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# Association Between Inflammatory Components and Physical Function in the Health, Aging, and Body Composition Study: A Principal Component Analysis Approach

Fang-Chi Hsu,[1] Stephen B. Kritchevsky,[2,3] Yongmei Liu,[4] Alka Kanaya,[5] Anne B. Newman,[6] Sara E. Perry,[7] Marjolein Visser,[8] Macro Pahor,[9] Tamara B. Harris,[10] and Barbara J. Nicklas,[2,3] for the Health ABC Study

[1]Department of Biostatistical Sciences, [2]Sticht Center on Aging, [3]Department of Internal Medicine, [4]Department of Epidemiology and Prevention, Wake Forest University School of Medicine, Winston-Salem, North Carolina.
[5]Division of General Internal Medicine, University of California, San Francisco.
[6]Division of Geriatric Medicine, University of Pittsburgh, Pennsylvania.
[7]Department of Epidemiology, Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana.
[8]Institute of Health Sciences, VU University Medical Center, Amsterdam, the Netherlands.
[9]Department of Aging and Geriatric Research, University of Florida, Gainesville.
[10]Geriatric Epidemiology Section, National Institute on Aging, Bethesda, Maryland.

***Background.*** In older adults, studies demonstrate an inverse relationship between physical function and individual inflammatory biomarkers. Given that the inflammatory response is a complex system, a combination of biomarkers may increase the strength and consistency of these associations. This study uses principal component analysis to identify inflammatory "component(s)" and evaluates associations between the identified component(s) and measures of physical function.

***Methods.*** Principal component analysis with a varimax rotation was used to identify two components from eight inflammatory biomarkers measured in 1,269 older persons. The study sample is a subset of the Health, Aging, and Body Composition study.

***Results.*** The two components explained 56% of the total variance in the data (34%, component 1 and 22%, component 2). Five markers (tumor necrosis factor-alpha [TNF-α], sTNFRI, sTNFRII, interleukin [IL]-6sR, IL-2sR) loaded highest on the first component (TNF-α related), whereas three markers (C-reactive protein [CRP], IL-6, plasminogen activator inhibitor-1) loaded highest on the second component (CRP related). After adjusting for age, sex, race, site, sampling indicator, total lean and fat mass, physical activity, smoking, and anti-inflammatory drug use, knee strength and a physical performance battery score were inversely related to the TNF-α-related component, but not to the CRP-related component (knee strength: $\hat{\beta}_{TNF\alpha} = -2.71$, $p = .002$; $\hat{\beta}_{CRP} = -0.88$, $p = .325$; physical performance battery score: $\hat{\beta}_{TNF\alpha} = -0.05$, $p < .001$; $\hat{\beta}_{CRP} = -0.02$, $p = .171$). Both components were positively associated with 400-m walk time, inversely associated with grip strength, and not associated with 20-m walking speed.

***Conclusions.*** At least two inflammatory components can be identified in an older population, and these components have inconsistent associations with different aspects of physical performance.

***Key Words:*** Inflammation—Physical function—Aging—Principal component analysis.

A number of studies demonstrate inverse relationships of muscle strength and other measures of physical function with individual biomarkers of inflammation in the elderly population (1–7). Cross-sectional data show that high concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) and its soluble receptors (sTNFRI and sTNFRII) are associated with lower muscle strength (2,3,7), slower walking speed and endurance (2,6–8), and lower self-reported functional ability (1,6). Moreover, longitudinal data show that onset of disability is preceded by elevated inflammatory biomarkers (9–11). However, due to the lack of studies with measures of multiple biomarkers, it is not known whether any one of these alone—or in specific combinations—is a more important risk factor for aging-related loss of function.

The presence of multiple measures allows the creation of inflammatory indexes that might provide better classification of underlying inflammatory status compared with a single measure alone. Identification of a summary variable(s) that may be more strongly related to physical function may provide a more clinically useful measure of chronic inflammation. Although rarely addressed, most commonly this issue has been dealt with by summing the number of markers that are "elevated," and this number is then used to characterize individuals. This approach does not account for the underlying correlational structure between measures and also assumes that all combined measures

relate to the same underlying unmeasured inflammatory factor. To date, no study has used data reduction tools like principal component analysis to identify associations between common inflammatory markers and physical function.

The Health, Aging, and Body Composition (Health ABC) study is a large epidemiological cohort of older adults with a large number of measured inflammatory biomarkers ($n = 8$) and comprehensive assessments of physical function. Thus, it provides an excellent opportunity to determine whether physical function is more strongly associated with one or more summary inflammation variables than a single biomarker. Thus, this study uses principal component analysis to identify a single or multiple inflammatory components, and evaluates associations between identified "component(s)" and measures of physical function.

## Methods

### *Study Sample*

Health ABC is a cohort study investigating changes in body composition as a common pathway by which multiple diseases contribute to disability (12). A total of 3,075 participants were recruited from a random sample of white and all black Medicare beneficiaries residing within each ZIP code from the metropolitan areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee , from 1997 to 1998. Participants were eligible if they were aged 70–79 years; reported no difficulty walking one quarter of a mile, climbing up 10 steps, and performing mobility-related activities of daily living; denied radiation treatment or chemotherapy for cancer in the past 3 years; were not enrolled in a trial of a lifestyle intervention; and had no plans to move out of the area in the next 3 years. All participants had CRP, IL-6, TNF-α, and plasminogen activator inhibitor-1 (PAI-1) measurements. An ancillary case-control study, involving limitation as defined as difficulty with walking a quarter of a mile or climbing 10 steps, measured the other four biomarkers (IL-2sR, IL-6sR, sTNFRI, and sTNFRII) in a subset including three groups, limited, unlimited, and random control sample. Limited cases were selected according to the occurrence of limitation at different time points (by 6, 12, 18, and 24 months), corresponding random unlimited controls (one case vs one control) were selected at each time point, and another random control sample was randomly selected out of those who did not develop limitation during follow-up and also was not in the selected unlimited controls. The probability of ending up in the subset depended on the selection process. The sampling indicator describes how the participants were selected (from limited [case], unlimited [control], or random sample [not in case or control]). For the present analysis, participants were excluded if they were missing data on any of the eight inflammatory markers, leaving 1,269 participants for analysis. The study was approved by the Institutional Review Boards of the University of Pittsburgh and the University of Tennessee, and all participants provided written informed consent to participate in the study.

### *Inflammatory Markers*

Eight inflammatory markers, including CRP, IL-6, IL-2sR, IL-6sR, PAI-1, sTNFRI, sTNFRII, and TNF-α, were analyzed at baseline and all are included in the present analysis. Blood samples were obtained by venipuncture after an overnight fast in the morning and, after processing, the specimens were aliquoted into cryovials, frozen at −70°C, and shipped to the Health ABC Core Laboratory at the University of Vermont. Serum concentrations of cytokines and cytokine-soluble receptors were measured in duplicate by an enzyme-linked immunosorbent assay (ELISA) kit from R&D Systems (Minneapolis, MN). The detectable limit for IL-6 (using the HS600 Quantikine kit) was 0.10 pg/mL, 0.18 pg/mL for TNF-α (using the HSTA50 kit), 6.5 pg/mL for IL-6sR (using the DR600 kit), 3 pg/mL for sTNFRI (using the DRT100 kit), 1 pg/mL for sTNFRII (using the DRT200 kit), and less than 10 pg/mL for IL-2sR (using the DR2A00 kit). Serum levels of CRP were also measured in duplicate by ELISA based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay was standardized according to the World Health Organization's First International Reference Standard, with a sensitivity of 0.08 μg/mL. Blind duplicate analyses for IL-6, CRP, and TNF-α showed an average interassay coefficient of variation (CV) of 10.3%, 8.0%, and 15.8%, respectively (13–15). The PAI-1 level was measured from citrated plasma with a two-site ELISA (Center of Molecular and Vascular Biology, University of Leuven, Belgium). The assay is sensitive to free PAI-1 (both latent and active) but not to PAI-1 in complex with tissue plasminogen activator. The CV for this assay was 3.5% (16).

### *Physical Function Measures*

Dynamic knee extensor strength was measured at an angular velocity of 60°/s on a Kin-Com 125 AP isokinetic dynamometer (Kin-Com, Chattanooga, TN) as previously described (17). The CV (repeated testing of 63 participants) was 10.7%. Isometric handgrip strength (right and left) was determined in duplicate by a handheld dynamometer with the maximum summed value reported (Jamar; TEC, Clifton, NJ). The CV for handgrip strength was 2.7% (18).

Long-distance walking performance was assessed as time to walk 400 m after a 2-minute warm-up as previously described (19). Persons were excluded for safety reasons if they had baseline potentially acute electrocardiogram abnormalities, elevated blood pressure (>200/110 mmHg), resting heart rate more than 120 or less than 40 beats per minute (bpm), recent exacerbation of chest pain, shortness of breath, or reported a recent cardiac event or procedure. The test was stopped if heart rate exceeded 135 bpm or if a participant reported chest pain or dyspnea during the test (19).

Global physical function was determined by the Health ABC physical performance battery (HPPB) described previously (20). Briefly, the scale is an extension of the lower

extremity performance tests used in the Epidemiologic Studies of the Elderly and includes five repeated chair stands, usual 6-m walk time, a 6-m narrow walk between lines 20 cm apart, and a balance test (30-second semi- and full-tandem stands and a 30-second single-leg stand). A ratio score from 0 to 1 was created for each test and the four tests added to provide a continuous scale from 0 to 4.

*Covariates*

Age, sex, race, smoking history, alcohol usage, and medication usage were determined by an interviewer-administered questionnaire. Prevalent clinical pulmonary disease was defined as self-report of any of current asthma, current chronic bronchitis, emphysema, or chronic obstructive pulmonary disease, or use of a pulmonary drug or oral steroid. Prevalent heart disease was defined as self-report or Health Care Financing Administration report of prevalent coronary heart disease or prevalent cerebrovascular disease including myocardial infarction, carotid endarterectomy, transient ischemic attack, and stroke, or any bypass or angioplasty-related surgeries, or use of anti-anginal medication. Prevalent diabetes was defined by use of hypoglycemic agents, self-report of a physician diagnosis of diabetes, fasting plasma glucose level of 126 mg/dL or greater, or a postchallenge glucose level of 200 mg/dL or greater. Physical activity level was calculated as kcal/wk by multiplying the appropriate kcal score for each of the activities by the amount of time spent during the week doing the activity (21). Total lean mass and total fat mass were measured with the use of fan-beam dual-energy x-ray absorptiometry (Hologic QDR4500A, software version 8.21; Waltham, MA) (22).

*Statistical Analysis*

We applied principal component analysis to reduce the eight inflammatory biomarkers into a smaller set of principal components that account for most of the variance of the inflammatory variables. All the inflammatory biomarkers, except IL-6sR, were log transformed to approximate the normality assumption. The number of components was retained based on the following rules: (a) eigenvalues 1 or greater or (b) components above the break in the scree plot. A varimax rotation was used to obtain a set of independent and best interpretable components. The components were interpreted based on the loadings that relate the biomarkers to components. Loadings greater than 0.45 were used to identify the variables comprising a component. This cut point could also separate the components well. Principal component scores were calculated for each participant. They are standardized to yield a sample mean equal to 0 and a standard deviation equal to 1. The scores were also categorized into four levels based on their quartiles.

Sample means and standard deviations were computed for the continuous characteristics, and proportions were calculated for discrete characteristics by the four component levels. Tests for trend were assessed using linear regression models for continuous characteristics (with appropriate transformations if necessary) and using logistic regression models for binary characteristics and polytomous regression models for discrete characteristics with more than two categories.

The cross-sectional associations of the inflammatory scores with measures of physical function were assessed using linear regression models. Principal component scores were modeled as continuous independent variables. Age, sex, race, study site, sampling indicator, total lean and fat mass, smoking, physical activity, and anti-inflammatory drug use were used as covariates in the models. Standard regression diagnostics for influential points were performed for each model. The program SAS (SAS Institute, Cary, NC) was used for all analyses.

We were also interested in whether the inflammatory component scores were more strongly related to the measures of physical function when compared with the individual biomarkers. We compared the coefficient of determination ($R^2$) for each component and individual biomarker by fitting models with the same standardized covariates. After adjusting for the same covariates, a larger $R^2$ shows that the variable can explain more of the total variance of outcome.

## Results

Table 1 shows the correlation coefficients among the eight inflammatory biomarkers. All are pairwise related with each other, except IL-6sR and CRP. The strongest associations were observed between IL-6 and CRP ($r$ = .46), between sTNFRI and sTNFRII ($r$ = .72), and between both of these and IL-2sR ($r$s = .54 and .59). In addition, TNF-α was strongly associated with IL-2sR ($r$ = .42), sTNFRI ($r$ = .45), and sTNFRII ($r$ = .55).

Principal component analysis, resulted in two eigenvalues greater than 1, and a scree plot confirmed the presence of two independent inflammatory components (data not shown). The two components explained 56% of the total variance in the data (34%, component 1 and 22%, component 2). As shown in Table 2, five variables (TNF-α, sTNFRI, sTNFRII, IL-6sR, and IL-2sR) loaded highest on the first component (component 1, "TNF-α related"), and three variables (CRP, IL-6, and PAI-1) loaded highest on the second component (component 2, "CRP related"). The two components did not correlate with each other ($r$ = −.01, $p$ = .607).

Table 3 shows participant characteristics by quartiles of each component level. Several characteristics show different trend effects for the two components, including age, race, and sex. A lower age was associated with a lower TNF-α-related component. However, age was not associated with the CRP-related component. Interestingly, there was a higher percentage of black participants with low levels of the TNF-α-related component, but the inverse was

Table 1. Pearson Correlation Coefficients Between Inflammatory Biomarkers ($N$ = 1,269)

| Correlation Coefficient *p* Value | CRP* | PAI-1* | IL-6* | IL-6sR | IL-2sR* | sTNFRI* | sTNFRII* | TNF-α* |
|---|---|---|---|---|---|---|---|---|
| CRP (mg/L) | 1 | | | | | | | |
| PAI-1 (ng/mL) | .22 | 1 | | | | | | |
| | <.001 | | | | | | | |
| IL-6 (pg/mL) | .46 | .22 | 1 | | | | | |
| | <.001 | <.001 | | | | | | |
| IL-6sR (mg/mL) | −.02 | .12 | .05 | 1 | | | | |
| | .588 | <.001 | .066 | | | | | |
| IL-2sR (mg/mL) | .10 | .08 | .18 | .23 | 1 | | | |
| | <.001 | .004 | <.001 | <.001 | | | | |
| sTNFRI (mg/mL) | .25 | .15 | .28 | .30 | .54 | 1 | | |
| | <.001 | <.001 | <.001 | <.001 | <.001 | | | |
| sTNFRII (mg/mL) | .20 | .10 | .24 | .23 | .59 | .72 | 1 | |
| | <.001 | <.001 | <.001 | <.001 | <.001 | <.001 | | |
| TNF-α (pg/mL) | .14 | .22 | .25 | .19 | .42 | .45 | .55 | 1 |
| | <.001 | <.001 | <.001 | <.001 | <.001 | <.001 | <.001 | |

*Notes*: CRP = C-reactive protein; IL = interleukin; PAI = plasminogen activator inhibitor; sTNFR = soluble TNF receptor; TNF = tumor necrosis factor.
*Variables have been log transformed.

true for the CRP-related component (ie, more blacks with high levels of the CRP-related component). Likewise, women were more likely to have low levels of the TNF-α-related component and more likely to have high levels of the CRP-related component. For the TNF-α-related component, a higher percentage of former smokers was observed in the highest quartile compared with never smokers, but there was no trend effect when comparing current smokers with never smokers. For the CRP-related component, there was a trend effect for both current and former smokers when compared with never smokers. There was no association between physical activity and the TNF-α-related component, but the CRP-related component was inversely related to physical activity. Diabetes was more prevalent in those with high levels of the CRP-related component, but not in those with high levels of the TNF-α-related component, whereas pulmonary and heart diseases were more prevalent in those with high levels of both inflammatory components. There was no association between total lean mass or fat mass and the TNF-α-related component, but the CRP-related component was positively related to both lean and fat mass.

The trend effects for the physical function measures were markedly different for the inflammatory components (Table 3). Global physical function, assessed as HPPB, was the only function measure associated with the TNF-α-related component, with a lower HPPB score associated with a higher component level. In contrast, there was a significant positive linear trend between the CRP-related component and 400-m walk time and negative linear trends between the CRP-related component and 20-m walking speed, HPPB, and grip strength, indicating lower physical function in participants in the higher quartiles of the CRP-related component.

Linear regression models were used to examine the association of principal component scores with physical function measures (Table 4). After adjusting for age, sex, race, site, sampling indicator, total lean mass, physical activity, smoking, and anti-inflammatory drug use, knee strength was inversely related to the TNF-α-related component, but not the CRP-related component, and 20-m walking speed was inversely associated with the CRP-related component, but not the TNF-α-related component. Both components were positively associated with 400-m walk time, and inversely associated with HPPB and grip strength. After additional adjustment for total fat mass, knee strength and the physical performance battery score was inversely related to

Table 2. Descriptive Statistics for Inflammatory Biomarkers and Rotated Component Loadings ($N$ = 1,269)

| | | | Rotated Component Loadings | |
|---|---|---|---|---|
| | Median (range) | Log-Transformed Median (range) | Component 1 | Component 2 |
| CRP (mg/L) | 1.67 (0.22–62.85) | 0.98 (0.20–4.16) | 0.0352 | 0.8156 |
| PAI-1 (ng/mL) | 22 (3–280) | 3.09 (1.10–5.63) | 0.0806 | 0.5454 |
| IL-6 (pg/mL) | 1.89 (0.30–14.43) | 1.06 (0.26–2.74) | 0.1470 | 0.7806 |
| IL-6sR (mg/mL) | 35.0 (1.3–69.7) | None required | 0.4878 | –0.0982 |
| IL-2sR (mg/mL) | 1.26 (0.28–10.22) | 7.14 (5.64–9.23) | 0.7817 | 0.0537 |
| sTNFRI (mg/mL) | 1.47 (0.27–3.91) | 7.29 (5.61–8.27) | 0.8068 | 0.2507 |
| sTNFRII (mg/mL) | 3.43 (1.73–47.19) | 8.14 (7.45–10.76) | 0.8511 | 0.1796 |
| TNF-α (pg/mL) | 3.17 (0.57–29.55) | 1.43 (0.45–3.42) | 0.6719 | 0.2387 |

*Note*: CRP = C-reactive protein; IL = interleukin; PAI = plasminogen activator inhibitor; sTNFR = soluble TNF receptor; TNF = tumor necrosis factor.

Table 3. Participant Characteristics by Inflammatory Component Level: TNF-Related Component and CRP-Related Component ($N$ = 1,269*)

| Variable | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | $P$ for Trend |
|---|---|---|---|---|---|
| TNF-α-related component | | | | | |
| Age (y) | 73.0 ± 2.9 | 73.5 ± 2.7 | 73.8 ± 2.9 | 74.1 ± 2.9 | <.001 |
| Black (%) | 65.1 | 43.7 | 30.8 | 25.2 | <.001 |
| Female (%) | 58.8 | 53.5 | 45.6 | 47.3 | .001 |
| Physical activity (kcal/wk) | 842 ± 1,431 | 1,074 ± 1,822 | 1,131 ± 1,989 | 1,045 ± 2,062 | .781† |
| Smoking (%) | | | | | |
| Never | 49.4 | 45.4 | 41.8 | 40.4 | |
| Current | 12.6 | 9.5 | 9.4 | 10.7 | .857 |
| Former | 38.1 | 45.1 | 48.7 | 48.9 | .005 |
| Alcohol use (%) | | | | | |
| None in past year | 50.6 | 47.8 | 49.5 | 58.5 | |
| Less than once/wk | 22.3 | 19.6 | 19.2 | 17.1 | .049 |
| Once to –seven times/week | 18.6 | 26.6 | 25.2 | 15.5 | .130 |
| More than seven times/wk | 8.5 | 6.0 | 6.0 | 8.9 | .725 |
| Prevalent clinical pulmonary disease (%) | 10.4 | 10.5 | 14.5 | 15.2 | .019 |
| Prevalent heart disease (%) | 21.8 | 29.1 | 35.3 | 31.2 | .003 |
| Prevalent diabetes (%) | | | | | |
| Not impaired | 61.3 | 60.8 | 65.5 | 58.9 | |
| Impaired fasting glucose | 17.7 | 19.9 | 16.8 | 16.6 | .620 |
| Diabetic fasting glucose | 4.8 | 5.6 | 2.5 | 2.2 | .037 |
| Known diabetic | 16.1 | 13.7 | 15.2 | 22.3 | .079 |
| Anti-inflammatory drug use (%) | 49.7 | 57.8 | 62.6 | 56.8 | .035 |
| Total lean mass (kg) | 46.4 ± 10.3 | 46.7 ± 10.1 | 47.5 ± 9.7 | 46.8 ± 9.8 | .4213 |
| Total fat mass (kg) | 26.6 ± 8.8 | 27.2 ± 9.2 | 27.4 ± 8.8 | 27.5 ± 8.8 | .2307 |
| Knee strength (Nm/kg) | 108.8 ± 42.8 | 106.1 ± 42.8 | 107.2 ± 37.7 | 102.5 ± 35.8 | .098 |
| 400-m walk time | 332.9 ± 59.9 | 328.8 ± 63.6 | 328.5 ± 71.6 | 335.8 ± 58.2 | .661† |
| Walking speed for 20 m | 1.30 ± 0.25 | 1.35± 0.27 | 1.34 ± 0.25 | 1.33 ± 0.25 | .210 |
| HPPB | 2.20 ± 0.51 | 2.17 ± 0.56 | 2.17 ± 0.57 | 2.08 ± 0.65 | .014 |
| Grip strength | 30.3 ± 10.5 | 29.6 ± 10.0 | 30.1 ± 10.4 | 29.0 ± 9.8 | .211† |
| CRP-related component | | | | | |
| Age (y) | 73.7 ± 2.8 | 73.8 ± 2.9 | 73.6 ± 2.9 | 73.4 ± 2.9 | .158 |
| Black (%) | 29.7 | 36.5 | 41.3 | 57.4 | <.001 |
| Female (%) | 47.3 | 49.4 | 51.7 | 56.8 | .014 |
| Physical activity (kcal/wk) | 1,305 ± 2,064 | 997 ± 1,712 | 918 ± 1,621 | 872 ± 1,922 | <.001† |
| Smoking (%) | | | | | |
| Never | 47.3 | 51.3 | 42.6 | 35.8 | |
| Current | 8.2 | 8.5 | 9.5 | 16.1 | <.001 |
| Former | 44.5 | 40.3 | 48.0 | 48.1 | .009 |
| Alcohol use (%) | | | | | |
| None in past year | 48.4 | 49.4 | 54.8 | 53.9 | |
| Less than once/wk | 19.6 | 23.6 | 18.4 | 16.7 | .088 |
| Once to seven times/wk | 25.0 | 22.3 | 19.9 | 18.6 | .027 |
| More than seven times/wk | 7.0 | 4.7 | 7.0 | 10.7 | .151 |
| Prevalent clinical pulmonary disease | 7.9 | 9.8 | 16.5 | 16.5 | <.001 |
| Prevalent heart disease | 20.4 | 28.4 | 32.1 | 36.6 | <.001 |
| Prevalent diabetes (%) | | | | | |
| Not impaired | 74.4 | 67.1 | 54.7 | 50.3 | |
| Impaired fasting glucose | 12.8 | 17.9 | 19.7 | 20.5 | <.001 |
| Diabetic fasting glucose | 1.3 | 1.9 | 5.2 | 6.7 | <.001 |
| Known diabetic | 11.5 | 13.1 | 20.4 | 22.4 | <.001 |
| Anti-inflammatory drug use (%) | 56.7 | 56.6 | 56.2 | 57.4 | .879 |
| Total lean mass (kg) | 45.5 ± 9.9 | 46.8 ± 10.5 | 47.0 ± 9.6 | 48.1 ± 9.6 | .0012 |
| Total fat mass (kg) | 22.9 ± 6.7 | 26.8 ± 8.2 | 27.6 ± 8.1 | 31.4 ± 10.2 | <.0001 |
| Knee strength (Nm/kg) | 108.1 ± 39.8 | 107.4 ± 39.7 | 105.7 ± 39.4 | 103.33 ± 41.1 | .143 |
| 400-m walk time | 315.1 ± 55.4 | 329.4 ± 56.0 | 335.6 ± 70.7 | 351.6 ± 69.2 | <.001† |
| Walking speed for 20 m | 1.40 ± 0.26 | 1.35± 0.25 | 1.32 ± 0.24 | 1.25 ± 0.25 | <.001 |
| HPPB | 2.32 ± 0.48 | 2.18 ± 0.58 | 2.14 ± 0.56 | 1.97 ± 0.62 | <.001 |
| Grip strength | 30.6 ± 10.7 | 30.2 ± 10.37 | 30.0 ± 9.85 | 28.1 ± 9.63 | .010† |

*Notes*: CRP = C-reactive protein; HPPB = Health ABC physical performance battery; TNF = tumor necrosis factor.

*Sample size was 1,269 except for smoking ($n$ = 1,268), alcohol use ($n$ = 1,267), prevalent heart disease ($n$ = 1,236), prevalent diabetes ($n$ = 1,246), anti-inflammatory drug use ($n$ = 1,266), total lean mass ($n$ = 1,258), total fat mass ($n$ = 1,258), knee strength ($n$ = 1,099), 400-m walk time ($n$ = 928), walking speed for 20 m ($n$ = 1,095), HPPB ($n$ = 1,246), and grip strength ($n$ = 1,200).

†After log transformation.

Table 4. Regression Coefficients Between Principal Component Scores and Physical Function Measures

| | *N* | Component 1 (TNF-α related), $\hat{\beta} \pm SE\ (\hat{\beta})$ (*p* value) | Component 2 (CRP related), $\hat{\beta} \pm SE\ (\hat{\beta})$ (*p* value) |
|---|---|---|---|
| Basic adjustment* | | | |
| Knee strength (Nm/kg) | 1,088 | −3.245 ± 0.864 (<.001) | −1.635 ± 0.878 (.063) |
| 400-m walk time† | 917 | 6.211 ± 1.947 (<.001) | 7.133 ± 1.993 (<.001) |
| Walking speed for 20 m (m/s) | 1,083 | −0.007 ± 0.007 (.293) | −0.019 ± 0.007 (.007) |
| HPPB | 1,231 | −0.064 ± 0.014 (<.001) | −0.041 ± 0.015 (.005) |
| Grip strength† | 1,186 | −0.469 ± 0.193 (.012) | −0. 849 ± 0.196 (<.001) |
| Basic adjustment* + total fat mass | | | |
| Knee strength (Nm/kg) | 1,088 | −2.710 ± 0.868 (.002) | −0.879 ± 0.892 (.325) |
| 400-m walk time† | 917 | 4.376 ± 1.921 (.019) | 3.910 ± 2.004 (.036) |
| Walking speed for 20 m (m/s) | 1,083 | −0.001 ± 0.007 (.936) | −0.008 ± 0.007 (.274) |
| HPPB | 1,231 | −0.051 ± 0.014 (<.001) | −0.020 ± 0.015 (.171) |
| Grip strength† | 1,186 | −0.339 ± 0.192 (.044) | −0.607 ± 0.198 (.005) |

*Notes*: CRP = C-reactive protein; HPPB = Health ABC physical performance battery; SE = standard error; TNF = tumor necrosis factor.

*Adjusting for age, sex, race, study site, sampling indicator, total lean mass, physical activity, smoking, and anti-inflammatory drug use.

†*p* value is calculated after log transformation.

the TNF-α-related component, but not the CRP-related component (for knee strength: $\hat{\beta}_{TNF\alpha} = -2.71$, $p = .002$; $\hat{\beta}_{CRP} = -0.88$, $p = .325$; for physical performance battery score: $\hat{\beta}_{TNF\alpha} = -0.05, p < .001$; $\hat{\beta}_{CRP} = -0.02, p = .171$). Both components were positively associated with 400-m walk time, inversely associated with grip strength, and not associated with 20-m walking speed. To check whether comorbidity may confound the results, we further adjusted for prevalent clinical pulmonary disease, heart disease, and diabetes. The results were similar to those without adjusting for the three prevalent diseases (data not shown).

We also analyzed associations between physical function measures and each individual biomarker when adjusting for the same covariates listed in Table 4 (basic adjustment + total fat mass). Because the covariate adjustment in each model is the same, we can directly compare $R^2$ to determine the relative importance of each individual biomarker or component (Table 5). Neither principal component score showed the highest $R^2$ compared with the single biomarkers. Among the five biomarkers loaded on the TNF-α-related component, IL-6sR by itself had the highest $R^2$ for grip strength, IL-2sR by itself had the highest $R^2$ for 20-m walking speed, sTNFRI by itself had the highest $R^2$ for 400-m walk time, and TNF-α by itself had the highest $R^2$ for knee strength and HPPB. Among the three biomarkers loaded on the CRP-related component, CRP by itself had the highest $R^2$ for 400-m walk time and 20-m walking speed, PAI-1 had the highest $R^2$ for HPPB, and IL-6 by itself had the highest $R^2$ for knee strength and grip strength (data not shown).

## Discussion

We found that at least two components (TNF-α-related component and CRP-related component) can be used to summarize eight different inflammatory biomarkers in a population of white and black community-dwelling older adults. The two components differed in their associations with measures of physical function. Knee strength and HPPB were inversely related to the TNF-α-related component, but not

Table 5. Coefficient of Determination ($R^2$) Summary of Models Between Inflammatory Biomarkers and Components and Physical Function Measures After Adjusting for Age, Sex, Race, Study Site, Sampling Indicator, Total Lean Mass, Total Fat Mass, Physical Activity, Smoking, and Anti-Inflammatory Drug Use ($N = 809$*)

| $R^2$ | Knee Strength (Nm/kg) | 400-m Walk Time | Walking Speed (for 20 m m/s) | HPPB | Grip Strength |
|---|---|---|---|---|---|
| Covariates only | .5861 | .3846 | .2686 | .2872 | .6540 |
| IL-6sR (mg/mL) | .5861 | .3846 | .2687 | .2873 | **.6550** |
| IL-2sR (mg/mL) | .5874 | .3892 | **.2700** | .2882 | .6542 |
| sTNFRI (mg/mL) | .5882 | **.3897** | .2686 | **.2893** | .6540 |
| sTNFRII (mg/mL) | .5861 | .3852 | .2693 | .2875 | .6541 |
| TNF-α (pg/mL) | **.5899**† | .3874 | .2689 | **.2893** | .6543 |
| TNF-α-related component | .5892 | .3876 | .2686 | .2888 | .6540 |
| CRP (mg/L) | .5865 | **.3893** | **.2703** | .2873 | .6541 |
| PAI-1 (ng/mL) | .5861 | .3877 | .2687 | **.2881** | .6541 |
| IL-6 (pg/mL) | **.5880** | .3847 | .2686 | .2875 | **.6592** |
| CRP-related component | .5864 | .3875 | .2691 | .2873 | .6564 |

*Notes*: CRP = C-reactive protein; HPPB = Health ABC physical performance battery; IL = interleukin; PAI = plasminogen activator inhibitor; sTNFR = soluble TNF receptor; TNF = tumor necrosis factor.

*A complete data set without missing values was used to allow for comparisons across models.

†Bolded is the highest value in each dimension.

the CRP-related component. Both components were positively associated with 400-m walk time, inversely associated with grip strength, and not associated with 20-m walking speed. These associations are consistent with several other reports in older persons. For example, higher concentrations of CRP, IL-6, and TNF-α (and its soluble receptors) are associated with lower muscle strength (2,3,7), slower walking speed and endurance (2,6–8), and lower self-reported functional ability (1,6). Our data show a strong relationship between the TNF-α-related component and knee strength, but no relationship between the CRP-related component and knee strength, as has been previously reported in this cohort for individual biomarkers of TNF-α and IL-6 (3).

Only a few studies to date report using data reduction tools, such as principal component analysis or factor analysis, to identify common inflammatory components or factors (23–25). One advantage of this type of analysis is that, because it does not require a priori biologic assumptions, it could uncover potential unknown interactions between inflammatory components. To our knowledge, no other study has used data reduction tools to identify summary inflammatory measures in a healthy older population and explored the associations between these summary measures and physical function. The identified TNF-α-related component included TNF-α and the four soluble receptors, and the CRP-related component included CRP, IL-6, and PAI-1. These two components are similar to those identified by Koukkunen and associates (23) and are mostly supported by biologically plausible evidence, especially that showing that the principle regulator of CRP transcription is IL-6 (26). Notably, IL-6 and its receptor were placed in different components. Our explanations are, first, that there are data showing that infusion of IL-6 into humans results in increased IL-6 receptor expression in muscle (27). Second, stimulation of the IL-6 receptor activates the Janus kinase signal transducer and activation signaling pathway, which, in turn, induces the suppressor of cytokine-signaling proteins to inhibit IL-6 (28,29). Thus, systemic levels of IL-6sR may not track with systemic levels of IL-6, as is the case in this study. However, we are unaware of any other data that show either a biologic or epidemiological link between IL-6sR and TNF-α. There are potential unknown interactions between the inflammatory components due to the complexity of the biologic system. Moreover, univariate correlations in our data showed a greater link between CRP and IL-6 than between CRP and TNF-α. The highest univariate correlations among the eight markers were between TNF-α and its soluble receptors, as well as between TNF-α, soluble TNF receptors, and IL-2sR. This is also consistent with evidence that shedding of the TNF receptors are induced by TNF-α itself (30). Soluble cytokine receptors are generally more stable in the circulation and they may reflect previous biologic effects of the initial response cytokines (31). Therefore, the relation between each of the cytokine-soluble receptors may be linked to the timing of the blood measure.

We explored the relationships between the two components and several demographic characteristics and function measures to evaluate the construct validity of the components. Interestingly, the linear trend effects of the two components differed for many characteristics. Blacks were more likely to have a low TNF-α-related component score but more likely to have a high CRP-related component score. This is consistent with studies showing that CRP is greater in blacks than whites, especially among women (32,33). In addition, a prior analyses in Health ABC showed that, compared with whites, blacks had higher IL-6 but lower TNF-α (3). Furthermore, there was no relationship between physical activity and the TNF-α-related component, but physical activity was strongly inversely associated with the CRP-related component. This is consistent with a prior finding in the Health ABC study in which higher levels of moderate–vigorous exercise were associated with lower CRP, IL-6, and TNF-α; but higher levels of nonexercise daily activity were only associated with lower levels of CRP and IL-6, and not TNF-α (34). Thus, the two components appear to possess convergent validity (seeing how closely the new component is related to other variables of the same construct to which it should be related) and discriminant validity (seeing how closely the new component is not correlated with dissimilar and unrelated measures).

Using a principal component approach to generate summary measures could offer an advantage in predicting health outcomes because it considers the correlational structure between measures and mitigates the multiple testing concerns. However, when we examined the contribution of the summary component measures compared with the individual inflammatory measures to physical function, neither component score showed the highest $R^2$ value with any of the functional measures. Because principal component analysis is a linear combination of each individual measure, the variance of one component is not greater than the variance from an individual measure that has the largest variance among all. While relating to physical function, which is an independent concept, the summary measure (component) may not be more closely related than the individual measures. Thus, in this subset of Health ABC participants, it appears that calculation of summary variables using a principal component approach does not strengthen associations between inflammation and physical function compared with a single biomarker. Furthermore, the additional $R^2$ (differences between any of the inflammatory components or individual measure and covariates only) from each inflammatory marker or its component is small (all less than .01). It suggests that factors other than inflammatory markers or components may have more prominent associations with physical function measures.

There are several strengths of this study. The sample size is large enough to have confidence in the results, and a reasonable number of biomarkers were evaluated. Also due to the effort of reducing variables, the issue of multiple

comparisons was minimized. Further, a large number of covariates were considered when evaluating the association between the components and physical function. However, we are limited by the cross-sectional nature of this analysis, allowing no conclusions to be drawn about a causal effect. Moreover, all Health ABC participants were initially selected for high functioning at baseline. If those with a lower functioning level and higher inflammation were underrepresented in this cohort, a bias would result leading to an underestimate of association between inflammation and function in the general older population. Also, to have complete inflammatory marker data, only a subset of Health ABC participants was used for analysis in this study (1,269 out of 3,075). This subset had a higher use of anti-inflammatory drugs and a higher fat mass compared with the rest of the Health ABC cohort (data not shown). Thus, our results may not be automatically generalized to the general population. Nevertheless, our study is an initial attempt to examine clustering of inflammatory biomarkers and how they relate to physical function. Ultimately, identification of a set of biomarkers that are most strongly related to physical function in older individuals may provide for more clinically useful measures of underlying chronic inflammation as risk predictors for aging-related disability.

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### Correspondence

Address for correspondence to Fang-Chi Hsu, PhD, Department of Biostatistical Sciences, Wake Forest University School of Medicine, 100 North Main Street, Suite 2323, Winston-Salem, NC 27101. Email: fhsu@wfubmc.edu

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