ASSOCIATION BETWEEN RATIO-INDEXES OF BODY COMPOSITION PHENOTYPES AND METABOLIC RISK IN ITALIAN ADULTS

Megan POWELL[1], Jose LARA[2,3], Gabriele MOCCIARO[3], Carla M. PRADO[4], Alberto BATTEZZATI[5], Alessandro LEONE[5], Anna TAGLIABUE[6], Ramona DE AMICIS[5], Laila VIGNATI[5], Simona BERTOLI[5#], Mario SIERVO[3#]

[1] School of Biomedical Sciences, Faculty of Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

[2] Department of Applied Sciences, Faculty of Health and Life Sciences, Northumbria University, Ellison Building Room A324, Newcastle upon Tyne NE1 8ST, UK

[3] Human Nutrition Research Centre, Institute of Cellular Medicine, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK

[4]Department of Agricultural, Food and Nutritional Sciences, University of Alberta, Edmonton, AB, Canada

[5]International Center for the Assessment of Nutritional Status, (ICANS Department of Food, Environmental and Nutritional Sciences (DeFENS), University of Milan, Sandro Botticelli, 21, 20133 Milano, Italy

[6]Human Nutrition and Eating Disorders Research Centre, Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Via Bassi, 21 - 27100 Pavia, Italy

Running title: Body composition phenotypes and metabolic risk

Keywords: obesity, sarcopenia, bioimpedance, ultrasound, visceral fat, metabolic syndrome

*Corresponding author: Dr Mario Siervo (mario.siervo@ncl.ac.uk)

#Shared last authorship

The material presented in this manuscript is original and it has not been submitted for publication elsewhere while under consideration for Clinical Obesity

Conflict of interest statement: The authors have no conflict of interest to declare.

Type of Manuscript: Research Paper

Abstract word count: 248

Main text word count: 3326

References: 40

Table: 5

Figures: 1

Online Supplementary Material: 1

What is already known about this subject

- Sarcopenic obesity, defined as the concomitant presence of high adiposity and low muscle mass, has been proposed as a novel body composition phenotype
- Several definitions have been proposed to define sarcopenic obesity with implications for prevalence estimates and disease risk predictions
- Ratio models of body composition phenotypes have been proposed to improve disease risk prediction

What this study adds

- Compare for the first time two independent ratio indexes for the load-capacity model
- There is no real advantage in using either VAT:FFMI or FMI:FFMI ratios as a predictor of metabolic risk

Abstract

Background/Objectives: The ratio between fat mass (FM) and fat free mass (FFM) has been used to discriminate individual differences in body composition and improve prediction of metabolic risk. Here, we evaluated whether the use of a visceral adipose tissue-to-fat free mass index (VAT:FFMI) ratio was a better predictor of metabolic risk than a fat mass index-to-fat-free mass index (FMI:FFMI) ratio.

Subjects/Methods: Cross-sectional study including 3441 adult participants (age range 18-81; men/women: 977/2464). FM and FFM were measured by bioelectrical impedance analysis and VAT by ultrasonography. A continuous metabolic risk Z score and harmonised international criteria were used to define cumulative metabolic risk and metabolic syndrome (MetS), respectively. Multivariate logistic and linear regression models were used to test associations between body composition indexes and metabolic risk.

Results: In unadjusted models, VAT:FFMI was a better predictor of MetS (OR 8.03, 95%CI 6.69-9.65) compared to FMI:FFMI (OR 2.91, 95%CI 2.45-3.46). However, the strength of association of VAT:FFMI and FMI:FFMI became comparable when models were adjusted for age, sex, clinical and sociodemographic factors (OR 4.06, 95%CI 3.31-4.97; OR 4.25, 95%CI 3.42- 5.27, respectively). A similar pattern was observed for the association of the two indexes with the metabolic risk Z score (VAT:FFMI: unadjusted b=0.69 ± 0.03, adjusted b=0.36 ± 0.03; FMI:FFMI: unadjusted b=0.28 ± 0.028, adjusted b=0.38 ± 0.02).

Conclusions: Our results suggest that there is no real advantage in using either VAT:FFMI or FMI:FFMI ratios as a predictor of metabolic risk in adults. However, these results warrant confirmation in longitudinal studies.

Introduction

Healthy ageing is associated with physiological changes in body composition across the life course, including a steady increase in fat mass (FM) and a decrease in fat free mass (FFM).(1) However, significant deviations from this norm through obesity and sarcopenia may have physiological, metabolic and functional implications which is associated with an increased morbidity and mortality.(2,3) Both sarcopenia and obesity are major areas of research, which has been prompted by the finding that sarcopenia may often co-exist with obesity. This has led to the introduction of a novel body composition phenotype, sarcopenic obesity.(4)

The concomitant excess adiposity and reduced muscle mass (primary component of FFM), characteristic of the sarcopenic obese phenotype, has been proposed to impose a greater morbidity and mortality risk on individuals than either component alone.(5) Sarcopenic obesity has been associated with greater levels of physical disability(6), increased risk of cardiovascular disease (7) and an increased likelihood of adverse surgical outcomes.(8) However, there has been variability in these findings(5,9,10) which have been partially attributed to a lack of consensus surrounding the diagnostic criteria for sarcopenic obesity.(11)

Sarcopenic obesity has been defined using different parameters as indicators of sarcopenia, obesity, body composition techniques and diagnostic cut-offs.(11) Body mass index (BMI)(9,12,13), waist circumference (7,14,15), FM % (5,6,16,17), fat mass index (FMI)(8,18) and visceral fat area(19-21) have all been used as parameters to define obesity. Whilst, appendicular skeletal muscle mass (16,20-23), skeletal mass index (5,17,24), skeletal muscle mass percentage (9,12), FFM index (FFMI)(8) and thigh muscle cross-sectional area(25) have all been parameters used to define sarcopenia. The cut-off values used for each of these parameters have differed between studies and have been sex-specific(5), cohort-specific(17) or derived from a reference young healthy population.(19) Dual energy X-ray absorptiometry (DXA) (11) has been frequently identified as an accurate method to assess body composition phenotypes such as sarcopenic obesity; however other indirect methods such as bioelectrical impedance analysis (BIA) have been frequently used in consideration of practicality and affordability.(26) Sarcopenic obesity has also been associated with an increased risk of metabolic syndrome (MetS)(12,16,27) and may represent a greater risk factor than obesity alone. Visceral adiposity is a strong risk factor of MetS, more strongly so than other obesity parameters such as BMI.(28) A few studies have used visceral adiposity for the diagnosis of sarcopenic obesity and found significant associations with MetS.(21) (22) (27) A summary of the studies using BIA to assess the sarcopenic obese phenotype is reported in **Table S1 of the Online Supplementary Material.**

Wells has proposed a load-capacity model to reflect the physiological roles of adiposity and FFM to improve the prediction of metabolic risk(29). The model is conceptualised around the contribution of two contrasting traits: 'metabolic capacity', which refers to the organs and tissues that maintain homeostasis, and 'metabolic load', which derives from other body components, or from behaviours (dietary intake, sedentary behaviour) that may challenge the maintenance of homeostasis (29). The applicability of this model has been attempted by assigning "metabolic load" and "metabolic capacity" to FM and FFM components, respectively (11). This has been subsequently operationalised by Siervo et al(30) by proposing two independent ratio indexes of body composition phenotypes using FM and appendicular skeletal mass and truncal FM and appendicular skeletal mass derived from DXA measurements. A higher value of either ratio would indicate a greater metabolic burden determined by a co-existing excess adiposity and lower FFM in the same individual.

Here, we propose to further test the load-capacity model hypothesis and use visceral adipose tissue (VAT)-to-FFMI (VAT:FFMI) and FM-to-FFM (FM:FFM) ratios, measured by ultrasonography and BIA, to examine their association with metabolic risk in a cohort of 3441 Italian adults. We specifically evaluated whether a high VAT:FFMI ratio was a better predictor of metabolic risk compared to the FM:FFM ratio, based on the hypothesis that VAT, combined with low FFM, would be more closely linked to the pathogenesis of MetS.

Methods

Subjects and study protocol

Full description of the study methodology is defined elsewhere (18,31). In brief, participants were selected from those recruited between February 2010 and September 2013 as part of a large on-going cohort, (Milan) followed at the International Center for the Assessment of Nutritional Status (ICANS, University of Milan). Participants attended the outpatient clinics for the assessment of the nutritional status and included healthy individuals as well as patients with diseases requiring assessment of nutritional status and dietetic therapy. A total of 3465 adult Caucasian men and women were recruited (age range 18-81; BMI range: 18.7 – 60.1 kg/m^2, men/women 987/2478). We excluded subjects with a BMI <18.5 and subjects with missing data, resulting in an analytic sample of 3441 adult participants (age range 18-81; men/women: 977/2464). Participants with medical conditions or medication use were not excluded to enhance the inclusiveness and representativeness of the sample. All participants gave written informed consent and the study procedure was approved by the University of Milan Ethical Committee. This work is reported in adherence with the STROBE guidelines for cross-sectional studies.(32)

Smoking, physical activity and health status

Current smoking habits were recorded as current smokers, never smoked or former smokers. A detailed medical interview was conducted and self-reported diagnosis of medical conditions was collected. Disease count including major chronic diseases, such as cancer, thyroid and adrenal disorders, systemic inflammatory diseases (i.e., Crohn's Disease, Ulcerative Colitis, Sjögren's Syndrome, Systemic Lupus Erythematosus, Systemic Sclerosis), HIV, and acute and chronic kidney failure, was calculated for each subject. Physical activity level was assessed using the short version of the International Physical Activity Questionnaire (IPAQ)[25].

Anthropometry

Body weight was measured by Column scale (Seca 700 balance, Seca Corporation, Hanover, MD, USA) to 100 g with subjects wearing only light underwear and after bladder emptying. Body height was measured to the nearest 0.1 cm using a vertical stadiometer. BMI was calculated as weight/height^2. Waist circumference was measured twice, with a flexible tape, in line with the umbilicus and to the nearest 0.1cm.

Bioelectrical Impedance Analysis

FM and FFM were calculated using BIA. A tetrapolar 8-point tactile electrode system (InBody 720, Biospace, Seoul, Korea) was used to measure impedance at 1, 5, 50, 250, 500 and 1000 kHz. Participants were in contact with a total of eight electrodes (two for each foot and for each hand). FM and FFM were estimated using manufacturer's equations. To adjust for height, a FMI and FFMI was calculated by dividing FM (kg) and FFM (kg) respectively by height in squared meters^2.

Abdominal Ultrasonography

VAT and subcutaneous adipose tissue (SAT) were measured using abdominal ultrasonography. VAT was measured as the distance between the anterior wall of the aorta and the posterior surface of the rectus abdominis muscle and SAT was measured as the distance between the epidermis and the external face of the rectus abdominis muscle. The measurements were taken by the same operator on fasting participants using a Logiq 3 Pro (GE Healthcare, Milwaukee, WI, USA). Both VAT and SAT were measured three times, one centimetre above the umbilicus, and a mean measurement was calculated.(31)

Laboratory Measurements

Fasting blood samples were drawn between 8:30 and 9:00 AM and analysed in the same morning at the ICANS laboratory. Fasting glucose, triglycerides and HDL cholesterol were measured using an enzymatic method (Cobas Integra 400 Plus, Roche Diagnostics, Rotkreuz, Switzerland). Resting blood pressure was measured in sitting position after participants had rested for at least ten minutes following the JNC-7 guidelines [30].

Definition of Body Composition Phenotypes

The classification of body composition phenotypes was based on the calculation of two indices in the whole population: FM:FFM and VAT:FFMI. Scores for both ratios were then divided into quintiles.(17,24) Those in the highest quintile (Q5) for either ratio were categorised as having high adiposity and low FFM (HA-LF) compared to the rest of the population (Q1-Q4), which for simplicity has been defined as having a normal body composition phenotype. The primary analyses were conducted in the whole population and a sensitivity analysis was conducted by stratifying the population by gender.

Metabolic Syndrome

Participants were diagnosed with MetS if they had three or more of the following criteria: waist circumference ≥ 102 cm in men and ≥ 88 cm in women, high density lipoproteins (HDL) < 40 mg/dL in men and <50mg/dL in women, triglycerides ≥ 150 mg/dL, systolic blood pressure (BP) ≥ 130 mmHg and/or diastolic blood pressure ≥ 85mmHg and fasting glucose ≥ 100 mg/dL. This criteria is in concordance with the harmonised international definition of the metabolic syndrome.(33) A continuous metabolic risk Z score was also calculated using the average of the individual Z scores for the following variables: triglycerides, HDL, systolic BP, diastolic BP and glucose. The Z score for HDL was reversed to indicate a higher metabolic risk with decreasing values. The method has been previously described.(34)

Statistical Analyses

Data are presented as mean ± SD (continuous variables) and frequency and percentage (categorical variables). Variables were checked for normality using Q-Q plots and appropriate transformations were applied to restore normality. Continuous variables were compared using an independent T-test and categorical variables were compared using a Chi-square test. Binary logistic regression models were created to evaluate the risk of MetS associated with HA-LF as defined by VAT:FFMI and FMI:FFMI. Unadjusted models were generated with presence of MetS as the dependent variable and body composition phenotypes (as defined by either ratio) as the main independent variable. The

model was then adjusted for potential covariates: age, sex, number of pathologies, BMI, physical activity levels, smoking status, marital status, education and employment. Beta coefficients (β, SE) and odds ratios (OR, 95% CI) are reported. Multiple linear regression models were created to assess HA-LF (as defined by VAT:FFMI and FMI:FFMI) as a predictor of individual metabolic biomarkers (glucose, systolic blood pressure, diastolic blood pressure, triglycerides and HDL) and total metabolic risk Z scores. Models were adjusted for potential covariates. Intercepts (α) and regression coefficients (*b*±SE) are reported. A sensitivity analysis was also conducted to check the performance of the regression models after exclusion of participants with pathologies that may affected body composition and/or metabolic health (endocrine disorders, cancer, inflammatory bowel diseases, cirrhosis, immunodeficiency, neurological disorders, kidney failure). Significance was defined as *p* value ≤0.05. Analyses were carried out using Microsoft Excel 2013 for Windows (Version 15.0, Microsoft Corp., Redmond, WA, USA) and IBM SPSS for Windows (Version 22.0, IBM Corp., Armonk, NY, USA).

Results

Sample Characteristics

Characteristics of the 3441 subjects included in this study are displayed in **Table 1.** Male subjects had a greater height, weight, BMI and waist circumference (p<0.001). SAT did not differ between male and female subjects (p=0.06), but VAT was significantly greater in males (p<0.001). Females had a greater FMI whereas male subjects had a greater FFMI (p<0.001). Metabolic parameters including glucose, systolic blood pressure, diastolic blood pressure and triglyceride levels were significantly greater in male subjects but HDL levels were greater in females (p<0.001). The number of pathologies did not differ between the two groups (p=0.15).

Characteristics of Body Composition Phenotypes

Table 2 displays the characteristics of the body composition phenotypes classified according to the two ratio indexes. Subjects in the HA-LF phenotype were generally older and had a greater BMI compared to the normal group (*p*<0.001). The HA-LF phenotype defined by either ratio was characterised by greater VAT, FMI and FFMI (*p*<0.001) compared to a normal phenotype. Metabolic parameters including glucose, systolic blood pressure, diastolic blood pressure and triglycerides were significantly greater in subjects classified as HA-LF by either ratio. HDL was significantly lower in the HA-LF phenotype defined by VAT:FFMI (p<0.001) but was not in those defined by the FMI:FFMI (p=0.19) ratio. The HA-LF phenotype was characterised by a greater number of pathologies (p<0.001), as was the percentage of those who did no physical activity (p<0.001).

Metabolic Risk and MetS

The prevalence of MetS and the mean metabolic risk Z scores for each ratio are displayed in **Figure 1**. In general, metabolic risk was significantly greater in the HA-LF compared to a normal phenotype. However, the mean metabolic risk Z scores (**Figure 1A**) and the prevalence of MetS (**Figure 1B**) were higher in the HA-LF phenotype defined by the VAT:FFMI index.

Logistic Regression

The HA-LF phenotype, defined by either ratio, was associated with an increased risk of MetS in both the unadjusted and adjusted models. The greatest risk for MetS was seen in the VAT:FFMI unadjusted model (OR=8.03, 95%CI 6.69-9.65). However, the adjustment for clinical, anthropometric and sociodemographic factors determined a reduced performance of the prediction model (OR=4.06, 95%CI 3.31-4.97). The risk for MetS associated with the HA-LF phenotype determined by FMI:FFMI was smaller in the unadjusted model (OR=2.91, 95%CI 2.45-3.46), but an increase in performance was observed after covariate adjustment (OR=4.25, 95%CI 3.42- 5.27) (**Table 3)**.

Multiple Linear Regression

In both adjusted and unadjusted models, the HA-LF phenotype showed a positive association with all individual metabolic biomarkers and total metabolic risk. HA-LF as defined by VAT:FFMI was a greater predictor of glucose (b = 0.73 ± 0.04), systolic BP (b = 0.86 ± 0.04), diastolic BP (b = 0.74 ± 0.04), triglycerides (b = 0.60 ± 0.04), HDL (b = 0.54 ± 0.04) and total metabolic risk score (b = 0.69 ± 0.03) compared to the FMI:FFMI definition (b = 0.28 ± 0.04, 0.49 ± 0.04, 0.46 ± 0.04, 0.11 ± 0.04, 0.05 ± 0.04, 0.28 ± 0.03 respectively) in unadjusted models. However, once clinical, anthropometric and sociodemographic factors were included in the model, differences between the two SO indexes were significantly reduced (**Table 4 and Table 5)**.

The stratification of the analyses by gender did not change the results of the multivariate models as prediction of metabolic risk was similar between the two ratio indexes for both men and women **(Table S2 of supplementary material)**. In addition, the exclusion of participants with diseases that may have influenced body composition and metabolic outcomes did not modify the results as ratios performed almost equally in the fully adjusted models **(Table S3 and S4 of supplementary material).**

Discussion

This is the first study to perform a comparison of the two body composition ratios for the prediction of metabolic risk in adults. We found a positive association between the HA-LF phenotype and MetS

for either ratio indexes. Contrary to our hypothesis, we found that the HA-LF phenotype, as defined by VAT:FFMI, was a better predictor of metabolic risk only in unadjusted regression models. When age, sex, clinical and sociodemographic factors were adjusted for, the strength of association of the two indexes with metabolic risk was comparable. This seems to suggest that the risk for impaired metabolic health attributable to VAT is largely explained by socio-demographic, lifestyle and health outcomes but, most importantly, the predictive value is not superior to FMI. This could simply mean that the FMI:FFMI model could be applied to predict disease risk prediction as these two body components are easily measured by user-friendly and largely available body composition methods such as BIA, DXA or air displacement plethysmography. However, the validity of these results require confirmation in prospective cohort studies.

The use of VAT:FFMI to define the HA-LF phenotype and examination of its relationship with MetS has not been previously investigated to the best of our knowledge. A similar approach was developed by Kim *et al*.(22), which used the ratio of skeletal muscle mass to VAT area as a new index of sarcopenic obesity. Like in our study, Kim *et al.* found that the new index was a significant risk factor for MetS in unadjusted models (OR=14.02), but the risk decreased in fully adjusted models (OR=5.85). Lim *et al.*(27) also used a similar ratio of VAT to thigh muscle area and evaluated its association with MetS. The highest quartile of the ratio had the greatest risk of the MetS in the unadjusted model (OR=19.77) but this dropped considerably in the fully adjusted model (OR=8.89).

Concurrent high FM and low FFM are the core components to define the sarcopenic obese phenotype. Siervo *et al.*(30) have integrated FMI:FFMI into a load-capacity model to improve disease-risk prediction but have yet to use it to examine risk of specific diseases. Prado *et al.*(11) have proposed FM:FFM to be a sensitive predictor of metabolic risk in those with sarcopenic obesity in a theoretical model presented in an extensive review on the topic, although this has yet be tested. Biolo *et al*.(35) have defined sarcopenic obesity as a FM:FFM>0.8 but this data was only used to examine the prevalence of sarcopenic obesity in their study.

The regional distribution of adipose tissue as a risk factor of MetS represents a large area of interest. VAT has been associated with a greater risk of MetS(28) and cardiovascular events(36) than SAT, regardless of BMI. Increase in VAT has been associated with elevated circulating levels of inflammatory cytokines and adipokines including; c-reactive protein, interleukin 6, monocyte chemotactic protein 1(14), serum adipocyte fatty acid-binding protein (23) and leptin(25). In people with sarcopenic obesity, these cytokine and adipokine levels have been found to be even greater than in those who are solely obese(14,19). This low grade inflammation stimulates muscle catabolism and exacerbates sarcopenia which may promoting insulin resistance.(37) Insulin

resistance is proposed to have a significant role in the pathophysiology of MetS(38) and has been suggested by many to be included in its definition.(39,40) Insulin resistance may be suggested as the link between sarcopenic obesity and an increased risk of MetS but more work is required to establish the exact causation.

Our study involved the comparison of two different ratio body composition indices (VAT:FFMI and FMI:FFMI) of sarcopenic obesity as predictors of metabolic risk. To our knowledge, only three other studies in Asian adults have also compared different indices of measurement for sarcopenic obesity in relation to MetS. These studies used very different diagnostic criteria for sarcopenic obesity compared to our study(12,16,21). In addition, Lu *et al*.(12) are the only other authors who have also used BIA to examine the relationship between a and MetS. They found that sarcopenic obesity was associated with a greater risk of MetS (OR=11.59), even greater than obesity (OR=7.53) and sarcopenia (OR=1.98) individually. One of the novel features of our study was the examination of associations between body composition phenotypes and metabolic risk Z scores. Siervo *et al.* have used a similar method to identify lifestyle and body composition predictors of cardiovascular risk factors and cumulative metabolic risk in a study examining age-related changes in basal substrate oxidation and visceral adiposity and their association with the MetS.(31) However, to the best of our knowledge, the analysis has not been carried out in the context of sarcopenic obesity.

Some limitations must be considered when interpreting our results. Our cross-sectional design, restricts the identification of causal associations. In addition, the study population were all recruited from a national health centre and therefore may not be fully representative of the Italian general population. The cohort consisted of considerably fewer men than women and therefore the results may have been biased towards females. Unlike other studies, we did not exclude people with medical conditions or medication use in order to enhance the inclusiveness of the sample. However, this meant that the body composition of participants with certain medical conditions might have been influenced by the condition itself, which in turn would impact the results. The number of pathologies was significantly associated with MetS and metabolic risk throughout the analyses, however, the mean number of pathologies only differed very slightly between HA-LF and normal body phenotypes when defined by either ratio.

Conclusions

A HA-LF phenotype is associated with an increased risk of MetS when defined by either VAT:FFMI or FMI:FFMI indexes. The results of this study showed that there is no real advantage in using either ratio as a predictor of metabolic risk. Our study has added novel findings from a large, adult,

Caucasian cohort to reinforce the associations between body composition models of sarcopenic obesity and metabolic risk. However the limitations of a cross-sectional design remain and longitudinal studies are required to determine causality and examine the association with the potential long-term consequences of MetS such as type 2 diabetes and cardiovascular events.

Statement of Authorship

The manuscript was conceived by MS, JL and MP who analysed the data and wrote the first draft of the manuscript. Data were collected by AL, SB, AB and AT. All authors contributed to critical interpretation subsequent of results. All authors contributed to the final revision of the manuscript. The corresponding author (MS) is the guarantor for the manuscript and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis reported in the manuscript.

Conflict of Interest

The authors declare no conflict of interest

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Figure Legends

Figure 1 The mean metabolic risk Z scores (A) and prevalence of the metabolic syndrome (B) in subjects identified with a HA-LF phenotype as defined by VAT:FFMI and FMI:FFMI

VAT:FFMI visceral adipose tissue-to-fat free mass ratio, FMI:FFMI fat mass index-to-fat free mass index ratio, HA-LF high adiposity – low fat free mass

P-values correspond to independent t-tests

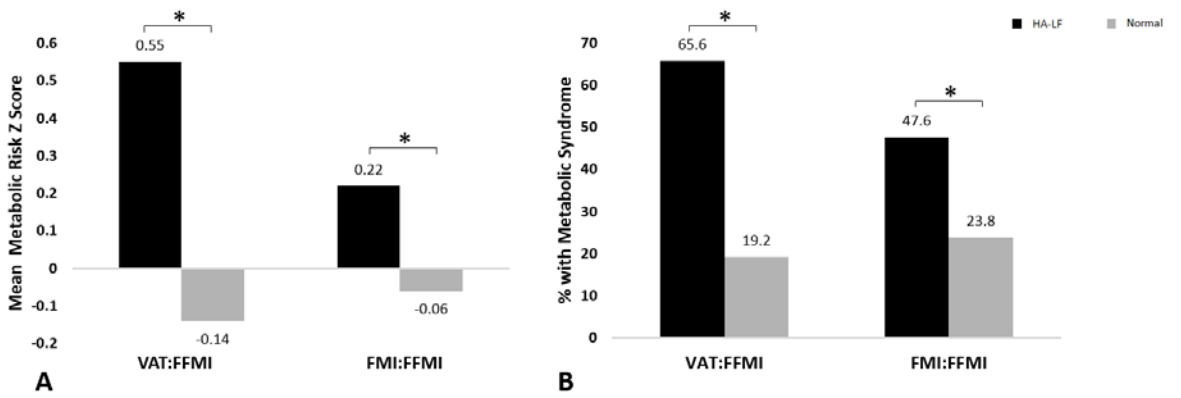
Mean Metabolic Risk Z Score
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
0.55
-0.14
0.22
-0.06
*
*
VAT:FFMI
FMI:FFMI
A
% with Metabolic Syndrome
70
60
50
40
30
20
10
0
65.6
19.2
47.6
23.8
HA-LF
Normal
VAT:FFMI
FMI:FFMI
B

Figure 1

Table 1
Main characteristics of the study population stratified by sex

	All	**Female**	**Male**	
	(N=3441)	**(*N*=2464)**	**(*N*=977)**	
	Mean ± SD			
Age (years)	45.7 ± 12.7	45.2 ± 12.8	47.3 ± 12.5	<0.001
Anthropometry				
Height (cm)	165.3 ± 8.9	161.5 ± 6.4	175.2 ± 6.5	<0.001
Weight (kg)	80.6 ± 18.0	74.8 ± 14.8	95.4 ± 17.2	<0.001
BMI (kg/m²)	29.3 ± 5.5	28.7 ± 5.6	31.1 ± 5.1	<0.001
WC (cm)	96.4 ± 14.8	92.2 ± 13.1	107.3 ± 13.5	<0.001
Adipose tissue determined by Ultrasound				
VAT (cm)	5.4 ± 2.7	4.6 ± 2.3	7.5 ± 2.7	<0.001
SAT (cm)	2.9 ± 1.2	2.9 ± 1.2	2.9 ± 1.3	0.057
Bioelectrical Impedance				
FM (kg)	29.3 ± 11.7	29.1 ± 11.4	29.6 ± 12.3	0.26
FFM (kg)	51.3 ± 11.2	45.6 ± 5.7	65.7 ± 8.2	<0.001
FMI (kg/m²)	10.8 ± 4.4	11.2 ± 4.5	9.7 ± 4.0	<0.001
FFMI (kg/m²)	18.5 ± 2.4	17.5 ± 1.6	21.4 ± 1.9	<0.001
Metabolic parameters				
Glucose (mg/dL)	95.0 ± 16.1	92.8 ± 14.3	100.7 ± 18.8	<0.001
Systolic BP (mmHg)	123.6 ± 14.3	120.7 ± 13.6	131.1 ± 13.7	<0.001
Diastolic BP (mmHg)	77.3 ± 9.7	75.3 ± 9.2	82.4 ± 9.2	<0.001
Triglycerides (mg/dL)	108.8 ± 70.8	95.7 ± 54.0	142.2 ± 93.9	<0.001
HDL (mg/dL)	59.9 ± 16.0	64.5 ± 15.2	48.3 ± 11.4	<0.001
Number of Pathologies	2.6 ± 2.0	2.6 ± 2.1	2.67 ± 2.0	0.158

SD standard deviation, N number of subjects, BMI body mass index, WC waist circumference, VAT visceral adipose tissue, SAT subcutaneous adipose tissue, FMI fat mass index, FFMI fat free mass index, BP blood pressure, HDL high density lipoproteins

Table 2 Clinical, anthropometric, metabolic and sociodemographic characteristics of HA-LF and normal body composition phenotypes as defined by VAT:FFMI and FMI:FFMI

	VAT:FFMI			FMI:FFMI		
	HA-LF (*N*=689)	**Normal (*N*=2752)**	***p***	**HA-LF (*N*=681)**	**Normal (*N*=2760)**	***p***
	Mean ± SD	**Mean ± SD**		**Mean ± SD**	**Mean ± SD**	
Age	54.1 ± 11.1	43.7 ± 12.2	<0.001	48.9 ± 13.5	45 ± 12.4	<0.001
Anthropometry						
BMI (kg/m²)	34.4 ± 5.9	28.1 ± 4.7	<0.001	36 ± 5.5	27.7 ± 4.2	<0.001
WC (cm)	112.2 ± 12.8	92.5 ± 12.6	<0.001	108.4 ± 13.3	93.5 ± 13.7	<0.001
Adipose tissue determined by Ultrasound						
VAT (cm)	9.6 ± 1.9	4.40 ± 1.7	<0.001	7.0 ± 2.8	5.0 ± 2.5	<0.001
SAT (cm)	3.0 ± 1.3	2.9 ± 1.2	0.164	3.9 ± 1.3	2.7 ± 1.1	<0.001
Bioelectrical Impedance						
FMI (kg/m²)	14.4 ± 4.9	9.9 ± 3.8	<0.001	17.5 ± 3.5	9.2 ± 2.8	<0.001
FFMI (kg/m²)	20 ± 2.6	18.2 ± 2.3	<0.001	18.5 ± 2.3	18.6 ± 2.5	0.649
Metabolic parameters						
Glucose (mg/dL)	104.5 ± 23.3	92.7 ± 12.7	<0.001	98.7 ± 18.9	94.1 ± 15.2	<0.001
Systolic BP (mmHg)	133.5 ± 14.1	121.2 ± 13.3	<0.001	129.2 ± 14.4	122.2 ± 14.0	<0.001
Diastolic BP (mmHg)	83.1 ± 9.2	75.9 ± 9.3	<0.001	80.9 ± 9.3	76.4 ± 9.6	<0.001
Triglycerides (mg/dL)	142.7 ± 86	100.4 ± 63.8	<0.001	114.9 ± 58.1	107.4 ± 73.7	0.004
HDL (mg/dL)	53.0 ± 14.4	61.6 ± 15.9	<0.001	59.2 ± 15.1	60.1 ± 16.2	0.192
	N (%)	**N (%)**		**N (%)**	**N (%)**	
Sex			<0.001			<0.001
Female	351 (50.9)	2113 (76.8)		632 (92.8)	1832 (66.4)	
Number of Pathologies	3.7 ± 2.3	2.3±1.9	<0.001	3.2 ± 2.3	2.4 ± 2.0	<0.001
Hours/week PA			<0.001			<0.001
Nothing	540 (78.4)	1697 (61.7)		539 (79.1)	1698 (61.5)	
Low (<2h/week)	90 (13.1)	527 (19.1)		89 (13.1)	528 (19.1)	
Moderate (2-4h/week)	40 (5.8)	343 (12.5)		41 (6)	342 (12.4)	
High (4-7h/week)	17 (2.5)	146 (5.3)		10 (1.5)	153 (5.5)	
Very High (>7h/week)	2 (0.3)	39 (1.4)		2 (0.3)	39 (1.4)	
Smoking status			<0.001			0.682

Smoker	130 (18.9)	568 (20.6)		130 (19.1)	568 (20.6)	
Non-Smoker	323 (46.9)	1573 (57.2)		382 (56.1)	1514 (54.9)	
Ex-Smoker	236 (34.3)	611 (22.2)		169 (24.8)	678 (24.6)	
Marital Status			<0.001			<0.001
Unmarried	151 (21.9)	1160 (42.2)		225 (33)	1086 (39.3)	
Married	466 (67.6)	1370 (49.8)		395 (58)	1441 (52.2)	
Widow	28 (4.1)	44 (1.6)		26 (3.8)	46 (1.7)	
Divorced	44 (6.4)	178 (6.5)		35 (5.1)	187 (6.8)	
Education			<0.001			<0.001
Elementary school	23 (3.3)	28 (1)		20 (2.9)	31 (1.1)	
High school lower level	125 (18.1)	270 (9.8)		132 (19.4)	263 (9.5)	
High school medium level	351 (50.9)	1359 (49.4)		357 (52.4)	1353 (49)	
High school higher level	3 (0.4)	28 (1)		9 (1.3)	22 (0.8)	
University	170 (24.7)	1007 (36.6)		145 (21.3)	1032 (37.4)	
Other	17 (2.5)	60 (2.2)		18 (2.6)	59 (2.1)	
Employment			<0.001			<0.001
Unemployed	9 (1.3)	55 (2)		19 (2.8)	45 (1.6)	
Student	1 (0.1)	159 (5.8)		21 (3.1)	139 (5)	
Housewife	60 (8.7)	142 (5.2)		80 (11.7)	122 (4.4)	
Retired	139 (20.2)	186 (6.8)		115 (16.9)	210 (7.6)	
Workman	30 (4.4)	85 (3.1)		29 (4.3)	86 (3.1)	
Employee/Office worker	282 (40.9)	1472 (53.5)		310 (45.5)	1444 (52.3)	
Freelancer	47 (6.8)	177 (6.4)		26 (3.8)	198 (7.2)	
Other	121 (17.6)	476 (17.3)		81 (11.9)	516 (18.7)	

Data presented as mean ± SD for continuous variables and frequency (percentage) for categorical variables.

N number of subjects, VAT:FFMI visceral adipose tissue-to-fat free mass ratio, FMI:FFMI fat mass index-to-fat free mass index ratio, BMI body mass index

HDL high density lipoproteins, PA physical activity, HA-LF high adiposity – low fat free mass

P-values correspond to t-tests for continuous variables and Chi-square tests for categorical variables

Table 3 Logistic regression to evaluate the risk of the metabolic syndrome associated with HA-LF (as defined by VAT:FFMI and FMI:FFMI) unadjusted (Model 1) and adjusted (Model 2) for age, sex, clinical and sociodemographic factors.

	VAT:FFMI			FMI:FFMI		
	B (SE)	**OR (95% CI)**	***p***	**β (SE)**	**OR (95% CI)**	***p***
Model 1[a]						
HA-LF	2.08 (0.09)	8.03 (6.69-9.65)	<0.001	1.07 (0.09)	2.91 (2.45-3.46)	<0.001
Model 2[b]						
HA-LF	1.40 (0.10)	4.06 (3.31-4.97)	<0.001	1.45 (0.11)	4.25 (3.42- 5.27)	<0.001
Age	0.02 (0.01)	1.02 (1.01-1.03)	<0.001	0.03 (0.01)	1.03 (1.02-1.04)	<0.001
Sex	1.19 (0.10)	3.28 (2.70-3.98)	<0.001	1.83 (0.10)	6.24 (5.08-7.65)	<0.001
Number of Pathologies	0.17 (0.02)	1.19 (1.14-1.25)	<0.001	0.19 (0.02)	1.21 (1.15-1.26)	<0.001
Hours/week PA						
Low (<2h/week)	-0.21 (0.12)	0.81 (0.64-1.03)	0.086	-0.23 (0.12)	0.8 (0.63-1.01)	0.059
Moderate (2-4h/week)	-0.33 (0.15)	0.72 (0.54-0.96)	0.026	-0.43 (0.15)	0.65 (0.48-0.87)	0.004
High (4-7h/week)	-0.78 (0.25)	0.46 (0.28-0.75)	0.002	-0.77 (0.25)	0.46 (0.29-0.75)	0.002
Very High (>7h/week)	-2.07 (0.74)	0.13 (0.03-0.54)	0.005	-2.32 (0.75)	0.1 (0.02-0.43)	0.002

VAT:FFMI visceral adipose tissue-to-fat free mass ratio, FMI:FFMI fat mass index-to-fat free mass index ratio, β regression coefficient, SE standard error, OR odds ratio, CI confidence interval, HA-LF high adiposity – low fat free mass, PA physical activity

[a] *Unadjusted model*

[b] *Adjusted for age, sex, number of pathologies, hours per week of physical activity, smoking status, marital status, education and employment*

Table 4 *Multiple linear regression to assess HA-LM (as defined by VAT:FFMI and FMI:FFMI) as a predictor of individual metabolic biomarkers both adjusted (Model 1[a]) and unadjusted (Model 2[b]) for clinical, anthropometric and sociodemographic factors*

	Glucose (mmol/L)						Systolic BP					
	VAT:FFMI			FMI:FFMI			VAT:FFMI			FMI:FFMI		
	b	**SE**	**p**	***b***	**SE**	**p**	***b***	**SE**	**p**	***b***	**SE**	**p**
Model 1[a]												
R2	0.09			0.01			0.12			0.04		
Intercept	-0.88	0.05	<0.001	-0.34	0.05	<0.001	-1.03	0.05	<0.001	-0.58	0.05	<0.001
HA-LM	0.73	0.04	<0.001	0.28	0.04	<0.001	0.86	0.04	<0.001	0.49	0.04	<0.001
Model 2[b]												
R2	0.16			0.16			0.27			0.29		
Intercept	-1.53	0.19	<0.001	-1.54	0.19	<0.001	-1.49	0.18	<0.001	-1.84	0.18	<0.001
HA-LM	0.42	0.04	<0.001	0.3	0.04	<0.001	0.41	0.04	<0.001	0.55	0.04	<0.001

	Diastolic BP						Triglycerides					
	VAT:FFMI			FMI:FFMI			VAT:FFMI			FMI:FFMI		
	b	**SE**	**p**	***b***	**SE**	**p**	***b***	**SE**	**p**	***b***	**SE**	**p**
Model 1[a]												
R2	0.09			0.03			0.06			0.002		
Intercept	-0.89	0.05	<0.001	-0.55	0.05	<0.001	-0.72	0.05	<0.001	-0.13	0.05	0.019
HA-LM	0.74	0.04	<0.001	0.46	0.04	<0.001	0.6	0.04	<0.001	0.11	0.04	0.013
Model 2[b]												
R2	0.2			0.24			0.14			0.14		
Intercept	-1.09	0.18	<0.001	-1.51	0.18	<0.001	-0.22	0.19	0.246	-0.17	0.19	0.387
HA-LM	0.37	0.04	<0.001	0.57	0.04	<0.001	0.32	0.04	<0.001	0.19	0.04	<0.001

	HDL					
	VAT:FFMI			FMI:FFMI		
	b	**SE**	**p**	***b***	**SE**	**p**
Model 1[a]						
R2	0.05			<0.001		

Intercept	-0.65	0.05	<0.001	-0.06	0.05	0.236
SO	0.54	0.04	<0.001	0.05	0.04	0.212
Model 2[b]						
R2	0.25			0.25		
Intercept	0.28	0.18	0.122	0.14	0.18	0.436
SO	0.3	0.04	<0.001	0.31	0.04	<0.001

VAT:FFMI visceral adipose tissue-to-fat free mass ratio, FMI:FFMI fat mass index-to-fat free mass index ratio, b raw regression coefficient, SE standard error, R^2 coefficient of determination, HA-LM high adiposity – low fat free mass

[a] *Unadjusted model*

[b] *Adjusted for age, sex, number of pathologies, hours per week of physical activity, smoking status, marital status, education and employment*

Table 5 Multiple linear regression to assess HA-LM (as defined by VAT:FFMI and FMI:FFMI) as a predictor of cumulative metabolic risk, both adjusted (Model 1) and unadjusted (Model 2) for clinical, anthropometric and sociodemographic factors

	Metabolic Risk Z score					
	VAT:FFMI			**FMI:FFMI**		
	b	SE	*p*	*b*	SE	*p*
Model 1[a]						
R^2	0.17			0.03		
Intercept	-0.83	0.03	<0.001	-0.33	0.04	<0.001
HA-LM	0.69	0.03	<0.001	0.28	0.03	<0.001
Model 2[b]						
R^2	0.4			0.41		
Intercept	-0.81	0.11	<0.001	-0.98	0.11	<0.001
HA-LM	0.36	0.03	<0.001	0.38	0.02	<0.001
Age	0.006	0.001	<0.001	0.008	0.001	<0.001
Sex	0.65	0.02	<0.001	0.8	0.02	<0.001
Number of Pathologies	0.04	0.005	<0.001	0.04	0.005	<0.001
Hours/week PA						
Low (<2h/week)	-0.07	0.02	0.007	-0.07	0.02	0.007
Moderate (2-4h/week)	-0.09	0.03	0.002	-0.1	0.03	0.001
High (4-7h/week)	-0.13	0.04	0.002	-0.12	0.04	0.005
Very High (>7h/week)	-0.18	0.08	0.027	-0.2	0.08	0.014

VAT:FFMI visceral adipose tissue-to-fat free mass ratio, FMI:FFMI fat mass index-to-fat free mass index ratio, b raw regression coefficient, SE standard error, R^2 coefficient of determination, HA-LF high adiposity – low fat free mass, PA physical activity

[a] Unadjusted model

[b] Adjusted for age, sex, number of pathologies, hours per week of physical activity, smoking status, marital status, education and employment

Table S1: Sarcopenic Obesity Research Using Bioelectrical Impedance

Author, Year	Aims	Results	Subjects (n)	Age (years)	Subjects Background	Pathology	Obesity Definition	Sarcopenia Definition	Sarcopenic Obesity Definition
Srikanthan et al., (9) 2010	Identify if sarcopenia is associated with impaired insulin sensitivity in obese/non-obese individuals	Sarcopenia is associated with insulin resistance independent of obesity.	14,528 F=7511 M=7017	20+	Non Hispanic White- 42.2% Non Hispanic Black 27.3% Hispanic 26.4% Other 4.18%	Not pregnant, no pacemakers or limb amputees	BMI ≥30 kg/m^2	SMI= SM (kg)/body mass (kg) × 100 <31.0% in men and <22.0% in women	**SO= Sarcopenia and Obesity Criteria**
Gomez-Cabello et al.,(17) 2011	To find the prevalence of OW, OB, SO in a Spanish elderly population Analyse the effect of lifestyle on adiposity.	84% OW/OB 15% SO-increases with age, occurs earlier in men than women Sedentary lifestyles are associated with increased adiposity	3037 F=2335 M=702	65+	Non-institutionalised Spanish	No dementia/ cancer	%BF quintiles: Women: ≤35.06; 35.07 - 38.28; 38.29 - 40.90; 40.91- 43.90; ≥43.91. Men: ≤25.18; 25.19 - 27.82; 27.83 -30.33; 30.34 -33.07; ≥33.08	RMM quintiles : Janssen equation(41) for skeletal muscle (kg)/ height^2 Women: ≤5.8; 5.81-6.19; 6.20-6.56; 6.57-7.00; ≥7.01 Men: ≤8.11; 8.12-8.61; 8.62-9.01; 9.02-9.50; ≥9.51	High BF: %BF upper two quintiles Low MM: RMM lower two quintiles Normal: %BF lower three quintiles RMM upper three quintiles 4 groups: Normal BF and Normal MM High BF and Normal MM Normal BF and Low MM **High BF and Low MM= SO**
Siervo et al.,(18) 2012	Prevalence of LMM and LMM-HA in adult women.	BMI least inclusive of LMM-HA FM% most inclusive of LMM-HA	763 F=763 M=0	Mean: 45.4 ± 18.8	Outpatient dietetic clinic of the University Federico II of Naples (Italy).	Excluded if acute or chronic systemic disorders which could have determined body composition or affected bioelectrical impedance measurement.	Excess adiposity: BMI ≥ 30.0 kg/m^2 WC > 88.0 cm FM% ≥ 35.0% FMI ≥ 9.5 kg/m^2	SMI calculated as skeletal muscle (kg) (Janssen equation)/height^2 low muscle mass defined as having a value of SMI below 6.76 kg/m^2	**SO= The simultaneous presence of both low muscle mass and high adiposity**
Batsis et al.,(5) 2012	SO and mortality risk	Sarcopenia in women associated with increased mortality, no association with SO in males or females	4652 F=2369 M= 2283	60+	Non Hispanic White- 84.9% Non Hispanic Black 7.8% Hispanic American 2.4% Other 4.9%	No exclusion based on pathological conditions	% BF Baumgartner's criteria of obesity: ≥27% in men ≥38% in women.	Skeletal muscle mass index: Janssen equation(41) for skeletal muscle (kg) /height^2 Men normal: 10.76 kg/m^2; class I sarcopenia: 8.51–10.75 kg/m^2 class II sarcopenia:	**Sarcopenia and obesity criteria= SO**

								≤ 8.50 kg/m^2
								Women normal:
								6.76 kg/m^2
								class I sarcopenia:
								5.76–6.75 kg/m^2
								class II sarcopenia:
								≤ 5.75 kg/m^2	

Lu et al.,(12) 2013	Association between SO and the metabolic syndrome	SO is a major risk factor for the metabolic syndrome	600 F=456 M=144	Mean: 63.6 +/- 10.1 years	Community-dwelling Northern Taiwan	No exclusion based on pathological conditions	BMI ≥ 25 kg/m^2	SMI = skeletal muscle mass (kg)/weight (kg) × 100. Sarcopenia:: ≦ 37% in men ≦ 27.6% in women	4 groups: normal, sarcopenia, obesity, **SO= Sarcopenia and OB criteria**
Visser et al.,(8) 2013	Association between SO and adverse clinical outcome after heart surgery	SO is associated with an increased likelihood of adverse clinical outcome after cardiac surgery.	325 F=90 M=235	≥ 65 = 186 <65= 139	Patients from the cardio-thoracic surgery department at the Academic Medical Centre of the University of Amsterdam	Patients admitted for elective coronary artery bypass grafting (CABG) and/or heart valve surgery.	FMI was calculated by dividing FM (kg) by squared body height (m^2) A high FMI: women ≥11.8 kg m^{-2} men ≥8.3 kg m^{-2}	FFMI calculated by dividing FFM by squared body height (m^2) A low FFMI: women ≤14.6 kg m^{-2} men ≤16.7 kg m^{-2}	**SO= A low FFMI and high FMI.**
Biolo et al.,(35) 2015	Investigating the predictive ability of 'A Body Shape Index' (ABSI) based on waist circumference on FFMI	ABSI may help define SO	200 F=111 M=89	Mean: 51 ± 12	Overweight/ obese from obesity clinics in Italy and Slovenia.	No diabetes or related comorbidities.	FM	FFM	FM:FFM <0.4 metabolically healthy obese 0.4-0.8 obese but FFM adequately maintained **>0.8 SO**
De Rosa et al., (13) 2015	Prevalence of sarcopenia amongst an obese population using two different sarcopenia indexes- SMP and SMI	Sarcopenia prevalence varies depending on criteria used.	131 F=80 M= 51	45-67	Obesity Outpatient Clinic in Naples, Italy All white and had lived in southern Italy for 3 generations min.	Excluded if had diabetes, cardiovascular disease, organ failure, chronic inflammatory disease, malignancy, endocrine disease, and pregnancy.	BMI ≥30 kg/m^2	SMP= SM (kg)/body mass (kg) × 100 SMI= SM (kg)/ height$(m)^2$ Mild sarcopenia-within -1 to -2SD of control population: Women-23.1% to 28.4% 6.49 to 7.32 kg/m^2 Men-28.8% to 35.6% 8.44 to 9.53 kg/m^2	**SO= Sarcopenia and Obesity Criteria**

								Severe sarcopenia: >-2SD of control population: Women≤23% ≤6.48 kg/m^2 Men ≤28.7% ≤8.43 kg/m^2	
Pedrero-Chamizo et al.,(24) 2015	To evaluate the association between fitness levels, health related quality of life and SO.	SO = Lower fitness levels Higher fitness levels associated with a reduced risk of SO.	2747 F=2102 M=645	65+	Non-institutionalised Spanish	No dementia/ cancer	%BF quintiles as published by Gómez-Cabello et (above)	RMM quintiles as published by Gómez-Cabello et al.	High BF: %BF upper two quintiles Low MM: RMM lower two quintiles Normal: %BF lower three quintiles RMM upper three quintiles 4 groups: Normal BF and Normal MM High BF and Normal MM Normal BF and Low MM **High BF in Low MM= SO**
OW = Overweight, SO = Sarcopenic Obesity, BF = Body Fat, RMM = Relative Muscle Mass, MM = Muscle Mass, SM= Skeletal muscle, F = Female, M =Male, OB = Obese, FM = Fat mass, FFM = Fat free mass LMM = Low Muscle Mass, HA = High Adiposity, FMI = Fat mass index, FFMI = Fat free mass index, SMI = Skeletal mass index, SMP= Skeletal muscle mass percentage									