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Chronic Inflammation Is Associated With Low Physical Function in Older Adults Across Multiple Comorbidities

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Background. Chronic subclinical inflammation may contribute to impaired physical function in older adults; however, more data are needed to determine whether inflammation is a common mechanism for functional decline, independent of disease or health status.

Methods. We examined associations between physical function and inflammatory biomarkers in 542 older men and women enrolled in four clinical studies at Wake Forest University between 2001 and 2006. All participants were at least 55 years and had chronic obstructive pulmonary disease, congestive heart failure, high cardiovascular risk, or self-reported physical disability. Uniform clinical assessments were used across studies, including grip strength; a Short Physical Performance Battery (SPPB; includes balance, 4-m walk, and repeated chair stands); inflammatory biomarker assays for interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP); and anthropometric measures.

Results. Higher levels of CRP and IL-6, but not TNF-α, were associated with lower grip strength and SPPB scores and longer times to complete the 4-m walk and repeated chair stands tests, independent of age, gender, and race. More importantly, these relationships were generally independent of disease status. Further adjustment for fat mass, lean mass, or percent body fat altered some of these relationships but did not significantly change the overall results.

Conclusions. Elevated CRP and IL-6 levels are associated with poorer physical function in older adults with various comorbidities, as assessed by a common battery of clinical assessments. Chronic subclinical inflammation may be a marker of functional limitations in older persons across several diseases/health conditions.

Key Words: Inflammation—Physical function—Aging—Comorbidities.

DUE to the impending public health burden associated with the loss of physical function with age (1), it is imperative to identify risk factors for functional decline. Impaired physical function and subsequent disability can occur as a result of age-related losses of muscle mass and strength (eg, sarcopenia) or an acute event (ie, stroke or hip fracture), or as a consequence of chronic diseases (ie, osteoarthritis, cardiovascular disease, congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD], and cancer) (2). Although the primary disease etiologies may differ (2–4), sarcopenia is a common consequence that likely contributes to the initial onset and progression of physical disability (5, 6).

The mechanisms of sarcopenia and physical disability are not fully understood; however, research suggests a role of chronic, subclinical inflammation. Aging is accompanied by increases in circulating levels of inflammatory cytokines and acute-phase proteins, and factors including increased fat mass, subclinical infections, and chronic diseases may contribute to this low-grade inflammatory status (7). Inflammatory biomarkers such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) may contribute to loss of function via direct effects on muscle catabolism (8–10). Both cross-sectional and longitudinal studies have shown that these inflammatory cytokines and the acute-phase reactant C-reactive protein (CRP) are associated with muscle mass, strength, sarcopenic obesity, physical function, and disability (11–17).

Evidence for a direct effect of inflammatory cytokines on muscle catabolism, along with the knowledge that inflammation is elevated with aging, provides additional rationale for inflammation as a common mechanism for functional decline, independent of whether it is initiated by an acute event, chronic disease, or aging. However, clinical assessments of physical function generally differ depending on the disease studied, making it difficult to compare individuals with different diseases or health conditions. We have data from several populations of older adults with various aging-related diseases/conditions who have completed a standard battery of physical function tests. Thus, we examined whether circulating levels of CRP, IL-6, and TNF-α are associated with physical function in older persons, independent of disease

Table 1. Study Descriptions

Study Name	*N*	Primary Disease	Age (y)	Exclusion Criteria
Reconditioning Exercise And Chronic Obstructive Pulmonary Disease Trial II	160	COPD with expiratory airflow limitation such that $FEV_1/FVC \leq 70\%$ and $FEV_1 \geq 20\%$ of predicted	55–80	Active treatment for cancer, severe CHF, stroke, CAD; inability to perform exercise due to physical disability or positive stress test
Pharmacological Intervention in the Elderly	52	Diastolic heart failure according the NHANES scoring system	≥65	Valvular or any other medical disorder as the primary etiology of CHF, recent or debilitating stroke, cancer or other noncardiac diseases with life expectancy <2 y
Trial of ACE Inhibition and Novel Cardiovascular Risk Factors	289	High cardiovascular risk, defined as stroke, coronary disease, peripheral vascular disease, or diabetes, and another risk factor	55–80	Current use of or hypersensitivity to ACE inhibitor, previous myocardial infarction, surgery in <6 months ago, significant renal disease
Power Training in Older Adults	41	Mild-to-moderate self-reported physical disability	≥65	Active treatment for cancer, coronary artery disease, or other major illness; inability to perform exercise; MMSE <24

Note: ACE = angiotensin converting enzyme; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; FEV_1 = 1-s forced expiratory volume; FVC = forced vital capacity; MMSE = Mini Mental State Examination; NHANES = National Health and Nutrition Examination Survey.

status. Given the importance of body fat and lean mass, we also determined whether these associations were independent of body composition.

Methods

Participants

This analysis included participants enrolled in four clinical studies at Wake Forest University (WFU) between 2001 and 2006. These studies assessed common measures of physical function, inflammation, and body composition in older persons (≥55 years) with COPD (Reconditioning Exercise And COPD Trial II [REACT II]), CHF (Pharmacological Intervention in the Elderly [PIE]), high cardiovascular risk (Trial of ACE Inhibition and Novel Cardiovascular Risk Factors [TRAIN]), or self-reported disability (Power Training in Older Adults [POWER]). Table 1 provides a description of each study including sample size, primary disease, and major exclusion criteria. All participants provided written informed consent. These studies were approved by the WFU's Institutional Review Board.

Measurements

All physical function, inflammatory biomarker, and body composition assessments were completed by trained personnel in the same clinical or research laboratories following rigorous quality control measures.

Physical function.—A common battery of physical function assessments was used across studies. The Short Physical Performance Battery (SPPB) is a standardized measure of lower extremity physical function comprising a timed usual pace 4-m walk, repeated chair stands, and a balance test (15, 18–20). Each of these measures is scored from 0 to 4, with 4 indicating the highest level of performance and 0 the inability to complete the test. A summary score ranging from 0 (worst performers) to 12 (best performers) is calculated by adding the three individual scores together.

Walking speed was assessed by asking participants to walk at their usual pace over a 4-m course. The faster of two walks was used to compute walking speed. The repeated chair stands test was performed using a straight-backed chair placed against a wall. Participants were asked to stand from a sitting position without using their arms. If able to perform the task, they were then asked to stand up and sit down five times as quickly as possible. Walking speed and chair stands performance were scored based on data from the Established Populations for Epidemiologic Studies of the Elderly (20). We also report continuous data from these tests as the time to complete each task in seconds, with shorter times indicating better performance. For the balance test, participants were asked to maintain balance in three positions characterized by a progressive narrowing of the base of support: side-by-side, semi-tandem, and tandem. For each position, participants were timed for less than or equal to 10 seconds and scored as previously described (20).

Grip strength was measured in both hands using an adjustable grip strength dynamometer (Jamar Model No. BK-7498; Fred Sammons, Inc., Burr Ridge, IL). Participants performed the test three times with each hand, and the maximum overall value was used in the analyses. Grip strength was not measured in the POWER study.

Inflammatory biomarkers.—Inflammatory biomarker concentrations were measured from blood samples collected in the morning after an overnight fast. Blood draws were rescheduled if participants reported current use of antibiotic medication, fever, or any other acute infection (such as a respiratory or urinary tract infection). Fasting plasma IL-6 and TNF-α concentrations were determined by high-sensitivity Quantikine immunoassay kits (R&D Systems, Minneapolis, MN). CRP was measured using an automated immunoanalyzer (Immulite; Diagnostics Products Corp.,

Table 2. Participant Characteristics, Body Composition, Physical Function, and Inflammatory Biomarker Concentrations in Each Study and in All Studies Combined

Characteristics	REACT II	PIE	TRAIN	POWER	Combined
N	160	52	289	41	542
Female, %	43.8	80.8	43.6	73.2	49.4
Whites, %	89.0	86.3	74.1	90.2	80.5
Age, y*	69.1 (9.2)	70.4 (7.7)	66.0 (7.4)	75.3 (5.9)	68.0 (8.3)
BMI, kg/m^2*	28.1 (5.9)	30.0 (5.0)	29.7 (5.4)	29.6 (5.6)	29.2 (5.6)
Total body fat, %*	32.7 (8.0)	38.3 (7.7)	33.1 (8.3)	38.1 (6.4)	33.9 (8.2)
Fat mass, kg*	27.2 (10.4)	30.8 (9.4)	29.1 (9.8)	30.4 (8.3)	28.8 (9.9)
Lean mass, kg*	52.5 (12.0)	46.9 (9.6)	55.9 (11.7)	47.3 (12.0)	53.4 (12.0)
SPPB score, 0–12*	10.6 (1.5)	9.8 (1.6)	10.3 (1.5)	9.2 (1.8)	10.3 (1.6)
Grip strength, kg*	36.7 (12.3)	28.8 (8.7)	39.5 (13.5)	—	37.7 (13.0)
4-m walk, s*	3.9 (1.1)	3.5 (0.7)	3.4 (0.9)	4.3 (1.2)	3.6 (1.0)
Chair rise, s*	13.0 (5.0)	15.0 (3.8)	13.9 (4.2)	18.4 (7.5)	14.0 (4.9)
CRP, mg/L†	4.3 (1.9–9.2)	6.5 (2.8–15.9)	2.5 (1.0–5.0)	5.0 (1.7–8.1)	3.3 (1.5–7.9)
IL-6, pg/mL†	2.5 (1.6–3.8)	2.4 (1.7–4.5)	2.9 (2.3–4.2)	3.4 (1.8–5.3)	2.8 (1.9–4.2)
TNF-α, pg/mL†	1.2 (0.9–1.5)	0.8 (0.6–1.1)	—	0.9 (0.6–1.2)	1.0 (0.8–1.4)

Notes: BMI = body mass index; CRP = C-reactive protein; IL-6 = interleukin-6; PIE = Pharmacological Intervention in the Elderly; POWER = Power Training in Older Adults; REACT II = Reconditioning Exercise And COPD Trial II; SPPB = Short Physical Performance Battery; TNF-α = tumor necrosis factor alpha; TRAIN = Trial of ACE Inhibition and Novel Cardiovascular Risk Factors.

*Values are in mean (standard deviation).

†Values are in median (interquartile range).

Los Angeles, CA). Samples were measured in duplicate with the average value used for data analyses. Intraassay and interassay coefficients of variation (CVs) for IL-6 were 7% and 16%, respectively, and 8% and 23%, respectively, for TNF-α. Intraassay and interassay CVs for CRP were 7% and 8%, respectively. TNF-α was not measured in the TRAIN study.

Body composition.—Body mass was measured in kilograms on a standard calibrated scale, and height was measured in centimeters using a stadiometer. Body mass index (BMI) was calculated as body mass in kilograms divided by height in meters squared. Total body fat, fat mass, and lean mass were assessed using dual energy x-ray absorptiometry on a Hologic scanner.

Statistical Analysis

CRP, IL-6, and TNF-α levels were not normally distributed and were log-transformed for all analyses. Multiple linear regression was used to characterize the strength of the relationship between physical function measures (grip strength, SPPB, 4-m walk time, and chair rise time) and inflammatory biomarker concentrations (CRP, IL-6, and TNF-α) within each study while controlling for age, gender, and race (individual study model). Multiple linear regression was used to determine the association between physical function and inflammatory biomarkers in all participants combined, controlling for study, in addition to age, gender, and race (combined model). Linear model assumptions were checked for each model fitted. Residual versus predicted value plots were used to check linearity of the relationship between physical function and inflammatory biomarkers and homoscedasticity (constant variance). Quantile-Quantile (QQ) plots of residuals were used to check for normality. Leverage points were also checked based on Cook's distance. We investigated the consistency of relationships across studies by testing for interactions between study and inflammatory biomarker. This was done by adding an interaction term in the combined model described previously. If the test for the interaction is statistically significant, it indicates that the relationship between physical function measure and inflammatory biomarker depends on disease status (unequal slopes); otherwise we conclude that the relationship is consistent across study populations (equal slopes). Additional adjustments were performed to examine whether these relationships were independent of fat mass, lean mass, percent body fat, and BMI, for both individual study models and combined models. A p value $\leq .05$ was considered statistically significant for all comparisons, except for the tests of interaction ($p \leq .10$). All analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

Results

Table 2 contains descriptive statistics for participant characteristics, body composition, physical function, and inflammatory biomarker concentrations for participants in each study and for all 542 participants combined. The mean (standard deviation) age of the combined study population was 68.0 (8.3) years. Study participants were predominately White and overweight, with low physical function and high levels of CRP, IL-6, and TNF-α.

Using multiple linear regression analyses, we examined associations between physical function and CRP for each study and for all studies combined (Figure 1). In the combined analysis, after adjusting for age, gender, race, and study, higher levels of CRP were associated with lower

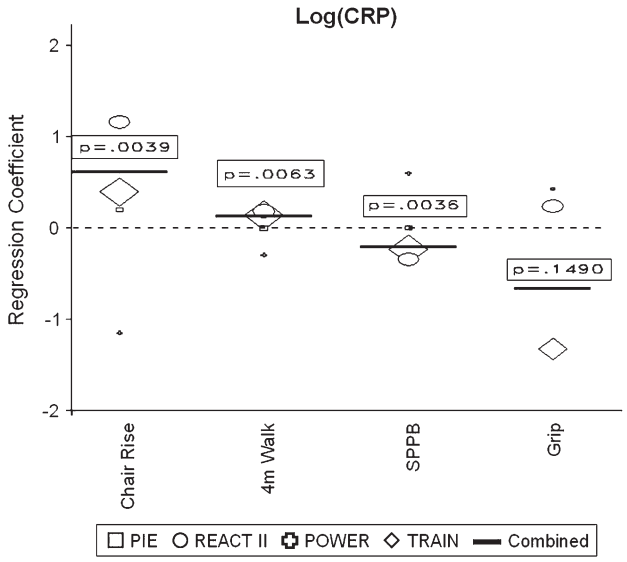

Figure 1. Changes in physical function measures per 1 *SD* increment in log(CRP) after adjustment for age, gender, and race. In the combined analyses, coefficients are also adjusted for study. The *p* values are from the test for slope = 0 in the combined analyses. The size of the symbol is proportional to the sample size. A positive coefficient for chair rise and walk times and a negative coefficient for SPPB scores and grip strength are indicative of poorer physical function. CRP = C-reactive protein; PIE = Pharmacological Intervention in the Elderly; POWER = Power Training in Older Adults; REACT II = Reconditioning Exercise And COPD Trial II; SPPB = Short Physical Performance Battery; TRAIN = Trial of ACE Inhibition and Novel Cardiovascular Risk Factors.

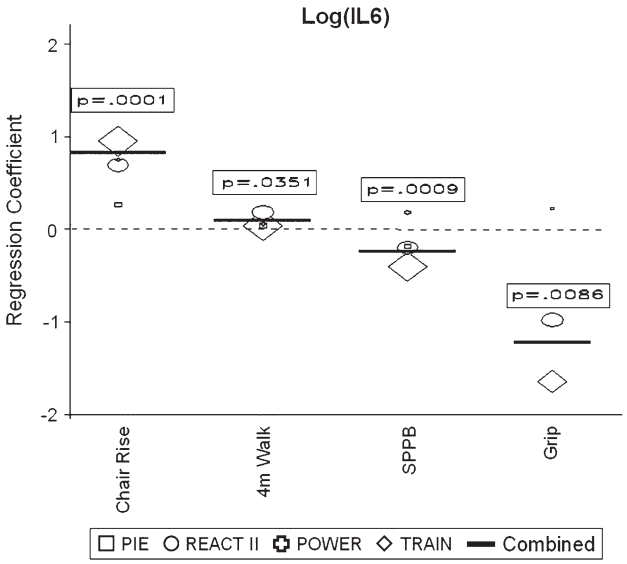

Figure 2. Changes in physical function measures per 1 *SD* increment in log(IL-6) after adjustment for age, gender, and race. In the combined analyses, coefficients are also adjusted for study. The *p* values are from the test for slope = 0 in the combined analyses. A positive coefficient for chair rise and walk times and a negative coefficient for SPBB scores and grip strength are indicative of poorer physical function. IL = interleukin-6; PIE = Pharmacological Intervention in the Elderly; POWER = Power Training in Older Adults; REACT II = Reconditioning Exercise And COPD Trial II; SPPB = Short Physical Performance Battery; TRAIN = Trial of ACE Inhibition and Novel Cardiovascular Risk Factors.

SPPB scores ($p = .004$) and longer 4-m walk ($p = .006$) and chair rise times ($p = .004$). There was no significant association between CRP and grip strength. Higher levels of IL-6 were associated with longer 4-m walk ($p = .04$) and chair rise times ($p = .001$), as well as lower grip strength ($p = .009$) and SPPB scores ($p = .009$; Figure 2). TNF-α was not associated with any physical function measures (Figure 3). The overall test of equality of slopes across studies relating inflammatory biomarkers to physical function differed only for CRP and SPPB ($p = .082$), TNF-α and SPPB ($p = .009$), and TNF-α and chair rise time ($p = .067$). Specifically, the relationship between CRP and SPPB was similar in all studies, except in POWER (Figure 1). Conversely, the relationships between TNF-α and both SPPB and chair rise time were similar in REACT II and POWER but not in PIE (Figure 3). Thus, the observed relationships were mostly consistent across studies, even though the strength of the associations varied by study.

Associations between physical function and inflammatory biomarker concentrations in all studies combined are presented in Table 3. To permit direct comparisons between inflammatory biomarkers, regression coefficients were reported as the increase/decrease in physical function per 1 *SD* increment in inflammatory biomarker concentration. Compared with CRP, IL-6 had a stronger association with grip strength and chair rise time but a similar relationship with SPPB and 4-m walk time. On the other hand, the associations between TNF-α and physical function were smaller and not significant. In analyses adjusting for body composition, the associations between chair rise time and both CRP and IL-6 were attenuated after controlling for fat mass (Model 2). In contrast, adjusting for lean mass (Model 3) resulted in stronger associations between inflammatory biomarkers (CRP and IL-6) and grip strength. Inclusion of BMI or percent body fat did not significantly affect the results (data not shown).

Discussion

We examined associations between inflammatory biomarkers and physical function in older adults with various diseases/conditions. Our data show that increased CRP and IL-6 were associated with poorer physical function, independent of age, gender, race, and body composition. Most importantly, the associations between physical function and inflammation were generally independent of disease status. Specifically, these associations were consistent among individuals with COPD, CHF, high cardiovascular risk, and self-reported disability, but no major illnesses, with a few exceptions where the relationship between inflammation and physical function was not uniform across studies. Of note, the relationship between CRP and SPPB was different in the POWER study (disease-free participants at risk for disability), whereas the relationships between TNF-α and SPPB and chair rise time were different in the PIE study (CHF patients). The reasons for these differences are not readily apparent.

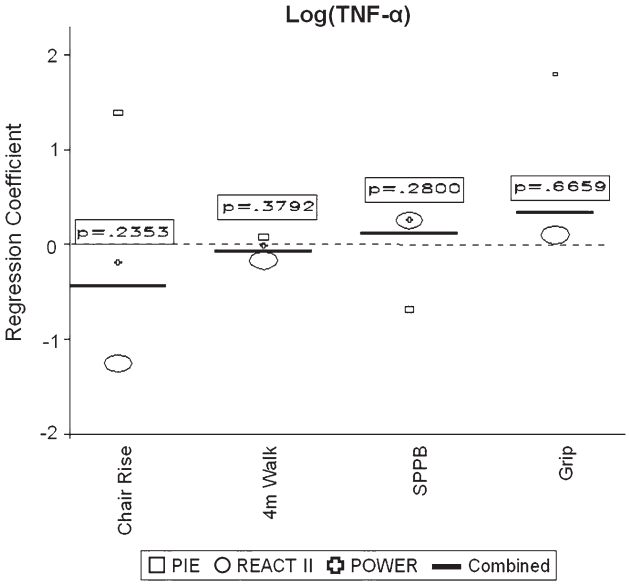

Figure 3. Changes in physical function measures per 1 *SD* increment in log(TNF-α) after adjustment for age, gender, and race. In the combined analyses, coefficients are also adjusted for study. The *p* values are from the test for slope = 0 in the combined analyses. The size of the symbol is proportional to the sample size. A positive coefficient for chair rise and walk times and a negative coefficient for SPPB scores and grip strength are indicative of poorer physical function. PIE = Pharmacological Intervention in the Elderly; POWER = Power Training in Older Adults; REACT II = Reconditioning Exercise And COPD Trial II; SPPB = Short Physical Performance Battery; TNF = tumor necrosis factor alpha; TRAIN = Trial of ACE Inhibition and Novel Cardiovascular Risk Factors.

Nevertheless, although previous cross-sectional studies show that increased inflammatory biomarker concentrations in the elderly are related to impaired physical function (15–17), this study is the first to report an association between inflammation and physical function using standardized measures across multiple study populations.

There is substantial evidence of an association between physical function and inflammation in a number of chronic disorders of the elderly. For example, muscle loss and wasting are associated with chronic systemic inflammation in COPD (21). Similarly, elevated cytokine concentrations in CHF patients are associated with reduced muscle mass and strength (22). Additionally, inflammatory biomarkers are strong independent risk factors for cardiovascular disease and predict cardiovascular outcomes, disability, and mortality in older persons (23). By performing uniform clinical assessments across multiple study populations, our results provide further evidence that chronic inflammation and impaired physical function are strongly related in various age-related diseases/health conditions.

In the present study, we could not reject the null hypothesis that TNF-α was not associated with physical function. Given that TNF-α was not measured in the TRAIN study (n = 289), the sample size for TNF-α was smaller than the other two biomarkers (IL-6 and CRP). The highest partial correlation we found between TNF-α and physical function was −.08 after adjusting for age, gender, race, and study; thus, we would need at least 1,250 participants in order to have adequate power to detect the effect of TNF-α. We calculated confidence intervals for the regression coefficient estimates so as to gain some insight on interpreting the results (data not shown). We found that the associations with TNF-α were generally much smaller than those for CRP and IL-6, suggesting that the relationship between TNF-α and physical function may simply be weaker in our study population. In patients with knee osteoarthritis, associations with physical function have been reported to be stronger for circulating levels of TNF-α receptors than for TNF-α itself (17). Soluble TNF-α receptors are able to modulate TNF-α activity (24) and may therefore modify its association with physical function and disease severity indicators. Because cytokines such as TNF-α are generally less stable in circulation over time than their receptors (25), soluble cytokine receptors could potentially be more reliable markers of the inflammatory response.

The association between inflammation and functional impairment may be partially due to the catabolic effect of inflammatory cytokines on muscle. For example, in humans, there is a positive correlation between whole-body protein

Table 3. Associations Between Inflammatory Biomarkers (per 1 *SD* increment) and Physical Function Measures in All Studies Combined With Adjustment for Different Covariates

	Log(CRP), mg/L			Log(IL-6), pg/mL			Log(TNF-α), pg/mL		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Grip strength, kg	−.67	−.75	−1.00*	−1.22†	−1.26†	−1.57‡	.34	.38	.19
SPPB score, 0–12	−.21†§	−.17*	−.21†	−.23‡	−.19†	−.22†	.12§	.13	.13
4-m walk, s	.13†	.12†	.14†	.10*	.09	.11*	−.06	−.06	−.06
Chair rise, s	.62†	.39	.58†	.83‡	.61†	.76‡	−.43§	−.46	−.46

Notes: Values are regression coefficients. Model 1: Adjusted for age, gender, race, and study. Model 2: Adjusted for age, gender, race, study, and fat mass. Model 3: Adjusted for age, gender, race, study, and lean mass. CRP = C-reactive protein; IL-6 = interleukin-6; POWER = Power Training in Older Adults; SPPB = Short Physical Performance Battery; TRAIN = Trial of ACE Inhibition and Novel Cardiovascular Risk Factors; TNF-α = tumor necrosis factor alpha.

*$p \leq .05$.

†$p \leq .01$

‡$p < .001$.

§Significant interaction between study and inflammatory biomarker concentration, $p \leq .10$. TNF-α was not measured in the TRAIN study (n = 289), and grip strength was not measured in the POWER study (n = 41).

breakdown and TNF-α production (26). Additionally, myosin heavy chain protein synthesis rates are inversely correlated with muscle TNF-α expression (27), as well as plasma levels of CRP and IL-6 (28). In rats, direct infusion of TNF-α induces skeletal muscle protein degradation (8, 10). Similarly, IL-6 infusion results in muscle atrophy and a loss of myofibrillar protein (9). Thus, elevated inflammatory biomarkers may contribute to functional decline and physical disability via decreases in skeletal muscle protein content and loss of muscle mass and strength.

Inflammatory biomarkers may also have an effect on physical function by promoting age-related changes in body composition, primarily fat gain and muscle loss. It was previously reported that the relationship between inflammation and sarcopenia was mostly explained by obesity (14). Although increased fat mass contributes to increased production of inflammatory cytokines, which in turn contribute to muscle catabolism and loss of muscle mass, we found that the associations between inflammation and physical function generally remained significant even after adjusting for lean mass, fat mass, percent body fat, or BMI. These results indicate that inflammatory biomarkers have an independent effect on physical function.

The major limitation of this study is that it is cross-sectional, and therefore, we cannot determine the underlying mechanisms for the observed association between inflammatory biomarkers and physical function. In addition, we were not able to fully account for anti-inflammatory medication use, although participants in the TRAIN study (more than half of the combined study population) were not on these medications. Moreover, although we studied patients with diseases/health conditions that are common in older individuals, these findings may not be applicable to all aging-related diseases. Nevertheless, the strength of the current investigation lies in the use of standardized measures and common resources across multiple study populations.

In conclusion, we found that increased concentrations of CRP and IL-6 were associated with impaired physical function in older adults with various diseases/conditions. Our data suggest that higher levels of inflammatory cytokines may be a marker of functional limitations in older persons across several diseases/health conditions. It is also possible that elevated inflammatory cytokine concentrations are markers of increased disease severity or other underlying factors that may drive the association between inflammation and physical function. Given the prevalence of low-grade inflammation in older persons, interventions aimed at reducing inflammatory biomarker concentrations may help slow the decline of physical function with age and disease.

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