Increased odds of having the metabolic syndrome with greater fat-free mass: counterintuitive results from the National Health and Nutrition Examination Survey database

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Abstract

Background It is well established that body composition influences metabolic health, but emerging data are conflicting with the largely purported idea that a large fat-free mass (FFM) has a protective effect on health. A potential explanation for these discrepancies is the way FFM is represented. The first objective is to determine the association between the metabolic syndrome (MetS) and FFM when the latter was represented in three different ways: 1—absolute FFM; 2—relative to squared height (FFMi); and 3—relative to body weight (FFM%). The second objective is to assess the impact of FFM on the relative risk of having the MetS after taking fat mass, physical activity, and sociodemographic variables into account.

Methods A total of 5274 individuals from the National Health and Nutrition Examination Survey database were studied. Age-specific and sex-specific quartiles of the three representations of FFM were defined, and the prevalence of MetS was determined in each of them. Quartiles of FFMi (kg/m^2) were used to calculate the odds ratios of having the MetS independently of FM, physical activity levels, and sociodemographic variables.

Results The prevalence of MetS decreased with increasing quartiles of whole-body FFM% (Q1: 40%; Q4: 10%) but grew with increasing quartiles of absolute FFM (Q1: 13%; Q4: 40%) and FFMi (Q1: 10%; Q4: 44%). Similar results were observed for appendicular and truncal FFM. The odds ratios of having the MetS, independently of fat mass, physical activity, sociodemographic variables, were significantly greater in the fourth quartile of FFMi when compared with the first quartiles of each specific subgroup [Q4 vs. Q1: younger men: 4.16 (1.99–8.68); younger women: 5.74 (2.46–13.39); older men: 1.98 (1.22–3.22); older women: 2.88 (1.69–4.90); all $P \leq 0.01$].

Conclusions These results support the notion that the representation of FFM significantly influences its association with MetS and that a larger FFM, whether absolute or relative to height, is associated with alterations in cardiometabolic health.

Keywords Fat-free mass; Body composition; Muscle mass; Metabolic syndrome; Cohort study

Introduction

It is well known that body composition influences metabolic health. For instance, greater fat mass (FM) and visceral fat accumulations significantly increase the risk of having the metabolic syndrome (MetS),[1] type 2 diabetes (T2D),[2] and cardiovascular disease (CVD).[3] Furthermore, many studies have suggested that sarcopenia, a state of age-related reduced fat-free mass (FFM), is associated with an unhealthy metabolic health,[4–6] insulin resistance (IR), T2D,[7,8] and CVD.[9] In this regard, Lee *et al*. reported that a greater baseline FFM, relative to total body weight, was associated with a more favourable metabolic health after a 4 year follow-up.[6] Similarly, Atlantis *et al*. concluded that a greater FFM percentage (FFM∕total body weight × 100) was a strong protective factor against being classified with the MetS.[5]

The standpoint that having a large FFM is a protective factor for metabolic health is rationalized by two main and well-accepted mechanisms. First, it has long been established that FFM accounts for a large proportion of glucose uptake under insulin-stimulated conditions,[10] which led to the purported assumption that a larger FFM better regulates glucose homeostasis.[11] Second, considering the bioactive nature of FFM and the association between FFM and resting energy expenditure,[12] it is often claimed that a greater FFM may protect individuals from fat accumulations through greater resting energy expenditure.[13]

However, based on multiple results obtained from our research group[14–19] and others,[20–23] we recently reported, in contrast with the generally purported idea, that a greater FFM could be negatively associated with insulin sensitivity and metabolic health in various populations. The dissonance between these contradictory conclusions could stem from the different ways FFM is represented in the numerous pertinent studies. It was previously shown that representing FFM in different ways (relative to weight or relative to height) leads to different conclusions regarding the association with insulin sensitivity[8] or MetS.[4,24] For instance, Park and Yoon observed that the odds ratios of having greater waist circumference (WC), blood pressure (BP), and triglyceride (TG) level, as well as the MetS, were significantly reduced when FFM was presented relative to body weight in a Korean population.[4] In contrast with the results they obtained when representing FFM relative to body weight, reporting FFM relative to squared height (kg/m^2) led to greater FFM being associated with higher odds ratios of presenting altered metabolic characteristics or having the MetS.[4] While the percentage of FFM (FFM%) is a useful measure to identify the risk of having the MetS, it is effectively a representation of body composition and thus cannot be used to assess the impact of the quantity of FFM *per se* on metabolic health. Instead, FFM index (FFMi), a measure of whole-body FFM corrected for height, should be used. It is important to note that when using FFMi, neither Park and Yoon nor Scott

et al. adjusted for major confounding factors such as FM,[4,24] which may have biased their results. Supporting the need for these adjustments are the data of Bijlsma *et al*., who reported a deleterious impact of greater appendicular FFMi on IR assessed with homeostatic model assessment of insulin resistance (HOMA-IR). However, this association was nulled in women when adjusting for FM and remained significant, although to a lesser extent, in men.[8]

The objectives of this study were thus two-fold. First is to confirm the association between MetS and FFM when the latter was represented in three different ways: 1—absolute FFM (kg); 2—relative to squared height (FFMi); and 3—relative to body weight (FFM%). Second is to assess the impact of FFM, once isolated from confounding factors, on the relative risk of having the MetS, or specific MetS components, in age-specific subgroups of men and women.

Methods

Study population

This study used data from the 1999–2006 cohorts of the US National Health and Nutrition Examination Survey (NHANES). NHANES used a multistage, stratified, and weighted sampling design to recruit individuals who were representative of the US population.[25] Adults aged 20 to 79 were included in the analyses if they had available data for anthropometrics, body composition, and MetS components [WC, fasting glucose, high-density lipoprotein cholesterol (HDL-C), TG, and BP]. Considering the impact of age and sex on body composition,[26] analyses were performed separately in younger (20–49 years old) and older (50–79 years old) men and women (younger men: $n = 1662$ and younger women: $n = 1379$; older men: $n = 1128$ and older women: $n = 1105$). All participants provided written and informed consent, and the protocol was approved by the National Center for Health Statistics.

Anthropometric

Height and body weight were measured with participants wearing only light clothing. Results were used to calculate body mass index [BMI: body weight (kg)/height (m)^2]. Waist circumference was measured at the nearest 0.1 cm just above the ilium.

Body composition, fat-free mass, and fat mass representations and quartiles

Body composition was measured using dual-energy X-ray absorptiometry (Hologic densitometer QDR4500A, Hologic Inc.,

Bedford, MA, USA) to obtain FM, FFM, and bone mineral content (BMC). Absolute FFM (kg) was calculated as absolute FFM, excluding BMC. Appendicular FFM was calculated as the sum of FFM from both arms and legs, excluding BMC. Then, FFMi was calculated by dividing absolute FFM by squared height [FFM (kg)/height (m^2)]. FFM% was calculated using the following equation: (absolute FFM⁄body weight) × 100. The same equations were used to determine absolute FMi. The benefit of normalizing FFM and FM relative to squared height is that it better considers the impact of stature on both variables, which then allows to better compare individuals of different sizes.[14] Furthermore, the determination of appendicular FFM allows the assessment of the impact of skeletal muscle *per se* by excluding the impact of other lean tissues (e.g. organs).[14]

Lastly, considering the previously reported impact of age and sex on body composition,[26] the quartiles of FFM and FM were calculated separately in younger and older men and women. The cut-offs for 25th, 50th, and 75th percentiles were used to establish quartiles of FFM and FM in younger and older men and women.

Metabolic syndrome

Individuals with three or more of the components listed in the succeeding text were considered as having the MetS, as defined by the Adult Treatment Panel III definition from the National Cholesterol Education Program.[27] The Adult Treatment Panel III definition recognizes the following cut-offs for defining MetS: (i) WC > 102 cm for men or >88 cm for women; (ii) systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg; (iii) TG ≥ 1.7 mmol/L; (iv) HDL-C < 1.04 mmol/L for men or <1.30 mmol/L for women; and (v) fasting glucose ≥6.1 mmol/L.

Blood pressure was measured three consecutive times on the right arm after a 5 min rest, and the average of the two or three available measures was calculated. Participants were excluded if they had only one available BP reading. Serum samples were collected following a 9 h overnight fast. Glucose and TG measurements were performed at first on Hitachi Model 917 Analyzer (Roche Diagnostics, Indianapolis, IN, USA) using the hexokinase method and the colorimetric Trinder assay, respectively. HDL-C was quantified using a heparin–manganese precipitation method or a direct immunoassay technique on Hitachi 704, Hitachi 717, and Hitachi 912 analysers (Roche Diagnostics).

Confounding factors

Information was obtained for sociodemographic covariates such as ethnicity (Mexican American, other Hispanic ethnicities, non-Hispanic White, Non-Hispanic Black, and other eth-

nicities), education (<9th grade, 9th to 11th grade, high school grade or equivalent, some college or Associate of Arts degree, and college graduate or above), and income, assessed with the poverty income ratio. The poverty income ratio is the ratio of family income to poverty threshold as determined by the Department of Health and Human Services. The values range from 0 (i.e. no income) to 5, representing a revenue five-fold over the poverty threshold. Any values over 5 are coded as 5 in the database for disclosure concerns.

Physical activities over the last 30 days were assessed using the Physical Activity and Physical Fitness Questionnaire. Individuals were then characterized according to their level of physical activity following the Canadian Physical Activity: (i) physically active = both resistance exercises and either moderate or vigorous aerobic activities over the past 30 days; (ii) moderately active = at least one of moderate, vigorous, or resistance exercise; and (iii) inactive = neither aerobic nor resistance exercise.

Statistical analyses

Continuous data are presented as mean ± standard deviation, unless otherwise specified. Given that the objective of this study is not to characterize the American population *per se*, non-weighted analyses were conducted with the 1999–2006 NHANES dataset. A few abnormal data were removed from the dataset prior to statistical analyses (e.g. value of diastolic BP of 0). Between-group differences were assessed using one-way analyses of variance, and Bonferroni *post hoc* tests were used to identify specific differences. χ^2 tests of independence (χ^2) were used for differences in the distribution of ethnicities. Differences in MetS prevalence between quartiles of FFM, FFMi, and FFM% were also assessed with χ^2.

Binary logistic regressions were performed to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of having the MetS or specific MetS components in younger (20–49) and older (50–79) men and women with increasing quartiles of FFMi. FMi, physical activity level, ethnicity, education, and poverty income ratio were included in the model as covariates. The classification cut-offs in the regressions were determined on whole-sample prevalence of the MetS and/or specific components. Statistical significance was set at $P \leq 0.05$. All analyses were performed using SPSS 25 for Windows (IBM Corp., Armonk, NY, USA).

Results

Overall, 5274 individuals (46.4 ± 16.1 years) with an average BMI of 27.5 ± 5.0 kg/m^2 from the NHANES 1999–2006 dataset were included in the analyses. Descriptive characteristics for age-specific and sex-specific subgroups are presented in *Table* 1. Men displayed greater height and body weight than

Table 1 Descriptive characteristics

	Younger 20–49 years old		Older 50–79 years old	
	Men (*n* = 1662)	Women (*n* = 1379)	Men (*n* = 1128)	Women (*n* = 1105)
Age (years)	34.3 ± 8.8	34.9 ± 8.8	62.5 ± 7.8[a,b]	62.4 ± 7.8[a,b]
Ethnicity				
Mexican American (%)	26.7	23.2	23.2	24.7
Other Hispanic (%)	4.9	5.1	3.8	4.3
Non-Hispanic White (%)	43.6	46.5	54.8[a,b]	51.7[a]
Non-Hispanic Black (%)	20.8	21.7	15.1[a,b]	16.2[a,b]
Other (%)	4.0	3.6	3.1	3.1
Anthropometric variables				
Height (m)	1.75 ± 0.07	1.62 ± 0.07[a]	1.74 ± 0.08[a,b]	1.60 ± 0.07[a,b,c]
Weight (kg)	82.5 ± 15.2	72.5 ± 16.2[a]	84.6 ± 14.4[a,b]	72.4 ± 14.3[a,c]
BMI (kg/m^2)	26.9 ± 4.4	27.4 ± 5.9[a]	27.8 ± 4.2[a]	28.2 ± 5.2[a,b]
Absolute FFM (kg)	58.4 ± 8.5	42.2 ± 6.8[a]	57.1 ± 7.9[a,b]	40.2 ± 6.2[a,b,c]
Absolute FM (kg)	22.2 ± 8.2	28.8 ± 10.3[a]	25.4 ± 7.8[a,b]	30.8 ± 9.1[a,b,c]
Waist circumference (cm)	94.2 ± 12.4	90.2 ± 13.5[a]	101.9 ± 11.3[a,b]	95.3 ± 12.6[b,c]
Metabolic variables				
Systolic BP (mmHg)	119.6 ± 12.2	113.3 ± 13.7[a]	132.3 ± 19.5[a,b]	135.1 ± 21.7[a,b,c]
Diastolic BP (mmHg)	72.4 ± 11.6	70.2 ± 9.4[a]	73.6 ± 11.6[b]	72.0 ± 11.8[b,c]
Triglycerides (mmol/L)	1.66 ± 1.48	1.32 ± 1.12[a]	1.93 ± 2.26[a,b]	1.79 ± 1.29[b]
HDL-C (mmol/L)	1.23 ± 0.34	1.44 ± 0.40[a]	1.24 ± 0.35[b]	1.53 ± 0.43[a,b,c]
Glucose (mmol/L)	5.26 ± 1.43	5.02 ± 1.25[a]	6.23 ± 2.45[a,b]	5.99 ± 2.41[a,b,c]
MetS, *n* (%)	241 (14.5)	235 (17.0)	416 (36.9)[a,b]	474 (42.9)[a,b,c]

BMI, body mass index; BP, blood pressure; FFM, fat-free mass; FM, fat mass; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.
Results are presented as mean ± standard deviation unless otherwise specified.
[a]Different from younger men ($P < 0.05$).
[b]Different from younger women ($P < 0.05$).
[c]Different from older men ($P < 0.05$).

women ($P < 0.05$). Younger individuals had greater FFM and lower FM, resting BP, TGs, fasting glucose, and HOMA-IR (all $P < 0.05$) than older counterparts. The cut-offs for the 25th, 50th, and 75th percentiles used to determine age-specific and sex-specific quartiles of FFMi, appendicular FFMi, trunk FFMi, and FMi are displayed in *Table* 2.

Prevalence of metabolic syndrome by representations of fat-free mass

Altogether, 25.9% of the sample (*n* = 1366) presented a MetS. The most prevalent component was a high WC (47.3%),

followed by high resting BP (34.9%), low HDL-C (34.4%), high TG (32.5%), and high blood glucose (13.8%).

Figure 1 shows the prevalence of MetS for each quartile of the three representations of whole-body, appendicular, and truncal FFM. A greater prevalence of MetS was observed with increasing quartiles of whole-body FFM and FFMi (i.e. greater FFM and FFMi; $P < 0.001$). In contrast, prevalence decreased with greater quartiles of whole-body FFM% (i.e. greater percentage of FFM relative to body weight; $P < 0.001$). Similar results were observed for appendicular and trunk FFM (*Figure* 1), that is, a higher prevalence of MetS with increased FFM and FFMi and lower prevalence of MetS with greater FFM%.

Table 2 Cut-offs for body composition quartiles

	Percentiles	Younger 20–49 years old		Older 50–79 years old	
		Men (*n* = 1662)	Women (*n* = 1379)	Men (*n* = 1128)	Women (*n* = 1105)
Whole-body FFMi (kg/m^2)	25	17.42	14.24	17.43	14.08
	50	18.98	15.62	18.74	15.45
	75	20.49	17.38	20.10	17.01
Appendicular FFMi (kg/m^2)	25	7.79	5.90	7.50	5.67
	50	8.54	6.63	8.13	6.29
	75	9.33	7.54	8.81	7.01
Trunk FFMi (kg/m^2)	25	8.50	7.19	8.75	7.29
	50	9.25	7.89	9.43	8.00
	75	10.02	8.74	10.21	8.78
FMi (kg/m^2)	25	5.32	8.03	6.66	9.63
	50	7.04	10.38	8.16	11.72
	75	8.84	13.35	9.95	14.13

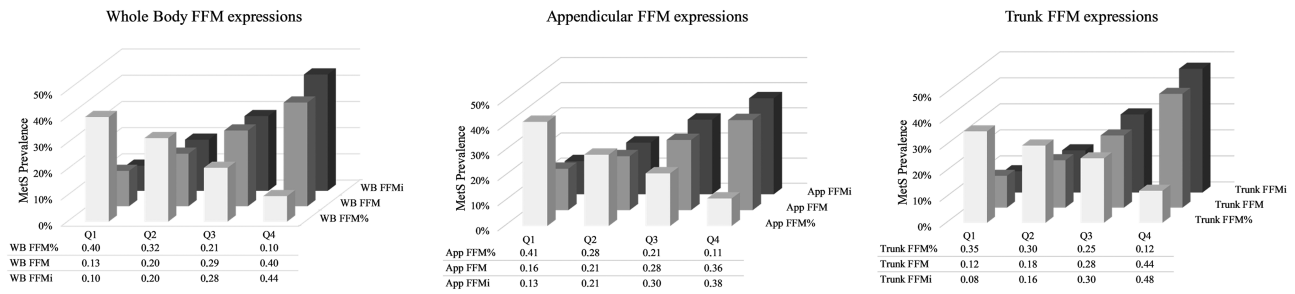FFMi, fat-free mass index; FMi, fat mass index.

Figure 1 Prevalence of metabolic syndrome (MetS) per quartile (Q) of absolute, appendicular, and trunk fat-free mass percentage (FFM/body weight × 100) (FFM%), absolute fat-free mass [FFM (kg)], and fat-free mass index [FFMi (kg/m^2)]. Matching quartiles were pooled to measure MetS prevalence (i.e. all Q1 pooled: 25% of young and older men and 25% of young and older women). WB, whole-body.

Odds ratios of having the metabolic syndrome or metabolic syndrome components

Odds ratios of having the metabolic syndrome

We then sought to verify if the increased prevalence of MetS with increasing quartiles of FFMi observed in the previous section was the consequence of covariates. Hence, FM index (kg/m^2), physical activity, ethnicity, education, and the poverty income ratio were included in the models. Further analyses were performed with whole-body FFMi (kg/m^2) representation because it accounts for height and characterizes the actual role of FFM on the MetS and not body composition, such as FFM%. Additionally, because appendicular and truncal compartments showed results similar to whole-body, only the latter was used in other analyses.

The ORs of having the MetS per quartiles of FFMi are presented in *Table* 3 for each age and sex subgroup. The ORs of having the MetS were significantly greater in Q4 of FFMi in every subgroup compared with its reference ($1.98 \le \beta \ge 5.74$; all $P < 0.01$), independently of covariates. In addition to Q4, the ORs of having the MetS were also significantly greater in Q2 and Q3 compared with Q1 of FFMi in younger and older women ($1.93 \le \beta \ge 3.41$; $0.001 \le P \ge 0.04$).

Odds ratios of having specific metabolic syndrome components

Given the increased ORs of having the MetS with a larger FFMi, we wanted to verify if a specific component of the MetS was driving these results. HDL-C and WC revealed a homogeneous response across groups (*Figure* 2). The ORs of having a large WC were significantly greater in almost every quartile of FFMi compared with Q1 ($1.75 \le \beta \ge 18.46$; $0.001 \le P \ge 0.04$). As for HDL-C, younger and older women and older men had greater ORs of having low HDL-C with increasing quartiles of FFMi ($1.50 \le \beta \ge 3.27$; $0.001 \le P \ge 0.051$).

Other components displayed a more heterogeneous response between age-specific and sex-specific subgroups. For instance, older women had greater odds of having high fasting glucose with increasing quartiles of FFMi ($2.16 \le \beta \ge 4.60$; $0.001 \le P \ge 0.004$), whereas no other group showed differences between quartiles. Furthermore, the ORs of having high plasma TG were either significantly or tended to be greater with increasing FFMi quartiles in younger indi-

Table 3 Odds ratios for metabolic syndrome by quartiles of FFMi

| Metabolic syndrome | Younger 20–49 years old | | | | | | Older 50–79 years old | | | | | |
| | Men (n = 1551) | | | Women (n = 1265) | | | Men (n = 1016) | | | Women (n = 955) | | |
	β	95% CI	P	β	95% CI	P	β	95% CI	P	β	95% CI	P
FFMi Q1 (ref)			0.000			0.000			0.053			0.000
FFMi Q2	1.27	0.58–2.77	NS	2.27	1.03–5.01	0.04	1.42	0.90–2.22	NS	1.93	1.25–2.97	0.003
FFMi Q3	1.61	0.76–3.40	NS	3.41	1.55–7.52	0.002	1.49	0.94–2.37	NS	3.02	1.90–4.81	0.000
FFMi Q4	4.16	1.99–8.68	0.000	5.74	2.46–13.39	0.000	1.98	1.22–3.22	0.006	2.88	1.69–4.90	0.000
Whole-body FMi	3.03	2.41–3.82	0.000	1.78	1.40–2.25	0.000	2.20	1.87–2.58	0.000	1.39	1.17–1.64	0.000
PA level	1.40	1.08–1.81	0.01	1.31	1.01–1.71	0.04	1.15	0.89–1.49	NS	1.52	1.18–1.98	0.002
Ethnicity	0.99	0.85–1.15	NS	0.85	0.74–0.99	0.03	0.86	0.74–0.99	0.04	0.79	0.69–0.91	0.001
Education	0.93	0.79–1.10	NS	0.91	0.78–1.07	NS	0.90	0.80–1.03	NS	0.87	0.76–1.00	0.05
PIR	1.06	0.94–1.19	NS	0.90	0.80–1.01	0.06	0.88	0.79–0.98	0.02	0.98	0.89–1.09	NS
Constant	0.001		0.000	0.017		0.000	0.107		0.000	0.174		0.000
Nagelkerke R^2	0.343			0.250			0.273			0.209		

CI, confidence interval; FFMi, fat-free mass index (kg/m^2); FMi, fat mass index (kg/m^2); PA, physical activity; PIR, poverty income ratio.
Overall n = 4787 due to missing data for sociodemographic and physical activity variables.

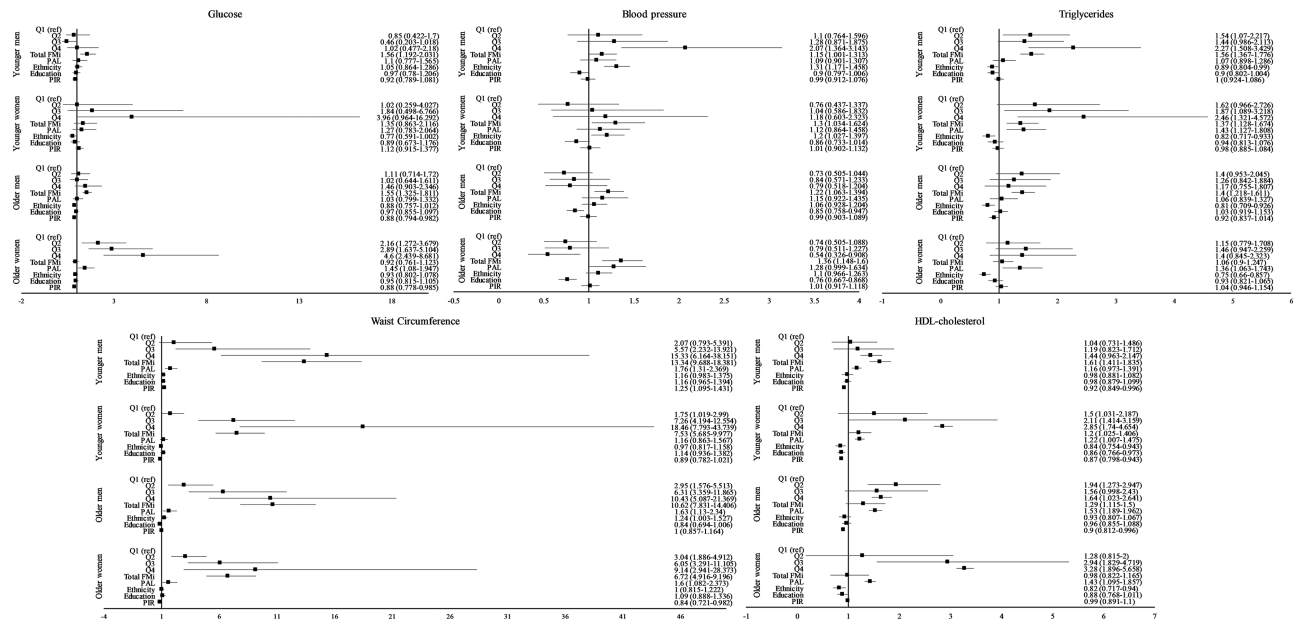**Figure 2** Odds ratios for metabolic syndrome components by quartiles of fat-free mass index [FFMi (kg/m^2)]. Overall $n = 4787$ due to missing data for sociodemographic and physical activity variables. Younger men: $n = 1551$; younger women: $n = 1265$; older men: $n = 1016$; older women: $n = 955$. FMi, fat mass index (kg/m^2); PAL, physical activity level; PIR, poverty income ratio; Q1–Q4: FFM index (kg/m^2) quartiles 1–4.

viduals ($1.44 \leq \beta \geq 2.46$; $0.001 \leq P \geq 0.07$), but not in older individuals ($1.15 \leq \beta \geq 1.46$; $0.09 \leq P \geq 0.5$).

Finally, the impact of FFMi on BP showed contrasting responses between groups with a higher ORs of having high BP in young men (Q4 vs. Q1: $\beta = 2.07$; $P = 0.001$) and lower ORs of high BP in older women (Q4 vs. Q1: $\beta = 0.54$; $P = 0.02$).

Discussion

The objectives of this study were to (i) determine the association between MetS and FFM when represented in three different ways (kg, FFMi, or FFM%) and (ii) assess the impact of FFM, once isolated from confounding factors, on the relative risk of having the MetS, or specific MetS components, in age-specific subgroups of men and women.

One main finding of this study is that the representations of FFM significantly and strongly influenced the direction of its association with MetS prevalence. This conclusion is of utmost importance considering the augmented risk for T2D and CVD with MetS and the largely purported idea that a greater FFM is beneficial for metabolic health. These results thus shed new light on previously published discrepant data reporting discordant associations between FFM and MetS and suggest that the different representations of FFM likely explain these discrepancies.

Our observations are in accordance with those of others.[4,21,24] For instance, Park and Yoon and Scott *et al.* re-

ported opposite associations between FFM and MetS depending on how FFM was represented: relative to weight (negative association) or relative to height (positive association).[4,24] However, despite these opposite associations, both research groups concluded that low FFM could play a role in the development of MetS based solely on the results from the negative association between FFM% and MetS.[4,24]

The contrasting associations with MetS among the different representations of FFM could be explained by the mediating role played by FM. Scott *et al.* argued that greater FFMi was positively correlated with FM and that the latter could have driven the risk of developing the MetS.[24] Yet similar concerns could be raised when representing FFM as a percentage of total body weight. It should be emphasized that at a three-compartment level, the body is made up of two main tissues: FFM (which includes muscle mass, ligaments, tendons, and organs) and FM. Hence, representing FFM as a percentage of body weight inherently represents FM and is thus indicative of tissue distribution, not FFM *per se*. While FFM% can accurately predict metabolic diseases,[4,24] it is inadequate to isolate the specific role of FFM on the risk of having the MetS and using it as such will lead to flawed inferences. A great example is from the article of Lee *et al.* who concluded that 'skeletal muscle mass may play a protective role against future metabolic deterioration' based on FFM% data.[6] However, in their study, appendicular FFM (expressed in kg) was similar between individuals progressing towards an unhealthy metabolic phenotype and those remaining healthy, leaving the only difference between groups to be a higher absolute

FM. We strongly believe that these flawed conclusions could be counteracted by using FFMi and further adjusting for FMi, thus allowing the assessment of FFM *per se* on the risk of having the MetS.

Applying this method led to the second main finding of this study: the ORs of having the MetS increased in younger and older men and women with larger FFMi, independently of multiple covariables. Although it opposes the widespread belief that FFM has a protective effect on metabolic health, this conclusion is in line with previous counterintuitive observations from multiple published studies.[4,15,17,18,20,23,24,28–31] The authors of these studies, however, have not always put forward, if discussed, their results. This phenomenon may contribute to a publication imbalance and perpetuate the notion that greater FFM is necessarily beneficial for metabolic health.

However, despite a rather constant response in the ORs of having the MetS with greater FFMi, some MetS components showed age-specific and/or sex-specific responses. For instance, the ORs of having elevated TGs were only significant in men and not in women. In contrast, the ORs for high plasma glucose were only significantly greater with FFMi in older women. This latter result is contrasting with some of our previous observations, in which we reported a relation between FFMi and glucose homeostasis in younger and older men and women,[14] that is, a greater IR with larger FFMi. These discrepancies could stem from the utilization of HOMA-IR in the previous study,[14] which give a broader perspective of glucose metabolism compared with simply using fasting glucose in this study. Another potential explanation for these age-specific and sex-specific responses could stem from the distribution of FFM, as shown by Peppa *et al*.[20] The authors showed that while whole-body FFMi or trunk FFMi was deleteriously associated with various cardiometabolic parameters (systolic BP, fasting insulin, HOMA-IR, QUICKI, HDL-C, and high sensitivity C-reactive protein), appendicular FFMi was only associated with BP.[20] Furthermore, when upper-body appendicular FFMi and lower-body appendicular FFMi were considered distinctly, lower-body appendicular FFMi was not associated with any cardiometabolic parameters, but upper-body appendicular FFMi was still associated with practically all variables estimated.[20] These observations suggest that upper-body and lower-body FFM may not have the same relation with metabolic health, which should further be investigated.

While other components showed group-specific and mild, weak, or no associations with FFMi, WC showed a robust and consistent positive association with greater FFMi across groups. This robust association was to be expected given the known relation between WC and BMI. Similar observations were reported by Scott *et al*. in Australian and Korean older adults.[24] Indeed, low appendicular FFMi had the greatest association with WC [OR = 0.12 (0.08–0.19)], mild

to moderate relation with TGs [OR = 0.52 (0.37–0.72)], HDL-C [OR = 0.55 (0.40–0.78)], and fasting plasma glucose [OR = 0.65 (0.45–0.95)], and no significant association with BP [OR = 0.79 (0.58–1.08)].[24]

Altogether, our results demonstrate a greater OR of having the MetS in the highest FFMi quartiles in younger and older men and women. These observations are in agreement with some of our previous results[15,17,18,28] and those of others,[8,20,22,29–31] but contrast with the observations of many.[4,7,32–34] Again, most studies concluding to a protective effect of a greater FFM on metabolic health used FFM% in their analyses,[4,7,32–34] which, based on our results, can likely explain discrepancies. It is worth mentioning that many of the previous studies reporting a positive association between FFMi and IR or MetS components were mainly led in older populations, specifically postmenopausal women[8,15–18,20,29,31] and older men.[8,29,31] In addition to confirming previous observations, our results showed that these associations extend to younger individuals. More broadly, our results suggest that low FFMi does not seem to be a contributing factor to the altered metabolic health observed in elder individuals and that other mechanisms are at play. This is in line with previous results from Goulet *et al*. who concluded that frail, lean older adults showed no differences in insulin sensitivity compared with normal healthy counterparts despite lower FFM.[35]

Considering the counterintuitive aspect of these results, no mechanistic study seems to have investigated this phenomenon. Our group has previously offered mechanistic hypotheses that could potentially explain the deleterious association between FFMi and MetS.[17,19] Briefly, a greater FFM is usually characterized by higher proportions of type 2 fibres, which have a lower oxidative capacity and a lower glucose-handling capacity compared with type 1 fibres.[36] Furthermore, muscle infiltration of lipids was shown to alter the insulin cascading pathways in inactive individuals[37] and could thus contribute to the development of MetS. Finally, a reduced capillary-to-fibre ratio and decreased capillary density in individuals with a higher FFM could also influence the association between FFMi and MetS because a limited exchange area and blood flow have been linked with IR.[38] Nevertheless, these all refer to muscle quality and are theoretical hypotheses that require further investigation and will be addressed in the near future.

It should be noted that the present study has some limitations. Our results are limited to non-Hispanic White, non-Hispanic Black, and Mexican American ethnicities and, therefore, may not be applicable to other ethnicities such as Asians and Indians. However, other large cohort studies have reported similar results in an Asian population.[24] Secondly, considering a substantial amount of missing data for smoking status and alcohol consumption in the NHANES database from 1999 to 2006, these confounding factors, previously associated with MetS and its components,[39]

could not be included in our analyses. Despite these limits, this study is strengthened by several aspects. One of them is the use of dual-energy X-ray absorptiometry, which is one of the most accurate methods to quantify body composition compartments and is considered the reference standard for muscle mass and FM measurements.[40] Furthermore, the large sample size from NHANES covering a wide range of demographic characteristics allowed the subgroup analyses by age and sex with sufficient statistical power. Finally, the analyses were corrected for multiple confounders including ethnicity, education level, and income. Furthermore, albeit self-reported, controlling for physical activity allowed us to take into account one of the most potent confounding factors in the association between FFM and metabolic status.

Conclusions

Taken together, these results shed new light on the association between metabolic status and FFM. First, we showed that the prevalence of MetS relative to FFM varies depending on the method used to represent the latter. Our findings also provide some indications of the role of FFM, independently of multiple confounders, on the ORs of having the MetS in an age-specific and sex-specific fashion. Specifically, we observed a greater OR of having the MetS

in higher quartiles of FFMi in young and ageing men and women. Hence, researchers and clinicians should be aware that the way FFM is represented can greatly affect their results and conclusions regarding associations between metabolic health and FFM. For instance, a misinterpretation of the data can lead to flawed or erroneous exercise recommendations in the context of weight loss or the prevention and management of chronic diseases (e.g. to increase or maintain muscle mass). At this point, future investigations phenotyping FFM are highly necessary to improve our understanding of the structural and metabolic mechanisms underlying our observations.

Conflict of interest

The authors report no conflicts of interest or competing interests.

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