Sarcopenia, obesity, and inflammation—results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study1–3


ABSTRACT
Background: Age-related body-composition changes are associated with health-related outcomes in elders. This relation may be explained by inflammation and hemostatic abnormalities.

Objectives: Our objectives were to evaluate the relation between body-composition measures [body mass index (BMI), total fat mass, and appendicular lean mass (aLM)] and C-reactive protein (CRP), interleukin 6 (IL-6), and plasminogen activator inhibitor 1 (PAI-1) and to explore the effect of obesity and sarcopenia on CRP, IL-6, and PAI-1 concentrations.

Design: The data are from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study baseline visit (n = 286; mean age = 66.0 y). Total fat mass and aLM were assessed with a dual-energy X-ray absorptiometry scan. Linear regressions were performed between body-composition measures and CRP, IL-6, or PAI-1 concentrations. The effect of sarcopenia and obesity (defined as the percentage of fat mass) on CRP, IL-6, and PAI-1 concentrations was evaluated with the use of analyses of covariance.

Results: CRP and IL-6 were positively associated with both BMI [β = 0.027 (P = 0.03) and β = 0.048 (P < 0.001), respectively] and total fat mass [β = 0.049 (P < 0.001) and β = 0.055 (P < 0.001), respectively] and were inversely associated with fat-adjusted aLM [β = −0.629 (P = 0.002) and β = −0.467 (P = 0.02), respectively]. PAI-1 was positively associated with both BMI (β = 0.038, P = 0.005) and total fat mass (β = 0.032, P = 0.007). No significant interaction was found between either obesity or sarcopenia and CRP, IL-6, and PAI-1 concentrations. Obesity remained significantly associated with high CRP and IL-6 concentrations after adjustments for sarcopenia.

Conclusions: CRP and IL-6 are positively associated with total fat mass and negatively associated with aLM. Obesity-associated inflammation may play an important role in the age-related process that leads to sarcopenia. The relation of inflammation with sarcopenia was not independent of any of the considered obesity indexes.

KEY WORDS Sarcopenia, obesity, inflammation, fibrinolysis, skeletal muscle, aging

INTRODUCTION
Sarcopenia, defined as the involuntary loss of skeletal muscle that occurs with advancing age (1, 2), is an important correlate of impairment and physical disability in older persons (1–5) and is associated with a decrease in muscular strength and endurance and a loss of autonomy in older persons (5–9). The age-related decrease in muscle mass and strength is mainly caused by atrophy of muscle fibers, especially the type IIa fibers (1). This is associated with a decline in protein synthesis, particularly in the synthesis of myosin heavy chains (1). It has been suggested that this loss of muscle mass is not isolated, but is strongly connected with a parallel increase in fat mass (10). This mechanism may lead to the concomitant presence of sarcopenia and obesity (2, 10).

Inflammation is linked not only to physical disability (11–13), but also to obesity (14, 15) and to body composition (16). Cytokines, which are produced by adipocytes, may have a direct effect on physical function by accelerating the changes in body composition that are typical of the aging process, namely fat gain and loss of muscle mass (12). Moreover, the endocrine role played by adipose tissue has been suggested as an explanation for the health-related events that are associated with increased fat mass, such as cardiovascular diseases (14, 17). Furthermore, a strong relation between inflammation and hemostatic abnormalities has been shown in clinical conditions that are characterized by body-composition changes, such as insulin resistance syndrome (18).

Despite the growing interest in age-related body-composition changes that may explain major negative outcomes in older

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persons, limited evidence is available about the relation of sarcopenia and obesity with markers of inflammation and fibrinolysis. Of the few studies available, Visser et al. (19) reported an inverse association of muscle mass and strength with concentrations of interleukin 6 (IL-6) and tumor necrosis factor α.

The present study evaluated the cross-sectional relations between 2 measures of sarcopenia that are based on appendicular lean mass (20, 21) and a proinflammatory cytokine (IL-6), an acute phase protein [C-reactive protein (CRP)], and an inhibitor of the fibrinolytic process [plasminogen activator inhibitor 1 (PAI-1)]. We also investigated the relation between markers of inflammation and fibrinolysis and body mass index (BMI) and total fat mass. Moreover, we investigated the effects of sarcopenia and obesity (as dichotomous variables) on CRP, IL-6, and PAI-1 concentrations. To provide a more accurate estimate of fat mass than the one provided by BMI, obesity was defined in this instance according to age-, sex-, and race-specific cutoffs of body fat mass (22).

SUBJECTS AND METHODS

Subjects

The present analyses were performed with the use of data from the baseline evaluation of participants who were enrolled in the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study. The TRAIN study is a double-blind, crossover, randomized, placebo-controlled trial aimed to assess the biological mechanisms by which angiotensin-converting enzyme (ACE) inhibition may improve clinical outcomes in persons aged >55 y who have a high cardiovascular disease risk profile.

To be included in the TRAIN study, the participants had to meet more than one of the following criteria: 1) coronary heart disease, 2) peripheral vascular disease, 3) history of stroke (>6 mo), 4) diabetes along with more than one other cardiovascular disease risk factor [hypertension, total cholesterol >200 mg/dL, HDL cholesterol <40 mg/dL, for men or <50 mg/dL for women, triacylglycerols ≥150 mg/dL, current cigarette smoking, BMI (in kg/m²) ≥30], known microalbuminuria, or any evidence of previous vascular disease), and 5) evidence of clinical or subclinical cardiovascular disease and another risk factor (same as in point 4). Exclusion criteria for the TRAIN study were the current use of or a known hypersensitivity to ACE inhibitors, a diagnosis of specific cardiovascular conditions (including previous myocardial infarction, ejection fraction <40%, syncopal episodes that were likely because of life-threatening arrhythmias, or planned cardiac surgery or angioplasty within 3 mo), conditions that would affect results of the trial (significant renal disease, life-threatening illness, recent surgical procedure, or simultaneous enrollment in another experimental drug trial), or plans to leave the area in the next 3 mo. All the inclusion and exclusion criteria were based on medical history, reviews of medical records, physical examinations, and the laboratory data of participants.

The participants were recruited from the communities of Winston-Salem and Greensboro, NC, through several recruitment strategies. The participants were first screened by a phone interview for eligibility (n = 2347; Figure 1). A clinical prescreening visit, which was aimed at reviewing medical history and records of potential participants, was arranged for those participants who successfully completed the phone interview (n = 576). The subjects who successfully completed the prescreening visit (n = 401) were entered in a screening and single-blind run-in phase, in which compliance and the tolerability of the ACE inhibitor fosinopril were evaluated. The participants who successfully completed all of the preliminary phase interviews and visits (n = 295) were then randomly assigned to either the placebo or the intervention branch (treatment with fosinopril) of the study during the baseline clinical visit. After 6 mo and 3 midterm follow-up clinical visits, the crossover occurred. After a further 6 mo and 3 midterm clinical visits, the participants made closeout visits. For the present analysis, we used baseline cross-sectional data from 286 participants, after excluding participants (n = 9) with missing values for inflammatory markers or body-composition variables. All of the participants signed an informed consent form for the study at the screening visit. The Institutional Review Board of Wake Forest University approved the study protocol.

Markers of inflammation and fibrinolysis

To minimize circadian rhythm and other fluctuations in the markers’ concentrations, all of the participants had their blood drawn by venipuncture after fasting for 6 h in the mornings of the screening and of each clinical visit. After the specimens were processed in the cold within 1 h of collection, they were divided into aliquots and placed into cryovials, which were then frozen and stored at −70 °C until analyzed.

Serum concentrations of IL-6 were assessed with a highsensitivity immunoassay kit (R&D Systems, Minneapolis, MN), which has synthetic peptides and highly specific monoclonal antibodies. The immunoassay had a sensitivity of <0.10 pg IL-6/mL and an expected detection range of 0.15–10.0 pg IL-6/mL.
Serum concentrations of CRP were measured with an enzyme-linked immunosorbent assay with the use of purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay had a sensitivity of 0.08 μg/μL and a standard reference range of 0.5-2.5 mg/L. In our previous studies, the mean CV for CRP across assay runs was 4.2% (23). Serum concentrations of PAI-1 antigen were measured with a 2-site enzyme-linked immunosorbent assay. The analytic CV for this assay is 3.47%.

**BMI and body-composition measures**

For the present analyses we related CRP, IL-6, and PAI-1 concentrations to BMI and total fat mass. BMI was defined as body weight (in kg)/height² (in m). Weight was measured with the use of a Delphi (Hologic Inc, Bedford, MA) dual-energy X-ray absorptiometry (DXA) scan. Height was self-reported by the participants. Total fat mass was defined as the percentage of fat mass, relative to whole body mass, that was determined by the DXA. These 2 measures of obesity and adipose tissue were considered as predictive variables in our models because the production of inflammatory and fibrinolysis markers from adipocytes was already shown (18, 24).

We also explored the relation between markers of inflammation and fibrinolysis and 2 different measures of sarcopenia based on appendicular lean mass (20, 21). Appendicular lean mass was defined as the sum of the lean mass (in kg) that was measured in each participant’s arms and legs with a DXA scan. The first measure, fat-adjusted appendicular lean mass, was defined with the use of the residuals of a linear regression model that predicted the dependent variable appendicular lean mass (in kg) from height (in m) and total fat mass (in kg) (20). Newman et al (20) suggested that for a better estimate of sarcopenia, especially in women and obese individuals, fat mass should be considered together with muscle mass. Moreover, the measure of muscle mass adjusted for fat mass was shown to be associated with lower extremity functional limitation (20). A positive fat-adjusted appendicular lean mass indicates a relatively muscular individual, whereas negative values indicate relatively sarcopenic individuals. A second measure of sarcopenia was defined as the residuals of a linear regression analysis between the dependent variable appendicular lean mass (in kg) and height (in m). Fat-adjusted and non-fat-adjusted appendicular lean mass were considered as dependent variables in our analyses, which explored their relation with CRP, IL-6, and PAI-1 because of the reported negative effects of inflammation on muscle mass (16, 25, 26).

To provide an accurate definition of obesity, we used the age-, sex-, and race-specific cutoffs for percentage total body fat (assessed with a DXA scan) previously reported by Gallagher et al (22). We defined obesity on the basis of percentage total body fat rather than on the basis of the more common BMI ranges to avoid misclassification as a result of 1) increases in fat that occur with aging even when BMI remains constant, 2) ethnic differences, or 3) differences in health status between the subjects and their counterparts with similar BMIs. On the basis of these cutoffs (22), persons aged <60 y were defined as obese if the percentage of body fat was >29% in white men, >27% in African American men, >29% in Asian men, >41% in white women, >39% in African American women, and >41% in Asian women. Persons aged 60-79 y were defined as obese if the percentage of body fat was >31% in white men, >29% in African American men, >29% in Asian men, >43% in white women, >41% in African American women, and >41% in Asian women. Participants from other ethnic groups or aged >80 y (n = 17), for which these estimates were not available, were excluded from these analyses.

**Covariates**

Sociodemographic characteristics (age, sex, race, and smoking status), self-reported clinical conditions (diabetes, angina, myocardial infarction, cancer, and stroke), and serum albumin concentrations were considered potential confounders of the relation between body-composition measures and markers of inflammation and fibrinolysis. Serum albumin concentrations were measured with a Roche-Hitachi Modular System-Modular D (Roche Diagnostics, Tokyo, Japan).

**Statistical methods**

Means (±SDs) and proportions were calculated for all of the variables of interest. Median values with 25th-75th percentile ranges were reported for nonnormally distributed variables. Given the nonnormal distribution of CRP, IL-6, and PAI-1, these marker concentrations were log transformed to make them normally distributed. To permit direct comparisons between CRP, IL-6, and PAI-1 concentrations, all of the results are shown per SD increases in log biomarker. Unadjusted and adjusted linear regression analyses were used to identify regression coefficients (with SE) in BMI and body-composition measures for CRP, IL-6, and PAI-1 concentrations. In the analysis of the relation between fat measures (BMI and percentage of total fat) and markers of inflammation and fibrinolysis, the latter were used as dependent variables. Fat-adjusted and nonfat-adjusted appendicular lean masses were considered dependent variables when analyses were performed between lean measures and markers of inflammation and fibrinolysis. Race and sex interactions were assessed by adding the interaction term for sex (or race) × marker concentrations in the adjusted model. Two-factor analyses of covariance were used to assess the possible interaction of sarcopenia and obesity with CRP, IL-6, or PAI-1 (in log values). If the interaction term was not significant, the models were re-performed after the term exclusion. Obesity was defined as previously described (22). Sarcopenia was defined by the lowest sex-specific tertile of fat-adjusted appendicular lean mass; the cutoffs for residuals of fat-adjusted appendicular lean mass were −0.47135 for the men and −2.79396 for the women. The statistical software SPSS version 10.1.0 (SPSS Inc, Chicago, IL) was used for the statistical analyses.

**RESULTS**

The main sociodemographic characteristics of the sample population (n = 286) are shown in Table 1. The mean (±SD) age of the participants was 66.0 ± 7.4 y. Male sex (57.0%) and white race (75.2%) were the predominant characteristics.

Unadjusted and adjusted linear regression models were fit between body-composition measures and markers of inflammation and fibrinolysis (per SD increase). The association between the inflammatory and the fibrinolysis markers (the dependent variables) and obesity and adipose tissue measures (BMI and percentage of total fat mass) and markers of inflammation and fibrinolysis, the latter were used as dependent variables. Fat-adjusted and nonfat-adjusted appendicular lean masses were considered dependent variables when analyses were performed between lean measures and markers of inflammation and fibrinolysis. Race and sex interactions were assessed by adding the interaction term for sex (or race) × marker concentrations in the adjusted model. Two-factor analyses of covariance were used to assess the possible interaction of sarcopenia and obesity with CRP, IL-6, or PAI-1 (in log values). If the interaction term was not significant, the models were re-performed after the term exclusion. Obesity was defined as previously described (22). Sarcopenia was defined by the lowest sex-specific tertile of fat-adjusted appendicular lean mass; the cutoffs for residuals of fat-adjusted appendicular lean mass were −0.47135 for the men and −2.79396 for the women. The statistical software SPSS version 10.1.0 (SPSS Inc, Chicago, IL) was used for the statistical analyses.

Table 1
positively and significantly associated with both BMI ($\beta = 0.027, SE = 0.013, P = 0.03$) and total fat mass ($\beta = 0.049, SE = 0.011, P < 0.001$); serum concentrations of IL-6 were also positively and significantly associated with both BMI ($\beta = 0.048, SE = 0.013, P < 0.001$) and total fat mass ($\beta = 0.055, SE = 0.012, P < 0.001$). Significant results were also found from adjusted linear regression models between PAI-1 and both BMI ($\beta = 0.038, SE = 0.013, P = 0.005$) and total fat mass ($\beta = 0.032, SE = 0.012, P = 0.007$).

The results from linear regression models that explored the relation between appendicular lean mass measures (dependent variables) and inflammatory and fibrinolysis markers are reported in Table 3. Negative and statistically significant associations were reported between fat-adjusted appendicular lean mass and both CRP ($\beta = -0.629, SE = 0.199, P = 0.002$) and IL-6 ($\beta = -0.467, SE = 0.193, P = 0.02$) and between appendicular lean mass and CRP ($\beta = -0.428, SE = 0.210, P = 0.04$). No significant race or sex interactions were found for the relation of CRP, IL-6, and PAI-1 with either BMI or measures of body composition ($P > 0.05$ for all).

Finally, we performed 2-factor analyses of covariance to evaluate the interaction between sarcopenia (defined as the lowest sex-specific tertile of fat-adjusted appendicular lean mass) and obesity [defined as the age-, sex-, and race-specific percentage of total fat mass (22)] and CRP, IL-6, and PAI-1 concentrations, but no significant interactions were found ($P > 0.1$ for all interactions). In models that included only sarcopenia and obesity as factors, obese participants had significantly ($P < 0.01$) higher concentrations of both CRP (log value: 1.349; 95% CI: 1.125, 1.574) and IL-6 (log value: 1.258; 95% CI: 1.156, 1.359) than did nonobese participants [log values (95% CI) for CRP and IL-6: 0.770 (0.602, 0.938) and 1.074 (0.997, 1.151), respectively]. No significant differences for PAI-1 or between sarcopenic and nonsarcopenic participants were found.

**DISCUSSION**

In the present study we explored the relations between inflammatory and fibrinolysis markers (CRP, IL-6, and PAI-1) and BMI, total fat mass, and 2 measures of sarcopenia. Our findings showed that all of the considered markers of inflammation and fibrinolysis were strongly correlated with obesity and total fat mass. Concentrations of CRP and IL-6, but not of PAI-1, were inversely associated with fat-adjusted appendicular lean mass. In our sample population, CRP concentrations showed a slightly stronger association with sarcopenia than did IL-6 concentrations. Our findings also showed that the association of higher concentrations of inflammatory markers with sarcopenia was mostly explained by the concurrent presence of adipose tissue.

**TABLE 1**
Sociodemographic characteristics of the sample population

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>66.0 ± 7.4(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>43.0</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>75.2</td>
</tr>
<tr>
<td>African American</td>
<td>22.7</td>
</tr>
<tr>
<td>Asian</td>
<td>0.7</td>
</tr>
<tr>
<td>Other</td>
<td>1.4</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>11.5</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22.0</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>7.7</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>5.2</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>14.7</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>8.0</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>2.51 (1.06–5.04)(^2)</td>
</tr>
<tr>
<td>Interleukin 6 (pg/mL)</td>
<td>2.91 (2.24–3.93)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>28.5 ± 4.8</td>
</tr>
<tr>
<td>Total fat mass (%)</td>
<td>32.1 ± 8.3</td>
</tr>
<tr>
<td>Appendicular lean mass (kg)</td>
<td>24.1 ± 5.9</td>
</tr>
</tbody>
</table>

\(^1\) ± SD (all such values).
\(^2\) Median; 25th–75th percentile range in parentheses (all such values).

**TABLE 2**
Association between body fat measures and concentrations of C-reactive protein, interleukin 6, and plasminogen activator inhibitor 1 (dependent variables) per SD increase in log value\(^3\)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (SE)</td>
<td>$P$(^5)</td>
</tr>
<tr>
<td>C-reactive protein(^6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.036 (0.012)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total fat mass (%)</td>
<td>0.043 (0.007)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interleukin 6(^7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.039 (0.012)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total fat mass (%)</td>
<td>0.022 (0.007)</td>
<td>0.003</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor 1(^8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>0.037 (0.012)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total fat mass (%)</td>
<td>−0.001 (0.007)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

\(^1\) $n = 286$.
\(^2\) Adjusted for age, sex, race, smoking, diabetes, angina, myocardial infarction, cancer, stroke, and serum albumin concentrations.
\(^3\) Linear regression models.
\(^4\) SD for log = 1.09424.
\(^5\) SD for log = 0.48534.
\(^6\) SD for log = 0.83576.
TABLE 3
Association between lean mass measures (dependent variables) and concentrations of C-reactive protein, interleukin 6, and plasminogen activator inhibitor 1 per SD increase in log values 

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th></th>
<th>Adjusted†</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta ) (SE)</td>
<td>( P^i )</td>
<td>( \beta ) (SE)</td>
<td>( P^i )</td>
</tr>
<tr>
<td>Fat-adjusted appendicular lean mass*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein†</td>
<td>-0.792 (0.203)</td>
<td>&lt;0.001</td>
<td>-0.629 (0.199)</td>
<td>0.002</td>
</tr>
<tr>
<td>Interleukin 6*</td>
<td>-0.502 (0.207)</td>
<td>0.02</td>
<td>-0.467 (0.193)</td>
<td>0.02</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor 1*</td>
<td>0.232 (0.207)</td>
<td>0.26</td>
<td>0.009 (0.192)</td>
<td>0.96</td>
</tr>
<tr>
<td>Appendicular lean mass*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein*</td>
<td>-0.541 (0.214)</td>
<td>0.01</td>
<td>-0.428 (0.210)</td>
<td>0.04</td>
</tr>
<tr>
<td>Interleukin 6*</td>
<td>-0.261 (0.214)</td>
<td>0.22</td>
<td>-0.208 (0.201)</td>
<td>0.30</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor 1*</td>
<td>0.375 (0.213)</td>
<td>0.08</td>
<td>0.148 (0.200)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

† n = 286.
‡ Adjusted for age, sex, race, smoking, diabetes, angina, myocardial infarction, cancer, stroke, and serum albumin concentrations.
§ Linear regression models.
* Defined as the residuals of linear regression analysis between the dependent variable appendicular lean mass (in kg) and height (in m) and total fat mass (in kg).
* Defined as the residuals of linear regression analysis between the dependent variable appendicular lean mass (in kg) and height (in m).

Sarcopenia, which is the involuntary loss of skeletal muscle that occurs with advancing age (1), is characterized by a decrease of muscular strength and endurance and is significantly associated with a loss of autonomy in older persons (1, 27). In a review, Roubenoff (10) suggested the presence of a vicious cycle between fat gain and loss of muscle, which act synergistically to lead to physical disability (2). In fact, even if the muscle loss is the result of several different underlying causes, muscle loss still represents the major contributor to fat gain, which in turn reinforces muscle loss. The loss of metabolically active cell mass and the weakness that results from the loss of muscle lead to a reduction in resting metabolic rate and physical activity. With an increased fat mass and a reduced muscle mass, physical activity becomes progressively more difficult, and the habitual level of physical activity decreases further. This mechanism leads to sarcopenic obesity, a major risk factor for the onset of physical disability (2, 7, 28). Our findings from the present study support this hypothesis. In fact, inflammatory markers were strongly and negatively associated with fat-adjusted appendicular lean mass; only CRP showed low significance when we tested a lean mass measure without taking fat mass into account. This finding supports evidence that suggests that fat mass should be considered in estimates of the prevalence of sarcopenia (2, 20).

In the present study we also explored the possible presence of an interaction of sarcopenia and obesity with concentrations of inflammatory markers. No interactions were found. Our analyses showed that obesity explains most of the association between sarcopenia and inflammation. In fact, when the dichotomous variables of obesity and sarcopenia were simultaneously added to the models, only the former remained significantly associated with inflammatory marker concentrations.

Inflammation has been indicated as a potential explanation to the age-related changes in body composition that lead to sarcopenia (1, 9, 16, 26, 29, 30). Several theories hypothesize that inflammation plays an important role during the aging process (31, 32), and a significant increase in production of IL-6 has been reported with advancing age (33). However, the relation between inflammation, adipose tissue, and muscle mass is very close. Major inflammatory markers, such as cytokines, are secreted by adipocytes, and their concentrations have been shown to be associated with obesity (14, 24, 34, 35). At the same time, evidence from humans (25, 36) as well as animal models (37–39) shows a direct negative influence of cytokines on muscle mass, and increased concentrations of inflammatory markers have been associated with a reduced lean mass (19, 36, 40). Previous studies have reported that weight gain and lean tissue anabolism are associated with the use of cytokine inhibitors (25). Moreover, a direct effect of inflammation on physical function, which accelerates changes in body composition that are typical of the aging process (ie, fat gain and loss of muscle mass), has also been suggested (12). Despite this, obese persons tend to have a higher amount of lean tissue as a result of a higher total body mass.

Several indirect mechanisms through which inflammation can affect body composition have also been shown. In fact, inflammation may enhance catabolic mechanisms (16), which promotes the onset of insulin resistance (41, 42), reduces the dietary energy intake (16), or lowers concentrations of insulin-like growth factor 1 (9, 26). It has also been suggested that age-related changes in body composition might be related to reduced physical activity, which is inversely related to inflammation (43).

In a well-functioning population aged 70-79 y, Visser et al (19) showed that plasma concentrations of IL-6 and tumor necrosis factor α were inversely associated with muscle mass and strength. Our study extends these findings to CRP, an inflammatory marker that is more widely used, and in a population characterized by a higher cardiovascular disease risk. Our results also confirm evidence from previous studies that showed a relation between BMI and total fat mass and markers of inflammation and fibrinolysis (14, 18, 24, 35). Given the well-established relation between BMI and total fat mass and cardiovascular diseases (17, 44), our results indirectly provide further support for the role played by CRP, IL-6, and PAI-1 as risk factors for cardiovascular disease.
Some limitations of the present study should be mentioned. The cross-sectional design of the study did not allow us to investigate the cause-effect relation between markers of inflammation and fibrinolysis and body-composition measures. The TRAIN study population is composed of highly selected subjects with a high cardiovascular disease risk profile. Therefore, our findings might have been driven by the presence of subclinical conditions that predispose the subjects to cardiovascular diseases. Additional studies are needed to confirm our results in the general population. Finally, we used self-reported height to calculate BMI and to derive residuals of appendicular lean mass (both unadjusted and fat-adjusted). Self-reported height may not be as accurate as measured heights, especially in older persons. However, the high correlations reported between self-reported and measured heights may have limited a potential bias in our findings (45, 46).

In conclusion, our study showed that obesity, a major risk factor for health-related outcomes, is strongly and positively associated with CRP, IL-6, and PAI-1 concentrations. Inflammatory markers are also inversely associated with appendicular lean mass independent of fat mass, which is consistent with an effect of inflammation on muscle mass. Our findings suggest a possible role of obesity-associated inflammation in the age-related process that leads to sarcopenia.

MC was involved in the study design, the data analyses, and the writing of the manuscript. SBK and MP were involved in the study design, the writing of the manuscript, and the critical review of the manuscript. RNB was involved in the study design and the critical review of the manuscript. HHA, LL, and RPT were involved in the data collection and the critical review of the manuscript. BWJHP was involved in the critical review of the manuscript. WTA was involved in the data management, the data analyses, and the critical review of the manuscript. SLF was involved in the data management and the critical review of the manuscript. None of the authors had any conflicts of interest.

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