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Associations between sarcopenia with asthmatic prevalence, lung function and comorbidity

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Abstract

Background

Sarcopenia was listed as a treatment trait in behavioral/risk factors of severe asthma, but studies between asthma and sarcopenia were scant. This study plans to determine the associations between sarcopenia with asthmatic prevalence, symptoms, lung function and comorbidity.

Methods

15404 individuals from the China Health and Retirement Longitudinal Study(CHARLS) and 10263 individuals from Study on global AGEing and adult health(SAGE) in China were included in this study. Four components of this study were respectively used to assess bidirectional association in the prevalence between sarcopenia with asthma, and estimate the relationships between sarcopenia with asthmatic symptoms, lung function and comorbidity via generalized additive models. The 10-item Center for Epidemiological Studies–Depression Scale≥12 scores was classified as depression in CHARLS.

Results

In CHARLS and SAGE, the prevalence of sarcopenia in asthmatics was higher than those without asthma. Asthmatics with sarcopenia had a significantly increased prevalence of severe shortness of breath(sarcopenia yes vs no, adjusted OR=3.71, 95%CI: 1.43-9.60) and airway obstruction in SAGE(sarcopenia yes vs no, adjusted OR=6.82, 95%CI: 2.54-18.34) and an obvious reduction of PEF in CHARLS and SAGE(sarcopenia yes vs no, adjusted RR=0.86, 95%CI: 0.82-0.91) compared to asthmatics without sacropenia. The presence of sarcopenia was positively associated with the prevalence of chronic obstructive pulmonary disease(sarcopenia yes vs no, adjusted OR=5.76, 95%CI:2.01-16.5) and depression(sarcopenia yes vs no, adjusted OR=1.87, 95%CI:1.11-3.14) in asthmatics.

Conclusions

Our findings indicated that sarcopenia partakes in the development of asthma by affecting lung function and comorbidity and maybe considered a treatable trait of asthma management.

Introduction

In 2018, approximately 339 million individuals suffer from asthma with respiratory symptoms and sudden episode of airflow limitation worldwide.[1] Frequent exacerbations of asthma puts a huge physiological and economic burden on patients and their family, even leads to disability and mortality. Worsening lung function and comorbidities(such as depression and chronic lung diseases) were two independent risk factors of asthmatic exacerbations [1]. In recent years, treatable traits are regarded as a

new paradigm for asthma management, one key of which involves early identification of pulmonary, extrapulmonary, and behavioral/risk factors with relation to asthmatic exacerbations [2–5]. Recent study demonstrated that targeting treatable traits may reduce acute exacerbations, and improve the quality of life and asthma control in individuals with severe asthma [2].

Sarcopenia is defined as a age-related loss of skeletal muscle mass plus loss of muscle strength and/or reduced physical performance with the age cutoffs at either 60 or 65 years old in Asian Working Group for sarcopenia(AWGS) 2019 [6]. The diagnose of sarcopenia requires to have the measurement of appendicular skeletal muscle mass(ASM), muscle strength and physical performance. According to AWGS 2014 criteria, the prevalence of sarcopenia was from 5.5–25.7% with male predominance. AWGS 2019 recommends that the cutoff of gait speed rose from 0.8 m/s to <1.0 m/s [6], which may increase the prevalence of sarcopenia. Sarcopenia with muscle fiber atrophy may cause immune senescence [7], the deterioration of respiratory force generation [8] and pulmonary function [9], frailty [10], depression and mortality [10] in the general population. In the study of McDonald et al, sarcopenia was regarded as a treatment trait in behavioral/risk factors of severe asthma. However, studies about the associations between sarcopenia with asthmatic prevalence, lung function and comorbidity were very scant.

It can be hypothesized that muscle fiber atrophy and weakness secondary to sarcopenia potentially lead to the impairment of respiratory function, physical activity limitation and the increasing risk of developing depression or comorbidity in individuals with asthma. By using two national population-based studies in China, we evaluated the associations in the prevalence between sarcopenia with asthma. Subsequently, this study determined whether sarcopenia and its severity are associated with the reduction of lung function in elderly individuals with asthma. Finally, we investigated whether sarcopenia has significant relationships with comorbidities via generalized additive models.

Methods

Study population

The China Health and Retirement Longitudinal Study(CHARLS) started in between June 2011 and March 2012 and involved 17708 individuals aged more than 45 years, which represented a nationally population-based health, social and economic status with covering 450 urban or rural areas in 28 provinces of China. CHARLS uses a face-to-face computer-assisted personal interview(CAPI) with physical measurements, blood sample collection, and depression assessment. Follow-up was conducted every 2 years with the participation of new individuals in CHARLS. The Biomedical Ethics Review Committee of Peking University approved CHARLS. Written informed consents were collected in National School of Development of Peking University. More detailed description about CHARLS has been reported elsewhere [11].

Study on global AGEing and adult health(SAGE) is designed by the World Health Organization(WHO) and plans to assess and compare health status and socio-economic consequences of adult populations and the ageing process in six countries(China, Ghana, India, Mexico, Russian Federation and South Africa)

worldwide. SAGE in China wave 1 was created between 2007 and 2010, involved 15050 individuals and covered the eight provinces. In 2012, the date involving 19 districts in Shanghai and 9524 individuals were included in SAGE. WHO Ethical Review Committee and local ethics research review boards approved ethical and obtained written informed consent. All information and data were found in elsewhere[12] and the following link: https://apps.who.int/healthinfo/systems/survey data/index.php/catalog/sage/about(accessed on 30 May 2021) [12].

Definition of asthma, sarcopenia and depression

The diagnosis of asthma was based on a positive answer of the following question: Have you ever been diagnosed with asthma by a doctor. In WHO SAGE, we collected the relevant data about asthmatic medications treatment and symptoms (attacks, awakening, and severe shortness of breath) in the past 12 months. Severe shortness of breath was based on a positive answer of the following question: Have you had an attack of shortness of breath that came on without obvious cause when you were not exercising or doing some physical activity?.

According to the recommend of AWGS 2019 [6], muscle strength and physical performance in the diagnosis of sarcopenia were measured by using handgrip strength(<28.0 kg for men and <18.0 kg for women) and gait speed(<1.0 m/s) in CHARLS and WHO SAGE. In addition, CHARLS also provided 5-time chair stand test to measure low physical performance(≥12 s). The following anthropometric equation for the height-adjusted muscle mass (ASM/Ht^2) can be used to determine whether low ASM exists in Chinese population[6, 13]: ASM/Ht^2=(0.193*body weight + 0.107* height- 4.157* gender - 0.037*age-2.631)/$height^2$. Similar to previous studies

[14–16], the cut-off for defining low muscle mass was based on the ASM/Ht2 of the lowest 20th% percentile of the study population. Therefore, ASM/Ht^2 < 6.92 for men and < 5.14 for female are regarded as low ASM. The age cutoffs of sarcopenina are set at 60 years old [6]. Low ASM with low muscle strength or physical performance were defined as sarcopenia, meanwhile patients with severe sarcopenia were associated with low ASM, muscle strength and physical performance [6].

CHARLS assessed whether depression exists by using the 10-item Center for Epidemiological Studies–Depression Scale (CES-D10). The 10 items with 4 four answers were used to estimate the depressive feelings and behaviors of individuals over one week, and value of 0-3 is assigned to each answer. Previous studies identified that CES-D10 harbors adequate reliability and validity in the assessment of depression for the community-dwelling older Chinese population [17]. CES-D10≥ 12 scores with total scores of 0 to 30 scores was considered depression [17, 18].

Variables

In CHARLS, this study included the following demographic characteristics as adjusted confounding factors: sex, age, region, urban/rural, married status, alcohol, smoking, body mass index(BMI), night sleep duration and thirteen physician- diagnosed comorbidities (hypertension, dyslipidemia, hyperglycemia,

cancers, chronic lung diseases, liver diseases, heart diseases, stroke, kidney diseases, digestive diseases, emotional or psychiatric problems, memory-related diseases, and arthritis or rheumatism). Lung function was measured through peak expiratory flow(PEF) in CHARLS.

In WHO SAGE, the following variables were used to adjusted the associations between asthma and sarcopenia: sex, age, region, urban/rural, married status, alcohol, smoking, vigorous-intensity activity, moderate-intensity activity, BMI, night sleep duration, hypertension, diabetes, angina, stroke, chronic lung diseases and arthritis. This study evaluated lung function in individuals with asthma through the following variables: forced expiratory volume in the first second (FEV1), FEV1/forced vital capacity(FVC), PEF, forced expiratory flow rate, mid-exhalation (FEF25–75%). FEV1/FVC<0.7 was regarded as airway obstruction. Individuals with chronic lung diseases and FEV1/FVC<0.7 were diagnosed as having chronic obstructive pulmonary disease (COPD).

For Chinese adults, BMI was divided into four groups: underweight (< 18.5 kg/m^2), normal (18.5 to < 24.0 kg/m^2), overweight (24.0 to < 28.0 kg/m^2), and obesity (≥ 28.0 kg/m^2) [19]. Age was divide into three groups: 60-69, 70-79, and 80 years. More detailed groups of all variables were shown in Table 1 and Table 2.

Table 1
The characteristics of study population in the China Health and Retirement Longitudinal Study

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
N	12159	2350	895	
Age	66.7 ± 5.6	69.9 ± 6.7	73.9 ± 7.2	<0.01
Year				<0.01
2011	3604 (29.6%)	877 (37.3%)	310 (34.6%)	
2013	3846 (31.6%)	715 (30.4%)	259 (28.9%)	
2015	4709 (38.7%)	758 (32.3%)	326 (36.4%)	
Sex				0.09
Male	6303 (51.8%)	1199 (51.0%)	495 (55.3%)	
Female	5856 (48.2%)	1151 (49.0%)	400 (44.7%)	
Region				<0.01
Southwest	3271 (26.9%)	924 (39.3%)	322 (36.0%)	
South and central	6344 (52.2%)	1163 (49.5%)	447 (49.9%)	
North	2544 (20.9%)	263 (11.2%)	126 (14.1%)	
Urban/Rural				<0.01
Urban	7232 (59.5%)	1746 (74.3%)	671 (75.0%)	
Rural	4927 (40.5%)	604 (25.7%)	224 (25.0%)	
Married status				<0.01
Current unmarried	2021 (16.6%)	551 (23.4%)	302 (33.7%)	
Current married	10138 (83.4%)	1799 (76.6%)	593 (66.3%)	
Alcohol				<0.01
More than once a month	3170 (26.1%)	605 (25.7%)	220 (24.6%)	
Less than once a month	927 (7.6%)	144 (6.1%)	48 (5.4%)	
Never	8062 (66.3%)	1601 (68.1%)	627 (70.1%)	
Smoking				<0.01
Never	6806 (56.0%)	1175 (50.0%)	456 (50.9%)	
Ever	1556 (12.8%)	239 (10.2%)	119 (13.3%)	

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
Current	3797 (31.2%)	936 (39.8%)	320 (35.8%)	
Body mass index category				<0.01
Underweight	76 (0.6%)	834 (35.5%)	344 (38.4%)	
Normal	5996 (49.3%)	1512 (64.3%)	549 (61.3%)	
Overweight	4460 (36.7%)	4 (0.2%)	2 (0.2%)	
Obesity	1627 (13.4%)	0 (0.0%)	0 (0.0%)	
Night sleep duration				<0.01
<360 mins	4000 (32.9%)	931 (39.6%)	370 (41.3%)	
360-419 mins	2641 (21.7%)	459 (19.5%)	148 (16.5%)	
420-479 mins	2150 (17.7%)	308 (13.1%)	107 (12.0%)	
480-539 mins	2352 (19.3%)	427 (18.2%)	160 (17.9%)	
≥540 mins	1016 (8.4%)	225 (9.6%)	110 (12.3%)	
Hypertension				<0.01
No	8392 (69.0%)	1854 (78.9%)	675 (75.4%)	
Yes	3767 (31.0%)	496 (21.1%)	220 (24.6%)	
Dyslipidemia				<0.01
No	10637 (87.5%)	2185 (93.0%)	828 (92.5%)	
Yes	1522 (12.5%)	165 (7.0%)	67 (7.5%)	
Hyperglycemia				<0.01
No	11167 (91.8%)	2243 (95.4%)	858 (95.9%)	
Yes	992 (8.2%)	107 (4.6%)	37 (4.1%)	
Cancer				0.69
No	12054 (99.1%)	2331 (99.2%)	885 (98.9%)	
Yes	105 (0.9%)	19 (0.8%)	10 (1.1%)	
Chronic lung diseases				<0.01
No	10846 (89.2%)	1999 (85.1%)	773 (86.4%)	
Yes	1313 (10.8%)	351 (14.9%)	122 (13.6%)	
Liver diseases				0.002

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
No	11608 (95.5%)	2271 (96.6%)	871 (97.3%)	
Yes	551 (4.5%)	79 (3.4%)	24 (2.7%)	
Heart diseases				<0.01
No	10316 (84.8%)	2069 (88.0%)	786 (87.8%)	
Yes	1843 (15.2%)	281 (12.0%)	109 (12.2%)	
Stroke				0.02
No	11821 (97.2%)	2308 (98.2%)	867 (96.9%)	
Yes	338 (2.8%)	42 (1.8%)	28 (3.1%)	
Kidney diseases				0.48
No	11329 (93.2%)	2199 (93.6%)	842 (94.1%)	
Yes	830 (6.8%)	151 (6.4%)	53 (5.9%)	
Digestive diseases				0.01
No	9527 (78.4%)	1785 (76.0%)	680 (76.0%)	
Yes	2632 (21.6%)	565 (24.0%)	215 (24.0%)	
Emotional, nervous, or psychiatric problems				0.10
No	11997 (98.7%)	2327 (99.0%)	889 (99.3%)	
Yes	162 (1.3%)	23 (1.0%)	6 (0.7%)	
Memory-related diseases				0.76
No	11907 (97.9%)	2306 (98.1%)	875 (97.8%)	
Yes	252 (2.1%)	44 (1.9%)	20 (2.2%)	
Arthritis or rheumatism				0.34
No	8044 (66.2%)	1584 (67.4%)	607 (67.8%)	
Yes	4115 (33.8%)	766 (32.6%)	288 (32.2%)	
Asthma				<0.01
No	11671 (96.0%)	2228 (94.8%)	846 (94.5%)	
Yes	488 (4.0%)	122 (5.2%)	49 (5.5%)	
Depression				<0.01
No	8847 (72.8%)	1551 (66.0%)	588 (65.7%)	

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
Yes	3312 (27.2%)	799 (34.0%)	307 (34.3%)	
PEF	289.5 ± 119.5	237.5 ± 108.7	195.9 ± 105.3	<0.01

Table 2
The characteristics of study population in the Study on global AGEing and adult health from China

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
N	8998	753	512	
Age	68.8 ± 6.9	73.0 ± 7.2	76.1 ± 7.3	<0.01
Sex				<0.01
Male	4506 (50.1%)	312 (41.4%)	199 (38.9%)	
Female	4492 (49.9%)	441 (58.6%)	313 (61.1%)	
Region				0.01
North	2754 (30.6%)	195 (25.9%)	141 (27.5%)	
South	6244 (69.4%)	558 (74.1%)	371 (72.5%)	
Urban/Rural				<0.01
Urban	4985 (55.4%)	297 (39.4%)	151 (29.5%)	
Rural	4013 (44.6%)	456 (60.6%)	361 (70.5%)	
Married status				<0.01
Current unmarried	1790 (19.9%)	253 (33.6%)	205 (40.0%)	
Current married	7208 (80.1%)	500 (66.4%)	307 (60.0%)	
Alochol				0.05
Ever	2349 (26.1%)	175 (23.2%)	115 (22.5%)	
Never	6649 (73.9%)	578 (76.8%)	397 (77.5%)	
Smoking				0.73
Never	6302 (70.0%)	522 (69.3%)	371 (72.5%)	
Ever	888 (9.9%)	72 (9.6%)	44 (8.6%)	
Current	1808 (20.1%)	159 (21.1%)	97 (18.9%)	
Body mass index				<0.01
Underweight	131 (1.5%)	231 (30.7%)	146 (28.5%)	
Normal	3992 (44.4%)	521 (69.2%)	364 (71.1%)	
Overweight	3525 (39.2%)	1 (0.1%)	2 (0.4%)	
Obesity	1350 (15.0%)	0 (0.0%)	0 (0.0%)	

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
Moderate-intensity activity				<0.01
Yes	2840 (31.6%)	304 (40.4%)	188 (36.7%)	
No	6158 (68.4%)	449 (59.6%)	324 (63.3%)	
Vigorous-intensity activity				0.61
Yes	748 (8.3%)	66 (8.8%)	37 (7.2%)	
No	8250 (91.7%)	687 (91.2%)	475 (92.8%)	
Night sleep duration				<0.01
<360mins	751 (8.3%)	79 (10.5%)	62 (12.1%)	
360-419 mins	1210 (13.4%)	92 (12.2%)	53 (10.4%)	
420-479mins	1958 (21.8%)	126 (16.7%)	58 (11.3%)	
480-539mins	2890 (32.1%)	224 (29.7%)	122 (23.8%)	
≥540min	2189 (24.3%)	232 (30.8%)	217 (42.4%)	
Hypertension				<0.01
No	5359 (59.6%)	586 (77.8%)	403 (78.7%)	
Yes	3639 (40.4%)	167 (22.2%)	109 (21.3%)	
Diabetes				<0.01
No	8082 (89.8%)	718 (95.4%)	489 (95.5%)	
Yes	916 (10.2%)	35 (4.6%)	23 (4.5%)	
Stroke				0.22
No	8051 (89.5%)	685 (91.0%)	467 (91.2%)	
Yes	947 (10.5%)	68 (9.0%)	45 (8.8%)	
Angina				0.32
No	8486 (94.3%)	720 (95.6%)	483 (94.3%)	
Yes	512 (5.7%)	33 (4.4%)	29 (5.7%)	
Chronic lung diseases				<0.01
No	8101 (90.0%)	654 (86.9%)	434 (84.8%)	
Yes	897 (10.0%)	99 (13.1%)	78 (15.2%)	
Arthritis				0.01

	No sarcopenia	Sarcopenia	Severe sarcopenia	*P*
No	6879 (76.5%)	615 (81.7%)	376 (73.4%)	
Yes	2119 (23.5%)	138 (18.3%)	136 (26.6%)	
Asthma				0.1
No	8733 (97.1%)	724 (96.1%)	490 (95.7%)	
Yes	265 (2.9%)	29 (3.9%)	22 (4.3%)	
FEV1	1.7 ± 0.7	1.5 ± 0.7	1.3 ± 0.7	<0.01
FEV1/FVC				<0.01
≥0.7	7252 (80.6%)	555 (73.7%)	352 (68.8%)	
<0.7	1746 (19.4%)	198 (26.3%)	160 (31.2%)	
PEF	78.6 ± 19.9	76.6 ± 19.5	73.8 ± 21.0	<0.01
FEF25-75	2.0 ± 1.1	1.6 ± 1.1	1.3 ± 1.0	<0.01

Statistical analysis

Study populations were categorized into three groups: no sarcopenia, non-severe sarcopenia and severe sarcopenia. SPSS described categorical variables by counts and percentages (%), subsequently compared the difference between three groups via a chi-square test. Continuous variables were presented as means and standard deviations with Mann-Whitney U test for skewed continuous variables and Student's t test or one-way ANOVA for normally distributed continuous variables. Chi-square goodness-of-fit method tested the normality of distribution of the data. The first component of the study assessed the associations in the prevalence between sarcopenia and asthma via three generalized additive models with binomial regression.The adjusted variables of each model were shown in each table. Model 1 included patient demographic characteristics, model 2 added physical/behavioral factors, and model 3 added physical/behavioral factors and comorbidities. In CHARLS, the least absolute shrinkage and selection operator (LASSO) [20] and multivariate logistic analyses with binomial regression were used to screen the independent risk factors of sarcopenia in asthmatics. We also evaluated the relationships between sarcopenia with asthmatic medications and symptoms in the second component. Model 4 also included lung function on the basis of model 3 in Table 3. The third component was that three generalized additive models with Possion regression were used to compare the differences of lung function among three sarcopenia groups in asthmatics. In WHO SAGE, model 4 added the adjustments of asthmatic medications and symptoms. Finally, three generalized additive models with binomial regression were used to evaluate the associations between sarcopenia with depression and COPD in asthmatics. All statistical analyses were done in SPSS, Empower(R) (www. empowerstats.com; X&Y solutions, Inc., Boston MA). Odd ratios (ORs) for binomial regression and analysis and rate ratio(RR) for

Poisson regression analysis with 95% confidence intervals (CIs) represented the strength of association, meanwhile a two tailed P < 0.05 was considered statistically significant.

Table 3
The associations between sarcopenia and asthma-related symptoms in the Study on global AGEing and adult health from China

	Model 1	Model 2	Model 3	Model 4
Asthma-related attacks				
Sarcopenia(no vs yes)	0.97(0.40, 2.38)	0.82(0.32, 2.06)	0.72(0.28, 1.86)	0.53(0.19, 1.51)
Asthma-related awakening				
Sarcopenia(no vs yes)	1.72(0.69, 4.31)	1.97(0.74, 5.26)	2.02(0.73, 5.59)	2.66(0.90, 7.82)
Asthma-related severe shortness of breath				
Sarcopenia(no vs yes)	3.51(1.50, 8.20)[#]	3.63(1.50, 8.79)[#]	3.41(1.38, 8.42)[#]	3.71(1.43, 9.60)[#]

Model 1 adjusted the following variables: sex, age, region, urban/rural, married status and body mass index,

Model 2 adjusted the following variables: sex, age, region, urban/rural, married status, body mass index, alcohol, smoking, vigorous-intensity activity, moderate- intensity activity and night sleep duration.

Model 3 adjusted the following variables: sex, age, region, urban/rural, married status,body mass index, alcohol, smoking, vigorous-intensity activity, moderate- intensity activity, night sleep duration, hypertension, diabetes, angina, stroke, chronic lung diseases, and arthritis.

Model 4 adjusted the following variables: sex, age, region, urban/rural, married status, alcohol, smoking, vigorous-intensity activity, moderate-intensity activity, body mass index, night sleep duration, hypertension, diabetes, angina, stroke, chronic lung diseases, arthritis, FEV1, airway obstruction, PEF, and FEF 25%-75%).

[#] $P < 0.01$

Results

The characteristics in CHARLS and WHO SAGE

In three cycles of CHARLS (2011, 2013 and 2015), a total of 15404 individuals aged 67.6±6.2 years (range, 60–103 years) were included in this present study. More than half (51.9%) of individuals were male with predominantly never alcohol and smoking. The overall prevalence of sarcopenia was 21.1% with 5.8% of severe sarcopenia. The prevalence of sarcopenia showed an upward trend with the increase of age: 14.4%, 31.8%, and 51.2% in the 60-69, 70-79 and ≥ 80 years groups, respectively. 659 (4.3%)

individuals reported physician-diagnosed asthma. 4433 (28.7%) individuals were classified as depressive group (CES-D10≥12 scores).

A total of 10263 individuals with 69.5±7.2 years(range, 60–102 years) were selected from WHO SAGE. Predominantly female (51.1%) with high-proportioned never alcohol and smoking were shown in WHO SAGE. The overall prevalence of sarcopenia was 12.3% with 10.2% among male and 14.4% among female. 512(5%) individuals were diagnosed with severe sarcopenia. Prevalence of sarcopenia in three age groups also significantly increased and varied by 6.0%, 16.4% and 32.5%. 2104 (20.5%) individuals had airway obstruction(FEV1/FVC<0.7). The prevalence of asthma was 3.1% (316 individuals). 301 asthmatics provided the information about medications treatment (73.4%) and asthma-related symptoms. The proportions of asthma-related attacks, awakening, and activity limitation were 68.1%, 27.2% and 42.2%, respectively. More detailed data were shown in Table 1 and Table 2.

Associations in the prevalence between sarcopenia with asthma

In CHARLS, the prevalence of non-severe and severe sarcopenia among asthmatics were 18.5% and 7.4%, respectively(see Figure 1). 4.0% of individuals with sarcopenia had the diagnosis of asthma, which was higher than those of individuals without sarcopenia(2.9%, *P*=0.036). Model 3 indicated that sarcopenia and asthma have no significantly bidirectional association in the prevalence(see table S1). In asthmatics, LASSO and multivariate logistic regression analyses indicated that aged with rural (rural vs unban, adjusted OR=0.41, 95%CI: 0.23-0.75) and depression (CES-D10 < 12 scores vs ≥ 12 scores, adjusted OR=1.95, 95%CI: 1.16-3.27) harbored relatively high prevalence of sarcopenia.

In WHO SAGE, 9.2% and 7% of individuals with asthma could be diagnosed with non-severe and severe sarcopenia, which were higher than those in individuals without asthma(see Figure 1). The prevalence of asthma was 4.0% in individuals with sarcopenia. Three models observed no significantly association in the prevalence between asthma and sarcopenia(see table S2). LASSO and multivariate logistic regression analyses suggested that female, rural, aged and airway obstruction were indepedent risk factors of sarcopenia among asthmatics.

Sarcopenia and asthma-related symptoms

Four models also showed that asthma-related attacks and awakening had no significant associations with the presence of sarcopenia (see Table 3). However, sarcopenia was associated with significantly higher prevalence of asthma-related severe shortness of breath after adjusted demographic characteristics, physical/behavioral factors, comorbidities and lung function (adjusted OR=3.71, 95%CI: 1.43-9.60). The prevalence of sarcopenia demonstrated a rising tendency with the increasing numbers of asthma-related symptoms(see Figure 2).

Sarcopenia and lung function in asthmatics

In CHARLS, Possion regression analysis suggested that adjusted mean value of PEF were significantly declined in asthmatics with non-severe(adjusted RR=0.926, 95%CI: 0.910-0.934) and severe

sarcopenia(adjusted RR=0.759, 95%CI: 0.739-779) compared to no sarcopenia.

In WHO SAGE, four Possion regression analyses demonstrated that the more severe sarcopenia in asthmatics, the more obvious was lung function impairment (see Table 4 and Figure 3). Asthmatics with sarcopenia(adjusted RR=6.82, 95%CI: 2.54-18.34 in model 4) were associated with significantly higher prevalence of airway obstruction than those without sarcopenia. Sarcopenia had a significantly negative correlation with adjusted mean value of PEF in asthmatics(adjusted RR=0.86, 95%CI: 0.82-0.91 in model 4).

Table 4
The associations between sarcopenia and lung function of asthmatics in the Study on global AGEing and adult health from China

	Model 1	Model 2	Model 3	Model 4
FEV1				
Sarcopenia(no vs yes)	0.75(0.57, 1.01)	0.75(0.50, 1.12)	0.80(0.53, 1.20)	0.81(0.53, 1.22)
FEV1/FVC<0.7				
Sarcopenia(no vs yes)	5.44(2.25, 13.19)#	5.89(2.34, 14.82)#	5.37(2.09, 13.80)#	6.82(2.54, 18.34)#
PEF				
Sarcopenia(no vs yes)	0.87(0.82, 0.91)#	0.87(0.83, 0.92)#	0.89(0.85, 0.94)#	0.86(0.82, 0.91)#
FEF25%-75%				
Sarcopenia(no vs yes)	0.89(0.61, 1.30)	0.88(0.60, 1.29)	0.96(0.66, 1.42)	0.93(0.63, 1.38)

Model 1 adjusted the following variables: sex, age, region, urban/rural, married status and body mass index,

Model 2 adjusted the following variables: sex, age, region, urban/rural, married status, body mass index, alcohol, smoking, vigorous-intensity activity, moderate- intensity activity and night sleep duration.

Model 3 adjusted the following variables: sex, age, region, urban/rural, married status,body mass index, alcohol, smoking, vigorous-intensity activity, moderate- intensity activity, night sleep duration, hypertension, diabetes, angina, stroke, chronic lung diseases, and arthritis.

Model 4 adjusted the following variables: sex, age, region, urban/rural, married status, alcohol, smoking, vigorous-intensity activity, moderate-intensity activity, body mass index, night sleep duration, hypertension, diabetes, angina, stroke, chronic lung diseases, arthritis, asthma related medications and symptoms (attacks, awakenings and activity limitation).

# $P < 0.01$

Sarcopenia and comorbidities in asthmatics

In CHARLS, Adjusted OR values in the prevalence of depression respectively were 1.82(95%CI: 1.04-3.18) in nonsevere sarcopenia and 2.02 (95%CI: 1.01-4.10) in severe sarcopenia compared with no sarcopenia after adjusted demographic characteristics, physical/behavioral factors, and thirteen comorbidities. The presence of sarcopenia was associated with significantly higher prevalence of depression (adjusted OR=1.87, 95%CI:1.11-3.14 in model 3).

In WHO SAGE, sarcopenia was an idepedent risk factor of COPD in individuals with asthma(adjusted OR=5.76, 95%CI:2.01-16.5 in model 4). When model 3 added the adjustment of asthmatic medication and symptoms, the prevalence of COPD in nonsevere sarcopenia group(adjusted OR=9.11, 95%CI:2.69-30.8 in model 4) was significantly higher than that in no sarcopenia group.

Discussion

The study used two national population-based survey to determine the

associations between sarcopenia with asthma and found the following results: Firstly, the prevalence of sarcopenia and severe sarcopenia defined by AWGS 2019 was 12.3%-21.3% and 5%-5.8% in Chinese older asthmatics. There was no significantly bidirectional association in the prevalence between asthma and sarcopenia, but an upward trend of sarcopenia was associated with the increasing numbers of asthma-related symptoms. Secondly, the presence of sarcopenia, especially severe sarcopenia, was accompanied by a significantly increasing risk of airway obstruction and the obvious reduction of PEF. Thirdly, sarcopenia was positively associated with the prevalence of depression and COPD in terms of asthmatic comorbidity.

Studies about sarcopenia and asthma did not obtain enough attention and are very scant. This is the first study to estimate the prevalence of sarcopenia in Chinese population with asthma using AWGS 2019 criteria. Our studied demonstrated that approximately 17.6% and 5.5% of asthmatics may be diagnosed with sarcopenia and severe sarcopenia. The prevalence of sarcopenia in CHARLS was higher than that in WHO SAGE. A possible explanation was that more individuals came from rural in CHARLS. Previous studies have fully explored the adverse effects of sarcopenia on chronic obstruction pulmonary diseases[21, 22] and health status in the general population [23, 24]. Our study suggested that the prevalence of sarcopenia among asthmatics was higher than that among individuals without asthma. The screen and study of sarcopenia in asthmatics should not be neglected, especially for aging individuals with rural, depression and airway obstruction.

Persistent airway obstruction and lung function impairment are two important hallmarks of asthmatic deterioration [1]. Airway obstruction and declined lung function not only augment the risk of asthmatic exacerbations and reduce the quality of life, but also increase the difficulty of asthmatic medication treatment. [1] Short-term and long-term PEF monitoring may know expiratory airflow limitation and

contribute to early detection of asthmatic exacerbations and the assessment of asthma control level. Sarcopenia was found to have positive correlation with the prevalence of airway obstructive and the decline of PEF in our study. We also observed that asthmatics with sarcopenia were more prone to develop COPD than those without sarcopenia. It is reasonable to expect that sarcopenia along with systemic muscle fiber atrophy and weakness will inevitably lead to functional disability of respiratory muscles. The cross-talk between sarcopenia and adverse health consequences is mediated through complex mechanisms and pathways, including microRNAs, inflammatory processes, oxidative stress and etc [25–27]. The onset and development of asthma were known to involve the regulatory of microRNAs and inflammatory processes [28, 29]. In asthmatics, the expression levels of miR-21 and miR-34 had strongly negative associations with handgrip strength and ASM, whereas miR-133 and miR-206 showed significantly positive correlations with handgrip strength and ASM[30]. Sarcopenia along with low handgrip strength and ASM potentially reduces the levels of miR-133 and miR-206 in asthmatics. The decreasing miR-133a could up-regulate RhoA expression of bronchial smooth muscle in asthma model, which may lead to an augmentation of bronchial smooth muscle contraction and induce airway hyperresponsiveness(AHR) in individuals with asthma [31]. In 4,4'-methylene diphenyl diisocyanate induced asthma model, the reduction of miR-206-3p might increase inducible nitric oxide synthase transcription expression by targeting calcineurin/NFAT signaling, in turn leading to AHR. Increasing level of miR-21 not only promotes the differentiation of T cells towards Th2 in eosinophilic asthma, but also restrains HDAC2 levels and results in glucocorticoids insensitivity by up-regulated PI3K-mediated phosphorylation and nuclear translocation of pAKT in neutrophilic asthma [28]. Multiple studies have shown that sarcopenia is associated with the significant increase of pro-inflammatory cytokines, including TNF-α, IL-6, and C-reactive protein [32]. Taken together, microRNAs regulatory network and inflammatory processes can be considered the underlying pathophysiology linking sarcopenia with asthma.

Depression is classed as an important independent risk factor of asthma onset, exacerbations and mortality [1]. Our study suggested a bidirectional association between depression and sarcopenia in asthmatics, similar to the results in the general population[33, 34]. Sarcopenia, especially severe sarcopenia, was associated with significant increase of depression compared with no sarcopenia. Sarcopenia and depression harbor common pathophysiological pathways with regard to inflammation processes, neurotrophins and oxidative stress [33]. In addition, the onset of sarcopenia and depression may attribute to some same lifestyle behaviors, such as low physical activity, smoking, and malnutrition [33]. Depression caused by sarcopenia was likely to participate in the occurrence and development of asthma.

Our main strength is to firstly assess the relationships between sarcopenia with asthmatic prevalence, lung function and comorbidity in Chinese population by using two national population-based studies. However, several limitations also exist in our study. Firstly, the diagnoses of asthma and some comorbidities depend on the questionnaire's results with potential selection bias. Secondly, an

anthropometric equation, instead of Dual X-ray absorpometry (DXA) or Bioelectrical impedance analysis(BIA), is used to evaluate ASM. However, this equation has previously been validated in Chinese population [13]. Our cutoff of low ASM was substantially identical to that in the study of Wu and the colleagues [16]. Besides, the unlity of anthropometric equation to assess low ASM may obtain a cost-effective alternative to BIA or DXA to improve the diagnsis of sarcopenia, especially in large-sample population-based studies [35]. Thirdly, the cross-sectional nature of two studies restrains the capability to infer interactional causation between asthma and sarcopenia.

Conclusion

This study reports the prevalence of sarcopenia and severe sarcopenia in Chinese older population and asthmatics. Sarcopenia can contribute to the development of asthma by affecting lung function and comorbidity and maybe considered treatable traits of asthma management. Considering the high prevalence and significant effect of sarcopenia, It's worth making a routine screening for asthmatics.

Abbreviations

AHR - airway hyperresponsiveness

ASM - Appendicular skeletal muscle mass

AWGS - Asian Working Group for sarcopenia

BIA - Bioelectrical impedance analysis

BMI - Body mass index

CAPI - Computer-assisted personal interview

CHARLS - **T**he China Health and Retirement Longitudinal Study

CI - Confidence interval

DXA - Dual X-ray absorpometry

LASSO - least absolute shrinkage and selection operator

OR - Odds ratio

RR- Rate ratio

SAGE - Global Ageing and Adult Health

Declarations

Ethics approval and consent to participate

The study procedures were carried out by the Declaration of Helsinki. Written informed consents were collected in National School of Development of Peking University on the China Health and Retirement Longitudinal Study(CHARLS). WHO Ethical Review Committee and local ethics research review boards approved ethical and obtained written informed consent on Global Ageing and Adult Health (SAGE). All experiments were performed in accordance with relevant guidelines and regulations. All experimental protocols were approved by the Institutional Review Board at China, Three Gorges University. This study was deemed exempt for review by the Institutional Review Board at China, Three Gorges University.

Consent to publication

Not Applicable.

Competing interests:

The authors declare that they have no confict of interest.

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Authors' contributions:

Z.H. F.Z. and X.Y. wrote the main manuscript text. A.Y.and Y.T. prepared figures 1-3. All authors reviewed the manuscript.

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Figures

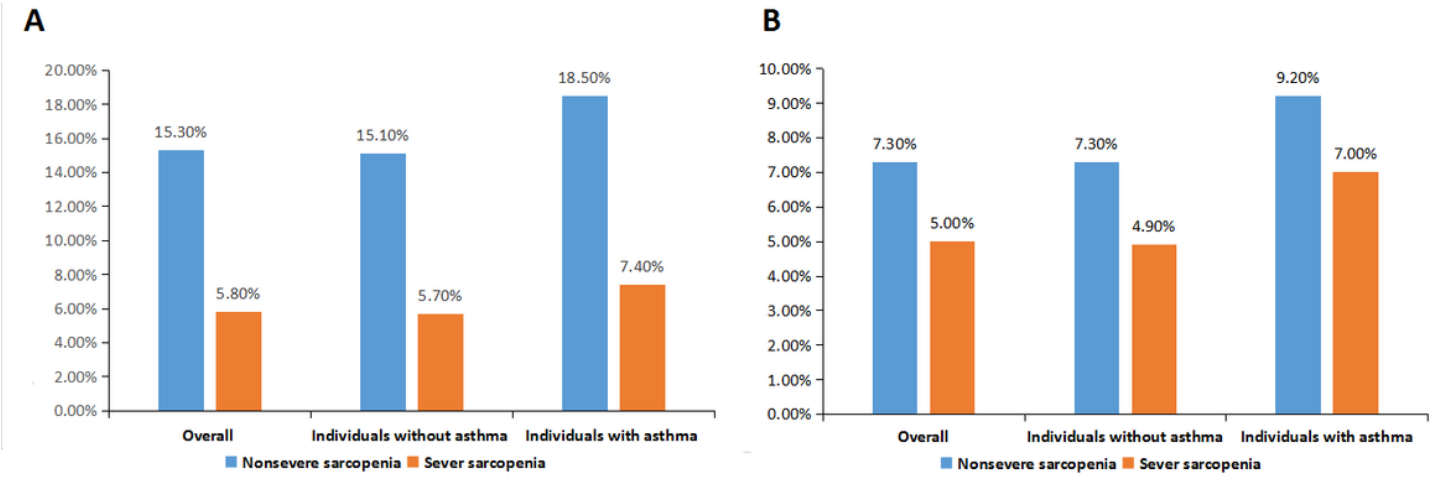

Figure 1

The prevalence of sarcopenia. A. In the China Health and Retirement Longitudinal Study; B. the Study on global AGEing and adult health from China.

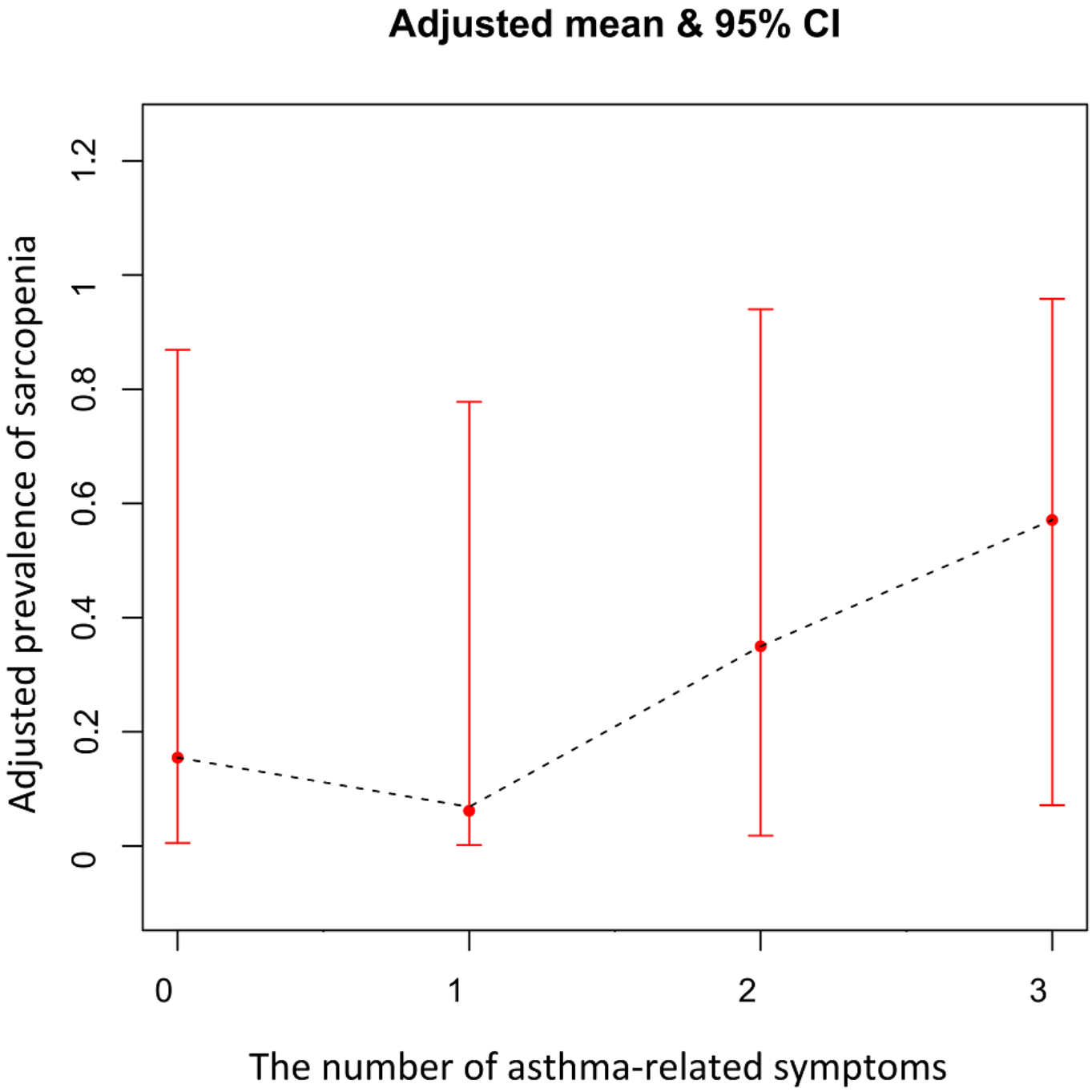

Figure 2

The associations between the prevalence of sarcopenia with the number of asthma-related symptoms in asthmatics from the Study on global AGEing and adult health from China.

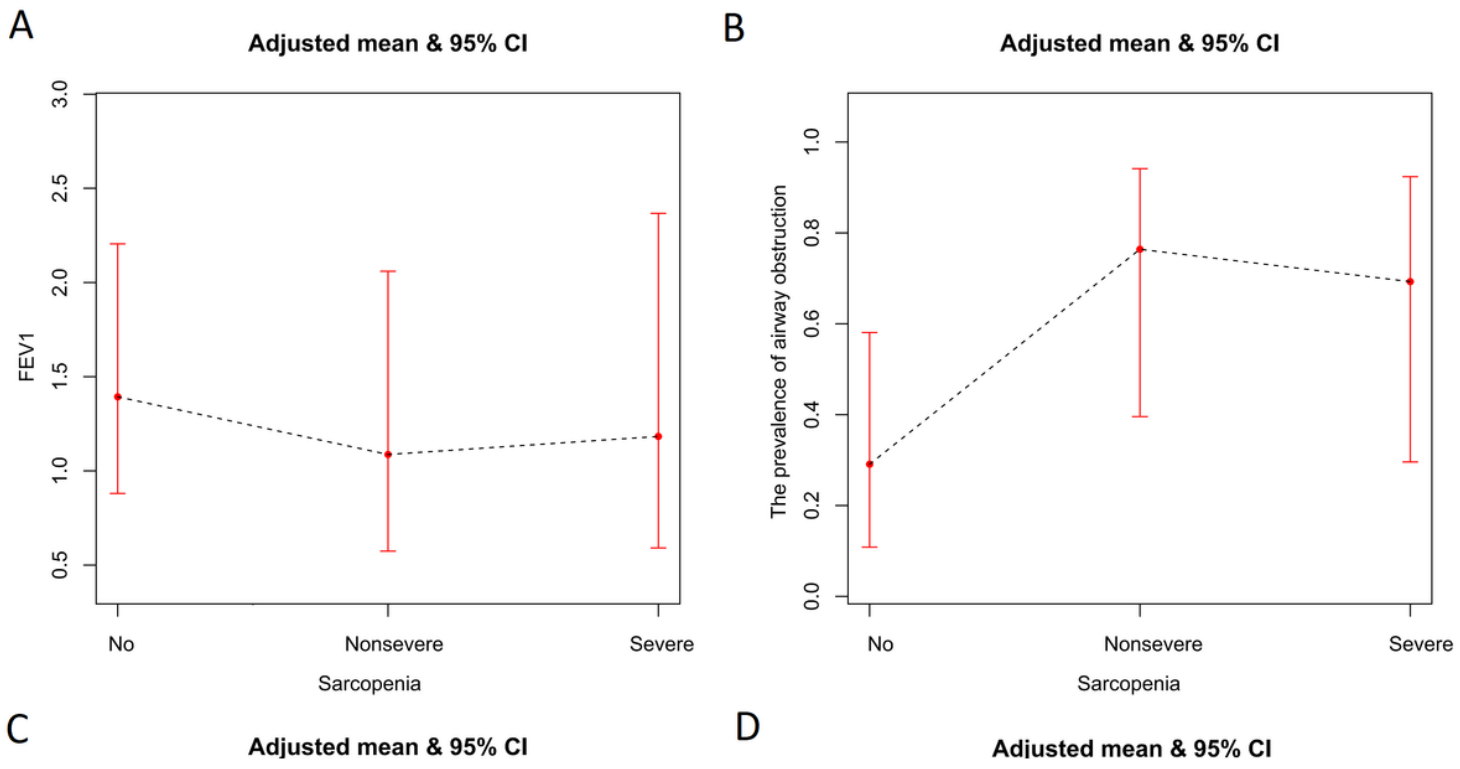

Figure 3

The associations between different grade of sarcopenia with lung function in asthmatics from the Study on global AGEing and adult health from China. A: FEV1; B: FEV1/FVC < 0.7; C: PEF; D: FEF 25%-75%.

Supplementary Files

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