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Muscle-to-fat ratio identifies functional impairments and cardiometabolic risk and predicts outcomes: biomarkers of sarcopenic obesity

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Abstract

Background Sarcopenic obesity aims to capture the risk of functional decline and cardiometabolic diseases, but its operational definition and associated clinical outcomes remain unclear. Using data from the Longitudinal Aging Study of Taipei, this study explored the roles of the muscle-to-fat ratio (MFR) with different definitions and its associations with clinical characteristics, functional performance, cardiometabolic risk and outcomes.

Methods (1) Appendicular muscle mass divided by total body fat mass (aMFR), (2) total body muscle mass divided by total body fat mass (tMFR) and (3) relative appendicular skeletal muscle mass (RASM) were measured. Each measurement was categorized by the sex-specific lowest quintiles for all study participants. Clinical outcomes included all-cause mortality and fracture.

Results Data from 1060 community-dwelling older adults (mean age: 71.0 ± 4.8 years) were retrieved for the study. Overall, 196 (34.2% male participants) participants had low RASM, but none was sarcopenic. Compared with those with high aMFR, participants with low aMFR were older (72 ± 5.6 vs. 70.7 ± 4.6 years, $P = 0.005$); used more medications (2.9 ± 3.3 vs. 2.1 ± 2.5, $P = 0.002$); had a higher body fat percentage (38 ± 4.8% vs. 28 ± 6.4%, $P < 0.001$), RASM (6.7 ± 1.0 vs. 6.5 ± 1.1 kg/m^2, $P = 0.001$), and cardiometabolic risk [fasting glucose: 105 ± 27.5 vs. 96.8 ± 18.7 mg/dL, $P < 0.001$; glycated haemoglobin (HbA1c): 6.0 ± 0.8 vs. 5.8 ± 0.6%, $P < 0.001$; triglyceride: 122.5 ± 56.9 vs. 108.6 ± 67.5 mg/dL, $P < 0.001$; high-density lipoprotein cholesterol (HDL-C): 56.2 ± 14.6 vs. 59.8 ± 16 mg/dL, $P = 0.010$]; and had worse functional performance [Montreal Cognitive Assessment (MoCA): 25.7 ± 4.2 vs. 26.4 ± 3.0, $P = 0.143$, handgrip strength: 24.7 ± 6.7 vs. 26.1 ± 7.9 kg, $P = 0.047$; gait speed: 1.8 ± 0.6 vs. 1.9 ± 0.6 m/s, $P < 0.001$]. Multivariate linear regression showed that age ($\beta = 0.093$, $P = 0.001$), body mass index ($\beta = 0.151$, $P = 0.046$), total percentage of body fat ($\beta = 0.579$, $P < 0001$) and RASM ($\beta = 0.181$, $P = 0.016$) were associated with low aMFR. Compared with those with high tMFR, participants with low tMFR were older (71.7 ± 5.5 vs. 70.8 ± 4.7 years, $P = 0.075$); used more medications (2.8 ± 3.3 vs. 2.1 ± 2.5, $P = 0.006$); had a higher body fat percentage (38.1 ± 4.7 vs. 28 ± 6.3%, $P < 0.001$), RASM (6.8 ± 1.0 vs. 6.5 ± 1.1 kg/m^2, $P < 0.001$), and cardiometabolic risk (fasting glucose: 104.8 ± 27.6 vs. 96.9 ± 18.7 mg/dL, $P < 0.001$; HbA1c: 6.1 ± 0.9 vs. 5.8 ± 0.6%, $P < 0.001$; triglyceride: 121.4 ± 55.5 vs. 108.8 ± 67.8 mg/dL, $P < 0.001$; HDL-C: 56.4 ± 14.9 vs. 59.7 ± 15.9 mg/dL, $P = 0.021$); and had worse functional performance (MoCA: 25.6 ± 4.2 vs. 26.5 ± 3.0, $P = 0.056$; handgrip strength: 24.6 ± 6.7 vs. 26.2 ± 7.9 kg, $P = 0.017$; gait speed: 1.8 ± 0.6 vs. 1.9 ± 0.6 m/s, $P < 0.001$). Low tMFR was associated with body fat percentage ($\beta = 0.766$, $P < 0.001$), RASM ($\beta = 0.476$, $P < 0.001$) and Mini-Nutritional Assessment ($\beta = -0.119$, $P < 0.001$). Gait speed, MoCA score, fasting glu-

cose, HbA1c and tMFR were significantly associated with adverse outcomes, and the effects of aMFR were marginal ($P = 0.074$).

Conclusions Older adults identified with low MFR had unfavourable body composition, poor functional performance, high cardiometabolic risk and a high risk for the clinical outcome.

Keywords Sarcopenia; Sarcopenic obesity; Muscle-to-fat ratio; Cardiovascular disease; Falls

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Introduction

Ageing is a complex process that involves a progressive decline in organ function, disrupted homeostasis, reduced physiological reserve and changes in body composition.[1,2] Overall, these changes result in the development of multimorbidity and disability that synergistically impacts the health outcomes of older people.[3–5] Unfavourable changes in body composition over time have pathological implications, such as obesity, osteoporosis and sarcopenia. In addition to the individual components of body composition, combinations of these components further suggest several at-risk conditions, such as sarcopenic obesity, osteosarcopenia or even osteosarcopenic obesity.[6] These conceptual proposals originated from the double burden assumption that two or more unfavourable conditions that occur together generate more adverse impacts than either alone. However, the obesity paradox weakened the potential impacts of sarcopenic obesity, the most common combination of the above-mentioned conditions.[7,8] Previous studies have repeatedly confirmed the importance of functional ability over individual diseases or multimorbidity in older adults,[3–5] and obesity increases the risk of cardiovascular diseases, immobility, falls and dementia.[7–9] Therefore, the health risk of obesity in late life should be addressed based on the health characteristics of older adults. Moreover, cardiometabolic risk related to obesity also substantially increases the risk of sarcopenia, frailty and dementia. Malnutrition secondary to strict control of the cardiometabolic risk should be balanced to evaluate the risk of obesity later in life.

Sarcopenia is a disease defined by the age-related loss of skeletal muscle mass together with a loss of muscle strength and/or reduced physical performance.[6] The adverse impacts of sarcopenia have been widely reported in the geriatric population and in patients with different clinical conditions, such as cancer, heart failure, chronic obstructive pulmonary disease, chronic kidney disease or liver disease.[10,11] However, older persons with sarcopenia may have two phenotypes, that is, lean or obese. Because of the potential survival benefits of the obesity paradox, the clinical impacts of sarcopenic obesity are still under debate.[12] Moreover, the operational definition of obesity in late life is controversial, and neither body mass index nor waist circumference satisfies the pathological definition of obesity.

The definition and diagnosis of sarcopenic obesity are also confusing. Some studies have shown that sarcopenic obesity increases the risk of metabolic syndrome, cardiovascular disease and impairment in instrumental activities of daily living,[13,14] but the overall impact of sarcopenic obesity in older adults remains unclear. In particular, some new approaches and biomarkers are needed to identify older persons at risk for both functional disability and cardiovascular disease, which justifies the original concept of sarcopenic obesity.

The muscle-to-fat ratio (MFR) has been reported to be a biomarker for cardiometabolic conditions and chronic kidney disease in older adults.[15,16] However, the ratio of total body muscle mass to total body fat mass is not completely compatible with the concepts of sarcopenia that use appendicular muscle mass and the focus on mobility. Hence, this study aimed to compare the clinical characteristics, functional ability, cardiometabolic risks, and clinical outcomes of biomarkers of unfavourable body composition, that is, relative appendicular muscle mass (RASM), the ratio of appendicular muscle mass to total body fat mass (aMFR), and the ratio of total body muscle to total body fat (tMFR), to explore the feasibility of using potential biomarkers to better define sarcopenic obesity.

Methods

Study design and participants

This study used the first-wave data of the Longitudinal Aging Study of Taipei, which recruited community-dwelling people aged 50 years and older living in the metropolitan area of Taipei, Taiwan.[17] However, data of participants under 65 years of age were not included in the analysis. This study was approved by the Institutional Review Board of National Yang Ming University (YM104121F-5). All participants provided written informed consent after a thorough explanation of the study by the research staff before enrolment. The study was designed and conducted in accordance with the princi-

ples of the Declaration of Helsinki; the cross-sectional, observational design and reporting format follow the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[18] and the ethical guidelines of the *Journal of Cachexia, Sarcopenia and Muscle*.[19]

Demographic data and functional assessment

Demographic characteristics, including age, sex, years of education, marital status, living status, smoking and drinking history, medical history and multimorbidity (evaluated using the Charlson Comorbidity Index), were collected. All participants underwent physical examinations, including blood pressure, body height and body weight. Muscle strength was measured by grip strength of the dominant hand, and the 6 m usual gait speed was used to evaluate physical performance. Moreover, the 6 min walking distance was used to evaluate muscle endurance, and the average energy expenditure of physical activity was evaluated using the International Physical Activity Questionnaire. Nutritional status was evaluated using the Mini-Nutritional Assessment (MNA). Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA), and depressive symptoms were evaluated by using the Center for Epidemiologic Studies - Depression Scale.

Body composition

Body composition, including the percentage of total body fat, lean body mass and estimated appendicular muscle mass, was evaluated using bioimpedance analysis (Inbody S10, Seoul, South Korea). Bone mineral density (BMD) was estimated by quantitative ultrasound at the calcaneus. Appendicular skeletal muscle mass was obtained by summing the lean tissue mass of all four limbs, and the RASM was calculated as appendicular skeletal muscle mass divided by the squared body height (in metres). In this study, low muscle mass was defined as the lowest quintile of sex-specific RASM measurements. The aMFR and tMFR were defined accordingly, and the sex-specific lowest quintile was used to define a low MFR.

Laboratory data

In this study, we used automated analysis (ADVIA Chemistry XPT, Siemens, Germany) to measure the serum levels of albumin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglycerides, glucose and high-sensitivity C-reactive protein. Whole-blood glycated haemoglobin (HbA1c) was measured using high-performance liquid chromatography (Bio-Rad D-100 System, Bio-Rad, USA). Serum levels of 25-hydroxyvitamin D were quantified by chemiluminescent immunoassay (LIAISON, DiaSorin, *Saluggia* VC. Italy).

Outcome measurements

All participants were clinically followed by the research staff every 3 months by telephone. Outcome events were defined as documented fractures and mortality during the follow-up period. Due to the low event rate during the study period, fractures and mortality were combined as the composite outcome for all participants. All participants were clinically followed for a mean of 32.6 months (range: 30–36 months).

Statistical analysis

In the present study, continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers or percentages. Comparisons of continuous variables were performed by independent *t*-tests, and χ^2 analysis was used to compare categorical variables. Non-parametric methods were used for statistical analyses of nonnormally distributed variables. Multivariate linear regression was used to explore the independent associations of low RASM, low aMFR or low tMFR with the other variables (including demographic characteristics, functional assessment and laboratory data). In particular, the association between aMFR or tMFR and the composite outcome (fracture and mortality) was also assessed, adjusting for other variables. Only confounders reached statistical significance in univariate analyses before selection for multivariate analyses. In linear regression analyses, betas were standardized coefficients. A two-sided P value of <0.05 was considered indicative of statistical significance. All statistical analyses were carried out using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Among 1060 community-dwelling adults aged 65 and older included in this study, 196 (34.2% male participants) were found to have a low RASM, but none of them were diagnosed with sarcopenia based on the 2019 consensus report of the Asian Working Group for Sarcopenia.[7] Compared with those with high RASM, participants with a low RASM were older (71.9 ± 5.7 vs. 70.7 ± 4.6 years, $P = 0.030$) and had a lower body weight (52.5 ± 7.9 vs. 61.9 ± 10.2 kg $P < 0.001$), BMI (20.3 ± 1.9 vs. 24.4 ± 3.0 kg/m^2, $P < 0.001$), percentage of body fat (27.0 ± 7.1 vs. 30.7 ± 7.1%, $P < 0.001$), and BMD (*T* score: −1.9 ± 1.1 vs. −1.6 ± 1.1, $P = 0.001$) (*Table* 1). In addition, participants with a low RASM had reduced handgrip strength (24.1 ± 7.1 vs. 26.3 ± 7.8 kg, $P < 0.001$), were less physically active (1620.9 ± 1301.7 vs. 2174.3 ± 1752.5 Kcal/week, $P < 0.001$) and had worse nutritional status (MNA: 25.7 ± 2.3 vs. 27.6 ± 1.8, $P < 0.001$); however, they had a better cardiometabolic risk profile (HbA1c: 5.7 ± 0.6 vs. 5.9 ± 0.7,

Table 1 Comparisons between participants with different skeletal muscle mass status

Variable	Total (n = 1060) *Mean ± SD*	Normal RASM (n = 864) *Mean ± SD*	Low RASM (n = 196) *Mean ± SD*	*P* value	Normal aMFR (n = 864) *Mean ± SD*	Low aMFR (n = 196) *Mean ± SD*	*P* value	Normal tMFR (n = 864) *Mean ± SD*	Low tMFR (n = 196) *Mean ± SD*	*P* value
Demographic characteristics										
Age (years)	71.0 ± 4.8	70.7 ± 4.6	71.9 ± 5.7	0.030	70.7 ± 4.6	72.0 ± 5.6	0.005	70.8 ± 4.7	71.7 ± 5.5	0.075
Male (n, %)	368 (34.7)	301 (34.8)	67 (34.2)	0.862	301 (34.8)	67 (34.2)	0.862	301 (34.8)	67 (34.2)	0.862
Education (years)	13.7 ± 3.7	13.6 ± 3.8	14.2 ± 3.3	0.075	13.8 ± 3.7	13.4 ± 3.9	0.367	13.8 ± 3.7	13.4 ± 4.0	0.444
Current smoker (n, %)	194 (18.3)	164 (19.0)	30 (15.3)	0.230	151 (17.5)	43 (21.9)	0.145	154 (17.8)	40 (20.4)	0.398
Current alcohol drinking (n, %)	760 (71.7)	636 (73.6)	124 (63.3)	0.004	622 (72.0)	138 (70.4)	0.657	624 (72.2)	136 (69.4)	0.426
Number of currently used medications	2.2 ± 2.7	2.3 ± 2.78	1.7 ± 2.0	0.012	2.1 ± 2.5	2.9 ± 3.3	0.002	2.1 ± 2.5	2.8 ± 3.3	0.006
Charlson Comorbidity Index	0.9 ± 1.1	0.8 ± 1.1	1.0 ± 1.2	0.219	0.9 ± 1.1	0.9 ± 1.1	0.874	0.86 ± 1.1	0.90 ± 1.2	0.844
Anthropometric measurements and body composition										
Height (cm)	159.2 ± 8.0	158.9 ± 7.9	160.5 ± 8.2	0.014	159.4 ± 7.9	158.3 ± 8.2	0.122	159.6 ± 7.9	157.6 ± 8.0	0.002
Weight (kg)	60.2 ± 10.5	61.9 ± 10.2	52.5 ± 7.9	<0.001	58.5 ± 9.7	67.5 ± 10.6	<0.001	58.6 ± 9.8	66.9 ± 10.8	<0.001
Body mass index (kg/m^2)	23.7 ± 3.2	24.4 ± 3.0	20.3 ± 1.9	<0.001	23.0 ± 2.8	26.8 ± 2.9	<0.001	22.9 ± 2.8	26.9 ± 2.9	<0.001
Waist-to-hip ratio	0.87 ± 0.11	0.87 ± 0.07	0.86 ± 0.20	<0.001	0.87 ± 0.11	0.90 ± 0.07	<0.001	0.87 ± 0.11	0.90 ± 0.07	<0.001
Total body fat (%)	30.0 ± 7.3	30.7 ± 7.1	27.0 ± 7.1	<0.001	28 ± 6.4	38 ± 4.8	<0.001	28.0 ± 6.3	38.1 ± 4.7	<0.001
RASM (kg/m^2)	6.5 ± 1.1	6.7 ± 1.0	5.8 ± 0.8	<0.001	6.5 ± 1.1	6.7 ± 1.0	0.001	6.5 ± 1.1	6.8 ± 1.0	<0.001
BMD T score	−1.7 ± 1.1	−1.6 ± 1.1	−1.9 ± 1.1	0.001	−1.7 ± 1.1	−1.6 ± 1.1	0.054	−1.7 ± 1.1	−1.6 ± 1.1	0.128
Functional assessment										
Handgrip strength (kg)	25.9 ± 7.7	26.3 ± 7.8	24.1 ± 7.1	<0.001	26.1 ± 7.9	24.7 ± 6.7	0.047	26.2 ± 7.9	24.6 ± 6.7	0.017
5-time chair-rise test (s)	9.4 ± 3.1	9.4 ± 3.2	9.6 ± 3.1	0.204	9.3 ± 3.1	10.1 ± 3.3	<0.001	9.3 ± 3.1	10.1 ± 3.2	<0.001
6 min walking distance (m)	505.3 ± 77.7	503.8 ± 77.0	511.4 ± 81.1	0.127	511.5 ± 76.9	477.6 ± 75.7	<0.001	511.9 ± 76.8	475.6 ± 75.0	<0.001
6 m gait speed (m/s)	1.9 ± 0.6	1.9 ± 0.6	1.9 ± 0.6	0.633	1.9 ± 0.6	1.8 ± 0.6	<0.001	1.9 ± 0.6	1.8 ± 0.6	<0.001
IPAQ (Kcal/week)	2072.0 ± 1691.5	2174.3 ± 1752.5	1620.9 ± 1301.7	<0.001	2034.2 ± 1584.3	2238.6 ± 2096.3	0.848	2060 ± 1647.4	2124.8 ± 1876.9	0.619
MNA	27.2 ± 2.1	27.6 ± 1.8	25.7 ± 2.3	<0.001	27.1 ± 2.1	27.8 ± 1.8	<0.001	27.1 ± 2.1	27.7 ± 1.8	<0.001
MoCA	26.3 ± 3.3	26.4 ± 3.1	26.1 ± 3.7	0.428	26.4 ± 3.0	25.7 ± 4.2	0.143	26.5 ± 3.0	25.6 ± 4.2	0.056
CES-D	2.4 ± 4.9	2.3 ± 4.7	2.8 ± 5.5	0.109	2.5 ± 4.9	2.2 ± 4.7	0.351	2.4 ± 4.9	2.4 ± 4.7	0.824
Laboratory data										
White blood cell count (/mm^3)	5.5 ± 1.5	5.5 ± 1.5	5.3 ± 1.4	0.093	5.4 ± 1.4	6.0 ± 1.6	<0.001	5.4 ± 1.4	6.0 ± 1.6	<0.001
Haemoglobin (g/dL)	14.0 ± 1.4	14.0 ± 1.4	13.9 ± 1.3	0.120	14 ± 1.3	14.1 ± 1.4	0.084	14.0 ± 1.3	14.1 ± 1.4	0.139
Vitamin D (ng/mL)	24 ± 7.3	23.7 ± 7.0	25.1 ± 8.2	0.009	24.4 ± 7.5	22.3 ± 5.6	<0.001	24.5 ± 7.5	22 ± 5.6	<0.001
Total cholesterol (mg/dL)	196.5 ± 34.6	195.5 ± 34.8	201.2 ± 33.5	0.028	196.5 ± 33.4	196.6 ± 39.6	0.403	196.2 ± 33.2	197.9 ± 40.4	0.835
Triglyceride (mg/dL)	111.1 ± 65.8	115.5 ± 69.8	91.8 ± 38.4	<0.001	108.6 ± 67.5	122.5 ± 56.9	<0.001	108.8 ± 67.8	121.4 ± 55.5	<0.001
HDL-C (mg/dL)	59.1 ± 15.8	57.6 ± 15.1	65.7 ± 16.9	<0.001	59.8 ± 16.0	56.2 ± 14.6	0.010	59.7 ± 15.9	56.4 ± 14.9	0.021
LDL-C (mg/dL)	114.2 ± 28.6	114.3 ± 28.9	114.0 ± 27.1	0.856	113.4 ± 27.7	117.8 ± 32.1	0.292	133.2 ± 27.5	118.5 ± 32.7	0.187
Albumin (mg/dL)	4.5 ± 0.2	4.5 ± 0.2	4.5 ± 0.2	0.985	4.5 ± 0.2	4.5 ± 0.2	0.061	4.5 ± 0.2	4.5 ± 0.2	0.143
Vitamin B12 (pg/mL)	743.9 ± 470.5	743.4 ± 489.1	746.4 ± 377.8	0.260	736.7 ± 453.6	776 ± 539	0.660	735.8 ± 452.7	779.7 ± 542.1	0.608
Fasting plasma glucose (mg/dL)	98.3 ± 20.9	98.9 ± 20.9	95.8 ± 20.7	0.001	96.8 ± 18.7	105 ± 27.5	<0.001	96.9 ± 18.7	104.8 ± 27.6	<0.001
HbA1c (%)	5.8 ± 0.7	5.9 ± 0.7	5.7 ± 0.6	0.001	5.8 ± 0.6	6.0 ± 0.8	<0.001	5.8 ± 0.6	6.1 ± 0.9	<0.001
Homocysteine (mmol/L)	13.6 ± 5.1	13.7 ± 4.5	13.2 ± 7.3	0.001	13.5 ± 5.3	14.3 ± 4.3	0.002	13.5 ± 5.3	14.2 ± 4.2	0.003
hs-CRP (mg/dL)	0.19 ± 0.47	0.19 ± 0.45	0.17 ± 0.53	0.005	0.17 ± 0.49	0.23 ± 0.35	<0.001	0.18 ± 0.49	0.23 ± 0.35	<0.001
Clinical outcome										
Mortality and fractures (n, %)	52 (4.9)	44 (5.1)	8 (4.1)	0.554	43 (4.9)	9 (5.1)	0.888	41 (4.7)	11 (5.6)	0.612

aMFR, appendicular muscle mass to total body fat mass; BMD, bone mineral density; CES-D, Center for Epidemiology Study-Depression; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; IPAQ, International Physical Activity Questionnaire; LDL-C, low-density lipoprotein cholesterol; MNA, Mini-Nutritional Assessment; MoCA, Montreal Cognitive Assessment; RASM, relative appendicular skeletal muscle; tMFR, total body muscle to total body fat.

P = 0.001; TG: 91.8 ± 38.4 vs. 115.5 ± 69.8 mg/dL, $P < 0.001$; HDL-C: 65.7 ± 16.9 vs. 57.6 ± 15.1 mg/dL, $P < 0.001$). The results of linear regression showed that older age (β coefficient: 0.145, $P < 0.001$), higher education years (β coefficient: 0.080, P = 0.003), lower BMI (β coefficient: −0.595, $P < 0.001$), higher percentage of total body fat (β coefficient: 0.292, $P < 0.001$), and higher serum levels of vitamin D (β coefficient: 0.068, P = 0.012) were independently associated with a low RASM. Sex-specific associations with a low RASM were identified and included age, medications used, BMD T score and serum levels of vitamin D (*Table* 2).

Compared with those with high aMFR, participants with a low aMFR were significantly older (72.0 ± 5.6 vs. 70.7 ± 4.6 years, P = 0.005); used more medications (2.9 ± 3.3 vs. 2.1 ± 2.5, P = 0.002); and had a higher BMI (26.8 ± 2.9 vs. 23.0 ± 2.8 kg/m^2, $P < 0.001$), waist-to-hip ratio (0.90 ± 0.07 vs. 0.87 ± 0.11, $P < 0.001$), body fat percentage (38 ± 4.8 vs. 28 ± 6.4%, $P < 0.001$), RASM (6.7 ± 1.0 vs. 6.5 ± 1.1 kg/m^2, P = 0.001), and cardiometabolic risk (fasting plasma glucose: 105 ± 27.5 vs. 96.8 ± 18.7 mg/dL, $P < 0.001$; HbA1c: 6.0 ± 0.8 vs. 5.8 ± 0.6%, $P < 0.001$; TG: 122.5 ± 56.9 vs. 108.6 ± 67.5 mg/dL, $P < 0.001$; HDL-C: 56.2 ± 14.6 vs. 59.8 ± 16.0 mg/dL, P = 0.010). Moreover, participants with a low aMFR had worse scores on all functional assessments, including MoCA (25.7 ± 4.2 vs. 26.4 ± 3.0, P = 0.143), dominant handgrip strength (24.7 ± 6.7 vs. 26.1 ± 7.9 kg, P = 0.047), 6 m gait speed (1.8 ± 0.6 vs. 1.9 ± 0.6 m/s, $P < 0.001$), five-time chair-rise test (10.1 ± 3.3 vs. 9.3 ± 3.1 s, $P < 0.001$) and 6 min walking distance (477.6 ± 75.7 vs. 511.5 ± 76.9 m, $P < 0.001$). The results of linear regression showed that age (β coefficient: 0.093, P = 0.001), BMI (β coefficient: 0.151, P = 0.046), total percentage of body fat (β coefficient: 0.579, $P < 0001$) and RASM (β coefficient: 0.181, P = 0.016) were positively associated with low aMFR. Sex-specific associations with a low aMFR were identified as MNA score and white blood cell count (*Table* 3).

Table 1 shows that participants with a low tMFR were older (71.7 ± 5.5 vs. 70.8 ± 4.7 years, P = 0.075); used more medications (2.8 ± 3.3 vs. 2.1 ± 2.5, P = 0.006); and had a higher BMI (26.9 ± 2.9 vs. 22.9 ± 2.8 kg/m^2, $P < 0.001$), waist-to-hip ratio (0.90 ± 0.07 vs. 0.87 ± 0.11, $P < 0.001$), body fat percentage (38.1 ± 4.7 vs. 28.0 ± 6.3%, $P < 0.001$), RASM (6.8 ± 1.0 vs. 6.5 ± 1.1 kg/m^2, $P < 0.001$), and cardiometabolic risk (fasting plasma glucose: 104.8 ± 27.6 vs. 96.9 ± 18.7 mg/dL, $P < 0.001$; HbA1c: 6.1 ± 0.9 vs. 5.8 ± 0.6%, $P < 0.001$; TG: 121.4 ± 55.5 vs. 108.8 ± 67.8 mg/dL, $P = < 0.001$; HDL-C: 56.4 ± 14.9 vs. 59.7 ± 15.9 mg/dL, P = 0.021) and that they had worse functional assessments (MoCA: 25.6 ± 4.2 vs. 26.5 ± 3.0, P = 0.056; handgrip strength: 24.6 ± 6.7 vs. 26.2 ± 7.9 kg, P = 0.017; 6 m gait speed: 1.8 ± 0.6 vs. 1.9 ± 0.6 m/s, $P < 0.001$; five-time chair-rise test: 10.1 ± 3.2 vs. 9.3 ± 3.1 s, P = 0.002; 6 min walking distance: 475.6 ± 75.0 vs. 511.9 ± 76.8 m, $P < 0.001$). Linear regression showed that a low tMFR was positively associated with the percentage of body fat (β coefficient: 0.766, $P < 0.001$) and RASM (β coefficient: 0.476, $P < 0.001$) and negatively associated with MNA score (β coefficient: −0.119, $P < 0.001$). Sex-specific associations with a low tMFR were identified for BMI, handgrip strength, MNA score, white blood cell count and HbA1c (*Table* 4).

Table 5 shows the independent factors associated with adverse clinical outcomes: tMFR, gait speed, MoCA score, fasting plasma glucose and HbA1c were all significantly associated with adverse outcomes, and the effects of aMFR were only marginal (P = 0.074).

Discussion

The results of this study support using the MFR, especially tMFR, as a potential biomarker for defining or diagnosing

Table 2 Sex differences in independent factors associated with low relative appendicular skeletal muscle mass (RASM) among study participants

	Total (n = 1060)			Men (n = 368)			Women (n = 692)		
	95% CI	β	P value	95% CI	β	P value	95% CI	β	P value
Demographic characteristics									
Age (years)	0.008, 0.017	0.145	<0.001	−0.004, 0.011	0.052	0.306	0.003, 0.015	0.100	0.003
Education (years)	0.003, 0.014	0.080	0.003	−0.004, 0.016	0.050	0.261	−0.001, 0.013	0.056	0.088
Number of currently used medications	−0.019, −0.001	−0.066	0.023	−0.026, 0.001	−0.095	0.070	−0.025, −0.001	−0.075	0.027
Anthropometric measurements and body composition									
Body mass index (kg/m^2)	−0.087, −0.066	−0.595	<0.001	−0.111, −0.071	−0.689	<0.001	−0.100, −0.074	−0.678	<0.001
Total body fat (%)	0.011, 0.021	0.292	<0.001	0.011, 0.031	0.315	<0.001	0.020, 0.033	0.398	<0.001
BMD T score	−0.045, −0.008	−0.073	0.006	−0.038, 0.025	−0.019	0.668	−0.049, −0.004	−0.074	0.020
Functional assessment									
Handgrip strength (kg)	0.006, 0.014	0.188	<0.001	−0.008, 0.006	−0.012	0.813	−0.004, 0.009	0.030	0.382
MNA	−0.054, −0.030	−0.216	<0.001	−0.073, −0.025	−0.211	<0.001	−0.056, −0.029	−0.234	<0.001
Laboratory data									
Vitamin D (pg/L)	0.001, 0.007	0.068	0.012	−0.002, 0.008	0.056	0.211	0.001, 0.008	0.073	0.024

BMD, bone mineral density; CI, confidence interval; MNA, Mini-Nutritional Assessment.

Table 3 Sex differences in independent factors associated with low appendicular muscle mass to total body fat ratio (aMFR) among study participants

	Total (n = 1060)			Men (n = 368)			Women (n = 692)		
	95% CI	β	P value	95% CI	β	P value	95% CI	β	P value
Demographic characteristics									
Age (years)	0.003, 0.013	0.093	0.001	−0.003, 0.011	0.055	0.262	−0.010, 0.003	−0.034	0.317
Anthropometric measurements and body composition									
Body mass index (kg/m^2)	0.000, 0.039	0.151	0.046	0.056, 0.127	0.679	<0.001	0.064, 0.122	0.725	<0.001
Total body fat (%)	0.024, 0.039	0.579	<0.001	0.007, 0.033	0.303	0.003	0.010, 0.028	0.292	<0.001
RASM (kg/m^2)	0.013, 0.124	0.181	0.016	−0.384, −0.168	−0.447	<0.001	−0.409, −0.180	−0.405	<0.001
Functional assessment									
MNA	−0.032, −0.008	−0.104	0.001	−0.030, 0.017	−0.027	0.576	−0.037, −0.011	−0.132	<0.001
Laboratory data									
White blood cell count (/mm^3)	−0.002, 0.027	0.046	0.084	−0.033, 0.009	−0.045	0.276	0.002, 0.038	0.069	0.030

CI, confidence interval; MNA, Mini-Nutritional Assessment; RASM, relative appendicular skeletal muscle mass.

sarcopenic obesity because it clearly demonstrates associations with functional performance, cardiometabolic risk and clinical outcomes. In this study, the associations between the MFR (either aMFR or tMFR), BMI, total fat percentage and RASM were strong, but the associations with functional performance, cardiometabolic risk and adverse clinical outcomes supported our hypothesis that the MFR could be used as a biomarker of sarcopenic obesity. The importance of sarcopenic obesity should be defined by its clinical significance, and ideally, a proper definition of sarcopenic obesity should include cardiometabolic health and functional performance. To echo the ideology of healthy ageing to promote intrinsic capacity and functional ability,[20–22] a biomarker of sarcopenic obesity should consider cardiometabolic health and functional performance.

Previous studies have shown the effectiveness of using the MFR to predict metabolic syndrome, insulin resistance and the development of chronic kidney disease,[15,16] which are still within the spectrum of cardiometabolic health. However, the most common outcome indicators for sarcopenia were falls, frailty, mobility difficulties, disability, hospitalizations and mortality.[10] Studies have shown that existing cardiovascular disease and diabetes significantly increase the risk of functional decline and disability,[23,24] so a biomarker that includes cardiometabolic health and functional decline is needed to clarify the health risk of sarcopenic obesity. The MFR is determined by the dynamics of muscle mass and fat mass that eventually represent various conditions. However, adiposity is the major pathoaetiological factor of cardiometabolic diseases, where muscle mass and its function are the main diagnostic components of sarcopenia. Therefore, the MFR should be an appropriate biomarker for the definition and diagnosis of sarcopenic obesity.

The accumulation of visceral fat and central obesity are the key features of age-related adipose tissue redistribution and contribute to the development of cardiometabolic diseases. Visceral fat accumulation is highly compatible with total body fat mass, so using total body fat mass as the denominator for the MFR is widely acceptable. However, unlike total body fat mass, selecting the numerator of the MFR is challenging because sarcopenia focuses on appendicular muscle mass instead of total body muscle mass.[25] Defining obesity in older adults is a considerable challenge because both BMI and waist circumference are not satisfactory measurements.[26,27] The MFR in this study, however defined, was consistent with

Table 4 Sex differences in independent factors associated with low total body muscle to total body fat ratio (tMFR) among study participants

	Total (n = 1060)			Men (n = 368)			Women (n = 692)		
	95% CI	β	P value	95% CI	β	P value	95% CI	β	P value
Anthropometric measurements and body composition									
Body mass index (kg/m^2)	−0.028, 0.009	−0.075	0.308	−0.002, 0.069	0.249	0.065	0.018, 0.076	0.370	0.001
Total body fat (%)	0.035, 0.049	0.766	<0.001	0.025, 0.051	0.579	<0.001	0.023, 0.040	0.478	<0.001
RASM (kg/m^2)	0.125, 0.233	0.476	<0.001	−0.185, 0.030	−0.125	0.158	−0.201, 0.028	−0.119	0.140
Functional assessment									
Handgrip strength (kg)	−0.005, 0.004	−0.005	0.897	−0.013, 0.000	−0.094	0.056	−0.013, −0.001	−0.071	0.029
MNA	−0.035, −0.011	−0.119	<0.001	−0.034, 0.012	−0.046	0.337	−0.039, −0.013	−0.144	<0.001
Laboratory data									
White blood cell count (/mm^3)	−0.003, 0.024	0.039	0.139	−0.042, 0.000	−0.080	0.054	0.005, 0.040	0.080	0.012
Triglyceride (mg/dL)	−0.001, 0.000	−0.063	0.026	0.000, 0.001	0.021	0.651	−0.001, 0.000	−0.031	0.368
HDL-C (mg/dL)	0.000, 0.003	0.061	0.049	−0.001, 0.005	0.050	0.299	0.000, 0.004	0.084	0.016
LDL-C (mg/dL)	−0.001, 0.001	−0.014	0.584	−0.002, 0.000	−0.087	0.050	−0.001, 0.001	−0.015	0.627
HbA1c (%)	−0.034, 0.068	0.0265	0.522	0.013, 0.161	0.142	0.021	−0.092, 0.041	−0.037	0.451

CI, confidence interval; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MNA, Mini-Nutritional Assessment; RASM, relative appendicular skeletal muscle mass.

Table 5 Independent factors associated with death and fractures among study participants

Variable	Total, n = 1060 (aMFR)			Total, n = 1060 (tMFR)		
	95% CI	β	P value	95% CI	β	P value
Demographic characteristics						
Age (years)	−0.003, 0.003	0.006	0.879	−0.003, 0.003	−0.003	0.941
Number of currently used medications	−0.002, 0.010	0.050	0.173	−0.002, 0.010	0.048	0.203
MFR	−0.062, 0.003	−0.074	0.074	−0.051, 0.000	−0.081	0.049
Functional assessment						
Handgrip strength (kg)	0.000, 0.004	0.073	0.094	−0.001, 0.004	0.064	0.130
5-time chair-rise test (s)	0.000, 0.011	0.076	0.060	0.000, 0.011	0.074	0.066
6 min walking distance (m)	0.000, 0.000	−0.060	0.202	0.000, 0.000	−0.053	0.253
6 m gait speed (m/s)	0.001, 0.056	0.080	0.043	0.001, 0.056	0.079	0.045
MNA	−0.010, 0.004	−0.030	0.412	−0.010, 0.004	−0.031	0.408
MoCA	−0.009, 0.000	−0.067	0.054	−0.009, 0.000	−0.070	0.047
Laboratory data						
White blood cell count (/mm^3)	−0.015, 0.003	−0.042	0.215	−0.015, 0.003	−0.042	0.217
Vitamin D (pg/L)	−0.003, 0.001	−0.031	0.361	−0.003, 0.001	−0.026	0.435
Triglyceride (mg/dL)	0.000, 0.000	−0.036	0.326	0.000, 0.000	−0.033	0.370
HDL-C (mg/dL)	0.000, 0.002	0.041	0.299	0.000, 0.002	0.048	0.212
LDL-C (mg/dL)				−0.001, 0.000	−0.006	0.863
Albumin (mg/dL)	−0.048, 0.069	0.011	0.733			
Fasting plasma glucose (mg/dL)	−0.002, 0.000	−0.110	0.031	−0.002, 0.000	−0.107	0.035
HbA1c (%)	0.010, 0.079	0.131	0.011	0.009, 0.077	0.126	0.014
Homocysteine (mmol/L)	−0.004, 0.001	−0.037	0.282			

aMFR, appendicular muscle mass to total body fat mass; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MNA, Mini-Nutritional Assessment; MoCA, Montreal Cognitive Assessment; tMFR, total body muscle to total body fat.

BMI, waist-to-hip ratio and total body fat percentage, so the characteristics of obesity should be sufficiently identified.

This study compared the aMFR and tMFR and showed that both definitions significantly differentiated older people by cardiometabolic risk profiles and functional performance. Moreover, the associations between the aMFR and these parameters showed fewer sex differences, but the tMFR was better for outcome prediction. Therefore, studies with longer observational periods are needed to explore the prognostic roles of the aMFR and tMFR. A sex-specific relationship is common in obesity and sarcopenia research,[28–30] but it also increases the difficulties of data interpretation.

In this study, both fasting plasma glucose and HbA1c were significantly associated with adverse outcomes but in opposite directions. The association between a higher HbA1c and adverse outcomes suggested the importance of long-term glycaemic control. On the other hand, the association between lower fasting plasma glucose and adverse clinical outcomes implied the adverse effects of potential silent hypoglycaemia. Glycaemic variability has been reported as a poor outcome indicator in diabetes care,[31,32] and the discrepancy between fasting plasma glucose and HbA1c in the association with clinical outcomes may be partly explained by glycaemic variability. Sex differences in the associations among body composition, clinical characteristics and outcomes were common in this study and have been reported in other studies.[28–30] Previous comparative studies found that in both men and women, Asian people had higher adiposity than Western individuals across different levels of obesity. On the other hand, older Asian women did not lose as much muscle as Caucasian women did, but older Asian men and Caucasian men lost equivalent amounts.[33,34] Therefore, the sex differences in the associations with anthropometric measurements, body composition and functional assessments were unsurprising.

As people age, both the aMFR and tMFR moved in an unfavourable direction in both men and women, and fewer sex-specific associations were observed in the aMFR. Accumulation of excessive fat mass and loss of muscle mass represent different health risks to older adults throughout the life course,[35–37] but the combined effects should be prioritized to define sarcopenic obesity. Compared with that of the tMFR, the efficacy of predicting adverse outcomes was only marginal at the mean 32.6 month follow-up, but using appendicular muscle mass reduced the sex-specific effects with a stronger emphasis on mobility function. The lean body mass estimated by bioimpedance was more strongly associated with nutritional status, unlike the association of appendicular muscle mass with the mobility function. From the results of this study, a lower MFR (both aMFR and tMFR) clearly identified the phenotypic presentation of worse physical and cognitive function, unfavourable body composition, worse nutritional status and higher cardiometabolic risk in older people. The MFR covers most of the health risks of interest related to sarcopenic obesity and may be considered a biomarker for the definition and diagnosis of sarcopenic obesity.

Despite all of the research efforts in this study, there were still some limitations. First, participants in this study were healthy, active and educated older persons, so their baseline functional and health statuses were better than those of typ-

ical community-dwelling older adults. The lack of sarcopenia and a mean walking speed of 1.8 m/s among all participants clearly reflected their health status, so extrapolation to other populations deserves further attention. Second, the observational period was a mean of 32.6 months, which may be short for these active and healthy older persons. Hence, a longer observational period or a larger sample size is needed to confirm the findings of the current study. Third, bioimpedance-estimated body composition may not be the gold standard compared with computerized tomography or magnetic resonance imaging. Nevertheless, for community-dwelling elderly individuals, it is a non-invasive, fast, low-cost, portable, easily conducted and safe method.[38] The measurements of multichannel bioimpedance have been shown to be comparable with those of dual X-ray absorptiometry.[39] This is why we selected bioimpedance-estimated body composition in this study.

In conclusion, the MFR, assessed by either appendicular muscle mass or total body mass divided by total body fat mass, clearly represented functional performance and cardiometabolic risk and may be suitable as a biomarker of sarcopenic obesity. Although the MFR significantly predicted the composite outcome of mortality and fractures, further study with a longer observational period is needed to evaluate its efficacy in predicting adverse clinical outcomes covering both sarcopenia and cardiometabolic conditions in older people.

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Conflicts of interest

All authors declared no conflicts of interest.

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