ORIGINAL RESEARCH

Association Between Adiposity and Lean Mass With Long-Term Cardiovascular Events in Patients With Coronary Artery Disease: No Paradox

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***Background*—**Prognosis based on body fat percentage (BF%) in patients with coronary artery disease has not been extensively studied. We tested the hypothesis that patients with coronary artery disease and increased BF% have a higher risk for major adverse cardiovascular events (MACEs) and that fat-free mass is associated with better prognosis.

***Methods and Results*—**We included 717 patients referred to cardiac rehabilitation after coronary artery disease events or procedures who underwent air displacement plethysmography to assess BF%; 75% were men, with a mean age 61.4±11.4 years and a mean body mass index of 30±5.4 kg/m^2. Follow-up was performed using a record linkage system. Patients were classified in sex-specific quartiles of BF% and fat-free mass index. The composite outcome of MACEs included acute coronary syndromes, coronary revascularization, stroke, or death from any cause. After a median follow-up of 3.9 years, 201 patients had a MACE. After adjusting for covariates, body mass index was not associated with MACEs (P=0.12). However, the risk of MACEs for those in the highest BF% quartile was nearly double when compared with those in the lowest quartile (hazard ratio, 1.89; 95% confidence interval, 1.30–2.77; P=0.0008). In contrast, fat-free mass was inversely associated with MACEs. The risk of MACEs for those in the fourth fat-free mass quartile was lower (adjusted hazard ratio, 0.53; 95% confidence interval, 0.35–0.82; P=0.004), when compared with those in the first quartile.

***Conclusions*—**In patients with coronary artery disease, there is no obesity paradox when measuring BF% instead of body mass index. BF% is associated with a higher risk of MACEs, whereas fat-free mass is associated with a lower risk of MACEs. Body mass index was not associated with MACEs. **(*J Am Heart Assoc*. 2018;7:e007505. DOI: 10.1161/JAHA.117.007505.)**

Key Words: adipose tissue • cardiac rehabilitation • coronary artery disease

The detrimental effects of obesity on general and cardiovascular health are well recognized.[1] Obesity is associated with an increased risk of coronary artery disease (CAD), heart failure, hypertension, atrial fibrillation, and many other cardiovascular conditions.[1] Adipose tissue is not a simple storehouse for fat, but rather an endocrine organ that is capable of synthesizing and releasing a variety of molecules, such as leptin, adiponectin, tumor necrosis factor-α, interleukin-6, and many others, that play a central role in the pathophysiological features of inflammation and CAD.[2] However, numerous publications have demonstrated the existence of an "obesity paradox," where overweight and obese people with CAD or heart failure have a better prognosis than normal weight people with similar conditions and cardiovascular risk factors.[3] Although the cause for the obesity paradox is unclear, several factors can contribute to it, such as the inability of the body mass index (BMI) to distinguish between body fat (BF) mass and fat-free mass in the general population[4] and particularly in patients with CAD.[5,6] Because of the fact that fat-free mass has protective metabolic effects, the inability of BMI to discriminate between fat-free and fat mass may lead to erroneous assumptions about the association between fatness and prognosis in patients with CAD. The prognosis in people with CAD based on actual fat measurement has not been extensively studied nor has the association between BMI and long-term nonfatal events.

We tested the hypothesis that patients with CAD and high BF content, as measured by air displacement,[7] but not a high BMI, will have a greater rate of long-term major adverse

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Clinical Perspective

What Is New?

- In patients with coronary artery disease, higher content of body fat is associated with adverse cardiovascular events.
- In patients with coronary artery disease, greater fat-free mass was associated with a lower risk of major adverse cardiovascular events.
- Contrary to what has been found in studies assessing the prognosis according to body mass index in patients with coronary artery disease, we found no obesity paradox when measuring body fatness.

What Are the Clinical Implications?

- Body mass index cannot discriminate between high fat content or low fat-free mass and does not add risk information in patients with coronary disease.
- Our results suggest that performing body composition analysis in patients with coronary artery disease may better identify people at risk for major adverse cardiovascular events.

cardiovascular events (MACEs) than lean people, and that fat-free mass may be inversely associated with MACEs.

Methods

Study Populations

In consideration of the privacy of patients, the data, the analytic methods, and the study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

We included all consecutive patients ≥18 years of age between January 1, 2002, and December 31, 2012, who enrolled in early outpatient (phase 2) cardiac rehabilitation (CR) because of CAD events or procedures and who underwent a body composition assessment as part of their entry evaluation. History of CAD events or procedures included a recent myocardial infarction (MI; ST- or non–ST-segment–elevation MI), stable or unstable angina, and previous revascularization by either coronary artery bypass grafting or percutaneous coronary intervention. Because the Rochester Epidemiology Project (REP) focuses on outcome assessment of local residents, all were residents of Olmsted County, Minnesota. We excluded underweight patients (defined as BMI ≤18.5 kg/m^2), because they generally have an excessively high mortality rate attributable to comorbidities; frailty; and other conditions not completely captured in a database. These conditions could introduce bias. We also excluded people that did not undergo body composition assessment and those with end-stage renal or liver disease or myxedema, because these patients could have increased extravascular fluids, leading to erroneous measurements of BF content. We excluded those who either refused the measurement or had other limitations, like claustrophobia or musculoskeletal problems, that would make the measurement of BF uncomfortable for patients.

Practically all medical care in Olmsted County is available to residents through Olmsted Medical Center or the Mayo Clinic and its allied hospitals. All medical records are linked in a dossier for each individual, regardless of the site of care, as part of the REP, a record linkage system that contains information on all Olmsted County residents who have provided research authorization as required by the state of Minnesota.[8] The REP regularly abstracts diagnosis, procedures, and other vital information from this dossier. All original records are available for review, serving as an ideal community-based infrastructure to analyze disease-related factors and outcomes.[9]

The baseline and outcome information was obtained using the electronic medical record in the REP. Baseline information was gathered within 3 months before CR program enrollment and included height (recorded to the nearest centimeter), weight (recorded to the nearest 0.1 kg), patient's clinical characteristics, blood pressure, type and date of CAD events/procedure, medications prescribed for the treatment of CAD, and laboratory values.

Patient's clinical characteristics were collected using the *International Classification of Diseases, Ninth Revision* (*ICD-9*).[10] To decrease false-positive results, 2 occurrences of a code (either the same code or 2 different codes within the code set for a given disease) separated by >30 days and occurring within 5 years before the index date were required for diagnosis, an approach that has been validated in the past.[11,12] The information was then reviewed for internal validation in duplicate by 2 physician investigators who were masked to the baseline characteristics of patients (J.M.I. and N.J.).

A medical history of diabetes mellitus was defined as having the clinical diagnosis, receiving medication for diabetes mellitus, or having fasting plasma glucose ≥126 mg/dL in 2 separate tests or a hemoglobin A1c level ≥6.5%. History of smoking was classified as ever versus never smoker. Hypertension was defined as having a documented clinical diagnosis of hypertension, receiving treatment for hypertension, or having a systolic blood pressure of >140 mm Hg or a diastolic blood pressure of >90 mm Hg. Dyslipidemia was defined as receiving lipid-lowering treatment before the index event or having a fasting plasma cholesterol level ≥200 mg/dL or triglycerides ≥150 mg/dL. A history of heart failure was based on a clinical diagnosis of heart failure documented in the electronic medical record.

Body composition was measured using air displacement plethysmography (Bod-Pod; COSMED, Concord, CA); detailed calculations and scanning procedures were followed, as

reported elsewhere.[7] Briefly, the Bod-Pod is a dual-chamber system in which each subject sits inside a plastic pod wearing a tight-fitting swimsuit and swimming cap while breathing normally. Body volume is obtained from chamber gas pressure difference under isothermal conditions, applying Boyle's and Poisson's laws. The principles of densitometry are then applied, where body density is calculated as total body mass in kilograms (kg)/body volume (L).[7,13–15] Then, body density is used in the Siri's formula to derive BF mass (BF mass=[4.95/body density−4.50]×100).[16] BF% is calculated on the basis of the fraction of BF mass/total body mass. Fat-free mass was calculated as total body mass (in kg) minus BF mass. Fat-free mass index was calculated by dividing fat-free mass by height squared in meters, and fat mass index was calculated by dividing BF mass by height squared in meters. BMI was calculated as weight (in kilograms)/height squared (in meters).

Outcome Measures

The primary outcome was the incidence of MACEs, defined as follows: (1) any diagnosis of a new acute coronary syndrome, including both ST- and non–ST-segment–elevation MI and unstable angina that required hospitalization; (2) coronary revascularization, including percutaneous coronary intervention or coronary artery bypass grafting; (3) stroke, including any nontraumatic brain hemorrhage or infarction; and (4) death from any cause. Mortality information was obtained directly from the REP, which records vital status from state vital statistics offices and the National Death Index. All patients were followed up passively through a review of the electronic medical records in the records-linkage system through December 1, 2014. Outcome data were abstracted by 2 physician investigators (J.M.I. and M.G.I.) who were blinded to baseline characteristics, including BF and BMI.

Only patients who had previously given consent to use their medical records for medical research were included in this study. The study protocol was reviewed and approved by the institutional review boards of both the Mayo Clinic and Olmsted Medical Center.

Statistical Analysis

We assessed baseline patient characteristics as frequencies with percentages, mean values and SDs, or medians and interquartile ranges, depending on the distribution of the variables. Selected patient characteristics were compared between BF% quartile with χ^2 tests, 2-sample *t* tests, or ANOVA, as appropriate. The κ statistic was used to assess interobserver agreement over comorbidities at baseline and MACEs.

The functional form of the association between the body composition measurements of interest (BMI, BF%, and fat-free mass index) and time to first MACE was initially investigated with splines in Cox proportional hazards regression models, adjusting for sex.[17] BF% and fat-free mass index were ultimately treated as sex-specific quartiles because this evaluation revealed that the relationships with MACEs were not completely linear. For BMI, clinically meaningful categories were used. The unadjusted associations between body composition categories with time to first recorded MACE were estimated with the Kaplan-Meier method and tested using log-rank tests. Cox proportional hazard regression models were estimated, adjusting for age and sex plus additional clinical variables associated with body composition in the univariate analysis. Fat-free mass index was also included in the model to further evaluate this relationship beyond the effect of fat-free mass. An additional exploratory model was created, including obesity-related factors that are known mediators of obesity and CAD. Findings were summarized using 3-year event-free rates, hazard ratios (HRs), and 95% confidence intervals (CIs). The assumption of proportionality for the Cox proportional hazards regression models was assessed graphically by plotting the cumulative hazards of the logarithms of the covariates.[18] The proportionality assumption was met for each model. In all cases, 2-tailed $P<0.05$ values were considered statistically significant. All analyses were completed using JMP, Version 12.0, or SAS, 9.4 (SAS Institute Inc, Cary, NC).

Results

During the study period, 2399 patients attended phase 2 CR with a confirmed diagnosis of CAD. Of those patients, 717 had adiposity measured at Mayo Clinic CR. The 1682 patients excluded because they did not have body composition measurements were slightly older (mean age, 65.5 versus 61.4 years; $P<0.001$), were more likely to be women (33.0% versus 25.0%; $P<0.001$), had higher prevalence of hypertension (51.4% versus 34.3%; $P<0.001$), had history of smoking (58.0% versus 38.1%; $P<0.001$), and had similar incidence of MACEs (the 3-year event-free survival rates were 80.0% versus 79%; log-rank $P=0.9$).

Mean age at baseline was 61.4±11.4 years, and 539 (75%) were men. Most patients were non-Hispanic whites (94.4%), 2.2% were black or African American, 2.2% were Asian, <1% were Hispanic or Latino, and <1% were Native American or Alaska Native. The average BF% was 31.9±7.2% and 42.6±8.0% for men and women, respectively ($P<0.001$). Average BMI was similar for men and women (29.7 and 29.4 kg/m^2, respectively; $P=0.5$). Interobserver agreement over both comorbidities ($\kappa=0.81$) and MACE outcome assessments ($\kappa=0.89$) was excellent. Additional baseline characteristics compared between sex-adjusted BF% quartiles are shown in Table 1.

Table 1. Baseline Patient Characteristics Among Sex-Adjusted BF% Quartiles

Characteristics	First Quartile (n=177)	Second Quartile (n=180)	Third Quartile (n=178)	Fourth Quartile (n=182)	Total (n=717)	*P* Value
Age, y	60.1±11.8	60.9±11.3	62.9±11.6	62.3±11.5	61.8±10.7	0.09
Male sex	134 (76)	134 (74)	133 (75)	138 (76)	539 (75)	0.9
Clinical history						
Heart failure	33 (18.6)	27 (15.0)	29 (16.3)	26 (14.3)	115 (16.0)	0.6
Hypertension	49 (27.7)	51 (28.3)	68 (38.2)	78 (42.9)	246 (34.3)	0.003
Diabetes mellitus	54 (30.5)	71 (39.4)	81 (45.5)	107 (58.8)	313 (43.7)	<0.0001
Ever smoking	105 (59.3)	102 (56.7)	101 (56.7)	108 (59.3)	416 (58.0)	0.9
Dyslipidemia	154 (87.0)	167 (92.8)	172 (96.6)	178 (97.8)	671 (93.6)	0.001
Medications						
Statins	142 (80.2)	143 (79.4)	150 (84.3)	151 (83.0)	586 (81.7)	0.6
β-Blocker use	134 (75.7)	133 (73.9)	151 (84.8)	142 (78.02)	560 (78.1)	0.05
ACE inhibitor use	80 (15.2)	79 (43.9)	79 (44.4)	76 (41.8)	314 (43.8)	0.9
CCB use	17 (9.6)	17 (9.4)	20 (11.2)	22 (12.1)	76 (10.6)	0.9
Diuretic use	43 (24.3)	39 (21.7)	51 (30.3)	61 (33.5)	197 (27.5)	0.04
BF%	24.9±5.4	32.3±4.9	37.2±5.2	43.5±6.1	34.6±8.7	<0.0001
Weight, kg	75.9±14.1	84.1±15.8	90.9±16.0	103.2±20.8	88.7±19.6	<0.0001
Fat mass, kg	18.7±4.2	26.9±4.9	33.6±6.5	45.0±11.5	31.1±12.1	<0.0001
Fat-free mass, kg	57.2±12.3	57.3±12.9	57.3±12.0	58.3±12.9	57.5±12.5	0.8
Height, cm	172.3±10.0	172.6±10.2	172.5±9.4	172.2±9.7	172.4±9.8	0.9
BMI, kg/m^2	25.4±3.3	28.0±3.2	30.31±4.1	34.6±5.6	29.6±5.4	<0.0001
Fat mass index, kg/m^2	6.3±1.5	9.1±1.8	11.3±2.3	15.2±4.0	10.5±4.2	<0.0001
Fat-free mass index, kg/m^2	19.1±2.9	19.1±3.0	19.1±2.6	19.5±3.0	19.1±2.9	0.4
MACEs, %*	82.1	81.9	84.6	72.6	80.4	0.0008

Values are mean±SD or number (percentage). *P*<0.05, with ANOVA or χ^2 accordingly, across BF% sex-adjusted quartiles. BF% sex-adjusted quartiles: men (1, <27; 2, 27–<32; 3, 32–<36.6; and 4, ≥36.6) and women (1, <37.6; 2, 37.6–<43; 3, 43–<48.6; and 4, ≥48.6). ACE indicates angiotensin-converting enzyme; BF%, body fat percentage; BMI, body mass index; CCB, calcium channel blocker; and MACE, major adverse cardiovascular event.

*Represents Kaplan-Meier 3-year event-free survival rates.

During a median follow-up of 3.9 years (interquartile range, 2.5–6.8 years), 201 patients had at least 1 MACE, 66 had an MI, 66 had unstable angina, 31 had coronary artery bypass grafting, 114 had percutaneous coronary intervention, 14 had strokes, and 34 died. Some patients had >1 event. BMI was not found to be a significant predictor for MACEs. With BMI <25 kg/m^2 as the reference, HRs for BMI of 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m^2 were 0.87 (95% CI, 0.58–1.28; *P*=0.49), 1.24 (95% CI, 0.82–1.88; *P*=0.29), 0.86 (95% CI, 0.46–1.60; *P*=0.64), and 1.62 (95% CI, 0.85–3.07; *P*=0.15), respectively (*P*=0.12 for trend).

Adiposity level, as measured by BF% quartiles, was associated with an increased risk of MACEs. The 3-year event-free-survival rates were 82.1%, 81.9%, 84.6%, and 72.6% for each of the BF% quartiles, respectively (log-rank *P*=0.0008) (Figure). After adjusting for age, sex, smoking, history of MI, and heart failure, BF% category remained a significant predictor for MACEs. The risk of MACEs for those in the fourth BF% quartile was higher in every case, when compared with the first quartile (HR, 1.82; 95% CI, 1.25–3.68; *P*=0.001), the second quartile (HR, 1.85; 95% CI, 1.27–2.71; *P*=0.001), and the third quartile (HR, 1.96; 95% CI, 1.34–2.91; *P*=0.0005) (*P*=0.0008 for trend) (Table 2 and Figure). This was unaffected after adjusting for fat mass index (adjusted HR, 1.89; 95% CI, 1.30–2.77; *P*=0.0008), when comparing the fourth quartile with the first quartile (Table 2).

In an exploratory model that also adjusted for obesity-mediating factors (diabetes mellitus, dyslipidemia, and hypertension), those in the fourth BF% quartile of BF% had a higher risk of MACEs: When compared with the first quartile, HR was 1.78 (95% CI, 1.21–2.65; *P*=0.003); when compared with the second quartile, HR was 1.85 (95% CI, 1.27–2.73; *P*=0.001); and when compared with the third quartile, HR was 1.91 (95% CI, 1.30–2.85; *P*=0.0009).

Fat-free mass and fat-free mass index were not different across quartiles of BF (*P*=0.8 and *P*=0.4, respectively)

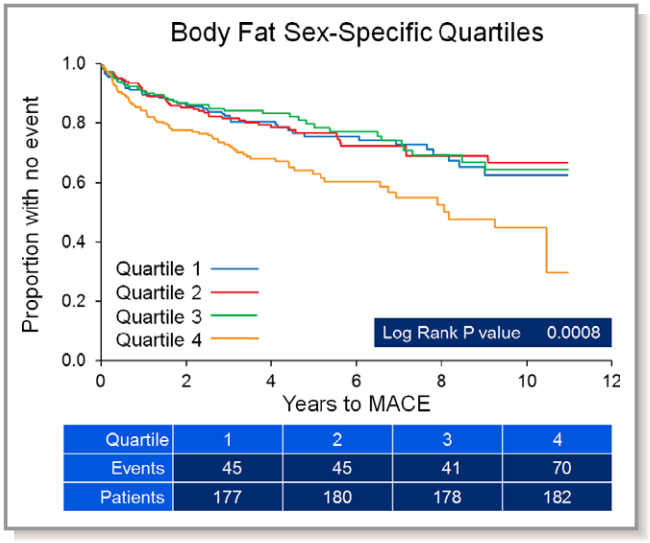

Figure. Kaplan-Meier curves showing the association between sex-specific body fat percentage (BF%) quartiles and major adverse cardiovascular events (MACEs). The figure displays survival curves for sex-specific adjusted BF% quartiles for the 717 patients who had adiposity measured at Mayo Clinic cardiac rehabilitation for the composite outcome of MACE.

(Table 1). After adjusting for age, sex, smoking, history of MI and heart failure, and fat mass indexes, lean mass represented by the fat-free mass index was associated with a decreased risk of MACEs. The risk of MACEs was lower for those in the fourth fat-free mass index quartile (HR, 0.53; 95% CI, 0.35–0.82; *P*=0.004) and the third fat-free mass index quartile (HR, 0.49; 95% CI, 0.32–0.74; *P*=0.007), and no different for those in the second fat-free mass index quartile (HR, 0.74; 95% CI, 0.51–1.07; *P*=0.1), when compared with those in the first fat-free mass index quartile (*P*=0.004 for trend) (Table 3).

Discussion

This population-based historical cohort study demonstrated that patients with known CAD and higher BF content had a greater risk of MACEs when compared with those with less BF. In addition, patients with higher fat-free mass had a lower risk of MACEs, whereas BMI was not associated with MACEs.

To the best of our knowledge, no other study has assessed the risk of MACEs, including nonfatal events, in patients with CAD, according to BMI or body composition in a population-based setting. These results suggest that increased body fatness has deleterious effects, whereas fat-free mass may have a protective effect, on patients with CAD, similar to what has been demonstrated in the general population and in studies excluding people with CAD. Our results also show that there is no obesity paradox, or a protective effect of obesity in

Table 2. Cox Proportional Hazard Models Testing the Association Between BF% Quartiles and MACEs

Measure	Unadjusted Model			Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
BF% quartile			0.001*			0.004*			0.0008*			0.0005*
1	Reference	…	…	Reference	…	…	Reference	…	…	Reference	…	…
2	0.96	0.63–1.45	0.8†	0.95	0.62–1.44	0.8†	0.98	0.65–1.49	0.9†	0.99	0.65–1.50	0.9†
3	0.91	0.59–1.40	0.7†	0.90	0.58–1.37	0.6†	0.93	0.60–1.42	0.7†	0.95	0.61–1.45	0.8†
4	1.73	1.20–2.54	0.003†	1.71	1.18–2.51	0.004†	1.82	1.25–2.68	0.001†	1.89	1.30–2.77	0.0008†

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, and history of myocardial infarction and heart failure. Model 3: model 2 in addition to fat-free mass index. Interactions between body mass index and BF (in a model with body mass index and BF), as well as between fat index and fat-free index (in a model with fat index and fat-free index), were not statistically significant. BF% sex-adjusted quartile: men (1, <27; 2, 27–<32; 3, 32–<36.6; and 4, ≥36.6) and women (1, <37.6; 2, 37.6–<43; 3, 43–<48.6; and 4, ≥48.6). BF% indicates body fat percentage; CI, confidence interval; HR, hazard ratio; and MACE, major adverse cardiovascular event.

*Represents *P* value for trend.

†Represents *P* value for pairwise comparison between individual quartile and reference category.

Table 3. Cox Proportional Hazard Models Testing the Association Between Fat-Free Mass Index (kg/m^2) Quartiles and MACEs

Measure	Unadjusted Model			Model 1			Model 2			Model 3		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Fat-free mass index (kg/m^2) quartiles			0.04*			0.003*			0.03*			0.004*
1	Reference	…	…	Reference	…	…	Reference	…	…	Reference	…	…
2	0.83	0.57–1.21	0.3†	0.84	0.58–1.22	0.3†	0.78	0.54–1.13	0.2†	0.74	0.51–1.07	0.1†
3	0.56	0.37–0.84	0.005†	0.57	0.37–0.85	0.006†	0.55	0.36–0.82	0.003†	0.49	0.32–0.74	0.0007†
4	0.80	0.55–1.17	0.2†	0.83	0.56–1.21	0.3†	0.68	0.46–1.01	0.05†	0.53	0.35–0.82	0.004†

Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, smoking, and history of myocardial infarction and heart failure. Model 3: model 2 in addition to body fat percentage quartile. Interactions between body mass index and body fat (in a model with body mass index and body fat), as well as between fat index and fat-free index (in a model with fat index and fat-free index), were not statistically significant. Fat-free mass index (kg/m^2) quartiles: men (1, <18.4; 2, 18.4–<19.8; 3, 19.8–<21.5; and 4, ≥21.5) and women (1, <14.9; 2, 14.9–<16.1; 3, 16.1–<15.5; and 4, ≥17.5). CI indicates confidence interval; HR, hazard ratio; and MACE, major adverse cardiovascular event.

*Represents *P* value for trend.

†Represents *P* value for pairwise comparison between individual quartile and reference category.

patients with CAD, when using direct measurements of fatness to determine obesity.

The link between excessive BF and CAD is thought to be mediated through intermediate conditions caused by obesity, like hypertension, dyslipidemia, and diabetes mellitus, all well-established risk factors for CAD. Adipose tissue might lead to CAD through direct effects on the cardiovascular system via different disease mechanisms, including an increase in free fatty acid circulation, low-grade inflammation, endothelial dysfunction, and metabolic dysregulation. Endothelial dysfunction is known to be a precursor for atherosclerosis and thrombosis and has been directly linked to an increased likelihood for cardiovascular events.[19]

Skeletal muscle is the organ where most of the glucose metabolism occurs, and studies have shown that increased muscle mass is associated with better insulin sensitivity, better glucose metabolism, and lower rates of type 2 diabetes mellitus and cardiovascular events.[20–22] Likewise, sarcopenia, defined as a loss of muscle mass and associated with frailty and overall decreased functionality and increased mortality, could have harmful effects in patients with CAD, as our results suggest.[23–25]

Overall, the inability of BMI to discriminate between fat-free mass, a protective factor, and fat mass, a factor associated with adverse outcomes, may lead to erroneous assumptions about risk of MACEs in patients with CAD and may explain why, in our cohort, BMI was not associated with MACEs.[5,6,26,27] Thus, the results of our study could not confirm the obesity paradox that has been reported in several other studies in those with CAD,[28–32] heart failure,[33–36] and atrial fibrillation.[37] The obesity paradox was addressed in a large meta-analysis of patients with CAD, where it was observed that subjects with a low BMI had an increased relative risk for total mortality and cardiovascular mortality, whereas obese patients had no increased risk or even a lower risk for total mortality or cardiovascular mortality.[3] Results showing the obesity paradox could be partially explained by the poor diagnostic accuracy of BMI to detect adiposity and its inability to differentiate between fat-free and fat mass, particularly among patients with CAD.[5,6,20] For example, a lower BMI could be related to sarcopenia rather than low fat mass, while being overweight may reflect increased muscle mass, rather than excessive adipose tissue. People with sarcopenia tend to have limited exercise capacity and reduced mobility, which are both associated with increased total mortality.[38]

There are only a few studies assessing the relationship of BF content and mortality in patients with CAD, and they have used the skin fold method to assess body fatness.[23,27] This technique has proved to be not better than BMI to assess body composition,[39] and this probably explains why those studies still show a paradoxical association between low fat

and increased mortality, similar to studies using BMI as a measure of fatness.[3]

This study has several strengths. Body composition was assessed by air displacement plethysmography, a valid and reliable method to assess body fatness.[7,13–15] A robust and valid source of information was used to obtain outcome data by using the record linkage system of the REP infrastructure, known to minimize unavailability for follow-up because it is applied to a relatively steady population. Clinician abstractors, who were blinded to body composition and BMI categories of patients, verified all outcomes. In addition, we used a composite end point of MACEs that combined nonfatal events and mortality to provide a clinically meaningful risk assessment, including clinically relevant outcomes, not just death. Last, our study had a considerably longer follow-up compared with other studies that assessed prognosis of patients with CAD.[3]

Limitations

The observational nature of our study makes it prone to several sources of bias, although efforts to overcome this were made during our analysis. Selection bias was likely present by including only patients with CAD who had their body composition measured with the Bod-Pod while attending CR, as demonstrated by the differences in clinical characteristics when comparing them with those without Bod-Pod measurements. In addition, prognosis based on BF could be different among those without CAD or patients with CAD not attending CR. However, these factors might affect the generalizability, but not the internal validity, of our study. Another limitation is the limited diversity of those living in Olmsted County, a population that is mostly non-Hispanic white. However, the epidemiological characteristics of Olmsted County for age, sex, morbidity, and mortality are comparable to those of the state of Minnesota and the entire United States.[40] Last, misclassification bias could potentially affect our sample; our estimates are based on a single measure of body composition as the exposure variable, assuming that body composition will not change through follow-up. However, it is an accepted strategy in epidemiologic studies to use baseline measures, including exposure and confounding variables.

Conclusion

Higher BF content is associated with a higher risk of MACEs in patients with CAD, whereas greater fat-free mass is associated with a lower risk of MACEs. There is no obesity paradox with BMI when assessing fatal and nonfatal MACEs. Measuring body composition in CR may be justified.

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Disclosures

None.

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Association Between Adiposity and Lean Mass With Long–Term Cardiovascular Events in Patients With Coronary Artery Disease: No Paradox

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