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Physical functioning related to C-reactive protein and fibrinogen levels in mid-life women

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Abstract

We investigated whether subclinical inflammatory markers high-sensitivity C-reactive protein (CRP) and fibrinogen are related to measures of physical functioning in midlife women. Our sample included 543 participants in the Michigan site of Study of Women's Health Across the Nation (SWAN). Predictors included CRP from serum and fibrinogen from plasma. Performance-based outcomes included measures of gait, hand grip strength, flexibility, stair climb, 40-foot walk, and chair rise. Perception of physical functioning was assessed with the Medical Outcomes Study Short-Form 36 questionnaire. Regression analyses adjusted for relevant covariates. Cross-sectional associations were identified between higher CRP and more time spent in double support (with both feet on the floor while walking), shorter forward reach, slower 2-lb lift, and slower stair climb. Higher CRP and fibrinogen were associated with worse perceived functioning in cross-sectional analyses. Predictive associations across time were found between higher CRP and increased time spent in double support, diminishing forward reach distance and grip strength and worse perceived physical functioning. Predictive associations across time were also found between higher fibrinogen and greater time spent in double support, slower stair climb and worse perceived physical functioning. Our results suggest that inflammatory processes are associated with poor physical functioning in midlife women.

Keywords

mobility limitation; inflammation; C-reactive protein; fibrinogen; body mass index; women

INTRODUCTION

Aging is associated with a progressive decline in physical functioning and for many, this decline begins in midlife. Results from the National Health Interview Survey indicate that 37% of persons 50–54 and 42% of those aged 55–59 had difficulty with at least one of the following functions: walking a quarter mile; climbing ten steps; standing two hours; sitting two hours;

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stooping, bending or kneeling; reaching over one's head; grasping small objects; carrying ten pounds; and/or moving large objects (Martin, 2009). Females report consistently greater difficulty in physical functions compared to males (Pleis and Lucas, 2009). In a large multi-ethnic sample of mid-life women aged 40–55 years, 19% were classified as moderately or substantially limited in physical functioning on tasks such as walking and climbing stairs (Pope, 2001).

The connection between inflammation and health outcomes, including physical functioning (Taaffe et al., 2000; Cesari et al., 2004; Davi et al., 2002), has been studied extensively in the elderly but data are sparse in younger populations. Understanding associations with inflammation are important in mid-aged populations because inflammatory markers are elevated (greater than 3.0 mg/l) in this age group. According to recent national survey results, inflammatory marker C-reactive protein (CRP) is elevated in 46% of Americans aged 45–65 years. Further, this marker was much more elevated in women (45%) compared to men (27%), as well as in those classified as obese (60.5%) compared to those without obesity (26.4%) (Cummings, 2006).

Research in the elderly suggests that chronically-elevated inflammatory response may compromise physical capacities, including strength, aerobic capacity, balance and coordination (Taaffe et al., 2000; Cesari et al., 2004; Davi et al., 2002). Some findings in humans and animals suggest that poor physical functioning is linked through a deleterious impact on muscle and strength (Cesari et al., 2004; Goodman, 1994; Goodman, 1991; Schaap et al., 2006). The association with poorer physical functioning may also involve pain (Whitson et al., 2009), particularly with flexibility (Lin et al., 2001). Finally, it is also possible that there is a bidirectional association of diminishing physical functioning leading to elevated inflammatory levels though increasing weight gain, which can curtail physical activity.

A loss in physical functioning often develops slowly over time, initiated by events that likely occur years or even decades before a decline in functioning becomes markedly apparent. And while numerous studies in the elderly have related explicit disease states and conditions such as obesity, stroke, cardiovascular disease, hypertension, diabetes, and arthritis to poorer physical functioning (Boult et al., 1994; Dunlop et al., 2002; Sarkisian et al., 2001; Mor et al., 1989; Woo et al., 1998; Gregg et al., 2002; Launer et al., 1994; Fine et al., 1998), much less is known about the occult physiological changes contributing to the natural history of functional decline.

This investigation examines associations between subclinical disease markers for inflammation [high-sensitivity CRP and fibrinogen] in relation to measures of physical functioning, while adjusting for relevant variables. The analyses addressed two questions 1) Are CRP or fibrinogen biomarker levels associated with physical functioning level at the same time point? 2) Do baseline and/or change in biomarkers predict change in physical functioning? All analyses related to CRP included a body size confounding variable that allowed us to statistically evaluate metabolic and non-metabolic effects of BMI separately.

MATERIALS AND METHODS

Sampling and Study Population

Study of Women's Health Across the Nation (SWAN) is a longitudinal study of multi-ethnic, midlife women recruited from seven US cities (Sowers et al., 2000). This analysis is limited to the Michigan site because performance-based physical functioning measures were measured only at this site. Eligibility at enrollment included being female, age 42–52 years, not using hormones, menses within 3 months prior to enrollment and recruitment of Caucasian and minority samples. The Michigan site includes a population-based sample of 543 African

American or Caucasian women. Consistent with their recruitment plan, 60% of participants were African American and 40% were Caucasian. Institutional Review Board approval was granted for the study protocol and written informed consent was obtained from each participant.

Measurements

Independent variables: Biomarker assays—During the year-5 (2001) visit, 98% of participants reported fasting at least 8 hours before their blood draw. Assays for high-sensitivity CRP and fibrinogen were undertaken at Medical Research Laboratories International, Inc (now GCL, Inc). CRP was quantified from serum using an ultrasensitive immunonephelometric method (Dade-Behring, Marburg, Germany). Fibrinogen was measured in frozen citrated plasma (MLA ELECTRA 1400C, Medical Laboratory Automation Inc., Mt. Vernon, NY) using a clot-based turbidometric detection system. The monthly interassay CVs were 2.3–3.5% and 2.6–3.6% at mean concentrations of 250 and 140 mg/dl, respectively.

Dependent variable: perceived physical functioning—Perceived physical functioning was quantified with responses to a 10-question subscale of the Medical Outcomes Study Short-Form 36 questionnaire (SF-36; Ware, 1995). Participants indicated whether they were limited a lot, a little or not limited in bathing, dressing, carrying groceries, bending, moderate and vigorous athletic activities, walking, and climbing stairs. Total points ranged from 0 – 100, with higher scores representing better functioning.

Women with a score below 50 points were classified as having substantial limitations; such individuals could have reported no limitations on, at most, five of the ten activities. Those with 51–85 points were classified as having moderate limitations; a woman with 85 points could have reported no limitations on, at most, eight of ten activities, allowing for some limitations in vigorous and moderate activities. Women with 86–100 points were considered not limited.

Dependent variables: performance-based physical functioning

Hand grip strength and chair rise: To assess hand grip strength, participants were asked to squeeze a standard adjustable handle dynamometer while seated in a chair with the forearm at a 90-degree elbow bend and hands placed with fingers and thumb parallel to the body (Bohannon, 2008). The average of three consecutive grip strength (kg) efforts was used. Chair rise time, considered a test of lower extremity and central strength, (Curb, 2006) was also evaluated. Participants were asked to rise from a standard height, armless chair with their arms folded over their chest. This variable captured movement time (in seconds) from onset of trunk motion on the chair to an upright standing position. Both chair rise and grip strength have been shown to have good discrimination across the range of physical function, including in younger, high-functioning persons (Curb, 2006).

2-lb lift: This test was designed to capture dynamic balance ability, joint coordination and initial posture for lifting, which have been related to functional status in mid-life women (Buhr, 1998). The measure quantified the time (seconds) to lift a 2-pound box from the floor to waist height. The box was placed at a standard distance (8") forward of the toes. Timing was stopped when the woman was standing upright again with the object at waist height.

Forward reach: Forward reach distance was used as a measure of flexibility and range of motion (Duncan, 1990). Participants were asked to stand perpendicular to the floor, extend their arm at a ninety-degree angle and then reach the greatest distance (cm) possible forward while keeping their arm parallel to the floor.

Measures of gait: We timed two purposeful walks down a 40 foot carpeted corridor. An instrumented gait mat with an active sensor area (Gaitrite, CIR Systems, Clifton, NJ) was

placed midway in the corridor where they had completed the 40-foot walk. Footsteps detected by the sensors (80 Hz sampling frequency) were recorded on a computer for subsequent analysis. Analysis of the electronic gait data required interactive editing of the "raw" footstep data collected by the gait mat software. The footsteps recorded during the walk were displayed on a computer screen, and incomplete footsteps were removed from the dataset (i.e., those footsteps at the beginning and ending of the walk that only partially contacted the sensor area of the mat). Data from both walking trials were combined to yield one set of gait data for each participant. Measures include seconds to complete the 40-foot walk and percent time in double support (i.e. when both feet have some contact with the floor) during one gait cycle. Both of these variables are considered important predictors of adverse health events (Cesari, 2009; Verghese, 2009).

Timed stair climb: We timed (seconds) the ascent and descent of three standard stairs. This measure is intended to capture a variety of physical functioning domains including strength, balance, and range of motion, and has also been used to capture functioning limitations associated with pain (Terwee, 2006). Movement time commenced at the toe-off of the leading leg at the start of ascent to final foot contact of the trailing leg after descent. Time from the second of two trials was used.

Covariates—Weight and height, measured using calibrated scales and a stadiometer, respectively, were used to calculate body mass index [BMI; weight (kg) / height (m²)]. Women characterized their economic stress by reporting whether it was very hard, somewhat hard, or not hard at all to pay for basics like food, housing, and health care. Presence of high blood pressure, diabetes, heart disease defined as history of heart attack or angina, and arthritis was self-reported and not verified with medical records. Current smoking exposure (Ferris, 1978; Coghlin et al., 1989), age and race were measured via questionnaire.

Statistical approach—Medians (interquartile ranges; IQR) were used to describe participant characteristics due to skewed distributions of some variables. Two main approaches were used to evaluate our two research questions. For question 1, whether biomarkers were associated with physical functioning at the same time point, we related levels of CRP or fibrinogen to physical functioning outcomes in cross-sectional analyses with data from the year 2001.

Associations with performance-based physical functioning were evaluated using linear regression models. To meet model assumptions, continuous variables with non-normal distributions were log transformed including CRP, fibrinogen, time in spent in double support during a gait cycle, 2-lb lift, timed stair climb, chair rise, 40-foot timed walk and BMI. Ordinal logistic regression models were used to evaluate cross-sectional associations with perceived physical functioning category (based on the SF-36 score) because the distribution of this score could not be normalized using simple transformations. Because SF-36 data were not available for 2001, data from the year 2002 were used. Tertiles of CRP and fibrinogen were used as independent variables for ease of interpretation. The proportional odds assumption was tested for each model using a chi-square test; therefore, each summary odds ratio represents the comparisons between no limitations vs. moderate/substantial limitations, as well as no/moderate limitations vs. substantial limitations.

For question 2, whether baseline and/or change in biomarkers predicted change in physical functioning, these predictive associations were evaluated using repeated measures analyses. First, we used longitudinal mixed models to relate baseline (1996) and five-year change (1996–2001) in biomarkers with three-year change in performance-based physical functioning outcomes (from 2001–2003). Change in CRP or fibrinogen was calculated as $\log_{\text{biomarker at 2001}} - \log_{\text{biomarker at 1996}}$. Continuous variables were transformed in a similar

fashion to the linear regression models. For perceived physical functioning outcomes (SF-36 category), repeated measures generalized estimating equations (GEE) models with an ordinal dependent variable were used. Change in perceived physical functioning spanned every two years from 2002 to 2006.

Cross-sectional models were adjusted for age, race/ethnicity, economic strain, smoking, heart disease, arthritis, high blood pressure, diabetes and BMI, as appropriate. All other models were adjusted for these variables plus the initial value of the dependent variable (e.g. year 2001 timed walk).

Due to collinearity between body fat and CRP, statistical models with CRP as the independent variable included residuals of BMI as the measure of body size confounding. The BMI residual variable represents the variation in BMI that remains following simple regression with CRP and therefore is not related to CRP (e.g., mechanical loading). It is thus assumed that the relationship between CRP and BMI that is metabolic is represented by the variable CRP. Models in which fibrinogen is the independent variable include BMI as a covariate.

The functional forms and fit of models were assessed graphically, using residual analyses and goodness-of-fit. Either CRP and residual BMI or fibrinogen and BMI were forced into models, while covariates were selected using a stepwise approach. A two-sided $\alpha < 0.05$ was applied. SAS 9.1 and Macro facilities (SAS Institute, Cary, NC) were used.

RESULTS

Median age in 2001 was 50 years and median BMI was 32.4 kg/m² (Table 1). The median (IQR) level of CRP was 3.9 (6.5) mg/L, and the 5-year increase from 1996 to 2001 was 0.2 (3.4) mg/L. Median (IQR) fibrinogen level was 292 (83) mg/dl, and the median 5-year decrease was 13 (64.0) mg/dl.

Approximately 41% (n=153) of women reported very little perceived physical functioning difficulties (based on the SF-36) while 36% (n=137) and 23% (n=88) of women were classified as having moderate and substantial physical limitations, respectively. The median (IQR) percent time in double support was 25.7 (8.3) seconds, and the median forward reach distance was 35.6 (10) cm (Table 1). Median time to lift a two-pound weight was 2.2 (1.0) seconds, and median stair climb time was 19.1 (6.6) seconds.

Twenty two percent (22%) of participants reported current cigarette smoking, 28% reported having high blood pressure, and 25% reported having arthritis. Twelve percent of participants reported that it was very difficult to pay for basics.

Cross-sectional associations between biomarkers and physical functioning measures

Higher $\log_{10}$ CRP was associated with greater percent time spent in double support [β (SE) 0.06 (0.01), p value <0.0001; Table 2]. Higher $\log_{10}$ CRP was also associated with shorter forward reach [β (SE) -1.3 (0.3), p value 0.0003] and slower 2-lb lift [β (SE) 0.06 (0.02), p value 0.001]. Slower timed stair climb was associated with higher $\log_{10}$ CRP [β (SE) 0.04 (0.01), p value 0.002]. $\log_{10}$ Fibrinogen was not associated with performance-based physical function measures in cross-sectional analyses.

Those with CRP values of ≥ 6.3 mg/L were classified into the highest CRP tertile, and those with value ranges from > 2.1 through 6.3 mg/L, and ≤ 2.1 mg/L, were classified into middle and lowest tertiles, respectively. Being in the highest tertile of CRP was associated with more than a two-fold greater odds of having greater limitations in perceived physical functioning compared to those in the lowest tertile [summary OR (95% CI) for the highest vs. lowest tertile

of CRP: 2.11 (1.25, 3.56); summary OR (95% CI) for the middle vs. lowest tertile of CRP: 1.12 (0.66, 1.92); Figure 1].

Those with fibrinogen values of > 316 mg/dl were categorized into the highest tertile, whereas those placed in the middle and lowest tertiles of fibrinogen had value ranges of > 267 through 316 mg/dl and ≤ 267 , respectively. Being in the highest tertile of fibrinogen was associated with a nearly two-fold likelihood of having greater limitations in perceived physical functioning compared to those in the lowest tertile of fibrinogen [summary OR (95% CI) for the highest vs. lowest tertile of fibrinogen: 1.93 (1.1, 3.38); summary OR (95% CI) for the middle vs. lowest tertile of fibrinogen: 1.44 (0.84, 2.46); Figure 1]. Body mass index was statistically significant ($p \leq 0.05$) in all models in which CRP or fibrinogen was significant.

Predictive associations across time

Relating baseline and five-year change in biomarkers and change in performance-based physical functioning—Higher baseline $\log_{10}$ CRP was associated with greater increase in time spent in double support during a gait cycle [β (SE) 0.01 (0.005), p value 0.01] and shortening of forward reach distance [β (SE) -0.45 (0.2), p value 0.01] (Table 3) over time. Greater five-year increase in $\log_{10}$ CRP was associated with greater decline in grip strength [β (SE) -0.42 (0.2), p value 0.03]. There were no significant predictive associations between $\log_{10}$ CRP and 2-lb lift, chair rise, timed walk or timed stair climb.

Higher baseline $\log_{10}$ fibrinogen was associated with increased time spent in double support [β (SE) 0.12 (0.05), p value 0.02] over time. Higher baseline and greater increase in $\log_{10}$ fibrinogen were associated with greater slowing in timed stair climb [β (SE) 0.08 (0.04), p value 0.03 and 0.12 (0.04), p value 0.005, respectively]. There were no significant predictive associations between $\log_{10}$ fibrinogen and hand grip strength, forward reach distance, 2-lb lift, chair rise, or timed walk.

Relating baseline and five-year change in biomarkers and change in perceived physical functioning—Neither baseline $\log_{10}$ CRP level nor baseline $\log_{10}$ fibrinogen level were associated with perceived physical functioning. Those with a greater five-year increase in $\log_{10}$ CRP were more likely to have a decline in perceived physical functioning (summary OR: 1.46; 95% CI: 1.07, 1.99). Those with greater five-year increase in $\log_{10}$ fibrinogen were also more likely to have a decline in perceived physical functioning (summary OR: 5.24; 95% CI: 1.34, 20.53).

DISCUSSION

We related two biomarkers of inflammatory processes to physical functioning outcomes in mid-life women. Both biomarkers were related to poorer perception of physical functioning in cross-sectional and longitudinal analyses. CRP was associated with poorer performance on four of seven physical functioning outcomes in cross-sectional analyses, and fewer in longitudinal analyses showing predictive associations across time. While fibrinogen was associated with no physical functioning outcomes in cross-sectional analyses, higher fibrinogen was related to decline in double support and timed stair climb in longitudinal analyses.

Inflammation, which increases with aging, may impact physical functioning directly through a deleterious impact on muscle mass and strength. This pathway is supported by investigations into the catabolic effects of inflammatory markers. Experimental studies of rats have reported that administration of IL-6 or TNF- α causes muscle breakdown (Goodman, 1994; Goodman, 1991), and prospective findings in humans suggest that higher levels of IL-6 and CRP are associated with loss of muscle strength after adjustment for BMI and other covariates (Schaap

et al., 2006). This pathway is relevant to our findings, as strength is integral to performance of hand grip strength, stair climb, and most physical actions listed on the perceived physical functioning questionnaire.

Higher BMI has been linked to poorer strength-supported physical functions in several studies (Houston et al., 2005a; Houston et al., 2005b; Ugur-Altun et al., 2005), and this relationship likely stems from the metabolic effects of increased fat mass. Fibrinogen and CRP are markers of a chronic, low-grade inflammatory process, and their levels rise with greater central adiposity (Ugur-Altun et al., 2005; Despres and Lemieux, 2006; Sesti, 2006).

In addition to direct catabolic effects, the inflammatory process may work indirectly through mechanisms related to insulin resistance. Insulin resistance often coexists with high central adiposity and may impact physical functioning through its association with lower muscle mass and strength (Guillet and Boirie, 2005; Abbatecola, et al., 2005; Karelis et al., 2007). Insulin resistance is reportedly involved in muscle protein loss (Guillet and Boirie, 2005); in aging muscle, there is a reduced response of protein metabolism to insulin at both the whole body and muscle levels. Additionally, because insulin resistance impairs glycogen synthesis and glucose uptake in skeletal muscle, (Sesti, 2006) fatigue and feeling of weakness could contribute to poorer functioning (Abbatecola et al., 2005).

In our investigation the variable CRP represented, in part, the metabolic effect of increased adiposity. But biomechanical encumbrances such as limited range of motion associated with higher body mass, or difficulty in carrying out physical tasks while supporting extra body weight might also play a role. The latter explanations are congruent with our reported associations with physical functions that are not markers of strength. Higher CRP was related to more time spent in double support and slower 2-pound lift, as well as a shorter forward reach. All three are largely measures of balance, while the latter two also capture flexibility and range of motion. An effect of CRP above and beyond that of body weight may involve the bodily pain associated with biological processes of inflammation. We chose not to adjust for pain because we hypothesized that it was in the causal pathway between inflammatory actions and poor physical functioning.

Our results showed that fibrinogen was associated with fewer physical functioning measures than CRP. Fibrinogen production is triggered in part by increased levels of proinflammatory cytokines, and plays a central role in blood hemostasis. Markers of coagulation including fibrinogen have been found to predict coronary heart disease and atherosclerosis (Folsom et al., 2001; Danesh et al., 2001) and it has been proposed that this relationship extends to physical functioning (Marenberg, 2003). Reports about the association between thrombotic blood markers and physical functioning, however, have been mixed with some studies finding that higher levels of these markers are associated with poorer functioning (McDermott et al., 2004; Cohen et al., 2003) and some finding no association (McDermott et al., 2005). While associations with fibrinogen were not consistently associated with physical functioning measures, high blood pressure was consistently associated with a variety of physical functioning outcomes in these models. Thus, while our results do suggest an association with vascular dysfunction, many of the associations with fibrinogen were not independent.

A strength of this investigation was inclusion of both performance-based and self-report measures of physical functioning. Performance-based measures provide an expanded scope of measurement, specifically designed to capture a wide range of functional abilities. According to Seeman (1994), performance-based functioning measures, including timed measures, provide a measurement tool that has greater discrimination of differences in ability, especially at higher levels of ability compared to self-report measures. Though floor and ceiling effects have been reported for the SF-36 physical functioning scale (McHorney, 1995), using self-

report is advantageous because it provides additional information not captured by performance-based measures (Wittink, 2003). Though both measures attempt to quantify an individual's ability to perform physical tasks, self-reported measures capture an individual's perception of their ability while performance-based measures aim to capture physical ability. For example, the SF-36 inquires about limitations in walking; however, the performance-based measure quantifies speed of walking in seconds.

A major advantage of this investigation was the availability of exposure data at two time points; however, a disadvantage was the relatively short follow-up period, which may be insufficient to detect associations with change in CRP for some physical functioning variables. It is important to acknowledge that bidirectional associations could be at play; i.e. poorer physical functioning leads to less activity and greater adiposity, thereby increasing inflammatory markers.

Nevertheless, our results provide some support for our hypothesized association between inflammatory markers and functional decline. Limited findings linking subclinical indicators with compromised physical function in mid-life persons allow the role of these indicators to be characterized prior to onset of overt disease (Kumari et al., 2004). If research evidence continues to support these associations, interventions could be developed to improve physical functioning, including weight loss, or treatment with anti-inflammatory drugs. Based on their review of the literature, Guillet and Boirie (2005) have suggested that beyond glucose homeostasis, insulin treatment in elderly people is an appropriate therapeutic strategy to optimize muscle protein gain and limit progression of sarcopenia. Investigating whether these treatments are appropriate for a younger population is an important question that is yet to be determined.

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Figure 1.

Odds ratios and 95% confidence intervals describing cross-sectional association between tertiles of CRP or fibrinogen and perceived physical functioning. These odds ratios summarize the comparisons between no limitations vs. moderate/substantial limitations, as well as no/moderate vs. substantial limitations. Models were adjusted for age, race/ ethnicity, economic stress, smoking, heart disease, arthritis, high blood pressure, diabetes and BMI as appropriate.

Table 1Descriptive characteristics of women in the SWAN study in 2001^a (N = 543)

	Median (Interquartile range)
Age (years)	50 (5)
BMI (kg/m ²)	32.4 (11.6)
Biomarker	
C-reactive protein (mg/l)	3.9 (6.5)
Fibrinogen (mg/dl)	292.0 (83.0)
Change in biomarker (1996 to 2001)	
C-reactive protein (mg/L)	0.2 (3.4)
Fibrinogen (mg/dl)	-13.0 (64.0)
Performance-based physical functioning	
Grip strength, dominant hand (kg)	27.3 (8.0)
Time in double support (%)	25.7 (8.3)
Forward reach (cm)	35.6 (10.0)
2-lb lift (seconds)	2.2 (1.0)
Chair rise (seconds)	1.3 (0.6)
40-foot timed walk (seconds)	9.1 (2.7)
Timed stair climb (seconds)	19.1 (6.6)
	%
Perceived physical functioning	
Not limited (SF-36 score >86 points)	40.5%
Moderately limited (SF-36 score 51–85 points)	36.2%
Substantially limited (SF-36 score <50 points)	23.3%
Race	
African American	60%
Caucasian	40%
Cigarette smoking	22.4%
Self-reported co-morbidities	
Heart disease	2.5%
High blood pressure	27.9%
Diabetes	9.1%
Arthritis	25.4%
Economic Stress	
Very difficult to pay for basics	12.2%
Somewhat difficult to pay for basics	34.1%
Not difficult at all to pay for basics	53.7%

^a Race and economic stress measured in 1996, perceived physical functioning measured in 2002

Table 2

Cross-sectional associations between CRP or fibrinogen and physical functioning measures

Independent variables	Log CRP β (SE)	Log Fibrinogen β (SE)
Grip strength, dominant hand (kg)	0.15 (0.3)	-1.6 (2.2)
Log Time in double support (%)	0.06 (0.01)^c	-0.1 (0.09)
Forward reach (cm)	-1.3 (0.3)^b	-3.5 (2.3)
Log 2-lb lift (seconds)	0.06 (0.02)^b	-0.05 (0.1)
Log Chair rise (seconds)	0.03 (0.02)	0.2 (0.1)
Log 40-foot timed walk (seconds)	0.01 (0.01)	0.03 (0.07)
Log Timed stair climb (seconds)	0.04 (0.01)^b	0.01 (0.09)

^a Models were adjusted for age, race/ ethnicity, economic stress, smoking, heart disease, arthritis, high blood pressure, diabetes and BMI as appropriate.

^b $p \leq 0.01$

^c $p \leq 0.0001$

Table 3

Associations between baseline or 5-year change in biomarker^a and 3-year change in physical functioning measures

Three-year change in independent variables	Log CRP		Log Fibrinogen	
	Baseline β (SE)	5-year change β (SE)	Baseline β (SE)	5-year change β (SE)
Grip strength, dominant hand (kg)	-0.18 (0.1)	-0.42 (0.2)^b	0.30 (0.8)	-0.13 (0.9)
Log Time in double support (%)	0.01 (0.005)^c	-0.004 (0.007)	0.12 (0.05)^b	0.09 (0.06)
Forward reach (cm)	-0.45 (0.2)^c	-0.05 (0.3)	0.49 (1.1)	0.60 (1.3)
Log 2-lb lift (seconds)	0.005 (0.008)	0.018 (0.01)	0.03 (0.06)	0.11 (0.07)
Log Chair rise (seconds)	0.02 (0.01)	0.007 (0.02)	-0.001 (0.07)	-0.02 (0.09)
Log 40-foot timed walk (seconds)	0.01 (0.006)	0.008 (0.009)	0.04 (0.04)	0.02 (0.05)
Log Timed stair climb (seconds)	0.002 (0.004)	0.01 (0.006)	0.08 (0.04)^b	0.12 (0.04)^c

^aTwo models were run for each outcome including either baseline and change in logCRP or baseline and change in logfibrinogen. Models were all adjusted for the initial value of the dependent variable. Models were also adjusted for age, race/ ethnicity, economic stress, smoking, heart disease, arthritis, high blood pressure, diabetes and BMI as appropriate.

^b
 $p \leq 0.05$

^c
 $p \leq 0.01$

^d
 $p \leq 0.0001$