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Race modifies the association between adiposity and inflammation in patients with chronic kidney disease: findings from the CRIC study

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Abstract

Objective—To examine the race-specific association of inflammation with adiposity and muscle mass in subjects with chronic kidney disease (CKD).

Design and Methods—Plasma concentration of IL-1β, IL-Receptor antagonist (IL-1RA), IL-6, IL-10, TNF-α, TGF-β, hs-CRP, fibrinogen, and serum albumin were measured in 3,939 Chronic Renal Insufficiency Cohort study participants. Bioelectric impedance analysis was used to determine body fat mass (BFM) and fat free mass (FFM).

Results—Plasma levels of hs-CRP, fibrinogen, IL-1RA, IL-6, and TNF-α increased and serum albumin decreased across the quartiles of body mass index. In multivariable analysis, BFM and

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Competing interests:
The authors have no competing interest.

FFM were positively associated with hs-CRP, fibrinogen, IL-1β, IL-1RA and IL-6. One standard deviation (SD) increase in BFM and FFM was associated with 0.36 (95% CI 0.33, 0.39) and 0.26 (95% CI 0.22, 0.30) SD increase in log transformed hs-CRP, respectively ($p<0.001$). Race stratified analysis showed that the association between biomarkers and BFM and FFM differed by race, with Caucasians demonstrating a stronger association with markers of inflammation than African Americans.

Conclusion—BFA and FFM are positively associated with markers of inflammation in patients with CKD. Race stratified analysis showed that Caucasians have a stronger association with markers of inflammation compared to African Americans.

Keywords

Bioelectric impedance analysis; cytokines; acute phase proteins; muscle mass; Body mass index; African Americans

Introduction

Findings from the Chronic Renal Insufficiency Cohort study showed that about 86% of subjects with chronic kidney disease (CKD) have some evidence of inflammation (1). Inflammatory state is characterized by activation of an array of soluble factors such as cytokine and chemokines. Elevated plasma cytokine levels in CKD could be a consequence of decreased elimination and/or increased generation. It is now well recognized that obesity is a chronic inflammatory state (2). A number of cross-sectional and longitudinal studies from diverse populations have revealed that higher body mass index is a risk factor for the prevalence and progression of CKD (3). Analysis of data from the United States Renal Data System (USRDS) showed that among incident patients with ESRD, mean BMI increased from 25.7 to 27.5 kg/m^2 during the years 1995 to 2002 (4). However, BMI does not discriminate between muscle mass and fat mass. The inflammatory response and prognostic implications of body fat mass (BFM) and muscle mass may be different (5). Although most of the circulating cytokines are secreted from activated macrophages and lymphocytes, adipocytes and skeletal muscle are also a possible source of these cytokines (6;7). Evidence from basic science laboratory and clinical translational studies indicate that pro-inflammatory cytokines mediate muscle protein catabolism (8–11). The association between inflammation and body composition has not been studied in a large cohort of racially diverse CKD patients with varying level of kidney function.

We hypothesized that inflammatory biomarkers are positively associated with BFM and negatively with fat free mass (FFM). We further hypothesized that the association between anthropometric measures and inflammation is modulated by race. Thus, in this study, we examine the association between inflammation and bio-electric impedance analysis (BIA)-derived measures of adiposity and muscle mass in CRIC study participants.

Methods and procedures

The CRIC Study

The organization, design, and methods of the CRIC study have been previously reported (12). Briefly, the CRIC study is a multi-center, prospective observational cohort study of 3,939 subjects with established CKD. The exclusion criteria in CRIC were monogenetic renal disease, cirrhosis, class III or IV heart failure, HIV, cancer, autoimmune disease, or current immunosuppressive therapy, polycystic kidney disease, pregnant women, subjects with organ or bone marrow transplant, and persons who had received immunotherapy for primary renal disease or systemic vasculitis within the past six month or had systemic chemotherapy. The study protocol was approved by the Institutional Review Board at each participating site. Written informed consent was obtained from all study participants.

CRIC Data Collection

Demographic and clinical characteristics were determined at baseline. Self-reported race/ethnicity was documented. Serum creatinine was measured by the Jaffe method on a Beckman Synchron System. Serum cystatin C was measured on a Dade-Behring BNII, with a coefficient of variation (CV) of about 1.7%. We calculated the glomerular filtration rate using the estimating equation derived from the CRIC cohort (eGFR) (13).

BMI was calculated as body weight in kg/ (height in meters)^2

Bioelectric Impedance Analysis

All CRIC study participants underwent BIA studies at baseline with a Quantum II analyzer employing standard techniques. The bioelectrical impedance analyzer vectors the impedance signal (Z, in ohms, Ω) into resistance (R, Ω) and reactance (Xc, Ω) as a direct series measurement. Values for FFM and BFM were determined using established predictive formulae (14). Muscle mass was derived using the equation that has been validated using magnetic resonance imaging (15) and applied to patients with CKD (16).

$$FFM = (a \times Ht^2) + (b \times Wt) + (c \times A) + (d \times R) + e$$

where Ht is height in cm, Wt is weight in kg, A is age, R is impedance (Ω), and a and e are constants provided by the manufacturer.

$$\text{Body fat mass (kg)} = BW - 0.55\,(Ht^2/R) - 16.69 \text{ (Males)} = BW - 0.55\,(Ht^2/R) - 11.49 \text{ (Females)}$$

BW is body weight in kg, Ht height in cm

Chertow et al (17) has shown that BIA is a sensitive tool for evaluating body composition in patients with kidney disease.

Measurement of Biomarkers of Inflammation

High sensitivity sandwich ELISAs (Quantikine HS, R&D Systems, Minneapolis, MN) were used to measure plasma interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α levels. Standard sandwich ELISAs (Quantikine, R&D Systems) were used to quantify IL-1

Receptor Antagonist (IL-1RA) and transforming growth factor (TGF)-β levels. Integrated performance of IL-1β, IL-1RA, IL-6, and TNF-α ELISAs were implemented using a robotic liquid handling platform (Biomek FXp, Beckman Coulter, Brea, CA). All cytokine assays were performed in duplicates and the mean value was used in the analysis. Several blood samples had a concentration of IL-1β below the minimal level for detection (0.125); to these samples we arbitrarily assigned a very low value for IL-1β at (0.00001). High sensitivity C-reactive protein (hsCRP) and fibrinogen were quantified in EDTA plasma samples using specific laser-based immunonephelometric methods on the BNII (Siemens Healthcare Diagnostics, Deerfield, IL).

Calculation of Inflammation Score

We computed a composite score ranging from 0 to 5 based on levels as reported by us earlier (1). When the levels of the following biomarkers were at or above the range indicated a score of "1" was assigned: (a) hsCRP >3 mg/L, (b) fibrinogen >350 mg/dL, (c) IL-6 ≥6 pg/mL, (d) TNF-α ≥7 pg/mL, and (e) IL-1β≥ 0.39 pg/ml. The cut-off values for individual biomarkers were chosen from published literature.

Statistical Analysis

Selected demographic and clinical characteristics of the study population were summarized by BMI quartiles. Continuous variables were presented as mean and standard deviation (SD), or median and interquartile range, and were compared across BMI quartiles using ANOVA or Kruskal–Wallis test, as appropriate. Categorical variables were presented as frequency and percentages and were compared across BMI quartiles using a chi-square test. Multivariable linear regression models were employed to estimate the association of BMI, BFM, and FFM with biomarkers of inflammation, adjusting for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid lowering medications, aspirin and ACE-I/ARB use, metabolic equivalent of tasks (METS), and eGFR, which was estimated using an equation developed within CRIC (13). Natural logarithm transformation (ln) was applied to the biomarkers of inflammation that had skewed distribution. In the regression analyses done in each instance, adjustment was only made for one cytokine or inflammatory marker in each model tested. Both the exposures (i.e. BMI, BFM and FFM) and outcomes of interest were standardized by dividing the SDs. An additional subgroup analysis estimated the association of BMI, BFM, and FFM with biomarkers of inflammation by eGFR group, dividing the CRIC participants into two groups: 1) individuals with advanced CKD with an eGFR <30 ml/min/1.73 m^2 (n=804) and individuals with an eGFR≥30 ml/min/1.73 m^2 (n=3,123). We dichotomized the cohort because the number of subjects in each stage of CKD was too small to derive meaningful conclusions. The analysis was adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid lowering medications, aspirin and ACE-I/ARB use, metabolic equivalent of tasks (METS), and eGFR. Subgroup analyses were done in Caucasian and African Americans and formal tests of effect modification by race were done by checking the significance of the interaction terms between race and biomarkers of inflammation. We also investigated the interaction between race and biomarkers of inflammation by eGFR level (eGFR ml/min/1.73 m^2 and eGFR≥30 ml/min/1.73 m^2). Subgroup analysis was not done in Hispanics because of the relatively

small sample size. All analyses were done with the SAS statistical software (V9.3, SAS Inc., Cary, NC).

Results

We studied 3,684 of the 3,939 (93.5%) CRIC study participants, in whom BIA and inflammation biomarker results were available. Baseline clinical and demographic characteristics according to the quartile of BMI are presented in Table 1. Subjects in the highest quartile were more likely to be African American, females with hypertension, insulin resistance and diabetes, who were physically inactive and received treatment with lipid lowering agents. They also had the lowest hemoglobin level and highest WBC count. Individuals in the lowest BMI group were more likely to be Caucasian, smokers, with a college level education, who consumed the highest amount of protein and calories. Although serum creatinine was not significantly different across the quartiles of BMI, eGFR was lower and cystatin C level was greater in patients in the highest quartile of BMI. As expected, waist circumference, BFM, and FFM were higher in the larger BMI groups. The ratio of FFM to BFM decreased across the higher BMI categories.

Plasma levels of hs-CRP, fibrinogen, IL-1RA, IL-6, and TNF-α increased significantly across increasing quartiles of BMI (Table 2). Serum albumin, on the other hand decreased significantly in the higher BMI group. There were 531 (14.4%) subjects with no evidence of inflammation (inflammation score "0") and 173 subjects (4.7%) with inflammation score ≥4. As shown in Figure 1, subjects with a higher inflammation score tend to have larger BMI, as well as higher BFM and FFM ($p<0.01$). Subjects with inflammation score ≥4 had a significantly higher BMI (34.2 ± 7.9 vs. 28.5 ± 5.4 kg/m^2, $p<0.001$), BFM (33.5 ± 16.2 vs. 24.8 ± 9.8 kg, $p<0.001$), and FFM (63.0 ± 16.1 vs. 59.6 ± 15.5 kg, $p=0.02$) compared to those with inflammation score of "0".

In multivariable linear regression, after adjusting for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid lowering medications, ACE-I/ARB, METS, aspirin use, and eGFR, BMI was positively associated with IL-1β, IL-1RA, IL-6, hs-CRP, and fibrinogen, but negatively with serum albumin (Table 3). Similar association between the biomarkers of inflammation with BFM and FFM was noted, except that the association between serum albumin and BFM was not significant. One SD increase in BFM and FFM was associated with a 0.36 (95% CI 0.33, 0.39) and a 0.26 (95% CI 0.22, 0.30) unit increase in ln hs-CRP, respectively ($p<0.001$ for both). FFM was weakly, but negatively associated with TNF-α and serum albumin. We examined whether the association between body composition and inflammation differs in patients with eGFR <30 ml/min/1.73 m^2 and ≥30 ml/min/1.73 m^2 (Table 4). Positive association between BFM, FFM, and IL-1β, FFM and IL-10 as well as negative association between TNF-α and FFM noted in those with higher eGFR did not retain significance in subjects with lower eGFR.

While examining the association between body composition and inflammation, significant interaction with race was evident. Interaction between race and BFM was noted for IL-6 ($p=0.03$), IL-1RA ($p=0.004$), and the inflammation score ($p=0.003$) in the full cohort (Figure 2). On sub-group analysis, such interaction was evident only in subjects with only in those

with eGFR ≥30 ml/min/1.73 m^2 (n=3,123) and confined to inflammation score (p=0.015) and IL-1RA (p=0.023; data not shown). Interaction was significant for IL-1RA (p=0.045) for FFM in the full cohort (Figure 3). On further analysis, such interaction was confined to those with eGFR <30 ml/min/1.73 m^2 (n=804) for fibrinogen, TGFβ and IL-1β (p-values of 0.04, 0.006, and 0.039, respectively; data not shown). These associations were stronger in Caucasians compared to African Americans.

Discussion

In this study, we examined the association between body composition determined by BIA and biomarkers of inflammation in a large, cohort of subjects with broad range of kidney function. In general, a robust positive association between BFM and several pro-inflammatory biomarkers was evident. However, contrary to our hypothesis, a positive association between FFM and some inflammatory markers was noted. Race stratified analysis showed that the association between inflammatory biomarkers and body composition differs by race, with Caucasians demonstrating a stronger association with markers of inflammation as compared to African Americans.

BMI is a simple index to classify adults as overweight or obese (18). We found that about 84.2% of the CRIC study participants were either overweight or obese, with 55.6% being obese. Not unexpectedly, we noted higher representation of African Americans females in the larger BMI category (Table 1). Obesity among African Americans has been variously attributed to genetics, weight misperception, and lower socioeconomic status. Several cross-sectional and longitudinal studies have shown that higher BMI is associated with prevalent CKD and a risk factor for the progression of CKD (3;19). Accordingly, we found that eGFR was lower and cystatin C higher across increasing quartiles of BMI (p<0.01). Cystatin C is claimed to be a more sensitive marker for kidney function than serum creatinine (20), and it has also greater association with inflammation (1). Re-analysis of the data using the traditional definition of obesity by BMI (21), did not change any of the observations except that those with BMI<18.5 and ≥35 had higher level of TNF-α compared to others. However, there were only 23 subjects in the BMI <18.5 category.

We found that the plasma level of pro-inflammatory cytokines (IL-6 and TNF-α) and positive acute phase proteins (hs-CRP and fibrinogen) increased across the quartiles of BMI (Table 2). Although the IL-1β level was not different, the plasma level of IL-1RA was significantly higher in subjects with larger BMI. Circulating cytokine receptors may provide additional information in chronic inflammatory conditions because they generally have a longer half-life than the cytokines themselves; therefore exhibiting more constant levels over time (22).

There is mounting evidence to suggest that BMI may not be an ideal measure of obesity, since it does not discriminate between fat mass and muscle mass (21). BIA determines electrical impedance of body tissues, from which BFM and FFM can be reliably estimated in subjects with and without kidney disease (14;17;23). Contribution of adipose tissue and skeletal muscle mass to the prevailing inflammatory state and clinical outcomes may be different (24). In response to inflammatory signals, adipocytes induce expression of several

mediators of inflammation (25). Adipocytokines, through autocrine, paracrine, and endocrine mechanisms, mediate changes in body composition (5). In order to clearly chart the association between inflammation and body composition, it is important to integrate information derived from multiple biomarkers as a measure of prevailing inflammatory state (1). We computed an inflammation score using multiple pro-inflammatory markers and found that the BMI, BFM, and FFM increased progressively and significantly with a higher intensity of inflammation (Figure 1).

In multivariable linear regression after adjusting for confounding variables, a positive association between several markers of inflammation and body composition was evident (Table 3). The association between inflammatory biomarkers and BFM and FFM was influenced by the level of eGFR (Table 4). These findings should be interpreted with caution, since the number of patients with eGFR<30 ml/min/1.73 m^2 was small. The relative contribution of adipocytokines released from adipocytes and myokines from skeletal muscle to the systemic inflammation is not known (10;24). Preliminary evidence indicates that skeletal muscle and adipose tissue contribute to about 12% and 10 to 35% of the circulating IL-6 respectively (11). Using arterio-venous balance studies and immunohistochemistry techniques, we showed that skeletal muscle is an important source of cytokines in patients with ESRD (7;10). When secreted from the muscle, IL-6 acts as a hormone, signaling and affecting the liver and adipose tissue. Besides its well-recognized role in mediating muscle protein catabolism, cytokines are also essential for successful muscle regeneration (10;26). In the present study, we noted that one SD increase in BFM and FFM were associated with 0.14 SD (95% CI [0.11, 0.18]) and 0.13 SD (95% CI [0.09, 0.17]) SD increase in ln(IL-6), respectively (Table 3). Surprisingly, we noted a weak but negative was association between serum albumin and FFM. Raj et al studied protein kinetics in patients with kidney disease using a three compartmental model and showed that IL-6 mediates muscle protein breakdown and the amino acid released from muscle is utilized for acute phase protein synthesis in the liver (10;27). However, the differential role for adipocytokines and myokines on albumin kinetics needs further investigation using techniques that determine muscle mass more precisely.

In a large prospective cohort study that examined the association between BMI and death rates among US adults, mortality rates increased with higher BMI, but less so for African Americans (28). In our study, we observed that the association between adiposity and inflammation is modified by race. The associations were more robust in Caucasians than in African Americans (Figure 2). African Americans have less visceral fat compared to Caucasians with similar waist to hip ratio and BMI (29;30). This may explain the lower degree of inflammation present in African Americans, since visceral fat is known to have higher expression of pro-inflammatory cytokines such as TNF-α and IL-6 (31). The amount of FFM also differs between ethnicities. African Americans have more FFM compared to Caucasians, which may also contribute to the racial differences observed between these ethnicities (32). The attenuated inflammatory signals from fat mass may explain in part the improved survival reported in obese members of the racial minority groups with kidney disease.

Our study has number of strengths, which includes a large cohort of patients with representation of different races, broad range of kidney function, study of a number of biomarkers, and determination of body composition using BIA. However, our findings should be considered within the context of several limitations: (a) this is a cross-sectional study and hence temporal associations and causality cannot be inferred; (b) cytokine profile and acute phase response exhibit inter- and intra-individual variability over time (33); (c) the determination of body composition by BIA could be influenced by changes in hydration(34); and (d) BIA does not distinguishes between visceral and subcutaneous adiposity. It has been shown that visceral fat is a stronger predictor of inflammation than fat deposits in other sites (35).

To summarize, we examined the association of adiposity and muscle mass with biomarkers of inflammation in CRIC Study participants and noted a strong positive association between several markers of inflammation and BFM. The association between FFM and inflammatory biomarkers was also positive in general, but less pronounced. Race stratified analysis showed that the association between adiposity and inflammation was stronger in Caucasians compared to African Americans. Additional studies aimed towards understanding the genetic and molecular mechanisms for the racial differences in inflammatory response to adiposity are warranted.

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Raj conceived the hypothesis; Raj, Wing, and Yang wrote the manuscript; Yang, Teal, and Tao performed the data analysis; Sankar Navaneethan, Akinlolu Ojo, Nicolas N. Guzman, Muredach Reilly, Melanie Wolman MPH, Sylvia E. Rosas, Magda Cuevas, Michael Fischer, Eva Lustigova, Stephen R. Master, Dawei Xie, Dina Appleby, Marshall Joffe, John Kusek, and Harold I Feldman reviewed and edited the manuscript and approve the final version of the manuscript.

Reference List

1. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association between Albuminuria, Kidney Function, and Inflammatory Biomarker Profile. Clin J Am Soc Nephrol. 2012; 7:1938–1946. [PubMed: 23024164]
2. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011; 29:415–445. [PubMed: 21219177]
3. Ejerblad E, Fored CM, Lindblad P, Fryzek J, McLaughlin JK, Nyren O. Obesity and risk for chronic renal failure. J Am Soc Nephrol. 2006; 17(6):1695–1702. [PubMed: 16641153]
4. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol. 2006; 17(5):1453–1459. [PubMed: 16597682]
5. Mak RH, Cheung W. Cachexia in chronic kidney disease: role of inflammation and neuropeptide signaling. Curr Opin Nephrol Hypertens. 2007; 16(1):27–31. [PubMed: 17143068]

6. Kimmel PL, Phillips TM, Phillips E, Bosch JP. Effect of renal replacement therapy on cellular cytokine production in patients with renal disease. Kidney Int. 1990; 38(1):129–135. [PubMed: 2385082]
7. Raj DSC, Dominic EA, Pai A, Osman F, Morgan M, Pickett G, et al. Skeletal muscle, cytokines and oxidative stress in End-stage renal disease. Kidney Int. 2005; 68:2338–2344. [PubMed: 16221238]
8. Raj DS, Shah H, Shah VO, Ferrando A, Bankhurst A, Wolfe R, et al. Markers of inflammation, proteolysis, and apoptosis in ESRD. Am J Kidney Dis. 2003; 42(6):1212–1220. [PubMed: 14655193]
9. Cheung WW, Paik KH, Mak RH. Inflammation and cachexia in chronic kidney disease. Pediatr Nephrol. 2010; 25(4):711–724. [PubMed: 20111974]
10. Raj DS, Moseley P, Dominic EA, Onime A, Tzamaloukas AH, Boyd A, et al. Interleukin-6 modulates hepatic and muscle protein synthesis during hemodialysis. Kidney Int. 2008; 73(9): 1054–1061. [PubMed: 18288103]
11. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. J Clin Endocrinol Metab. 1998; 83(3):847–850. [PubMed: 9506738]
12. Feldman HI, Appel LJ, Chertow GM, Cifelli D, Cizman B, Daugirdas J, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: Design and Methods. J Am Soc Nephrol. 2003; 14(7 Suppl 2):S148–S153. [PubMed: 12819321]
13. Anderson AH, Yang W, Hsu CY, Joffe MM, Leonard MB, Xie D, et al. Estimating GFR Among Participants in the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2012; 60(2):250–261. [PubMed: 22658574]
14. Bellizzi V, Scalfi L, Terracciano V, De NL, Minutolo R, Marra M, et al. Early changes in bioelectrical estimates of body composition in chronic kidney disease. J Am Soc Nephrol. 2006; 17(5):1481–1487. [PubMed: 16611719]
15. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol. 2000; 89(2):465–471. [PubMed: 10926627]
16. Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Association between renal insufficiency and malnutrition in older adults: results from the NHANES III. Kidney Int. 2001; 60(5):1867–1874. [PubMed: 11703605]
17. Chertow GM, Lowrie EG, Wilmore DW, Gonzalez J, Lew NL, Ling J, et al. Nutritional assessment with bioelectrical impedance analysis in maintenance hemodialysis patients. Journal of the American Society of Nephrology. 1995; 6(1):75–81. [PubMed: 7579073]
18. National Institute of Health. Clinical guidelines on the identification, Evaluation and Treatment of Overweight and Obesity in Adults. Bethesda, MD: NIH; 1998.
19. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004; 291(7):844–850. [PubMed: 14970063]
20. Muntner P, Winston J, Uribarri J, Mann D, Fox CS. Overweight, obesity, and elevated serum cystatin C levels in adults in the United States. Am J Med. 2008; 121(4):341–348. [PubMed: 18374694]
21. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. 2000. Report No.: World Health Organ Tech Rep Ser 894
22. Balakrishnan VS, Jaber BL, Natov SN, Cendoroglo M, King AJ, Schmid CH, et al. Interleukin-1 receptor antagonist synthesis by peripheral blood mononuclear cells in hemodialysis patients. Kidney Int. 1998; 54(6):2106–2112. [PubMed: 9853276]
23. Roubenoff R. Applications of bioelectrical impedance analysis for body composition to epidemiologic studies. Am J Clin Nutr. 1996; 64(3 Suppl):459S–462S. [PubMed: 8780363]
24. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor-alpha, in vivo. J Clin Endocrinol Metab. 1997; 82(12):4196–4200. [PubMed: 9398739]
25. Fain JN, Madan AK, Hiler ML, Cheema P, Bahouth SW. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. Endocrinology. 2004; 145(5):2273–2282. [PubMed: 14726444]

26. Serrano AL, Baeza-Raja B, Perdiguero E, Jardi M, Munoz-Canoves P. Interleukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. Cell Metab. 2008; 7(1):33–44. [PubMed: 18177723]
27. Boivin MA, Battah SI, Dominic EA, Kalantar-Zadeh K, Ferrando A, Tzamaloukas AH, et al. Activation of caspase-3 in the skeletal muscle during haemodialysis. Eur J Clin Invest. 2010; 40(10):903–910. [PubMed: 20636378]
28. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 341(15):1097–1105. [PubMed: 10511607]
29. Lovejoy JC, de la Bretonne JA, Klemperer M, Tulley R. Abdominal fat distribution and metabolic risk factors: effects of race. Metabolism. 1996; 45(9):1119–1124. [PubMed: 8781299]
30. Carroll JF, Chiapa AL, Rodriquez M, Phelps DR, Cardarelli KM, Vishwanatha JK, et al. Visceral fat, waist circumference, and BMI: impact of race/ethnicity. Obesity (Silver Spring). 2008; 16(3): 600–607. [PubMed: 18239557]
31. Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol. 2010; 314(1):1–16. [PubMed: 19682539]
32. Hull HR, Thornton J, Wang J, Pierson RN Jr, Kaleem Z, Pi-Sunyer X, et al. Fat-free mass index: changes and race/ethnic differences in adulthood. Int J Obes (Lond). 2011; 35(1):121–127. [PubMed: 20531353]
33. Nascimento MM, Pecoits-Filho R, Qureshi AR, Hayashi SY, Manfro RC, Pachaly MA, et al. The prognostic impact of fluctuating levels of C-reactive protein in Brazilian haemodialysis patients: a prospective study. Nephrol Dial Transplant. 2004; 19(11):2803–2809. [PubMed: 15496560]
34. Kushner RF, Gudivaka R, Schoeller DA. Clinical characteristics influencing bioelectrical impedance analysis measurements. Am J Clin Nutr. 1996; 64(3 Suppl):423S–427S. [PubMed: 8780358]
35. Beasley LE, Koster A, Newman AB, Javaid MK, Ferrucci L, Kritchevsky SB, et al. Inflammation and race and gender differences in computerized tomography-measured adipose depots. Obesity (Silver Spring). 2009; 17(5):1062–1069. [PubMed: 19165157]

What is already known about this subject?

- Adiposity is associated with inflammation
- Cytokines mediate muscle protein catabolism

What does this study add?

- Fat mass as well as muscle mass are associated with markers of inflammation in patients with chronic kidney disease
- Caucasians with CKD exhibit a stronger association between body composition and markers of inflammation than African Americans

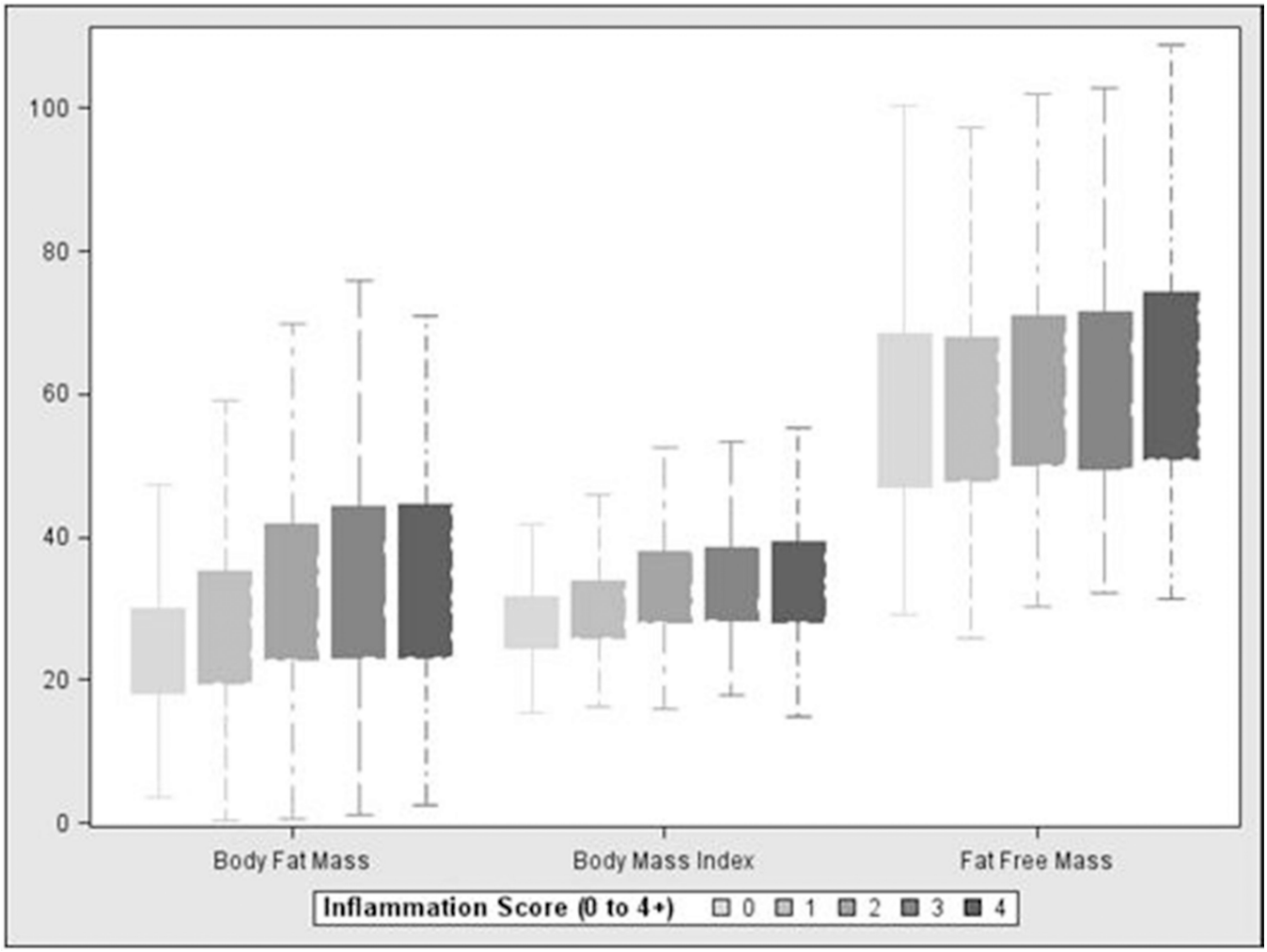

Figure 1.

Association between inflammation score and body mass index, body fat mass, and fat free mass in CRIC Study participants. All anthropometric measures were higher in CRIC study participants with higher inflammation score ($p<0.01$).

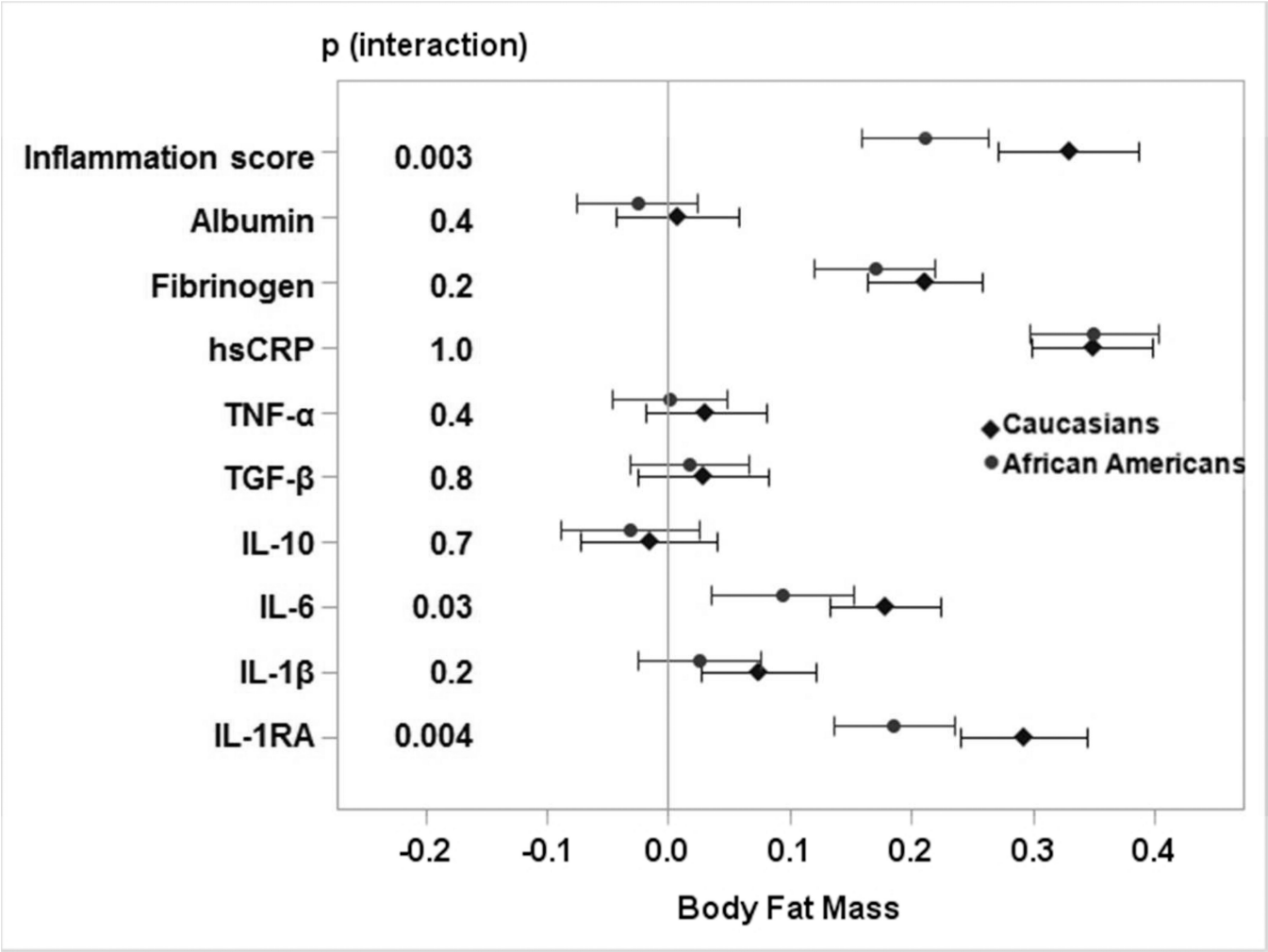

Figure 2.

Multivariable adjusted association between body fat mass and biomarkers of inflammation in Caucasians and African Americans. A significant interaction between race and BFM was noted for IL-6, IL-1RA, and the inflammation score.

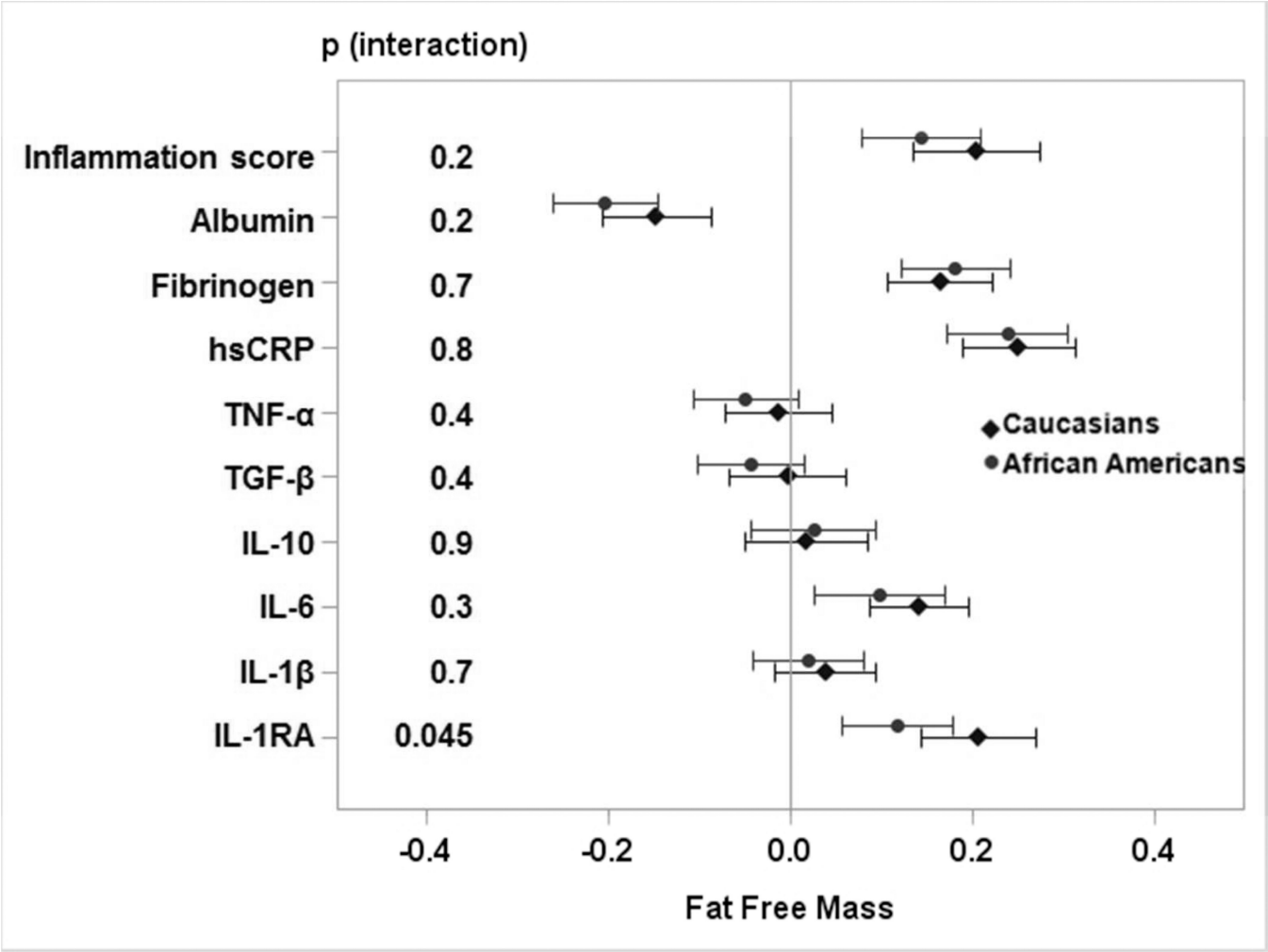

Figure 3.

Multivariable adjusted association between fat free mass and biomarkers of inflammation in Caucasians and African Americans. A significant interaction between race and FFM was evident for IL-1RA.

Table 1

Demography of the study population according to the quartiles of body mass index

Variable	Body Mass Index (kg/m^2)				P-value
	<26.8 (n = 915)	≥26.8 to <30.9 (n = 920)	≥30.9 to <36.1 (n = 928)	≥36.1 (n = 921)	
Age (years)	56.7 (12.3)	59.2 (10.9)	59.2 (10.2)	57.5 (10.4)	<0.01
Male Sex (%)	479 (52.4)	614 (66.7)	556 (59.9)	360 (39.1)	<0.01
Race/Ethnicity (%)					
Caucasians	459 (50.2)	411 (44.7)	377 (40.6)	319 (34.6)	<0.01
African Americans	290 (31.7)	343 (37.3)	402 (43.3)	492 (53.4)	
Hispanic	103 (11.3)	119 (12.9)	128 (13.8)	91 (9.9)	
Other*	63 (6.9)	47 (5.1)	21 (2.3)	19 (2.1)	
Diabetes (%)	288(31.5)	400 (43.5)	480 (51.7)	600 (65.2)	<0.01
Hypertension (%)	710 (77.6%)	796 (86.5%)	811 (87.4%)	851 (92.4%)	<0.01
Smokers (%)	167 (18.3)	120 (13.0)	105 (11.3)	88 (9.6)	<0.01
Educational Level (%)					
College graduate	370 (40.4)	325 (35.4)	278 (30.0)	200 (21.7)	<0.01
Some college education	223 (24.4)	265 (28.8)	286 (30.8)	299 (32.5)	
Higher secondary graduation	147 (16.1)	155 (16.9)	164 (17.7)	218 (23.7)	
Less than Higher secondary education	175 (19.1)	174 (18.9)	200 (21.6)	204 (22.2)	
Calorie intake (kcal/kg/day)	26.0 (11.5)	21.7 (9.5)	19.2 (8.4)	16.4 (7.6)	<0.01
Protein intake (grams/kg/day)	1.0 (0.5)	0.8 (0.4)	0.8 (0.4)	0.6 (0.3)	<0.01
Total METS (kcal/kg/hour)	168 (116–254)	170 (112–256)	167 (109–245)	153 (104–242)	0.03
HOMA-IR	4.1 (5.5)	5.9 (7.4)	6.9 (7.6)	9.1 (9.4)	<0.01
Hemoglobin (g/dL)	12.6 (1.8)	12.9 (1.8)	12.7 (1.7)	12.3 (1.7)	<0.01
WBC count (×10^3/μL)	6.3 (2.0)	6.4 (1.9)	6.6 (2.0)	7.0 (3.0)	<0.01
Serum Creatinine (mg/dL)	1.72 (0.60)	1.75 (0.57)	1.75 (0.57)	1.73 (0.56)	0.72
CRIC eGFR (mL/min/1.73 m^2)	46.8 (18.3)	46.2 (16.4)	45.4 (16.8)	41.9 (15.2)	<0.01
Cystatin C (mg/L)	1.45 (0.54)	1.46 (0.52)	1.50 (0.54)	1.62 (0.53)	<0.01
Total cholesterol (mg/dL)	187.1 (45.5)	184.3 (46.4)	183.1 (46.1)	181.9 (43.0)	0.08

Variable	Body Mass Index (kg/m^2)				P-value
	<26.8 (n = 915)	**≥26.8 to <30.9 (n = 920)**	**≥30.9 to <36.1 (n = 928)**	**≥36.1 (n = 921)**	
Low density lipoprotein (mg/dL)	103.9 (35.0)	103.8 (36.4)	101.5 (35.0)	102.2 (34.7)	0.37
Triglyceride (mg/dL)	130.8 (90.0)	160.3 (117.6)	170.7 (131.1)	166.7 (118.4)	<0.01
Body composition					
Body Fat Mass (kg)	18.0 (5.8)	25.2 (6.5)	32.3 (7.8)	48.4 (14.5)	<0.01
Fat Free mass (kg)	49.6 (10.2)	58.8 (11.3)	63.5 (14.0)	70.2 (17.5)	<0.01
FFM/BFM	3.4 (3.9)	2.7 (2.8)	2.6 (9.8)	1.8 (2.6)	<0.01
Waist circumference (cm)	87.5 (9.3)	100.2 (8.1)	109.7 (10.2)	126.1 (13.7)	<0.01
Lipid lowering drugs (%)	446 (49.2)	554 (60.8)	582 (62.9)	604 (66.1)	<0.01

Data presented as mean and SD or median and interquartile range

* Includes Asian/Pacific Islanders and Native Americans

Abbreviations: HS, high school; Grad, graduate; CHF, congestive heart failure; METS, metabolic equivalent of tasks; HOMA-IR, homeostasis model of assessment-insulin resistance

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Table 2

Biomarkers of inflammation according to the quartiles of body mass index

	Body Mass Index (kg/m^2)				
Variable	**<26.8 (n = 915)**	**≥26.8 to <30.9 (n = 920)**	**≥30.9 to <36.1 (n = 928)**	**≥36.1 (n = 921)**	**P-value**
Acute phase proteins					
hs-CRP (mg/L)	1.2 (0.6–3.2)	2.0 (0.9–5.0)	2.9 (1.3–6.6)	4.7 (2.1–9.1)	<0.01
Fibrinogen (mg/L)	3700 (3100–4400)	3900 (3300–4600)	4100 (3400–4800)	4500 (3800–5200)	<0.01
Albumin (g/dL)[1]	3.99 (0.51)	3.97 (0.46)	3.96 (0.45)	3.85 (0.43)	<0.01
Cytokines					
Interleukin-1β (pg/mL)	0.18 (0.06–1.1)	0.18 (0.06–1.1)	0.15 (0.06–1.3)	0.3 (0.06–1.4)	0.08
Interleukin-1RA (pg/mL)	503 (291–1177)	637 (358–1346)	692 (419–1471)	1086 (575–1909)	<0.01
Interleukin-6 (pg/mL)	1.4 (0.9–2.4)	1.7 (1.0–3.0)	2.0 (1.2–3.1)	2.4 (1.6–3.7)	<0.01
Interleukin-10 (>0 pg/mL)[2]	148 (16.3%)	132 (14.4%)	155 (16.8%)	148 (16.1%)	0.5
TNF-α (pg/mL)	2.1 (1.4–3.2)	2.1 (1.5–3.2)	2.2 (1.5–3.3)	2.3 (1.7–3.3)	0.006
TGF-β (pg/mL)	10.3 (6.1–17.7)	11.5 (6.4–18.4)	10.7 (6.2–17.5)	11.0 (7.1–17.8)	0.3

Data presented as median and interquartile range,

[1] Mean (SD),

[2] n (%) where Interleukin-10 is >0

Table 3

Multivariable adjusted association between body composition and biomarkers of inflammation

Outcome variable	Predictor variable					
	Body mass index		*Body fat mass*		*Fat free mass*	
	Est/1 SD(95% CI)	*P-value*	*Est/1 SD (95% CI)*	*P-value*	*Est/1 SD (95% CI)*	*P-value*
Acute phase proteins						
ln(hs-CRP + 1)/*1 SD*	0.34 (0.31, 0.37)	<0.001	0.36 (0.33, 0.39)	<0.001	0.26 (0.22, 0.30)	<0.001
Fibrinogen/*1 SD*	0.20 (0.17, 0.23)	<0.001	0.18 (0.15, 0.21)	<0.001	0.17 (0.14, 0.21)	<0.001
Serum Albumin/*1 SD*	−0.07 (−0.10, −0.04)	<0.001	0.02 (−0.01, 0.06)	0.2	−0.15 (−0.19, −0.11)	<0.001
Cytokines						
ln(IL1β + 1)/*1 SD*	0.05 (0.02, 0.08)	0.002	0.04 (0.01, 0.07)	0.02	0.05 (0.01, 0.09)	0.02
ln(IL-1RA + 1)/*1 SD*	0.20 (0.17, 0.24)	<0.001	0.22 (0.19, 0.25)	<0.001	0.16 (0.12, 0.20)	<0.001
ln(IL-6 + 1)/*1 SD*	0.15 (0.12, 0.18)	<0.001	0.14 (0.11, 0.18)	<0.001	0.13 (0.09, 0.17)	<0.001
ln(IL-10 + 1)/*1 SD*	−0.00 (−0.04, 0.03)	0.8	−0.01 (−0.05, 0.02)	0.5	0.03 (−0.01, 0.07)	0.2
ln(TGF-β + 1)/*1 SD*	0.00 (−0.03, 0.04)	0.8	0.01 (−0.02, 0.05)	0.4	−0.03 (−0.07, 0.01)	0.1
ln(TNF-α + 1)/*1 SD*	−0.01 (−0.04, 0.02)	0.6	−0.01 (−0.04, 0.02)	0.6	−0.04 (−0.08, −0.01)	0.03

Adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid lowering medications, aspirin and ACE-I/ARB use, metabolic equivalent of tasks (METS), and estimated GFR.

Table 4

Multivariable adjusted association between body composition and biomarkers of inflammation by eGFR.

Outcome variable	Predictor variable							
	Body fat mass				*Fat free mass*			
	eGFR <30 ml/min/1.73 m^2 (n=804)		*eGFR ≥ 30 ml/min/1.73 m^2 (n=3,123)*		*eGFR <30 ml/min/1.73 m^2 (n=804)*		*eGFR ≥ 30 ml/min/1.73 m^2 (n=3,123)*	
	Est/1 SD(95% CI)	*P-value*	*Est/1 SD (95% CI)*	*P-value*	*Est/1 SD (95% CI)*	*P-value*	*Est/1 SD (95% CI)*	*P-value*
Acute phase proteins								
ln(hs-CRP + 1)/*1 SD*	0.34 (0.27, 0.42)	<0.001	0.36 (0.33, 0.40)	<0.001	0.28 (0.18, 0.38)	<0.001	0.26 (0.22, 0.31)	<0.001
Fibrinogen/*1 SD*	0.17 (0.10, 0.25)	<0.001	0.19 (0.16, 0.22)	<0.001	0.27 (0.18, 0.37)	<0.001	0.15 (0.11, 0.19)	<0.001
Serum Albumin/*1 SD*	0.09 (0.01, 0.16)	0.03	0.00 (−0.03, 0.04)	0.9	−0.18 (−0.27, −0.08)	<0.001	−0.15 (−0.19, −0.10)	<0.001
Cytokines								
ln(IL1β + 1)/*1 SD*	0.02 (−0.05, 0.09)	0.6	0.05 (0.01, 0.08)	0.01	0.06 (−0.02, 0.15)	0.2	0.04 (−0.00, 0.09)	0.06
ln(IL-1RA + 1)/*1 SD*	0.21 (0.14, 0.28)	<0.001	0.22 (0.18, 0.26)	<0.001	0.18 (0.09, 0.26)	<0.001	0.16 (0.12, 0.21)	<0.001
ln(IL-6 + 1)/*1 SD*	0.11 (0.03, 0.19)	0.006	0.16 (0.12, 0.19)	<0.001	0.14 (0.04, 0.24)	0.006	0.13 (0.09, 0.18)	<0.001
ln(IL-10 + 1)/*1 SD*	−0.05 (−0.13, 0.03)	0.2	0.00 (−0.04, 0.04)	1.0	−0.06 (−0.16, 0.04)	0.3	0.05 (0.01, 0.10)	0.03
ln(TGF-β + 1)/*1 SD*	0.02 (−0.05, 0.09)	0.6	0.01 (−0.02, 0.05)	0.5	0.04 (−0.04, 0.13)	0.3	−0.04 (−0.09, 0.00)	0.05
ln(TNF-α + 1)/*1 SD*	0.01 (−0.05, 0.08)	0.7	−0.02 (−0.05, 0.02)	0.4	0.01 (−0.08, 0.09)	0.9	−0.06 (−0.10, −0.01)	0.01

Adjusted for age, sex, clinical center, diabetes, hypertension, smoking, total cholesterol, lipid lowering medications, aspirin and ACE-I/ARB use, metabolic equivalent of tasks (METS), and estimated GFR.