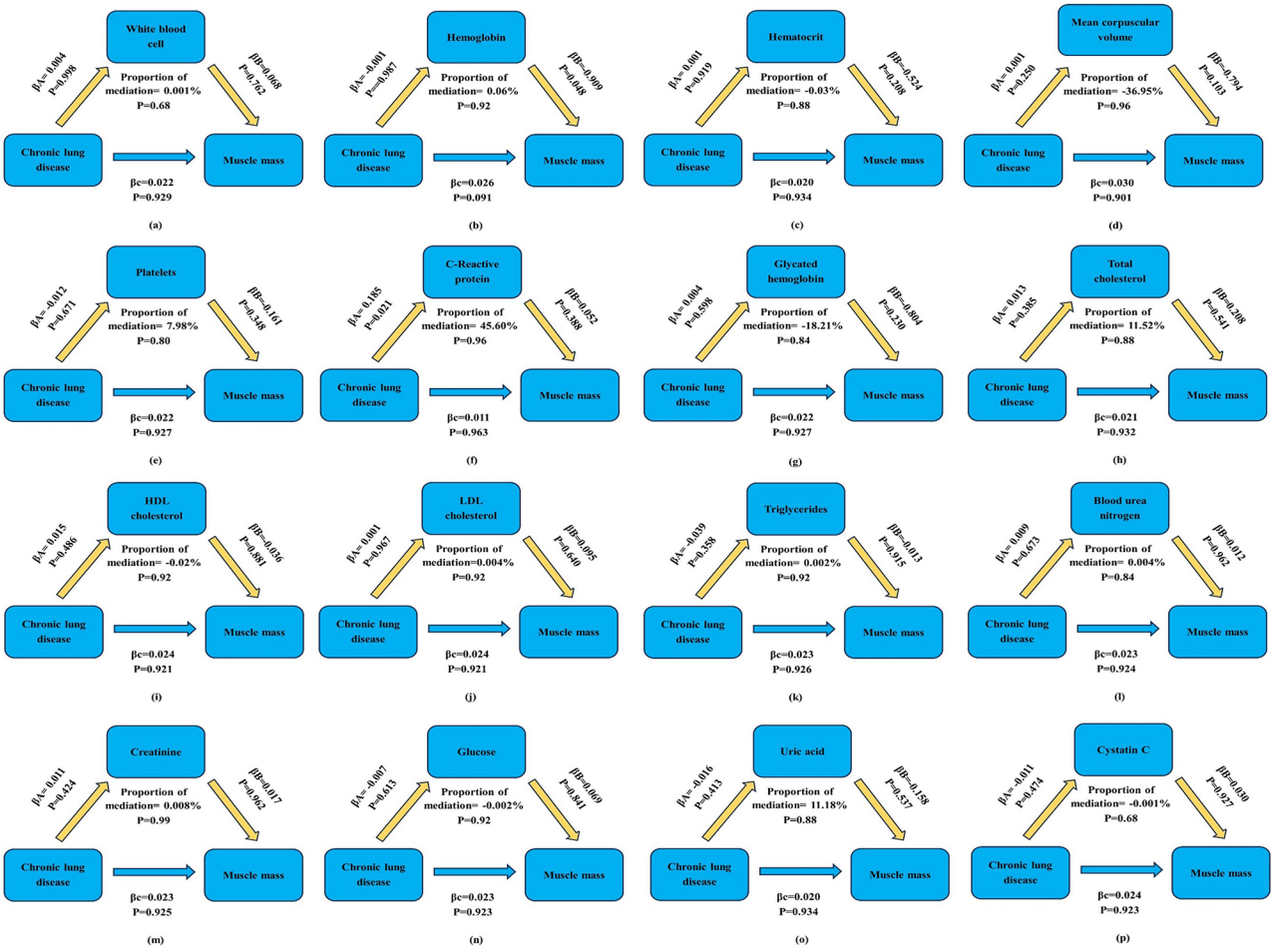

Fig. 5 Association between chronic lung disease, mediator variables, and muscle mass among Chinese adults aged 45 or above. (**a**)-(**p**): Using white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, platelets, C-reactive protein, glycated hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, blood urea nitrogen, creatinine, glucose, uric acid, and cystatin C as mediator separately, and the models were all adjusted for age, sex, marriage, education, smoking, alcohol consumption, BMI, disability, insurance, occupation, and residence. βA represents the effect of baseline chronic lung disease on the mediator; βB represents the effect of the mediator on muscle mass; and βC represents the effect of baseline chronic lung disease on muscle mass. The average causal mediation effect (ACME) represents the effect of baseline muscle mass on chronic lung disease via the mediator. The mediation proportion (Prop) was calculated using the formula ACME/(ADE + ACME)×100%. In causal mediation analysis, a linear regression model was used to estimate the relationship between the independent variable, the dependent variable, and the mediator, and a logistic regression model was used to estimate the relationship between the independent variable and the dependent variable. A p-value < 0.05 is considered significant

times per week, and increased protein intake, are recommended [41–44].

In the stratified analysis, participants with secondary and tertiary education and above, and unemployed individuals demonstrated were more likely to lose muscle mass. This may be due to middle-aged and older adults with secondary education or above probably prioritizing work and studies, leading to sedentary lifestyles and neglect of exercise, which contributes to lower estimated muscle mass. Conversely, less-educated individuals often engage in manual labor, supporting better muscle maintenance. Spruit et al. found that physical exercise can promote muscle cell synthesis, improve muscle metabolism, increase cardiorespiratory fitness, strengthen respiratory muscles, reduce dyspnea and fatigue, and improve estimated muscle mass [45]. Unemployed individuals exhibit a higher susceptibility to estimated low muscle mass compared to employed rural and urban workers, a phenomenon that may arise from multifactorial determinants. Firstly, the abrupt decline in physical activity levels resulting from unemployment accelerates muscle atrophy [46]. Secondly, heightened economic constraints restrict the intake of high-quality proteins and essential micronutrients, while the lack of health insurance coverage exacerbates vulnerability to reduced estimated muscle quality [10, 47]. Furthermore, chronic psychological stress induced by prolonged unemployment promotes muscle catabolism through the activation of inflammatory pathways [48]. Therefore, it is recommended that unemployed older adults increase their protein intake,

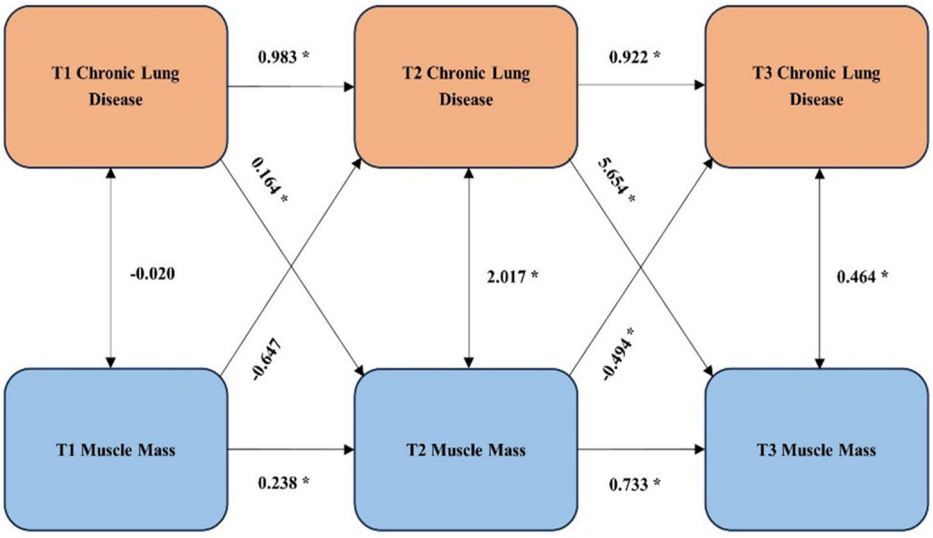

Fig. 6 Three-wave cross-lagged panel model of the bidirectional association between muscle mass and chronic lung disease. T1, T2, and T3 denote the years 2011, 2013, and 2015, respectively, which served as the temporal nodes for this longitudinal analysis. * $P < 0.05$

while middle-aged and older adults with secondary or higher education levels should engage in at least 30 min of moderate-intensity physical activities (such as jogging, yoga, tai chi, etc.) per week, in addition to performing regular daily activities (e.g., cleaning, laundry, cooking) [49].

In mediation analysis, it appears that low muscle mass may influence the development of CLD through cystatin C. However, there may not be a reciprocal effect of CLD on the progression of muscle mass via cystatin C. This asymmetry could arise from bidirectional mechanisms in which reduced estimated muscle mass exacerbates systemic inflammation, accelerates muscle proteolysis through the ubiquitin-proteasome system, and releases myokines into circulation. These processes may increase renal burden, subsequently elevating cystatin C levels while reducing glomerular filtration rates. The resulting elevation in cystatin C might then contribute to pulmonary pathogenesis [50]. Conversely, the primary mechanisms linking self-reported CLD to estimated muscle mass may involve mobility restrictions, chronic systemic inflammation, and inadequate nutritional intake—factors that could suppress muscle protein synthesis independently of cystatin C pathways [51]. Additionally, it is important to consider the potential limitations of the model, particularly regarding the possibility of insufficient case numbers in the self-report CLD-to-estimated muscle mass pathway.

Finally, although our study is based on a large national sample, there are several limitations to consider. First, self-reported CLD may be subject to potential misclassification and recall bias. For instance, a large-scale survey in China indicated that only 20.24% of participants who reported having lung disease (COPD) were confirmed through spirometry [52], suggesting that caution is warranted in interpreting our findings. While we utilized self-reported data for CLD, we also employed specific criteria for diagnosis, including follow-up assessments to confirm the presence of the condition, thereby minimizing the risks associated with misclassification and recall bias as much as possible. Second, a previous study demonstrated cross-validation between muscle mass estimation using bioelectrical impedance analysis (BIA) and predictive equations for muscle mass quantification, revealing no significant discrepancies between these methodologies [53]. Although the current investigation utilized formula-derived estimates of muscle mass rather than direct measurements from imaging modalities (e.g., DEXA or CT) - a potential source of misclassification bias - it is noteworthy that the employed estimation model has been specifically validated as an appropriate approach for assessing muscle mass in Asian populations. This validation process serves to minimize potential misclassification bias through methodological standardization. Third, this study was conducted in China, and therefore, the findings may be limited to countries with similar sociocultural contexts. However, there is currently no conclusive evidence suggesting inadequate generalizability of our results to other settings, which should be further explored in future cross-cultural studies. Fourth, although we controlled for a series of covariates in the analysis, we cannot rule out the potential influence of other unmeasured factors beyond those accounted for in the database when performing causal mediation analysis.

Conclusions

Drawing on data from the CHARLS, this study presents new evidence of a bidirectional relationship between muscle mass and the risk of CLD. The findings highlight the importance of early screening for both muscle mass loss and CLD in middle-aged and older adults in China, particularly in men and individuals with higher education. Special attention should be given to inflammatory markers, such as cystatin C. Targeted interventions to reduce the risk of self-report CLD and prevent estimated muscle mass decline could significantly improve health outcomes and quality of life in this population.

Abbreviations

CHARLS	China Health and Retirement Longitudinal Study
CLD	Chronic lung disease
BMI	Body mass index
HR	Hazard ratio
95% CI	95% Confidence interval
COPD	Chronic obstructive pulmonary disease
HDL Cholesterol	High-Density Lipoprotein cholesterol
LDL	Cholesterol, Low-Density Lipoprotein cholesterol
CLPM	Cross-lagged panel model
CFI	Comparative Fit Index
TLI	Tucker-Lewis Index
RMSEA	Root mean square error of approximation
SRMR	Standardized root mean square residual

Acknowledgements

We thank the staff and participants of the CHARLS study for their contributions.

Author contributions

JLL and LC conceived and designed the study; JY conducted statistical analyses; JLL, WXL, and LC supervised the data analyses; JY, WXL, RXZ, JJL, XLC, JLL, and LC contributed to manuscript writing. All authors have read and approved the final manuscript.

FUNDING

This work was supported by the Research Foundation for Advanced Talents of Hainan (Grant number 820RC649) and Research Fund for Key Research and Development Project in Hainan (ZDYF2021GXJS018). The funding body had no role in the design of the study and collection, analysis, and interpretation of data, and in writing the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All respondents of the China Health and Retirement Longitudinal Study (CHARLS) signed informed written consent before being interviewed, which was approved by the Institutional Review Board of Peking University (IRB00001052- 11015). Also, this study was conducted according to the approved guidelines.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 2 October 2024 / Accepted: 24 April 2025
Published online: 13 May 2025

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