Higher C-Reactive Protein and Soluble Tumor Necrosis Factor Receptor Levels Are Associated With Poor Physical Function and Disability: A Cross-Sectional Analysis of a Cohort of Late Middle-Aged African Americans

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Abstract. This cohort of “late middle-aged” African Americans has an excess of disability. We aimed to determine associations of circulating cytokine receptors (sTNFR1, sTNFR2, and sIL-6R) and C-reactive protein (CRP) with disability, physical function, and body composition.

Methods. Stratified sampling of two socioeconomically diverse strata of St Louis, Missouri, occurred in 2000–2001. Inclusion criteria were self-reported black or African American race, born 1936–1950 inclusive, and Mini-Mental State Examination score of 16 or greater. In-home evaluations of handgrip strength, lean body mass percentage (LBM%), physical performance, upper and lower body functional limitations (UBFLs and LBFLs), and basic and instrumental activities of daily living (BADLs and IADLs) were collected. Of the 998 participants, 368 had blood sampled at baseline. Serum was stored and assayed in 2006.

Results. Absolute risks were LBFLs of 2 or more, 46%; UBFLs of 1 or more, 23.5%; BADLs of 2 or more, 20.6%; and IADLs of 2 or more, 22.5%. Independent of age, sex, and underlying comorbid conditions, higher CRP and sTNFR were associated with poorer physical performance (β = −1.462, p < .001 and β = −0.618, p = .003), UBFLs (odds ratio [OR] 2.26, 95% confidence interval [CI] 1.1–4.64 and OR 1.39, 95% CI 0.96–2.02), LBFLs (OR 2.30, 95% CI 1.19–4.45 and OR 1.91, 95% CI 1.26–2.91), BADLs (OR 2.79, 95% CI 1.03–7.96 and OR 1.66, 95% CI 1.11–2.46), and IADLs (OR 2.13, 95% CI 1.03–4.41 and OR 1.43, 95% CI 0.99–2.08). Higher CRP (β = −3.251, p < .001), sIL-6R (β = −6.152, p = .013), and lower adiponectin (β = 2.947, p = .052) were associated with lower LBM%.

Conclusions. Higher CRP and sTNFR are independently associated with disability and physical dysfunction. Higher sIL-6R, CRP, and lower adiponectin associate with lower LBM%.

Key Words: Cytokine receptors—Aging—Disability.

The African American Health (AAH) project is a study of an urban group of African Americans of “late middle-age.” This cohort has been shown to have dysphoric symptoms and health-related quality of life below that of U.S. national averages (1,2) and an excess of subclinical and frank disability (3). The reason for the poor level of performance in this cohort has not been determined.

Epidemiological evidence has shown an association of cytokines (tumor necrosis factor [TNF] α, interleukin [IL]-6), their soluble receptors, and C-reactive protein (CRP) with lower skeletal muscle mass, strength, and aerobic capacity (4). Evidence also exists, particularly in older people, for an inverse association between self-rated health and circulating cytokines (5). Adiponectin is an anti-inflammatory adipokine that increases insulin sensitivity of skeletal muscle and adipose tissue, increases fatty acid oxidation, and may be protective against diabetes and atherosclerosis (6), two major contributors to the disability burden. Independent of body fatness, African Americans have been shown to have lower adiponectin levels than Caucasians (7). We have shown previously that for women in this cohort, adiponectin is lower in obese women and is associated with increased waist-to-hip ratio, triglyceride levels, and history of stroke (8).
It is therefore plausible to hypothesize that a reduction in skeletal muscle mass mediated by proinflammatory cytokines may contribute to impairments in performance, function, and disability. Such an association has been difficult to show in population and clinical studies, possibly due to the labile nature of circulating proinflammatory cytokines. There is physiological rationale for the measurement of soluble cytokine receptors as plasma concentrations reflect the chronic history of inflammatory immune activation (9). Furthermore, sIL-6Rs prolong the half-life of IL-6 in plasma (10) and enhance the signaling of IL-6 even in tissues lacking membrane-bound IL-6R (11,12). sTNFRs are induced by IL-6 (13) and neutralize the effects of TNFα by preventing the interaction of the cytokine with membrane-bound receptors (14). For this reason, soluble cytokine receptors rather than cytokines themselves were measured as markers of chronic inflammation in this cohort.

It was hypothesized that the poor level of performance of the AAH cohort may be due to a high level of chronic inflammation as indicated by elevated soluble cytokine receptors. This investigation examines the association of soluble cytokine receptors and CRP with body composition, physical performance, functional limitations, and disability.

Methods

Referent Population and Study Sample

The sampling and data collection procedures of AAH have been previously described in detail (1,3). Briefly, AAH is a population-based longitudinal study of 998 men and women aged 49–65 years at baseline, initiated to examine key issues of disability and frailty among urban-dwelling African Americans. Sampling was designed to recruit approximately equal proportions of participants from two socioeconomically diverse strata. One group was from a poor, inner-city area of St Louis, Missouri, and the other was from suburbs adjacent to the north and west of the city. Inclusion criteria were the following: (a) self-reported black or African American race; (b) birth year from 1936 to 1950, inclusive; and (c) Mini-Mental State Examination score of 16 or greater. Baseline evaluations were done between 2000 and 2001, and the response rate was 76%. The eligible study sample for the current investigation included 368 participants who donated blood at baseline. Of this group, there were 349 participants for whom complete data were available on all laboratory measures, and these participants were included in the current study.

Laboratory Methods

Blood was drawn for laboratory analyses shortly after the baseline, in-home assessment, or at the time of further clinical examinations required for special substudies. Serum was stored until analysis for cytokines in 2006. Adiponectin was determined using a commercially available radioimmunoassay kit (Linco Research, St Charles, MO), with intra-assay and inter-assay coefficients of variation (CVs) of 5.3% and 8.1%, respectively. CRP was measured with a commercially available High-Sensitivity Enzyme Immunoassay (hsCRP ELISA) kit from MP Biomedicals (Orangeburg, NY). The intra-assay and interassay CVs were 4.5% and 4.1%, respectively. Soluble IL-6R was measured with an ELISA kit from ICN-Biomedicals (Costa Mesa, CA). The intra-assay and interassay CVs were 5.0% and 5.9%, respectively. Soluble TNFR1 and sTNFR2 were measured using ELISA kits (BioSource, Camarillo, CA). Intra-assay and interassay CVs were 4.1% and 7.3% for sTNFR1 and 5.1% and 8.6% for sTNFR2.

Functional Status and Body Composition

Disability was assessed using activities of daily living scales. Basic activities of daily living (BADLs) included seven items (bathing, dressing, eating, transferring bed or chair, walking across a room, getting outside, and using toilet) from the Second Longitudinal Study of Aging (LSOA-II) (15). Instrumental activities of daily living (IADLs) included eight items (preparing meals, shopping for groceries, managing money, making phone calls, doing light housework, doing heavy housework, getting to places outside walking distance, and managing medications) from LSOA-II (15) and Lawton and Brody (16). Lower body functional limitations (LBFLs) included five items (walking a quarter of a mile, walking up and down 10 steps without rest, standing for 2 hours, stooping or kneeling, and lifting 10 pounds), and upper body functional limitations (UBFLs) included three items (reaching overhead, reaching out as if to shake hands, and reaching out to grasp an object). LBFL and UBFL items were from the Nagi’s (17) Physical Performance Scale. BADD, IADL, and LBFL scales were scored as the sum of items on which participants reported difficulty performing a task, and scores on each of these scales were dichotomized as 0–1 difficulty versus 2 or more difficulties. UBFL were scored as the total number of items on which participants reported difficulty performing a task, and scores were dichotomized as no difficulty versus 1 or more difficulties.

Physical performance was measured using the Short Physical Performance Battery (SPPB) (18,19). The SPPB is a summary measure of lower body performance based on three component tasks: standing balance, chairs stands, and usual walking speed. Each component task was scored as 0–4 (range 0 = worst to 4 = best), and a composite score was computed as the sum of scores on component tasks as 0–12 (range 0 = worst to 12 = best). Complete details on the composite SPPB score in AAH are provided by Miller and colleagues (19). Isometric grip strength was assessed using a handgrip dynamometer (Fabrication Enterprises, Inc., Irvington, NY). The mean of three maximal effort trials with the self-reported stronger hand was used in these analyses. The test was performed seated in a chair (without arm rests), with feet flat on the floor and the stronger arm held aligned with the self-reported stronger hand was used in these analyses. The test was performed seated in a chair (without arm rests), with feet flat on the floor and the stronger arm held aligned with the self-reported stronger hand was used in these analyses. The test was performed seated in a chair (without arm rests), with feet flat on the floor and the stronger arm held...
flat against the side with the elbow at 90°. Lean body mass percentage (LBM%) was assessed using a Tanita 2204 Ultimate Scale (Tanita Corporation of America, Inc., Arlington Heights, IL) and determined as 1 minus percent body fat.

Statistical Analysis

Analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, IL). Descriptive statistics are reported as percentages or $M \pm SD$. Values for sIL-6R, sTNFR1, sTNFR2, adiponectin, and CRP were not normally distributed, and due to this, these variables were log transformed for all univariable and multivariable analyses. Chi-square (discrete variables) and independent samples $t$ tests (continuous variables) were used to compare baseline characteristics of the study sample (i.e., AAH participants who donated blood at baseline) versus those not eligible for the study (i.e., AAH participants who did not donate blood or those with missing data on one or more laboratory tests). To examine the independent association of each of the cytokine receptors and CRP with each of the functional and disability outcomes, logistic regression models were computed for discrete outcomes (BADLs, IADLs, LBFL, and UBFL), and ordinary least squares regressions were computed for continuous outcomes (SPPB, maximum handgrip, and LBM%), adjusting for age and sex in each model. To assess the effect of chronic comorbidities on the associations of inflammatory markers with functional and disability outcomes, models were also computed with adjustment for chronic disease status (yes or no), including obesity, hypertension, arthritis, type 2 diabetes, stroke history, asthma, chronic heart disease, congestive heart failure, chronic obstructive pulmonary disease, cancer, and chronic kidney disease.

A factor score (linear combination of variables) was created for the sTNFR1 and sTNFR2 variables due to the high correlation between these variables and to handle multicollinearity in the ordinary least squares regressions. For consistency in the presentation of the results, the sTNFR1/sTNFR2 factor scores were used in all regression models. An alpha level of .05 was accepted as statistically significant.

**Results**

Table 1 provides sociodemographic, anthropometric, functional, and disability characteristics of the current study participants and other AAH participants. Table 2 shows LBM%, handgrip strength, and serum cytokine concentrations in the study sample ($N = 349$). The study sample was slightly older and reported higher BADLs, IADLs, LBFLs, and UBFLs than those not included herein. LBM%; handgrip strength; and serum concentrations of soluble cytokine receptors, CRP, and adiponectin are described in Table 2.

The age- and sex-adjusted associations of soluble cytokine receptor, CRP, and adiponectin concentrations with LBM%, handgrip strength, SPPB, LBFLs, UBFLs, and disability (BADLs and IADLs) are shown in Table 3. Higher sTNFR factor scores (odds ratio [OR] 1.49, $p = .004$) and higher CRP levels (OR 1.87, $p = .008$) were significantly associated with BADL of 2 or more. Higher sTNFR factor scores were significantly associated with IADL of 2 or more (OR 1.60, $p = .001$), LBFL of 2 or more (OR 2.03, $p < .001$), and UBFL of 1 or more (OR 1.42, $p = .008$). Both higher sTNFR factor scores ($\beta = -0.768, p < .001$) and higher CRP levels ($\beta = -1.296, p < .001$) were significantly

### Table 1. Sociodemographic, Anthropometric, Functional, and Disability Characteristics of the Current Study Participants and Other AAH Participants

<table>
<thead>
<tr>
<th>Variables*</th>
<th>Current Study Participants</th>
<th>AAH Participants</th>
<th>Not in Current Study</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N$</td>
<td>349</td>
<td>649</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>56.70 (4.4)</td>
<td>56.08 (4.5)</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>33.2</td>
<td>39.3</td>
<td>0.059</td>
<td></td>
</tr>
<tr>
<td>Geography (% inner city)</td>
<td>44.7</td>
<td>47.3</td>
<td>0.431</td>
<td></td>
</tr>
<tr>
<td>Household income (% &lt;20K p.a.)</td>
<td>40.4</td>
<td>38.4</td>
<td>0.563</td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 (0.1)</td>
<td>1.68 (0.1)</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86.92 (19.0)</td>
<td>86.29 (19.2)</td>
<td>0.636</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>31.54 (7.0)</td>
<td>30.66 (6.9)</td>
<td>0.071</td>
<td></td>
</tr>
<tr>
<td>BADLs (0–7)</td>
<td>0.88 (1.6)</td>
<td>0.65 (1.4)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>IADLs (0–8)</td>
<td>0.99 (1.7)</td>
<td>0.79 (1.5)</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>UBFLs (0–3)</td>
<td>0.37 (0.7)</td>
<td>0.28 (0.6)</td>
<td>0.057</td>
<td></td>
</tr>
<tr>
<td>UBFLs (1 % or more)</td>
<td>25.5</td>
<td>20.7</td>
<td>0.309</td>
<td></td>
</tr>
<tr>
<td>LBFLs (0–5)</td>
<td>1.83 (1.8)</td>
<td>1.5 (1.8)</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>LBFLs (2 % or more)</td>
<td>46.0</td>
<td>38.3</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>SPPB (0–12)</td>
<td>7.93 (3.2)</td>
<td>7.99 (3.3)</td>
<td>0.768</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** AAH = African American Health; BADLs = basic activities of daily living; BMI = body mass index; IADLs = instrumental activities of daily living; LBFLs = lower body functional limitations; SPPB = Short Physical Performance Battery; UBFLs = upper body functional limitations.

*Data presented are $M$ (±SD), except for dichotomized variables (gender, geography, household income, BADLs, IADLs, UBFLs, and LBFLs), where percentages are reported for a given category.

### Table 2. LBM%, Handgrip Strength, and Serum Cytokine Concentrations in the Study Sample ($N = 349$)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Minimum</th>
<th>Maximum</th>
<th>$M$</th>
<th>$SD$</th>
<th>$N$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LBM (%)</td>
<td>43.0</td>
<td>95.0</td>
<td>62.74</td>
<td>10.68</td>
<td>306</td>
</tr>
<tr>
<td>Handgrip strength (kg)</td>
<td>5.00</td>
<td>90.0</td>
<td>36.39</td>
<td>14.47</td>
<td>325</td>
</tr>
<tr>
<td>sIL-6R (ng/mL)</td>
<td>19</td>
<td>126</td>
<td>60.95</td>
<td>23.49</td>
<td>349</td>
</tr>
<tr>
<td>sIL-6R (log$_{10}$)</td>
<td>1.28</td>
<td>2.10</td>
<td>1.75</td>
<td>0.18</td>
<td>349</td>
</tr>
<tr>
<td>sTNFR1 (ng/mL)</td>
<td>1</td>
<td>46</td>
<td>3.33</td>
<td>4.37</td>
<td>349</td>
</tr>
<tr>
<td>sTNFR1 (log$_{10}$)</td>
<td>0.04</td>
<td>1.66</td>
<td>0.44</td>
<td>0.21</td>
<td>349</td>
</tr>
<tr>
<td>sTNFR2 (ng/mL)</td>
<td>2</td>
<td>132</td>
<td>8.14</td>
<td>10.73</td>
<td>349</td>
</tr>
<tr>
<td>sTNFR2 (log$_{10}$)</td>
<td>0.18</td>
<td>2.12</td>
<td>0.82</td>
<td>0.22</td>
<td>349</td>
</tr>
<tr>
<td>sTNFR1 and sTNFR2 factor score (log$_{10}$)</td>
<td>-1.96</td>
<td>6.16</td>
<td>0.0</td>
<td>1.0</td>
<td>349</td>
</tr>
<tr>
<td>CRP (ng/mL)</td>
<td>0</td>
<td>38</td>
<td>7.01</td>
<td>7.20</td>
<td>349</td>
</tr>
<tr>
<td>CRP (log$_{10}$)</td>
<td>-1.00</td>
<td>1.58</td>
<td>0.60</td>
<td>0.51</td>
<td>349</td>
</tr>
<tr>
<td>Adiponectin (µg/L)</td>
<td>1</td>
<td>39</td>
<td>8.32</td>
<td>5.47</td>
<td>349</td>
</tr>
<tr>
<td>Adiponectin (log$_{10}$)</td>
<td>0</td>
<td>1.59</td>
<td>0.84</td>
<td>0.27</td>
<td>349</td>
</tr>
</tbody>
</table>

**Notes:** CRP = C-reactive protein; LBM% = lean body mass percentage.

*Both raw and transformed data are presented for each variable, where applicable.
The associations of sIL-6R, CRP, and adiponectin with physical performance outcomes to a level of significance. The associations of sIL-6R, CRP, and adiponectin with LBFL%, handgrip strength, SPPB, UBFLs, and disability (BADLs and IADLs) are shown in Table 4. Adjustment for comorbidities strengthened the association of CRP with disability, functional limitation, and physical performance outcomes to a level of significance. The associations of sIL-6R, CRP, and adiponectin with LBFL% remained, although for adiponectin, the association became marginally significant ($p = .051$). The associations of the sTNFR factor score with BADLs, UBFLs, and SPPB did not change substantively but became marginally significant for IADLs of 2 or more ($p = .060$) and UBFLs of 1 or more ($p = .082$).

### Discussion

With the aging of the population, there is increased interest in the factors leading to frailty and disability (20,21). The present study in late middle-aged African American men and women shows strong and independent associations of CRP and higher serum-soluble TNF receptor concentrations with poorer physical performance and higher levels of UBFLs and LBFLs and disability. The etiologies of functional limitations and disability are complex and multifactorial involving processes of physical, cognitive, social, emotional, and behavioral decline. The outcome measures used in the present study reflect different combinations of these factors and thus implicate CRP and sTNFR pathways in physical performances such as balance and walking speed and multifaceted functions from walking across a room, lifting 10 pounds and reaching overhead, to dressing, eating and managing money, and medications.

These associations were independent of underlying chronic comorbidities as indicated by our adjusted models. Kuo and colleagues (22) reported similar independent associations for CRP and disability in men and women aged 60 years and older who participated in National Health and Nutrition Examination Survey between 1999 and 2002 (mean age 70.2 years). CRP was also shown to be associated with disability, independent of health conditions in a population of older adults in the Sacramento Area Latino Study on Aging (23). Leng and colleagues (24) showed an age-, race-, education-, body mass index (BMI)–, and smoking status–independent association of CRP with prevalent frailty in community-dwelling older women but did not adjust for chronic conditions. The present

<table>
<thead>
<tr>
<th>Outcomes*</th>
<th>BADLs (2 or more)</th>
<th>IADLs (2 or more)</th>
<th>LBFLs (2 or more)</th>
<th>UBFLs (1 or more)</th>
<th>Handgrip Strength</th>
<th>SPPB</th>
<th>LBM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIL-6R (log)</td>
<td>8.524 (2.94), $p = .004$</td>
<td>−2.019 (4.47), $p = .845$</td>
<td>0.636 (1.12), $p = .537$</td>
<td>1.20 (0.24–4.18), $p = .537$</td>
<td>−1.62 (0.92–2.87), $p = .10$</td>
<td>−1.374 (0.74), $p = .01$</td>
<td>−4.655 (−1.60), $p = .001$</td>
</tr>
<tr>
<td>sTNFR (log)</td>
<td>5.868 (1.03–3.40), $p = .041$</td>
<td>−8.95 (3.79), $p = .233$</td>
<td>1.296 (1.00–1.67), $p = .098$</td>
<td>1.21 (0.14–2.81), $p = .764$</td>
<td>1.49 (1.21–2.11), $p = .001$</td>
<td>0.768 (0.36), $p &lt; .001$</td>
<td></td>
</tr>
<tr>
<td>CRP (log)</td>
<td>−5.868 (1.03–3.40), $p = .041$</td>
<td>−1.60 (0.39–2.80), $p = .233$</td>
<td>1.296 (1.00–1.67), $p = .098$</td>
<td>1.21 (0.14–2.81), $p = .764$</td>
<td>1.49 (1.21–2.11), $p = .001$</td>
<td>0.768 (0.36), $p &lt; .001$</td>
<td></td>
</tr>
</tbody>
</table>

*Note: BADL = basic activities of daily living; CRP = C-reactive protein; IADL = instrumental activities of daily living; LBFL = lower body functional limitations; UBFL = upper body functional limitations; LBM = lean body mass percentage; SPPB = Short Physical Performance Battery; UBFLs = UBFLs, LBM%, handgrip strength, SPPB, LBFLs, and disability (BADL’s and IADLs) are shown in Table 4. Adjustment for comorbidities strengthened the association of CRP with disability, functional limitation, and physical performance outcomes to a level of significance.
Table 4. Age-, Sex- and Comorbidity-Adjusted Associations of Cytokines With Disability, Functional Limitations, Physical Performance, Handgrip Strength, and LBM%

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>BADLs (2 or more)</th>
<th>IADLs (2 or more)</th>
<th>LBFLs (2 or more)</th>
<th>UBFLs (1 or more)</th>
<th>SPPB</th>
<th>Handgrip Strength</th>
<th>LBM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIL-6R (log_{10})</td>
<td>0.85 (0.11–6.81), *p = .876</td>
<td>0.74 (0.10–5.38), *p = .762</td>
<td>0.51 (0.09–2.93), *p = .446</td>
<td>0.48 (0.07–3.29), *p = .453</td>
<td>0.598 (1.01), *p = .552</td>
<td>−2.058 (4.57), *p = .652</td>
<td>−6.152 (2.47), *p = .013</td>
</tr>
<tr>
<td>sTNFR (log_{10})</td>
<td>1.66 (1.11–2.46), *p = 0.0013</td>
<td>1.43 (0.99–2.08), *p = .060</td>
<td>1.91 (1.26–2.91), *p = .002</td>
<td>1.39 (0.96–2.02), *p = .082</td>
<td>−0.618 (0.21), *p = .003</td>
<td>−0.964 (0.94), *p = .074</td>
<td>−0.269 (0.62), *p = .001</td>
</tr>
<tr>
<td>CRP (log_{10})</td>
<td>2.79 (1.03–5.96), *p = .008</td>
<td>2.13 (1.03–4.41), *p = .042</td>
<td>2.30 (1.19–4.45), *p = .013</td>
<td>2.26 (1.10–4.64), *p = .027</td>
<td>−1.426 (0.35), *p &lt; .0001</td>
<td>−2.269 (1.58), *p = .303</td>
<td>−3.251 (0.84), *p &lt; .001</td>
</tr>
<tr>
<td>Adiponectin (log_{10})</td>
<td>2.63 (0.72–9.53), *p = .142</td>
<td>1.03 (0.30–3.34), *p = .359</td>
<td>1.14 (0.39–3.39), *p = .309</td>
<td>0.81 (0.25–2.68), *p = .732</td>
<td>−0.425 (0.62), *p = .494</td>
<td>−1.530 (2.84), *p = .591</td>
<td>2.947 (1.51), *p = .052</td>
</tr>
</tbody>
</table>

Notes: BADLs = basic activities of daily living; CRP = C-reactive protein; IADLs = instrumental activities of daily living; LBFLs = lower body functional limitations; LBM% = lean body mass percentage; SPPB = Short Physical Performance Battery; UBFLs = upper body functional limitations.

*Results of logistic regressions computed for discrete outcomes (BADLs, IADLs, LBFLs, and UBFLs) are reported as odds ratio (95% confidence intervals). Results of ordinary least squares regressions computed for continuous outcomes (SPPB, handgrip strength, and LBM%) are reported as unstandardized betas (standard errors). Models were adjusted for age, sex, obesity, hypertension, arthritis, type 2 diabetes, stroke history, asthma, chronic heart disease, congestive heart failure, chronic obstructive pulmonary disease, cancer, and chronic kidney disease.

†The sTNFR factor score was used in these analyses. Bold values were used to highlight statistically significant associations.
capacity. Higher TNFα levels were correlated with lower skeletal muscle mass, and higher TNFα and IL-6 levels were associated with reduced leg and forearm muscle strength (4). The same group also reported an increase in circulating sTNFR2 and reduced insulin-like growth factor-1 levels in old (72 ± 1 years) versus young (29 ± 2 years) volunteers of mixed gender and showed that sTNFR2, CRP, and IL-6 concentrations were inversely associated with myosin heavy chain (MyHC) protein synthesis rate (39). Intriguingly, in the present study, a less favorable body composition, as indicated by lower LBM% (increased fat mass%), was associated with a serum adipocytokine profile of higher sIL-6R and CRP and lower adiponectin levels but not with sTNFR. Moreover, there was no association of any cytokine with handgrip strength. On the basis of this finding, we speculate that much of the association of CRP and sTNFR with functional limitations and disabilities in this population may be due less to effects on crude muscle strength and more to negative effects on cognitive processes required for some functional tasks.

Mechanistically, however, there is strong evidence of cytokine pathway involvement in skeletal muscle atrophy, IL-6, TNFα, and IL-1β have been identified as contributors to myofiber degradation and skeletal muscle atrophy (40). The TNF and IL signaling pathways can regulate DNA fragmentation, apoptosis, and atrophy in skeletal muscle via phosphorylation of I Kappa B kinase and activation of nuclear factor kappa (NFkB) (41,42). In skeletal muscle, activation of NFkB induces translocation to the nucleus where it binds to DNA and increases the transcription of the ubiquitin E3 ligases Atrogin-1 (aka MAFbx) and muscle ring-finger protein-I (43,44). These events also inhibit myogenic differentiation by both suppressing the transcription and promoting the degradation of myosin D (45,46) and also inhibit the transcription of MyHC (47).

It is not possible to elucidate temporal effects of cytokine activation, changes in body composition, muscle strength and physical performance, incident functional limitations and disability, given the cross-sectional nature of this study. Although an effect of CRP is common, the otherwise differential cytokine profiles associated with LBM% compared with physical performance, functional limitations, and disability suggest that changes in body composition may be driven by different factors than functional changes and disability; it is possible that one may precede and predict the other (Figure 1). Such associations may be driven by an epigenetic interaction of psychosocial and environmental factors with high frequencies of (adipo) cytokine gene polymorphisms in the African American population. Well-designed longitudinal analyses are required to examine these hypotheses. It is also possible that measurement of IL-6 rather than the soluble receptor could have resulted in different associations with body composition, functional limitations, and disability.

Some selection bias may have occurred in this subsample of the AAH study cohort as participants with full data avail-

![Figure 1. The proposed associations between changes in body composition, cytokines, and progression along the disability continuum. This figure represents the associations between changes in body composition, circulating cytokines, and progression along the disability continuum. This basic model requires longitudinal interrogation using valid and reliable measurement of circulating cytokines (soluble receptors), body fat (including visceral adiposity), and direct measurements of physical (and cognitive) function and disability.](https://academic.oup.com/biomedgerontology/article-abstract/65A/3/274/572995)
laboratory assays. M.M.H., PhD, contributed to acquisition of data, drafting of the manuscript, and technical support. W.A.B., MD, contributed to the conception and design of the study; acquisition of data; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical, and material support, and supervision. J.E.M., MB BCH, was involved in the conception and design of the study and critical revision of the manuscript for important intellectual content, administrative, technical, and material support, and supervision. T.K.M. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. There are no conflicts of interest to declare for any of the authors. The funding agency had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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