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Sex influences the association between appendicular skeletal muscle mass to visceral fat area ratio and non-alcoholic steatohepatitis in patients with biopsy-proven non-alcoholic fatty liver disease

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Abstract

Sarcopenic obesity is regarded as a risk factor for the progression and development of non-alcoholic fatty liver disease (NAFLD). Since male sex is a risk factor for NAFLD and skeletal muscle mass markedly varies between the sexes, we examined whether sex influences the association between appendicular skeletal muscle mass to visceral fat area ratio (SVR), that is, an index of skeletal muscle mass combined with abdominal obesity, and the histological severity of NAFLD. The SVR was measured by bioelectrical impedance in a cohort of 613 (M/F = 443/170) Chinese middle-aged individuals with biopsy-proven NAFLD. Multivariable logistic regression and subgroup analyses were used to test the association between SVR and the severity of NAFLD (i.e. non-alcoholic steatohepatitis (NASH) or NASH with the presence of any stage of liver fibrosis). NASH was identified by a NAFLD activity score ≥5, with a minimum score of 1 for each of its categories. The presence of fibrosis was classified as having a histological stage ≥1. The SVR was inversely associated with NASH in men (adjusted OR 0·62; 95 % CI 0·42, 0·92, $P = 0·017$ for NASH, adjusted OR 0·65; 95 % CI 0·43, 0·99, $P = 0·043$ for NASH with the presence of fibrosis), but not in women (1·47 (95 % CI 0·76, 2·83), $P = 0·25$ for NASH, and 1·45 (95 % CI 0·74, 2·83), $P = 0·28$ for NASH with the presence of fibrosis). There was a significant interaction for sex and SVR ($P_{interaction} = 0·017$ for NASH and $P_{interaction} = 0·033$ for NASH with the presence of fibrosis). Our findings show that lower skeletal muscle mass combined with abdominal obesity is strongly associated with the presence of NASH only in men.

Key words: Non-alcoholic fatty liver disease: Non-alcoholic steatohepatitis: Presence of fibrosis: Appendicular skeletal muscle mass: Sarcopenic obesity: Visceral fat area

Non-alcoholic fatty liver disease (NAFLD) is a common metabolic liver disease which influences over ¼ of the world's adults[1,2]. NAFLD includes a range of liver conditions spanning from simple steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis or cirrhosis. Higher energy food intake and physical inactivity may contribute to the development and progression of NAFLD in genetically predisposed individuals. Patients with NAFLD often have more than one of the individual

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SVR, appendicular skeletal muscle mass to visceral fat area ratio.

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features of the metabolic syndrome, and insulin resistance provides a common pathogenetic link between both conditions[3,4]. It is known that male sex is a risk factor for NAFLD, but the explanation for this association is not entirely understood[5,6,7].

Abnormal body composition, typically characterised by reduced appendicular skeletal muscle mass as well as increased visceral fat mass, may also adversely affect the risk of NAFLD development and progression[8,9]. As one of the principal sites of insulin-mediated glucose uptake, a low skeletal muscle mass results in increased whole-body insulin resistance, thereby promoting the possibility of the metabolic syndrome as well as NAFLD[10,11]. Visceral adipose tissue accumulation also leads to increased whole-body insulin resistance and low-grade inflammation, making it an additional risk factor not only for NAFLD and the metabolic syndrome but also for CVD[12,13]. The phenomenon of excess adiposity combined with reduced skeletal muscle mass is called sarcopenic obesity[14,15]. Using bioelectrical impedance, a measurement of the appendicular skeletal muscle mass and the intra-abdominal visceral fat area can be estimated and the appendicular skeletal muscle mass to visceral fat area ratio, known as the SVR index, has been used as a marker that is suggestive of sarcopenic obesity[16,17,18,19].

Interestingly, body composition and fat distribution are markedly different between the sexes, with women having more fat around the buttocks and thighs, and men having more fat around the abdomen[20]. Women also have approximately two-thirds less skeletal muscle mass and twice as much adipose tissue than men[21]. It is well known that male sex is a risk factor for NAFLD, but the explanation for this is uncertain[5,6,7]. It is currently not known whether the aforementioned sex-related differences in body fat and muscle mass distribution may also differentially impact on the association between the SVR index[8,16,17] and the histological severity of NAFLD.

Therefore, our study tends to estimate whether there is sex difference in the effect of exposure (SVR) on an outcome (histological level of NAFLD) in a cohort of Chinese middle-aged individuals with biopsy-proven NAFLD. If differences in this association do exist between the sexes, improvements in abnormal body composition could provide a new focus for ameliorating NAFLD development and progression.

Materials and methods

Study subjects and design

A total of 1067 adults with presumed NAFLD (on the basis of high values of serum liver enzymes and/or proof of liver steatosis upon imaging tests) were prospectively enrolled at our hospital over 3 years consecutively (December 2016–September 2020). As shown in Fig. 1, among them, 454 subjects were excluded (including 114 with excessive alcohol intake (>70 g/week in women and >140 g/week in men), one with viral hepatitis A, 216 with viral hepatitis B, ten with viral hepatitis C, one with viral hepatitis D, twenty with autoimmune hepatitis, three with drug-induced liver injury; fifty-eight with histological evidence of ≤5 % of hepatocyte steatosis and thirty-one with missing bioimpedance data from InBody 720). As a consequence, a total of 613 middle-aged individuals with biopsy-proven NAFLD were involved in this research.

The research protocol was approved by the First Affiliated Hospital of Wenzhou Medical University ethical committee (2016-246, 1 December 2016) and recorded in the Chinese Clinical Trial Registry (ChiCTR-EOC-17013562). All procedures conformed with the ethical requirements of the Institutional Research Committee and were in accordance with the 1964 Helsinki declaration. Signed written informed consent was collected from every patient ahead of participation within the research.

Clinical and laboratory data

Anthropometric and laboratory data were collected within 1 d of the liver biopsy procedure, and all of the samples of blood were collected in fasting treating. Standing height as well as body weight was measured, in a condition of the subjects barefoot and wearing light clothing. Samples of venous blood were collected post overnight fasting, with a minimum of 8 h and up to 12 h, followed by analysis at the Clinical Sample Test Room in the hospital. All biochemical parameters were analysed via an automated laboratory analyzer (Abbott AxSYM) with standard methods. BMI was measured as kg over the square of height in metres. BMI ≥ 25 kg/m^2 was defined as overweight. Fasting glucose coupled with insulin concentrations was employed for the calculation of homoeostasis model assessment of insulin resistance like following: fasting glucose (mmol/l) × fasting insulin (mU/l)/22·5. Presence of diabetes mellitus was diagnosed by fasting glucose level ≥7·0 mmol/l or HbA1c level ≥6·5 % (≥48 mmol/mol) and/or use of any glucose-lowering drugs. Subjects were considered to have hypertension if their blood pressure was ≥130/85 mmHg or if they were taking any anti-hypertensive drugs. A dual bioelectrical impedance analyzer (InBody 720; Biospace) was employed to measure lean body mass of patient's limbs and to calculate visceral fat area. According to Heymsfield *et al.*[22], the addition of the lean soft tissues of arms as well as legs results in appendicular skeletal muscle. We calculated the appendicular skeletal muscle (kg) adjusted by visceral fat area (mm^2), or the SVR (an index of sarcopenia obesity expressed as g/mm^2).

Liver biopsy

Liver biopsy examination has been described previously[23,24]. Briefly, histological evidence of >5 % of steatotic hepatocytes was used as a diagnostic criterion to define NAFLD. Subjects with a NAFLD Activity Score of 5 or greater, and a score of 1 for every one of its three histological components (lobular inflammation, hepatic steatosis and ballooning) were diagnosed as having definite NASH. Stages of hepatic fibrosis were graded from zero to 4, in accordance with the Brunt's histological criteria[25]. The presence of liver fibrosis was defined as having a histological stage of 1 or greater.

Statistical analysis

In both men and women, clinical and biochemical data were stratified by tertiles (T) of SVR as follows: T1, <2·18 g/mm^2;

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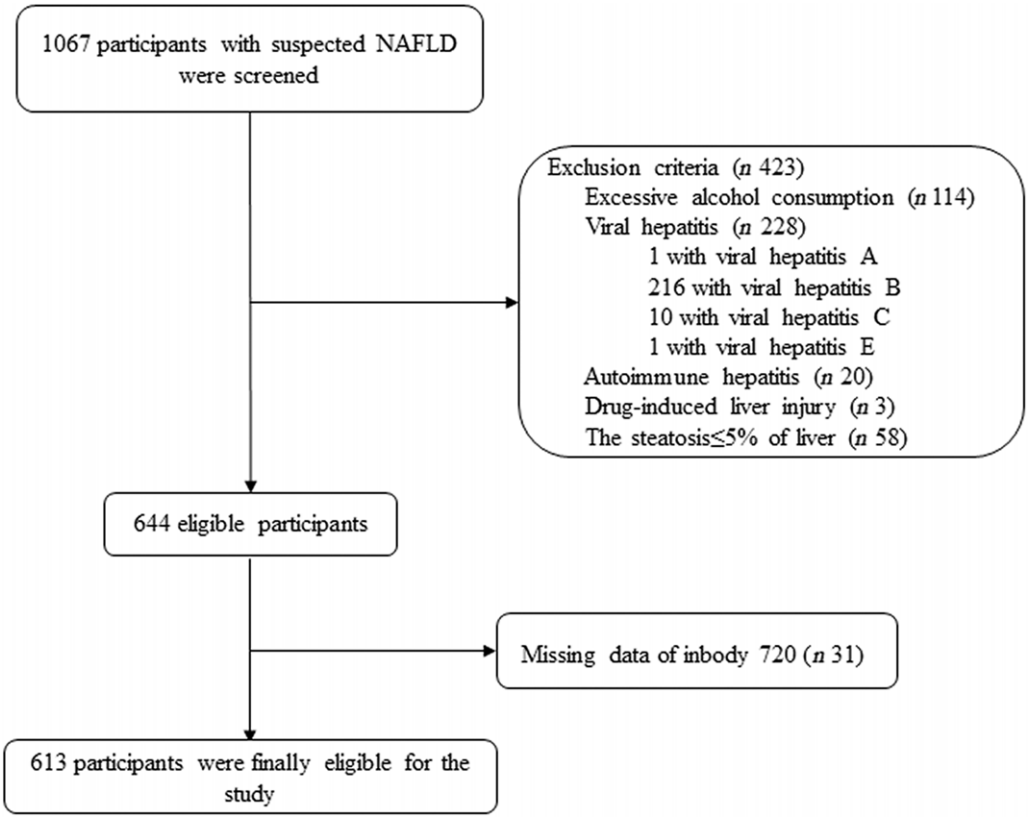

Fig. 1. Flow chart of the study.

T2, 2·18–2·63 g/mm^2; and T3, >2·63 g/mm^2 for men; and T1, <1·50 g/mm^2; T2, 1·50–1·88 g/mm^2; and T3, >1·88 g/mm^2 for women. Categorical variables and continuous strings of data were shown as percentages and means and standard deviation or medians (1st quartile, 3rd quartile), respectively. The one-way ANOVA and the Pearson's χ^2 test were employed to test significant differences in clinical and biochemical variables among the patient groups. Multivariable logistic regression analyses were used to examine the association between SVR (as the exposure variable) and the histological severity of NAFLD (i.e. presence of NASH or NASH with any stage of liver fibrosis, as the outcome measures) within both women and men. Subgroup and interaction analyses were also employed to test the association between decreasing SVR (as the exposure variable) and the presence of NASH or NASH with any stage of liver fibrosis (as the outcome measures). The likelihood ratio test was used to examine the interactions as well as modifications of different patient subgroups. Statistical significance was examined at two-sided *P*-value of 0·05. All statistical tests were performed with R software (version 3.5.2, R Foundation for Statistical Computing).

Results

Baseline characteristics of participants

Six hundred and thirteen biopsy-confirmed NAFLD were included, among which 72·3 % (*n* 443) were men. NASH was confirmed in 257 subjects (men: 176, 68·5 %). The major biochemical as well as clinical features and the liver histology features of participants, stratified by sex as well as SVR tertiles, are illustrated in Table 1. Men in the first tertile of SVR (i.e. reflecting a greater reduction in appendicular skeletal muscle mass:visceral fat area ratio) were more likely to be older and overweight/obese and to have type 2 diabetes than those belonging to the second and third tertiles of SVR. Notably, the former also had a greater proportion of definite NASH, as well as liver fibrosis, lobular inflammation and hepatocyte ballooning on histology. Conversely, women in the first tertile of SVR tend to be older and overweight/obese and to have hypertension than those belonging to the second and third tertiles of SVR. However, no significant differences were found in definite NASH and all its individual histological scores across SVR tertiles in women.

Association between appendicular skeletal muscle mass to visceral fat area ratio and severity of non-alcoholic fatty liver disease

Multivariable logistic regression analyses were used to estimate the effect of SVR (as the exposure variable) on the severity of NAFLD (as the outcome measures). As shown in Table 2, SVR showed a significant inverse association with either NASH (OR 0·77, 95 % CI 0·61, 0·91; $P = 0·022$) or NASH with the presence of any stage of liver fibrosis (OR 0·72, 95 % CI 0·56, 0·91; $P = 0·006$) in unadjusted logistic regression models. However, these associations were no longer significant after adjustment

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Table 1. Baseline characteristics of patients with biopsy-proven non-alcoholic fatty liver disease (NAFLD), stratified by sex and appendicular skeletal muscle mass:visceral fat area ratio tertiles (Numbers and percentages; mean values and standard deviations)

	Men							Women						
	T1		T2		T3			T1		T2		T3		
	Mean	SD	Mean	SD	Mean	SD	*P* value	Mean	SD	Mean	SD	Mean	SD	*P* value
n	148		148		147			57		57		56		
Demographics														
Age (years)	42	12	40	11	35	9*	<0·001	56	10	49	11†	45	10†	<0·001
Anthropometry														
Diastolic BP (mmHg)	83	11	82	11	80	10*	0·044	81	10	83	12	82	10	0·728
Systolic BP (mmHg)	129	14	127	15	126	15*	0·034	132	17	130	17	127	18	0·331
SVR (g/mm^2)	1·9	0·2	2·4	0·1	3·3	0·6	<0·001	1·2	0·3	1·7	0·1	2·3	0·4	<0·001
Concomitant diseases														
Type 2 diabetes														
n	35		33		19		0·044	26		20		17		0·229
%	23·6		22·3		12·9*			45·6		35·1		29·8		
Hypertension														
n	32		24		19		0·133	31		20		14		0·005
%	21·6		16·2		12·9			54·4		35·1		24·6†		
Overweight/obesity														
n	138		125		107		<0·001	42		46		33		0·034
%	93·2		84·5		72·3*			73·7		80·7†		57·9		
Clinical characteristics														
Total bilirubin (μmol/l)	14·8	7·2	15·3	7·9	14·7	6·5	0·739	11·2	3·9	11·2	4·6	12·1	5·1	0·489
Albumin (g/l)	47	44, 18	47	45, 50	47	45, 49	0·162	44	40, 46	45	43, 47	45	43, 48†	0·027
Platelet count (×10^9)	241	62	233	52	252	60*	0·014	239	65	269	67	253	72	0·062
AST (U/l)	36	26, 57	33	25, 54	33	25, 51	0·253	33	25, 54	35	24, 56	36	24, 49	0·960
ALT (U/l)	62	38, 107	52	33, 97	58	31, 100	0·225	38	22, 68	40	25, 69	40	22, 74	0·756
ALP (U/l)	79	68, 97	83	69, 98	79	67, 95	0·439	95	77, 109	79	69, 106	84	54, 102	0·070
GGT (U/l)	59	41, 97	59	37, 86	55	34, 85	0·251	38	24, 70	40	25, 83	39	23, 60	0·945
Fasting glucose (mmol/l)	5·4	4·9, 6·2	5·2	4·8, 6·0	5·2	4·9, 5·7	0·139	6·1	5·2, 7·9	6	5·1, 7·4	5·2	4·9, 6·6	0·059
Uric acid (mmol/l)	431	107	413	102	415	88	0·243	315	85	328	86	326	76	0·667
Total cholesterol (mmol/l)	5·4	1·3	5·2	1·1	5·1	1·1	0·080	4·9	1·2	5·4	1·0†	5·1	1·2	0·039
TAG (mmol/l)	2·1	1·6, 3·1	2·1	1·5, 3·0	1·9	1·3, 2·9	0·150	1·6	1·2, 2·3	1·8	1·3, 2·9	1·8	1·3, 2·4	0·393
HDL-cholesterol (mmol/l)	0·97	0·19	0·97	0·19	0·99	0·21	0·587	1·1	0·3	1·1	0·2	1·1	0·2	0·635
LDL-cholesterol (mmol/l)	3·2	1·0	3·0	0·8	3·0	0·9	0·096	2·7	0·8	3·0	0·8	2·9	0·9	0·147
Liver histology														
Steatosis							0·111							0·257
1														
n	51		69		68			27		19		20		
%	34·5		46·6		46·3			47·4		33·3		35·7		
2														
n	64		52		49			20		24		22		
%	43·2		35·1		33·3			35·1		42·1		39·3		
3														
n	33		27		30			10		14		14		
%	22·3		18·2		20·4			17·5		24·6		25·0		
Hepatocyte ballooning							0·048							0·398
0														
n	15		21		25			10		7		4		

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Table 1. (*Continued*)

	Men							Women						
	T1		T2		T3			T1		T2		T3		
	Mean	SD	Mean	SD	Mean	SD	*P* value	Mean	SD	Mean	SD	Mean	SD	*P* value
%	10·1		14·2		17·0			17·5		12·3		7·1		
1														
n	82		85		88			21		22		35		
%	55·4		57·4		59·9			36·8		38·6		62·5		
2														
n	51		42		34			26		28		17		
%	34·5		28·4		23·1			45·6		49·1		30·4		
Lobular inflammation							0·003							0·900
0														
n	9		25		18			4		7		5		
%	6·1		16·9		12·2			7·0		12·3		8·9		
1														
n	83		88		84			36		29		30		
%	56·1		59·5		57·1			63·2		50·9		53·6		
2														
n	52		33		42			15		21		21		
%	35·1		22·3		28·6			26·3		36·8		37·5		
3														
n	4		2		3			2		0		0		
%	2·7		1·4		2·0			3·5						
Fibrosis							<0·001							0·110
0														
n	58		64		75			18		24		23		
%	39·2		43·2		51·0			31·6		42·1		41·1		
1														
n	54		65		52			14		17		21		
%	36·5		43·9		35·4			24·6		29·8		37·5		
2														
n	31		15		18			20		11		10		
%	20·9		10·1		12·2			35·1		19·3		17·9		
3														
n	4		4		2			2		5		1		
%	2·7		2·7		1·4			3·5		8·8		1·8		
4														
n	1		0		0			3		0		1		
%	0·7							5·3				1·8		
NASH														
n	75		46		55		0·002	21		28		32		0·095
%	50·7		31·1		37·4			36·8		49·1		57·1		
NASH with the presence of fibrosis														
n	69		36		43		<0·001	18		26		27		0·124
%	46·4		24·3		29·3			31·5		45·6		48·2		

BP, blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; NASH, non-alcoholic steatohepatitis.
* *P* value < 0·05, *v.* T1 in men.
† *P* value < 0·05, *v.* T1 in women.

Table 2. Associations between appendicular skeletal muscle mass to visceral fat area ratio (SVR) and severity of non-alcoholic fatty liver disease (NAFLD) in the whole cohort of patients*
(Odds ratio and 95 % confidence intervals)

	Unadjusted model			Adjusted model 1			Adjusted model 2		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value	OR	95 % CI	*P* value
NASH									
	0·77	0·61, 0·96	0·022	0·59	0·44, 0·79	<0·001	0·75	0·54, 1·06	0·104
NASH with the presence of fibrosis									
	0·72	0·56, 0·91	0·006	0·58	0·43, 0·79	<0·001	0·79	0·55, 1·13	0·197

NASH, non-alcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HOMO-IR, homoeostasis model assessment of insulin resistance.
* Data are expressed as OR and 95 % CI tested by logistic regression analysis. Model 1 was adjusted for age and sex; Model 2 was adjusted for age, sex, BMI, serum albumin, AST, ALT, HDL-cholesterol, LDL-cholesterol, TAG, total cholesterol, HOMA-IR score, hypertension and type 2 diabetes.

by sex, age, BMI, hypertension, pre-existing type 2 diabetes and other potential confounding factors (adjusted models 2).

Subgroup analyses for the relevance of appendicular skeletal muscle mass to visceral fat area ratio with severity of non-alcoholic fatty liver disease

As detailed in Table 3, there were significant interactions of SVR with sex ($P_{interaction} = 0{\cdot}017$ for NASH, $P_{interaction} = 0{\cdot}033$ for NASH with the presence of fibrosis) and age ($P_{interaction} = 0{\cdot}009$ for NASH, $P_{interaction} = 0{\cdot}033$ for NASH with the presence of fibrosis), but not with overweight/obesity, hypertension or pre-existing diabetes (all $P_{interaction} > 0{\cdot}05$). In stratified analyses, after adjustment for potential confounders, SVR remained inversely relevant with the severity of NAFLD only within men (adjusted OR 0·62, 95 % CI 0·42, 0·92, $P = 0{\cdot}017$ for NASH; adjusted OR 0·65, 95 % CI 0·43, 0·99, $P = 0{\cdot}043$ for NASH with the presence of fibrosis), and in older individuals (adjusted OR 0·40, 95 % CI 0·22, 0·74, $P = 0{\cdot}003$ for NASH; adjusted OR 0·46, 95 % CI 0·25, 0·86, $P = 0{\cdot}014$ for NASH with the presence of fibrosis).

Discussion

We found that there are clear sex-related and age-related associations between a progressive reduction in SVR (i.e. reflecting a reduction in appendicular skeletal muscle mass to visceral fat area ratio) and the severity of NAFLD histology. In particular, we found that decreasing SVR is closely associated with NASH in both men and older individuals, but not in women or younger subjects. Notably, the interaction test between SVR and sex was significant for either definite NASH or NASH with the presence of any stage of liver fibrosis. According to our knowledge, this is the largest and first research to date that has investigated the impact of sex on the association of SVR as well as disease severity of liver for patients having NAFLD.

Over the past few years, the relationship between decreasing SVR and presence of cardiometabolic diseases (including NAFLD) has attracted increasing scientific interest[8,16,17,18,26]. However, no unified conclusion has been reached mainly due to different diagnostic methods of NAFLD and sarcopenic obesity. According to a cross-sectional research of Japanese individuals, Shida *et al.* published that SVR was inversely associated

Table 3. Adjusted associations between appendicular skeletal muscle mass to visceral fat area ratio (SVR) (as the exposure variable) and severity of non-alcoholic fatty liver disease (NAFLD) (as the outcome measure) in different patient subgroups*
(Odds ratio and 95 % confidence intervals)

	n	OR	95 % CI for NASH	*P* value	$P_{interaction}$	OR	95 % CI for NASH with the presence of fibrosis	*P* value	$P_{interaction}$
Sex					0·017				0·033
Men	443	0·62	0·42, 0·92	0·017		0·65	0·43, 0·99	0·043	
Women	170	1·47	0·76, 2·83	0·254		1·45	0·74, 2·83	0·275	
Age					0·009				0·033
≥44 years	280	0·40	0·22, 0·74	0·003		0·46	0·25, 0·86	0·014	
<44 years	330	0·96	0·66, 1·40	0·830		0·96	0·64, 1·43	0·835	
BMI					0·875				0·823
≥25 kg/m^2	417	0·73	0·47, 1·12	0·150		0·76	0·48, 1·21	0·253	
<25 kg/m^2	196	0·76	0·50, 1·16	0·201		0·81	0·52, 1·26	0·350	
Hypertension					0·268				0·289
Yes	140	0·53	0·26, 1·09	0·085		0·56	0·27, 1·18	0·127	
No	473	0·80	0·56, 1·13	0·204		0·84	0·58, 1·21	0·348	
Type 2 diabetes					0·384				0·705
Yes	150	0·58	0·29, 1·16	0·122		0·70	0·35. 1·41	0·325	
No	463	0·78	0·55, 1·11	0·175		0·81	0·56, 1·17	0·255	

NASH, non-alcoholic steatohepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HOMO-IR, homoeostasis model assessment of insulin resistance.
* All models and OR (95 % CI) have been estimated using a logistic regression. SVR was included as a continuous measure. All logistic regression models (reported above) were adjusted for age, sex, BMI, serum albumin, AST, ALT, HDL, LDL, TAG, total cholesterol, HOMA-IR score, hypertension and type 2 diabetes (with the exception of the specific variable used for stratifying each patient subgroup).

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with NAFLD for both sexes; however, in this research, the determination of NAFLD was obtained by ultrasonography and not by biopsy[8]. Another cross-sectional study performed in Chinese patients with type 2 diabetes found that SVR was inversely associated with the existence of ultrasonography-defined NAFLD only for women[18]. An independent association of sarcopenia with both NAFLD and NAFLD-related advanced fibrosis has been recently reported in a meta-analysis of three cross-sectional studies[27]. And, Seo *et al.* found that sarcopenia, as estimated from bioimpedance measurements, was related to a greater risk of having ultrasound-defined NAFLD only for men, in a large cross-sectional research from the Seoul Metabolic Syndrome Cohort[28]. Koo *et al.* claimed that sarcopenia was related to NAFLD, but this association became non-significant after adjustment for potential confounding elements. Among subjects with biopsy-proven NAFLD, sarcopenic patients tend to have NASH compared with their counterparts without sarcopenia[29]. However, these investigators did not perform separate statistical analyses stratifying by sex.

It is known that when skeletal muscle mass decreases and visceral adipose tissue increases, insulin-mediated skeletal muscle and adipose tissue's ability to use or store blood glucose decrease. Indeed, low skeletal muscle mass and increased visceral fat accumulation reduce whole-body insulin-mediated glucose uptake and may promote the development of NAFLD[8,30]. In our study, we found that the association between decreasing SVR and NASH (with or without accompanying liver fibrosis) was observed only in men and in older individuals (age ≥ 44 years). A possible explanation for this observed sex-related difference in the association between decreasing SVR and the severity of NAFLD histology is that there are sex differences in muscle pathophysiology as well as body fat deposition that might confound the association between SVR and whole-body insulin resistance. Sex differences in muscle capillary density, muscle fibre type composition and oestrogen receptors expressed in skeletal muscle may affect the ability of glycolytic *v.* oxidative substrate metabolism[31]. Additionally, women have more subcutaneous adipose tissue than men, which may affect circulating levels of adipokines. Circulating adipokines adversely affect skeletal muscle metabolism through receptor binding[31,32]. There is also evidence showing that appendicular muscle mass is inversely related to HOMA-estimated insulin resistance for regular-weight as well as obese men, however not for women[33], and that sarcopenic obesity occurs more frequently in older individuals, who lose muscle mass and become more centrally obese and directly affected by inflammation and insulin resistance with advancing years of life[34].

Our research has several significant limitations which should be listed. First of all, sarcopenia not only includes lower muscle mass but also includes lower hand-grip strength and gait speed. A confirmed diagnosis of sarcopenic obesity needs to include measures of both muscle mass and muscle function, but these latter were not measured in our study[14,35]. Second, due to the cross-sectional design of the research, a causal and temporal relationship cannot be established. And then, the gold standard method for measuring visceral fat area, i.e. the computed tomography, was not available in our study because of its high monetary cost as well as radiation exposure to each patient. However, we used a dual bioelectrical impedance analyzer, which is a reliable, non-radioactive as well as repeatable methodology. A good correlation has been reported between computed tomography scans and bioelectrical impedance analyzer for assessing abdominal visceral adiposity[36]. Finally, we did not include any detailed information about physical activities, menopausal status, sex hormone levels or current use of oestrogen and progestogen drugs.

To conclude, the findings of our research showed that a progressive appendicular skeletal muscle mass:visceral fat area ratio (as reflected by decreasing SVR) is strongly associated with the severity of NAFLD (i.e. NASH with varying levels of fibrosis) only for men, but not for women, after being adjusted for potential confounding factors. These findings provide a new focus for ameliorating NAFLD development and progression. However, future prospective and mechanistic researches are required to identify the linkage of sarcopenia obesity with the risk and progression of NAFLD better.

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