Original Article

Skeletal muscle mass indexes and nonalcoholic fatty liver disease in Chinese elders

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Background and Objectives: As an endocrine organ, the mass of skeletal muscle is closely related to human health. The present study aimed to investigate the relationship between regional skeletal muscle and nonalcoholic fatty liver disease (NAFLD) in Chinese elders. **Methods and Study Design:** A total of 1,328 participants (579 males and 749 females), aged 65 to 96 years were recruited between March to November 2020 in Qingdao, China. Of these, 400 cases and 400 healthy controls, matched by gender and age (±3 years), were included in the study. Skeletal muscle mass was measured by bioelectrical impedance analysis, and body weight was adopted to standardize skeletal muscle mass to obtain skeletal muscle mass indexes. **Results:** Inverse associations were observed for trunk muscle mass index (TMI) (OR=0.42; 95% CI: 0.19, 0.93; *p* for trend=0.083) and leg skeletal muscle mass index (LMI) (OR=0.41; 95% CI: 0.18, 0.97; *p* for trend=0.012) with NAFLD risk after adjustment for age, body mass index, glucose, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, dietary intakes of energy, carbohydrate, protein and fat, smoking, alcohol drinking, education and physical activity. Dose-response analysis indicated that per standard deviation increment of LMI was associated with 23% (95%CI: 0.63, 0.95) reduction of NAFLD risk. **Conclusions:** The present study demonstrates that higher TMI and LMI are associated with a lower NAFLD risk.

Key Words: nonalcoholic fatty liver disease, skeletal muscle mass indexes, elders, case-control study, epidemiology

INTRODUCTION

Nonalcoholic fatty liver diseases (NAFLD) are the most prevalent chronic liver disease, affecting about one quarter of the world's population.[1] It has been estimated that the prevalence of NAFLD was approximately 20.1-29.2% in Chinese adults.[2,3] Changes of lifestyle as well as environment exert significant effects responsible for the initiation and progress of NAFLD. As a progressive disease, NAFLD would potentially progress from simple steatosis into nonalcoholic steatohepatitis, cirrhosis, hepatocellular carcinoma and death.[4] Although NAFLD patients are asymptomatic in the initial stage, substantial evidence has demonstrated that NAFLD is associated with obesity, diabetes and other metabolic diseases, posing a major threat to public health.[5-7]

Skeletal muscle is an important endocrine organ for insulin-mediated glucose uptake and utilization, and plays an important role in glucose homeostasis and insulin resistance (IR). Besides, it participates in the processes of autocrine, paracrine, endocrine and inflammation.[8-10] Although a growing body of studies have shown inverse associations of total skeletal muscle mass and appendicular skeletal muscle mass (ASM) with NAFLD risk,[11-13] no study has focused on the relationship between regional skeletal muscle mass and NAFLD risk. Interestingly, one study demonstrated that the biological function of adipose tissue was location-related, and the distribution of adipose tissue in the upper and lower body showed an opposite biological function.[14] This study gives us a hint and raises a question: does the distribution of skeletal muscle show a similar pattern to adipose tissue? In addition, aging is significantly correlated with muscle mass loss and NAFLD incidence, respectively.[15,16] Therefore, the aim of the present study is to investigate the association between regional skeletal muscle and NAFLD risk, achieving this, we have conducted a population-based study to explore the relationship between regional skeletal muscle and NAFLD risk in Chinese elders.

METHODS

Study design and participants

China has a sound basic medical insurance system, which sets up electronic health records for people over 65 years

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Manuscript received 19 June 2021. Initial review completed 21 June 2021. Revision accepted 01 July 2021.
doi: 10.6133/apjcn.202109_30(3).0011

and provides free annual healthy check-up. Of these, 1,328 participants (579 males and 749 females) aged 65 to 96 years free-living in 2 neighborhoods (Fushan and Ningxia Community, Qingdao) completed the healthy examination at the local community service center between March to November 2020. Participants with lack of skeletal muscle mass data (n=190), or/and 3-day 24-hour dietary food records (n=17) were excluded in the study. Finally, 1,121 participants (493 males and 628 females) completed questionnaire and body composition analysis.

NAFLD was defined when participants' abdominal ultrasound diagnosed as fatty liver disease and weekly alcohol consumption ≤140 grams for males and ≤70 grams for females, excluding viral or autoimmune liver disease. The ultrasonic diagnostic criteria of fatty liver was based on the standard of the Chinese Liver Diseases Association.[17] To identify eligible NAFLD cases, the exclusion criteria were included: (1) malignancy or a history of malignancy, dementia, organ failure and so on; (2) specific diseases that could lead to steatosis, such as viral hepatitis, drug induced liver disease, total parenteral nutrition, Wilson's disease and autoimmune liver disease; (3) missing data on abdominal ultrasonography; (4) weekly alcohol consumption ≥140 grams for males and ≥70 grams for females, or excessive alcohol consumption in the past 12 months.[17] Ultimately, 471 participants were diagnosed as NAFLD, including 148 males and 323 females; the prevalence rate was 42%. Of these, 400 NAFLD patients were randomly selected as the cases. The controls were a random sample of those two neighborhoods that participated in physical check-up during the same period. Exclusion criteria were the same as cases, and abdominal ultrasonography confirmed the absence of fatty liver in the control group. Controls were individually matched to cases by age (±3 y) and gender. This study protocols were approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Qingdao University, China), and were carried out in accordance with the approved guidelines. Prior to participant this study, all participants provided written informed consent.

Muscle mass assessment and definition of muscle mass index

As a widely applied and effective method for assessing body composition, bioelectrical impedance analysis (BIA, InBodyS10, Biospace) was implemented to measure skeletal muscle mass after an overnight fasting.[18,19] Participants were instructed to sit quietly for 10 minutes to achieve a normal distribution of body fluids. The measurement process was performed by a professional nutritionist in accordance with the manufacturer's instructions. InBodyS10 used a z-axis for impedance, analyzed intracellular, extracellular fluid values and water content; and an x-axis for reactance, measured body cell mass. The InBodyS10 measured impedance of 5 regions of the body (trunk, right and left arms, and right and left legs).[20]

After obtaining each regional muscle mass using BIA, the skeletal muscle mass of each region was standardized by body weight to obtain the skeletal muscle mass index (SMI). For example, the appendicular skeletal muscle mass index (ASMI) was calculated by dividing the sum of the ASM in the bilateral upper and lower four limbs (kg) by body weight (kg) and expressed as a percentage = (ASM/body weight) × 100%.[19,21] Except for ASMI, total skeletal muscle mass index (TSMI), trunk muscle mass index (TMI), arm skeletal muscle mass index (AMI) and leg skeletal muscle mass index (LMI) were also calculated, respectively.

Questionnaire

Face-to-face interviews were performed to collect information demographic parameters, anthropometric parameters, lifestyles, chronic disease history, medication history, family genetic history and physical activity. In addition, 3-day 24-hour dietary records (2 working days and 1 weekend) were used to evaluate the energy and nutrients intake of the participants. Energy and nutrients were calculated by using the dietary software Nutrition system of Traditional Chinese Medicine Combining with Western Medicine (NCCWMX2/NCCW12.0).

Dietary diversity score (DDS) was calculated by 3-day 24-hour dietary records.[22] A minor modulation was performed to assess food groups, namely dairy; eggs, fish, shrimp, and meat; rice and grains; fruits; vegetables; beans; fat and oil, as previous reported.[22] The trial scored one point for each food groups, and the DDS score ≤5 and >5 were regarded as low- and high- dietary diversity, respectively.[23]

The physical activity of the participants was assessed with the physical activity scale for the elderly (PASE).[24] The physical activity index (PAI) was divided into low (≤123.6), medium (123.6-158.9) and high (>158.9), respectively.

Anthropometrical Measurements

Anthropometric measurements were implemented by trained investigators using standard methods, including height (m), weight (kg), waist circumference (WC) (cm), hip circumference (HC) (cm) and blood pressure (mmHg). Body mass index (BMI, kg/m^2) was calculated by dividing weight in kilograms by height in square meters.

Biochemical measurement

Fasting venous blood sample was obtained in into vacuum tubes, and the serum was collected for centrifugation at 3000 rpm for 15 minutes at 4℃. Biochemical indicators, in terms of hepatic functions and cardio-metabolic risk factors, were determined by automatic biochemical analyzer (Accute TBA-40FR autoanalyser, Toshiba, Japan) at the Affiliated Hospital of Qingdao University.

Statistical analysis

Shapiro-Wilk test was used to check the normal distribution of continuity variables. Data with normal distribution was represented by mean ± standard deviation (SD), while skewed variables were represented by median (interquartile rage). Normal distribution variables were compared by t-test, skewed variables were compared by rank sum test, and categorical variables were analyzed by chi-square test (χ^2).

The associations between NAFLD and regional SMIs were analyzed by fitting conditional logistic regression model. SMIs were divided into quartiles according to its distribution. Crude and multivariable-adjusted odds ratios

Table 1. General characteristic of study participants by NAFLD†

Characteristics	Case (n=400)	Control (n=400)	p‡
Age (year)	72 (68, 77)	71 (68, 75)	0.160
Sex (%)			1.000
Male	100 (25)	100 (25)	
Female	300 (75)	300 (75)	
Height (cm)	160 (155.5, 165.5)	160 (156, 165.5)	0.907
Weight (kg)	69.2 (63.3, 77.0)	62.5 (55.1, 69.8)	<0.001
BMI (kg/m^2)	26.9 (25.3, 28.9)	24.0 (22.2, 26.2)	<0.001
ALT (U/L)	25.0 (19.0, 35.0)	19.5 (15.0, 26.0)	<0.001
AST (U/L)	24.0 (20.0, 29.0)	23.0 (20.0, 27.0)	0.063
GLU (mmol/L)	6.1 (5.5, 7.3)	5.5 (5.1, 6.4)	<0.001
TG (mmol/L)	1.7 (1.2, 2.5)	1.2 (0.9, 1.8)	<0.001
TC (mmol/L)	6.1 (5.0, 7.0)	6.2 (5.2, 7.1)	0.220
LDL-C (mmol/L)	2.9 (2.3, 3.4)	3.0 (2.4, 3.5)	0.457
HDL-C (mmol/L)	2.0 (1.6, 2.3)	2.0 (1.7, 2.3)	0.217
SBP (mmHg)	137 (130, 152)	135 (126, 145)	0.001
DBP (mmHg)	79.0 (72.0, 85.0)	76.0 (69.0, 83.0)	0.001
Lifestyle factors, n (%)			
Physical activity index			0.745
Low (≤123.6)	153 (38.3)	144 (38.8)	
Medium (123.6-158.9)	131 (32.8)	113 (30.5)	
High (>158.9)	115 (28.8)	114 (30.7)	
Smoking status			0.034
Yes	21 (5.3)	33 (9.2)	
No	379 (94.7)	325 (90.8)	
Alcohol drinking status			<0.001
Yes	28 (7.0)	66 (18.4)	
No	372 (93.0)	293 (81.6)	
Educational level			0.387
Primary (≤6 y)	89 (22.3)	73 (20.2)	
Secondary (6-12 y)	269 (67.2)	239 (20.2)	
High (>12 y)	42 (10.5)	49 (13.6)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; DBP: diastolic blood pressure; GLU: glucose; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; SBP: systolic blood pressure; TG: triglyceride; TC: total cholesterol.

†Data are presented as median (interquartile range) for continuous variables with non-normal distributions or participants (percentage %) for categorical variables.

‡p for difference between groups was tested by chi-square and Wilcoxon rank sum test, respectively.

(ORs) with 95% confidence intervals (CIs) were calculated for NAFLD risk across quartiles of SMIs, with the lowest quartile as the reference. Multivariable-adjusted model was estimated by adjusting for the age, BMI, glucose (GLU), total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), energy, protein, fat, carbohydrate, smoking status (yes/no), alcohol drinking status (yes/no), education level (primary/secondary/high) and physical activity. Tendency test was performed by assigning a median value to each category and modeling the variables as continuous variables.[25]

A restricted cubic model with four nodes located in the 5th, 35th, 65th, and 95th percentiles of the exposure distribution in the adjusted model. Dose-response relationships between SMIs and NAFLD risk were evaluated by binary logistic regression models. The non-linear p value was calculated by testing the null hypothesis that the coefficient of the second spline was equal to zero. In addition, spearman correlation analysis was used to analyze the correlations between SMIs and anthropometric and biochemical parameters. Statistical analyses were performed by Stata 15.0 (Stata CORP, College Station, TX, USA), and two-tailed p<0.05 was considered as statistically significant.

RESULTS

Characteristics and dietary intake

Compared with the controls, the NAFLD cases tended to have significantly higher body weight, BMI, alanine transaminase (ALT), GLU, TG, higher systolic blood pressure (SBP) and diastolic blood pressure (DBP). No significant difference was found with respect to age, height, aspartate aminotransferase (AST), TC, LDL-C, HDL-C, and education levels between two groups. There were also significant differences among smoking and drinking status (Table 1). The dietary energy and various nutrients have no significantly difference between the case and control groups (Table 2).

Muscle mass indexes and NAFLD risk

Participants in the highest quartiles of TSMI (OR=0.48; 95% CI: 0.30, 0.76; p for trend=0.006), ASMI (OR=0.36; 95% CI: 0.22, 0.59; p for trend=0.001), TMI (OR=0.33; 95% CI: 0.21, 0.53; p for trend <0.001) and LMI (OR=0.28; 95% CI: 0.17, 0.46; p for trend <0.001) showed a significantly negative association with NAFLD risk compared with the references in crude logistic regression model, respectively (Table 3 and Figure 1 a and b). After adjusting for age, BMI, GLU, TC, TG, LDL-C, HDL-C, energy, protein, fat, carbohydrate, smoking sta-

Table 2. Average daily intake of major nutrients of the subjects[†]

Dietary nutrients	Case (n=400)	Control (n=400)	p[‡]
Energy (MJ)	7.21 (6.32, 8.47)	7.28 (6.08, 8.51)	0.536
Protein (g)	57.9 (45.3, 70.9)	59.5 (46.3, 70.3)	0.599
Carbohydrate (g)	209 (170, 255)	205 (163, 246)	0.077
Fat (g)	73.1 (62.3, 87.2)	73.3 (60.8, 89.4)	0.776
Vitamin A (μgRE)	460 (287, 684)	411 (277, 653)	0.211
Vitamin B-1 (mg)	0.8 (0.6, 1.0)	0.8 (0.6, 1.0)	0.770
Vitamin B-2 (mg)	1.1 (0.8, 1.3)	1.1 (0.8, 1.3)	0.971
Vitamin C (mg)	110 (74.4, 157)	105 (70.9,155)	0.748
Vitamin E (mg)	27.9 (23.5, 32.8)	27.2 (22.9, 33.4)	0.340
Vitamin PP (mg)	10.9 (8.3, 14.3)	10.9 (8.2, 14.7)	0.928
Potassium (g)	1.91 (1.52, 2.43)	1.93 (1.45, 2.43)	0.784
Sodium (g)	3.20 (2.89, 3.75)	3.20 (2.88, 3.69)	0.601
Calcium (mg)	452 (340, 612)	489 (337, 687)	0.099
Magnesium (mg)	272 (226, 353)	284 (217, 360)	0.685
Iron (mg)	17.4 (13.5, 21.0)	16.7 (13.1, 20.7)	0.496
Manganese (mg)	4.3 (3.3, 5.3)	4.1 (3.2, 5.3)	0.382
Zinc (mg)	7.9 (6.3, 9.7)	7.9 (6.1, 9.6)	0.835
Cuprum (mg)	1.5 (1.1,2.0)	1.5 (1.1, 2.0)	0.619
Phosphorus (g)	0.95 (0.77, 1.14)	0.98 (0.77, 1.19)	0.424
Selenium (μg)	41.3 (27.4, 60.9)	43.7 (29.2, 61.4)	0.377
Fiber (g)	13.8 (10.5, 18.6)	13.2 (9.9, 18.9)	0.388
SFA (g)	17.4 (14.7, 20.9)	17.3 (14.7, 21.1)	0.831
MUFA (g)	15.4 (13.3, 18.6)	15.3 (13.1,19.1)	0.935
PUFA (g)	9.9 (7.7, 12.9)	10.2 (7.7, 13.1)	0.468
TFA (g)	43.8 (36.9, 51.9)	41.5 (33.5, 51.8)	0.063

SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; TFA: total fatty acid.
[†]Data are presented as median (interquartile range).
[‡]p for difference between groups was tested by Wilcoxon rank sum test.

Table 3. Associations between muscle mass indexes and NAFLD risk

	Quartile of muscle mass				
	Q1	Q2	Q3	Q4	p for trend
TSMI					
Range (%)	<34.87	34.87-37.76	37.76-41.86	>41.86	
Case/Control (n)	111/90	113/86	91/109	85/115	
Crude OR (95%CI)	1 (Ref.)	1.05 (0.69, 1.59)	0.60 (0.39, 0.91)	0.48 (0.30, 0.76)	0.006
Adjusted OR (95%CI)	1 (Ref.)	1.12 (0.54, 2.32)	0.86 (0.43, 1.70)	0.62 (0.28, 1.38)	0.379
ASMI					
Range (%)	<25.61	25.61-27.99	27.99-31.06	>31.06	
Case/Control (n)	114/87	113/87	90/109	83/117	
Crude OR (95%CI)	1 (Ref.)	0.95 (0.64, 1.42)	0.48 (0.31, 0.75)	0.36 (0.22, 0.59)	0.001
Adjusted OR (95%CI)	1 (Ref.)	1.74 (0.82, 3.69)	0.65 (0.31, 1.36)	0.50 (0.21, 1.17)	0.294
AMI					
Range (%)	<6.53	6.53-7.12	7.12-7.98	>7.98	
Case/Control (n)	96/104	106/92	98/103	100/101	
Crude OR (95%CI)	1 (Ref.)	1.23 (0.84, 1.81)	1.01 (0.67, 1.54)	1.03 (0.65, 1.64)	0.661
Adjusted OR (95%CI)	1 (Ref.)	1.29 (0.66, 2.53)	0.82 (0.40, 1.67)	0.77 (0.36, 1.65)	0.685

NAFLD: nonalcoholic fatty liver diseases; TSMI: total skeletal muscle mass index; ASMI: appendicular skeletal muscle mass index; AMI: arm skeletal muscle mass index.
Model was adjusted for age, body mass index, glucose, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, dietary intakes of energy, carbohydrate, protein and fat, smoking, alcohol drinking, education and physical activity.

tus, alcohol drinking status, education level and physical activity, the association remained significantly regarding TMI (OR=0.42; 95% CI: 0.19, 0.93; p for trend=0.083) and LMI (OR=0.41; 95% CI: 0.18, 0.97; p for trend=0.012) (Figure 1 a and b). No significant correlations were found between AMI and NAFLD risk in crude (OR=1.03; 95% CI: 0.65, 1.64; p for trend=0.661) and multivariable-adjusted models (OR=0.77; 95% CI: 0.36, 1.65; p for trend=0.685) (Table 3).

The associations between NAFLD and muscle mass indexes in stratified by DDS are shown in Table 4. For participants' DDS ≤5, the highest quartile of LMI (OR=0.43; 95% CI: 0.23, 0.81; p for trend=0.024), was negatively associated with NAFLD risk compared with the lowest quartile in crude model. For participants' DDS >5, the highest quartile of ASMI (OR=0.56; 95% CI: 0.34, 0.93; p for trend=0.011), TMI (OR=0.42; 95% CI: 0.25, 0.71; p for trend=0.001) and LMI (OR=0.42; 95% CI: 0.25, 0.71; p for trend=0.001), were negatively associated with

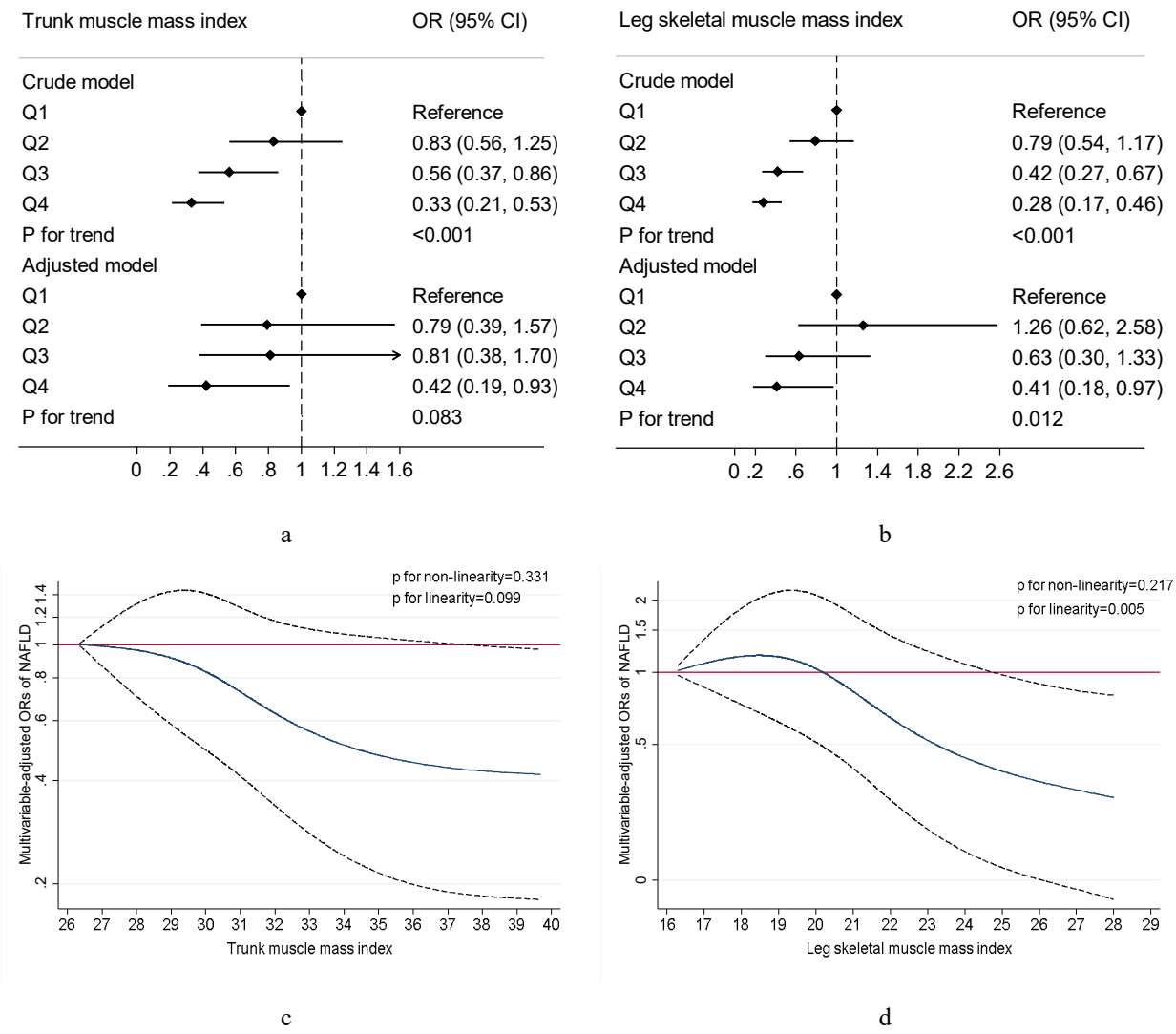

Figure 1. a: Association of trunk muscle mass index with NAFLD. Number of participants in each quartile (case/control): Q1, 117/83; Q2, 111/89; Q3, 97/103; Q4, 75/125; b: Q1, 119/81; b: Association of leg skeletal muscle mass index with NAFLD. Number of participants in each quartile (case/control): Q2, 112/88; Q3, 92/108; Q4, 77/123. c: Dose-response relationship between trunk muscle mass index increase and NAFLD risk. d: Dose-response relationship between leg skeletal muscle mass index increase and NAFLD risk. The solid line and dashed line represent the estimated ORs and the corresponding 95% CIs, respectively.

NAFLD risk compared with the lowest quartile in crude model. However, no significant associations were found between NAFLD risk and muscle mass indexes in the multivariable-adjusted model.

The associations between NAFLD and muscle mass indexes in stratified by PAI are shown in Table 5. For participants' PAI ≤123.6, the highest quartile of TMI (OR=0.43; 95% CI: 0.20, 0.92; *p* for trend=0.027) was negatively association with NAFLD risk compared with the lowest quartile in crude model. For participants' 123.6<PAI≤158.9, the highest quartile of TSMI (OR=0.36; 95% CI: 0.18, 0.72; *p* for trend=0.005), ASMI (OR=0.43; 95% CI: 0.22, 0.86; *p* for trend=0.011), TMI (OR=0.24; 95% CI: 0.12, 0.47; *p* for trend=0.001) and LMI (OR=0.33; 95% CI: 0.17, 0.66; *p* for trend=0.001) were negatively association with NAFLD risk in crude model. The significant correlations between muscle mass indexes and NAFLD risk were disappeared after adjustment for potential confounding factors.

By using restricted cubic model, a significant linear relationship was observed between LMI (*p* for non-linearity=0.217, *p* for linearity=0.005) and NAFLD risk, but not for TMI (*p* for non-linearity=0.331, *p* for linearity=0.099) (Figure 1 c and d). Dose-response analysis indicated that per SD increment of LMI was associated with 23% (95%CI: 0.63, 0.95; *p* for trend=0.014) reduction of NAFLD risk.

Correlation between muscle mass indexes and cardiometabolic parameters

Spearman correlation analysis showed that TSMI was negatively associated with BMI (r=-0.403, *p*<0.001), SBP (r=-0.111, *p*=0.002), WC (r=-0.231, *p*<0.001), HC (r=-0.218, *p*<0.001) and GLU (r=-0.079, *p*=0.026), respectively. ASMI was negatively associated with BMI (r=-0.364, *p*<0.001), SBP (r=-0.127, *p*<0.001), WC (r=-0.181, *p*<0.001), HC (r=-0.155, *p*<0.001) and GLU (r=-0.085, *p*=0.016), respectively. TMI was negatively associated with BMI (r=-0.459, *p*<0.001), SBP (r=-0.092, *p*=0.010), WC (r=-0.292, *p*<0.001), HC (r=-0.275, *p*<0.001) and GLU (r=-0.097, *p*=0.006), respectively. LMI was negatively associated with BMI (r=-0.429, *p*<0.001), SBP (r=-0.152, *p*<0.001), DBP (r=-0.075, *p*=0.035), WC (r=-0.235, *p*<0.001), HC (r=-0.208,

Table 4. Associations between muscle mass indexes and NAFLD risk stratified by DDS

	DDS ≤5					DDS >5				
	Quartile of muscle mass					Quartile of muscle mass				
	Q1	Q2	Q3	Q4	*p* for trend	Q1	Q2	Q3	Q4	*p* for trend
TSMI										
Range (%)	<34.87	34.87-37.76	37.76-41.86	>41.86		<34.87	34.87-37.76	37.76-41.86	>41.86	
Case/Control (n)	45/35	54/35	39/33	32/43		66/55	59/51	52/76	53/72	
Crude OR (95%CI)	1 (Ref.)	1.20 (0.65, 2.22)	0.82 (0.48, 1.74)	0.58 (0.31, 1.09)	0.213	1 (Ref.)	0.96 (0.57, 1.62)	0.57 (0.34, 0.94)	0.61 (0.37, 1.02)	0.032
Adjusted OR (95%CI)	1 (Ref.)	1.26 (0.59, 2.68)	1.25 (0.56, 2.77)	1.11 (0.45, 2.74)	0.639	1 (Ref.)	1.26 (0.64, 2.47)	1.12 (0.57, 2.19)	0.96 (0.47, 1.97)	0.893
ASMI										
Range (%)	<25.61	25.61-27.99	27.99-31.06	>31.06		<25.61	25.61-27.99	27.99-31.06	>31.06	
Case/Control (n)	47/36	50/26	43/39	30/45		67/51	63/61	47/70	53/72	
Crude OR (95%CI)	1 (Ref.)	1.47 (0.77, 2.80)	0.84 (0.46, 1.56)	0.51 (0.27, 0.96)	0.117	1 (Ref.)	0.79 (0.47, 1.30)	0.51 (0.30, 0.86)	0.56 (0.34, 0.93)	0.011
Adjusted OR (95%CI)	1 (Ref.)	1.43 (0.66, 3.12)	0.95 (0.44, 2.07)	0.94 (0.38, 2.30)	0.945	1 (Ref.)	1.27 (0.66, 2.46)	0.86 (0.43, 1.74)	1.05 (0.51, 2.16)	0.908
TMI										
Range (%)	<29.03	29.03-30.68	30.68-33.15	>33.15		<29.03	29.03-30.68	30.68-33.15	>33.15	
Case/Control (n)	47/34	53/29	42/36	28/47		70/49	58/60	55/67	47/78	
Crude OR (95%CI)	1 (Ref.)	1.32 (0.70, 2.49)	0.84 (0.45, 1.58)	0.43 (0.23, 0.82)	0.068	1 (Ref.)	0.68 (0.40, 1.13)	0.57 (0.34, 0.96)	0.42 (0.25, 0.71)	0.001
Adjusted OR (95%CI)	1 (Ref.)	1.23 (0.58, 2.62)	0.99 (0.44, 2.23)	0.87 (0.36, 2.09)	0.970	1 (Ref.)	0.70 (0.36, 1.36)	1.22 (0.60, 2.47)	0.62 (0.30, 1.28)	0.339
AMI										
Range (%)	<6.53	6.53-7.12	7.12-7.98	>7.98		<6.53	6.53-7.12	7.12-7.98	>7.98	
Case/Control (n)	38/39	46/32	46/36	40/39		58/65	60/60	52/67	60/62	
Crude OR (95%CI)	1 (Ref.)	1.48 (0.78, 2.78)	1.31 (0.70, 2.45)	1.05 (0.56, 1.98)	0.631	1 (Ref.)	1.12 (0.68, 1.85)	0.87 (0.52, 1.44)	1.08 (0.66, 1.79)	0.921
Adjusted OR (95%CI)	1 (Ref.)	0.80 (0.37, 1.71)	1.07 (0.48, 2.39)	1.08 (0.47, 2.51)	0.949	1 (Ref.)	1.41 (0.74, 2.69)	0.95 (0.49, 1.86)	1.25 (0.62, 2.52)	0.572
LMI										
Range (%)	<18.93	18.93-20.82	20.82-23.33	>23.33		<18.93	18.93-20.82	20.82-23.33	>23.33	
Case/Control (n)	49/33	54/30	37/36	30/47		70/48	58/58	55/72	47/76	
Crude OR (95%CI)	1 (Ref.)	1.21 (0.65,2.27)	0.69 (0.37,1.31)	0.43 (0.23,0.81)	0.024	1 (Ref.)	0.69 (0.41,1.15)	0.52 (0.32,0.87)	0.42 (0.25,0.71)	0.001
Adjusted OR (95%CI)	1 (Ref.)	1.51 (0.71,3.18)	0.88 (0.39,1.99)	1.04 (0.42,2.57)	0.824	1 (Ref.)	1.22 (0.62,2.39)	0.88 (0.44,1.74)	0.82 (0.39,1.69)	0.686

NAFLD: nonalcoholic fatty liver diseases; DDS: dietary diversity score; TSMI: total skeletal muscle mass index; ASMI: appendicular skeletal muscle mass index; TMI: trunk muscle mass index; AMI: arm skeletal muscle mass index; LMI: leg skeletal muscle mass index.

Model was adjusted for age, body mass index, glucose, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, dietary intakes of energy, carbohydrate, protein and fat, smoking, alcohol drinking, education and physical activity.

Table 5. Associations between muscle mass indexes and NAFLD risk stratified by PAI

	PAI ≤ 123.6					123.6 < PAI ≤ 158.9				
	Quartile of muscle mass					Quartile of muscle mass				
	Q1	Q2	Q3	Q4	*p* for trend	Q1	Q2	Q3	Q4	*p* for trend
TSMI										
Range (%)	<34.87	34.87-37.76	37.76-41.86	>41.86		<34.87	34.87-37.76	37.76-41.86	>41.86	
Case/Control (n)	48/36	32/28	27/30	15/21		44/25	50/29	40/44	28/44	
Crude OR (95%CI)	1(Ref.)	0.86 (0.44, 1.67)	0.68 (0.34, 1.33)	0.54 (0.24, 1.18)	0.124	1 (Ref.)	0.98 (0.50, 1.92)	0.52 (0.27, 0.99)	0.36 (0.18, 0.72)	0.005
Adjusted OR (95%CI)	1(Ref.)	0.85 (0.36, 1.98)	1.15 (0.46, 2.88)	1.15 (0.38, 3.45)	0.885	1 (Ref.)	1.06 (0.48, 2.36)	0.79 (0.35, 1.78)	0.66 (0.26, 0.71)	0.492
ASMI										
Range (%)	<25.61	25.61-27.99	27.99-31.06	>31.06		<25.61	25.61-27.99	27.99-31.06	>31.06	
Case/Control (n)	50/38	29/24	30/29	13/24		40/24	57/30	34/45	31/43	
Crude OR (95%CI)	1 (Ref.)	0.92 (0.46, 1.82)	0.79 (0.41, 1.52)	0.41 (0.19, 0.91)	0.088	1 (Ref.)	1.14 (0.58, 2.23)	0.45 (0.23, 0.89)	0.43(0.22, 0.86)	0.011
Adjusted OR (95%CI)	1 (Ref.)	1.07 (0.45, 2.60)	0.91 (0.37, 2.22)	0.92 (0.31, 2.78)	0.902	1 (Ref.)	1.46 (0.66, 3.21)	0.68 (0.29, 1.60)	0.93 (0.37, 2.36)	0.904
TMI										
Range (%)	<29.03	29.03-30.68	30.68-33.15	>33.15		<29.03	29.03-30.68	30.68-33.15	>33.15	
Case/Control (n)	46/30	36/30	23/29	17/26		50/26	50/32	37/30	25/54	
Crude OR (95%CI)	1 (Ref.)	0.78 (0.40, 1.53)	0.52 (0.25, 1.06)	0.43 (0.20, 0.92)	0.027	1 (Ref.)	0.81 (0.42, 1.56)	0.64 (0.33, 1.26)	0.24 (0.12, 0.47)	<0.001
Adjusted OR (95%CI)	1 (Ref.)	0.91 (0.39, 2.13)	0.77 (0.30, 1.97)	0.87 (0.30, 2.51)	0.678	1 (Ref.)	0.74 (0.35, 1.61)	0.87 (0.36, 2.08)	0.41 (0.17, 1.03)	0.139
AMI										
Range (%)	<6.53	6.53-7.12	7.12-7.98	>7.98		<6.53	6.53-7.12	7.12-7.98	>7.98	
Case/Control (n)	37/39	34/23	27/35	24/18		40/33	51/41	40/28	31/40	
Crude OR (95%CI)	1(Ref.)	1.56 (0.78, 3.12)	0.81 (0.41, 1.60)	1.41 (0.66, 3.00)	0.597	1 (Ref.)	1.03 (0.55, 1.90)	1.18 (0.60, 2.30)	0.64 (0.33, 1.23)	0.404
Adjusted OR (95%CI)	1(Ref.)	1.57 (0.65, 3.79)	0.45 (0.17, 1.18)	1.36 (0.47, 3.94)	0.983	1 (Ref.)	1.07 (0.51, 2.25)	1.08 (0.46, 2.50)	0.91 (0.38, 2.19)	0.967
LMI										
Range (%)	<18.93	18.93-20.82	20.82-23.33	>23.33		<18.93	18.93-20.82	20.82-23.33	>23.33	
Case/Control (n)	46/35	36/27	26/25	14/28		44/23	54/28	34/44	30/47	
Crude OR (95%CI)	1 (Ref.)	1.01 (0.52,1.97)	0.79 (0.39,1.60)	0.38 (0.17,0.83)	0.066	1 (Ref.)	1.01 (0.51,1.99)	0.40 (0.21,0.79)	0.33 (0.17,0.66)	0.001
Adjusted OR (95%CI)	1 (Ref.)	1.68 (0.72,3.93)	1.10 (0.43,2.79)	1.31 (0.44,3.90)	0.485	1 (Ref.)	1.47 (0.66,3.28)	0.68 (0.28,1.61)	0.79 (0.31,2.01)	0.717

NAFLD: nonalcoholic fatty liver diseases; PAI: physical activity index; TSMI: total skeletal muscle mass index; ASMI: appendicular skeletal muscle mass index; TMI: trunk muscle mass index; AMI: arm skeletal muscle mass index; LMI: leg skeletal muscle mass index.
Model was adjusted for age, body mass index, glucose, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein cholesterol, dietary intakes of energy, carbohydrate, protein and fat, smoking, alcohol drinking and education.

p<0.001), GLU (r=-0.107, p<0.002) and TG (r=-0.086, p=0.015), respectively. AMI was negatively associated with BMI (r=-0.103, p=0.004), HDL-C (r=-0.091, p=0.011) and TC (r=-0.094, p=0.008), respectively, and positively associated with ALT (r=0.084, p=0.018) (Figure 2).

DISCUSSION

In the present study, higher TMI and LMI were associated with a lower risk of NAFLD after adjustment for potential confounding factors. No significant associations were found between TSMI, ASMI, AMI and NAFLD risk. The findings of this study supported the hypothesis that lower muscle mass was positively associated with NAFLD risk, and different region muscle masses might perform different physiological functions.

Skeletal muscle mass, as an independent factor, is associated with NAFLD risk.[26-28] Cross-sectional studies have reported that higher ASMI and TSMI are inversely associated with NAFLD risk in different age groups.[11,13,28] Longitudinal study also demonstrated that increment in ASMI over time had favorable effects in prevention and remission of existing NAFLD.[21] However, it has been unclear whether regional muscle mass indexes are associated with NAFLD risk. In the present study, higher TMI and LMI were associated with reduced NAFLD risk in multivariate-adjusted model, indicating that TMI and LMI were independently associated with NAFLD risk. Previous study showed that higher leg and arm muscle masses to total body weight ratio could actively prevent metabolic syndrome.[29] Inconsistent with previous studies, no statistical significance was found with respect to AMI associated with NAFLD risk.

Dietary factors and physical activities play a pivotal role in the initiation and development of NAFLD.[30,31] Therefore, stratified analysis was performed to investigate whether DDS and PAI exerted the associations between muscle mass and NAFLD risk. Considering small sample-size and individual differences, no significant association was observed between muscle mass and NAFLD risk in stratified analysis after adjustment for confounding factors. We further explored the associations of SMIs with anthropometric and cardio-metabolic parameters. The results indicated that except for AMI, other SMIs, especially LMI, were negatively correlated with almost all anthropometric parameters, such as BMI, blood pressure, WC and HC. Elevated anthropometric parameters were associated with increasing risk of NAFLD.[32,33] The negative association between SMIs and NAFLD risk might be mediated by lowering these anthropometric parameters. Except for AMI, other SMIs also negatively correlated with blood glucose. Lower blood glucose can improve IR status and reduce the risk of diabetes in the elderly, thereby protecting against NAFLD.[34] In addition, LMI was negatively correlated with TG. Thus, appropriate muscle mass is critical for maintaining healthy anthropometric and biochemical parameters.

The mechanisms to explain why a higher skeletal muscle mass protected against NAFLD was summarized as follows (Figure 3). First, skeletal muscle is a glucose utilizing organ in response to insulin, and low skeletal muscle mass reduces glucose utilization and induces IR.[35,36] IR and its induced hyperinsulinemia can up-regulate sterol regulatory element binding protein-1c (SREBP-1c) expression and promotes the synthesis of excess TG in the liver.[37] SREBP-1c mainly expresses in liver, muscle and adipose tissue.[38] AMP-activated protein kinase (AMPK) activation via muscle exercise,[39] and high skele-

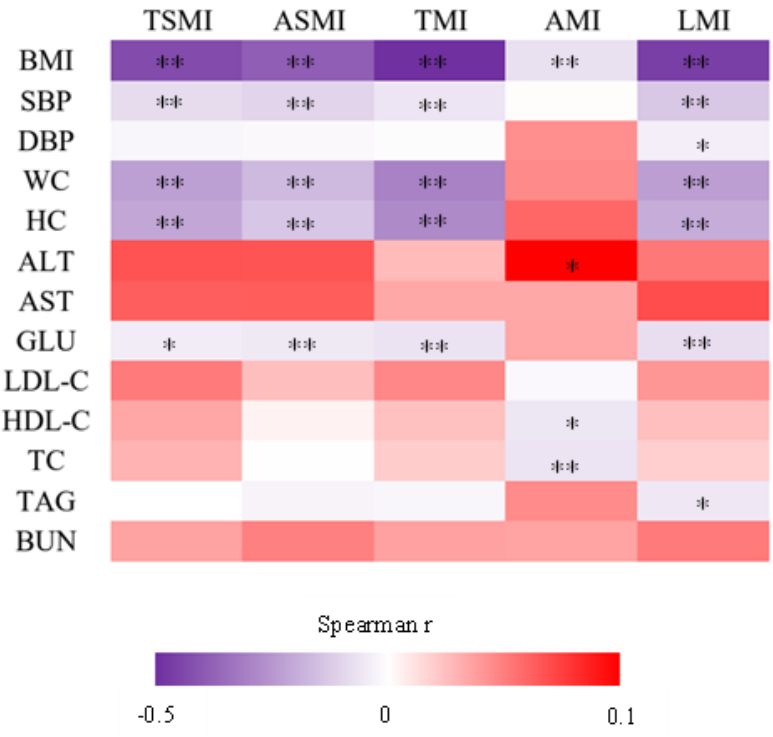

Figure 2. Correlation between muscle mass indexes and anthropometric parameters and biochemical indicator. The intensity of the colours represents the degree of association between muscle mass indexes and anthropometric parameters and biochemical indicator as measured by the Spearman correlations. The significance level was adjusted using the Bonferroni method. $^{*}p$<0.05, $^{**}p$<0.01.

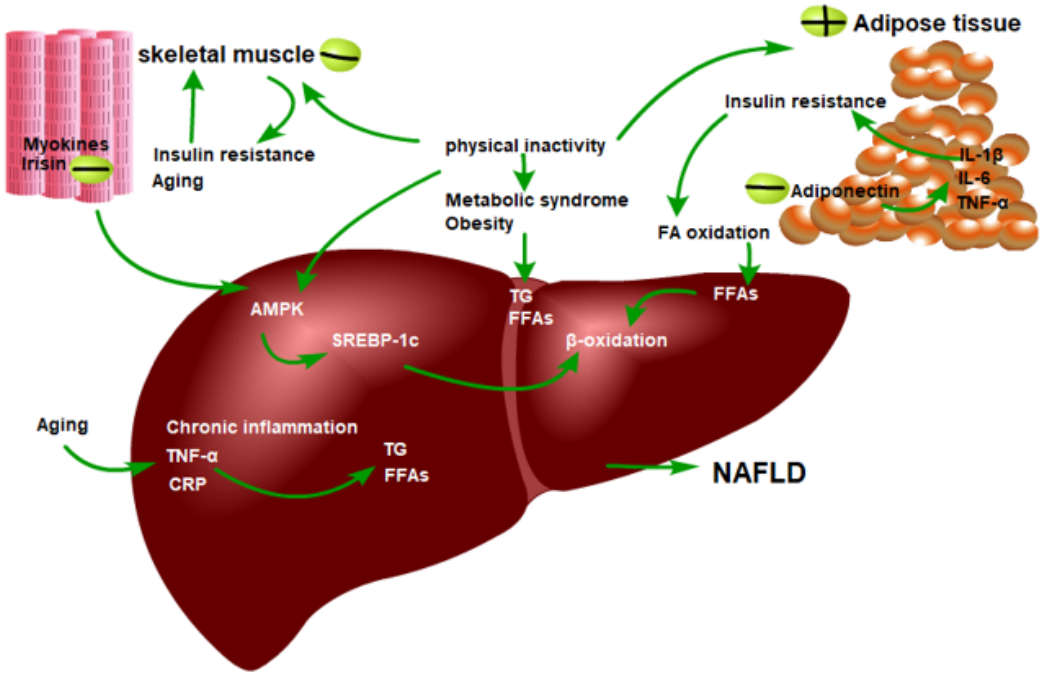

Figure 3. The possible mechanisms between skeletal muscle and NAFLD risk. Abbreviations: IL-1β, interleukin-1β; IL-6, interleukin-1; TNF-α, tumor necrosis factor-a; CRP, C-reaction protein; FA, fatty acid; TG, triglyceride; FFAs, free fatty acids; AMPK, AMP-activated protein kinase; SREBP-1c, sterol regulatory element binding protein-1c; NAFLD, non-alcoholic fatty liver disease.

tal muscle mass might down-regulate SREBP-1c expression. Second, skeletal muscle, as an endocrine organ, triggers and releases myokines.[40] Irisin, an exercise-inducible myokine, can increase β-oxidation in the liver.[41] It has been shown that irisin concentration is inversely associated with intrahepatic TG in obesity.[42] Consequently, low muscle mass might contribute to fatty liver disease by decreasing secretion of beneficial myokines. Third, age-related sarcopenia generally accompanies inflammatory disorders, forms chronic low-grade inflammatory status, increases concentration of pro-inflammatory cytokine such as tumor necrosis factor-α (TNF-α) and C-reactive protein (CRP).[36,43] TNF-α in the liver promotes fat accumulation and accelerates the formation of NAFLD by activating de novo fat synthesis.[44] The increase of CRP correlates with hepatic steatosis.[45] Fourth, sarcopenia patients tend to have high adipose mass.[46] Increased adipose tissue in the body results in decreased adiponectin secretion.[47] While studies have found that adiponectin can improve lipid oxidation, reduce insulin resistance, and improve the inflammatory state of body.[48,49] Exercise plays a beneficial role in inhibiting the pathogenesis of NAFLD,[50] simple exercise interventions (not changing diet) have shown to dramatically lower intrahepatic fat.[51] In the present study, there was a significant negative correlation between LMI and NAFLD risk, but not in AMI, we hypothesized that the leg muscles might play a crucial role in physical activities than arms.

The advantages of the present study deserve to be mentioned. First, this is the first study to investigate the association between regional skeletal muscle and NAFLD in China, indicating that the distribution of skeletal muscle might exert differential physiological functions. Second, using face-to-face interviews, the basic information is comprehensively collected regarding diet, lifestyle, and anthropometric parameters. Again, the community-based case-control design is more representative than hospital-based case-control studies. Nonetheless, several shortcomings in the study should be noted. First, this study is an observational study, the causal relationship between skeletal muscle and NAFLD cannot determine. Randomized controlled trials should be conducted to illuminate causal correlation between skeletal muscle mass and NAFLD. Second, the correlation between NAFLD severity and skeletal muscle mass may be different, and the severity of NAFLD is not classified in the present study. In addition, the correlation between skeletal muscle function (grip strength, gait speed, etc.) and NAFLD is not explored. Hence, skeletal muscle mass and function were combined to explore their correlation with NAFLD is a tendency in the further study. Third, the present study was conducted in elderly aged over 65 years, so the current results could not be generalized to the entire Chinese population.

The present study provides substantial evidence that the higher trunk muscle and leg skeletal muscle are associated with a lower risk of NAFLD. Appropriate exercise and dietary intake to maintain skeletal muscle mass of the trunk and legs are of great significance to the prevention of NAFLD in the elderly.

ACKNOWLEDGEMENTS

We appreciate faculty and staff at Fushan and Ningxia Community Hospital for their supports on the study.

AUTHOR DISCLOSURE

The authors declare no conflict of interest. This work was supported by the National Natural Science Foundation of China (NSFC: 81773433 and 82073538) and by the 2018 Chinese Nutrition Society (CNS) Nutrition Research Foundation-DSM

Research Fund (CNS-DSM2018A30). The funders have no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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