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Prospective associations between inflammatory and hemostatic markers and physical functioning limitations in mid-life women: Longitudinal Results of the Study of Women's Health Across the Nation (SWAN)

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Abstract

Background—Due to the public health burden of age-related declines in physical functioning, it is important to identify targets for intervention for the prevention of functional decline. We prospectively examined whether higher levels of inflammatory and hemostatic markers (high-sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA-ag), fibrinogen, and Factor VIIc (FVIIc)) were prospectively associated with reporting greater limitations in perceived physical functioning, and explored potential racial differences in the associations, in a multi-ethnic sample of mid-life women.

Methods—Women (45 – 56 years) in the Study of Women's Health Across the Nation who completed the physical functioning scale of the Medical Outcome Short Form (SF-36) at follow-up visits 4, 6, or 8 and had inflammatory/hemostatic measures in the preceeding year were included (n=2296). The continuous SF-36 physical function score was categorized as: no limitation (86–100 points), some limitation (51–85 points), and substantial limitation (0–50 points). Physical function category at time t was modeled a function of each biomarker, separately, at time t-1 using ordinal generalized estimating equations.

Results—After adjusting for age, race/ethnicity, body size, sociodemographic, medical and lifestyle factors, higher levels of tPA-ag and hs-CRP were associated with subsequently reporting greater limitations in physical functioning, although the latter was only marginally significant (p=0.13). For each standard deviation (SD) increase in $\log_{10}$ tPA-ag, the odds of some or substantial limitations was 1.18 (95%CI 1.09,1.27); for each SD increase in $\log_{10}$ hs-CRP, the odds of some or substantial limitation was (1.08, 95%CI 0.98,1.19). In African American women only, higher fibrinogen levels were associated with subsequently reporting greater limitations (OR=1.30, 95%CI 1.13,1.50, for each one SD increase in fibrinogen).

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Conclusions—Higher levels of inflammatory and hemostatic markers were prospectively associated with greater limitations in perceived physical functioning in mid-life women.

Keywords

Inflammation; Hemostasis; Physical Functioning; Women

1. Introduction

Limitations in physical functioning are defined as difficulty in performing basic body functions such as seeing, lifting, carrying, climbing or walking. Physical functioning limitations are burdensome due to their high prevalence, the continuing growth of the aging population, and their associations with decreased quality of life, increased risk of disability, and high health care expenditures (Freedman and Martin 1998; Fried et al., 2001; Stevens and Olson 2000; Verbrugge and Jette 1994; Wolinsky et al., 2007). Due to the public health burden of age-related declines in physical functioning, it is important to identify targets for early intervention for the prevention of functional limitations. Activations of the inflammatory and coagulant/fibrinolytic pathways are hypothesized mechanisms leading to age-related functional decline. In cross-sectional and longitudinal studies of older adults, higher levels of proinflammatory cytokines (Cesari et al., 2004; Cohen et al., 2003; Ferrucci et al., 2002; Figaro et al., 2006; Penninx et al., 2004; Tiainen et al., 2010; Walston et al., 2002) and markers of hemostasis (Barzilay et al., 2007; Cohen et al., 2003; Cohen et al., 1997; Currie et al., 1994; McDermott et al., 2005; Penninx et al., 2004; Pieper et al., 2000; Reiner et al., 2009; Walston et al., 2002) have been associated with impairments in physical functioning, functional decline, disability, and frailty.

However, functional limitations are not restricted to the elderly. Using data from the National Health Interview Survey, Martin et al. (2009) reported that 31% of persons aged 45–49, 37% of those aged 50–54, and 42% of those aged 55–59 reported difficulty with at least one of the following functions: walking a quarter mile; climbing ten steps; standing two hours; sitting two hours; stooping, bending or kneeling; reaching over one's head; grasping small objects; carrying ten pounds; and/or moving large objects (Martin et al., 2009). In addition, women report physical functioning limitations more frequently than men, even at relatively young ages (Pleis JR 2009). Self-reported functional limitations, assessed with the Medical Outcomes Study Short-Form 36 (SF-36) Physical Functioning Scale, were reported by 19% of women aged 40–55 screened for enrollment into the Study of Women's Health Across the Nation (SWAN) (Pope et al., 2001).

Despite the evidence consistently supporting an association between inflammation and hemostasis and physical functioning in older adults, few studies have examined these relationships in younger populations. Given the high prevalence of functional limitations in midlife and the fact that women experience an increase in inflammatory burden and alterations in hemostasis during the menopausal transition (Gebara et al., 1995; Pfeilschifter et al., 2002; Teede et al., 2000), studies in midlife women are particularly important. In a sub-sample of 543 midlife African American and Caucasian SWAN women, Tomey et al. (2009) reported, in both cross-sectional and longitudinal analyses, that both higher levels of CRP and fibrinogen were associated with poorer perception of physical functioning (Tomey et al., 2009). It is unclear if other hemostatic markers are associated with physical function and if there are racial/ethnic differences present in these relationships as women continue to progress through the menopausal transition. We hypothesize that higher levels of inflammatory and hemostatic markers [high-sensitivity C-reactive protein (hs-CRP), plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator antigen (tPA-ag), fibrinogen, and Factor VIIc (FVIIc)] in the prior visit would be associated with subsequently

reporting greater limitations in perceived physical functioning in a large, multi-ethnic sample of mid-life women.

2. Methods

SWAN is an ongoing, longitudinal, multi-ethnic study of the biological, physical, psychological, and social changes during the menopausal transition. The study design has been previously reported (Sowers M 2000). In brief, between 1996 and 1997, 3,302 participants aged 42–52 years were recruited from seven sites (Boston, MA; Detroit area, MI; Oakland, CA; Los Angeles, CA; Pittsburgh, PA; Chicago, IL; and Newark, NJ). The eligibility criteria were 1) an intact uterus and at least 1 ovary, 2) not pregnant or breastfeeding, 3) at least 1 menstrual period within the past 3 months, 4) no hormone therapy (HT) use within the past 3 months, 5) self-identifying race as African American, Caucasian, Chinese, Hispanic, or Japanese.

Of the 3,302 women enrolled in the SWAN cohort, 2911 women attended at least one of the SWAN follow-up visits used in the current analysis. Of these women, 2803 completed the Physical Function subscale of the Medical Outcomes Study Short-Form 36 (SF-36) as part of SWAN follow-up visits 04, 06, and/or 08. Inflammation and hemostasis were measured in the preceding follow-up visits, e.g. SWAN visits 03, 05, and 07. We excluded 76 women missing data on physical functioning at all three visits, 128 women missing all measures of inflammatory and hemostatic markers at all three visits, and 47 women without data on two consecutive visits. Having at least two consecutive visits is a requirement for lagged analysis to examine the influence of values at one exam on a subsequent exam. Due to administrative issues at the New Jersey Medical School, data collection was halted at the New Jersey site during the period included in this analysis, thus data from this site were excluded (n=255). One additional woman was excluded as <1 month elapsed between subsequent visits. The final sample available for this analysis was 2296 women with 5692 observations. (On average, a participant provided 2.48 observations to the analysis.) For the analysis of associations between physical functioning and hs-CRP, data from an additional 127 women whose hs-CRP values were >10 mg/dL were excluded to minimize the possibility of including women with an acute infection (Pearson et al., 2003).

The research protocols were approved by the institutional review board at each site and all participants provided written informed consent prior to enrollment.

2.1 Physical Functioning (PF) Limitation

The perception of physical function capacity was assessed by the 10-item PF subscale of the Medical Outcomes Study Short-Form 36 (SF-36) (Ware 1992), which has been extensively evaluated for construct validity, internal consistency, and test-retest reliability in diverse ethnic groups and age ranges. The physical function subscale uses a 3-item response scale of “limited a lot,” “limited a little,” or “not limited at all” to the following items: vigorous activities; moderate activities; lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or stooping; walking more than one mile; walking several blocks; walking one block; and bathing or dressing. Scores are summed and transformed to a score between 0–100 points, with higher scores representing better physical functioning (Ware 1993). Scores on the SF-36 are highly skewed and not normally distributed, with many respondents scoring 100 points (Achat et al., 2000; Michael et al., 1999; Rose et al., 1999). Therefore, SF-36 physical functioning scores were categorized into a 3-level physical function limitation variable using cutoffs as recommended by Rose et al. (Rose et al., 1999). Women with a score below 50 points were classified as having substantial limitations. Those with a score of 51–85 points were classified as having some limitations. Women with a score of 86–100 points were considered to have no limitation.

2.2 Biomarker assays

Fibrinogen, hs-CRP, FVIIc, PAI-1, and tPA-ag were measured in plasma. The hs-CRP was quantitated using an ultrasensitive rate immunonephelometric method (hs-CRP, Dade-Behring, Marburg, Germany). The sensitivity of the assay was 0.03 mg/dL and interassay coefficients of variations (CVs) at CRP concentrations of 0.05 and 2.2 mg/dl were 10–12% and 5–7%, respectively. Fibrinogen and FVIIc were measured in frozen citrated plasma (MLA ELECTRA 1400C, Medical Laboratory Automation Inc., Mt. Vernon, NY) using a turbidometric detection system. Fibrinogen monthly interassay CVs were 2.3–3.5% and 2.6–3.6% at mean concentrations of 250 and 140 mg/dl, respectively, and FVIIc monthly interassay CVs were 7.8%, 5%, and 4% for mean activities of 8%, 45%, and 99%, respectively. PAI-1 was measured with a sandwich procedure using a solid phased monoclonal antibody and enzyme labeled goat second antiserum for detection (IMUBIND plasma PAI-1 ELISA, American Diagnostica, Greenwich, CT). PAI-1 monthly interassay CVs were 5–9% and 4–9% at mean concentrations of 7 and 22.5 ng/dl, respectively. TPA-ag was measured in plasma using a double antibody in an enzyme linked immunosorbant assay (IMUBIND tPA ELISA, American Diagnostica, Greenwich, CT). The assay uses human single chain t(PA) as a standard calibrated against an international standard (NIBSAC, Hertfordshire, UK). Monthly interassay CVs were 4.7–8.7% and 3.8–7.8% at mean concentrations of 5.6 and 11 ng/dl, respectively.

Covariates were chosen a priori, based on a literature review. Race/ethnicity was based on self-report. Difficulty paying for basics was assessed as a proxy for socioeconomic status. Participants were asked to rank their degree of difficulty in paying for basics, such as food, housing, and health care on a three-item scale (very hard, somewhat hard, or not very hard at all). Age, education (less than or equal to a high school diploma, some college, college degree or post-college), marital status (single/never married, currently married/living as married, separated, widowed, divorced) and current smoking status (yes, no) were derived from questionnaires and interviews at each annual visit. Weight and height were measured annually and body mass index (BMI) was calculated as weight (kg)/height (m²). BMI was categorized as underweight/normal weight (BMI<25), overweight (25 BMI<30), and obese (BMI ≥ 30). Questions on medication use (verified by check containers when possible) and self-reported health history since previous examination were combined into five categories. We identified five health conditions of interest: heart condition including self-reported stroke, heart attack, angina, or high blood pressure, measured systolic blood pressure >130 mmHg or diastolic blood pressure ≥ 85 mmHg, or use of antihypertensive or anticoagulant medication; diabetes or use of insulin or diabetic medication; arthritis/osteoarthritis or use of arthritis medication or over-the-counter pain medication; thyroid condition or use of steroids; and depression, defined as a score of 16 or greater on the Center for Epidemiologic Studies Depression Scale (CESD) or use of depression medication. Physical activity was assessed at SWAN study baseline, visits 03, 05, and 06 via a Modified Baecke Scores of Habitual Physical Activity; with higher scores indicating greater physical activity (Baecke et al., 1982; Sternfeld et al., 1999). Last observation carried forward was used to fill in physical activity for SWAN visits 03, 05, and 07. Hormone therapy use since the previous annual visit was self-reported. Menopausal status was based on menstrual bleeding in the previous 12 months and was categorized as: (a) premenopausal: menstrual period in the past 3 months with no change in regularity over the past 12 months; (b) early perimenopausal: menstrual period in the past 3 months with some change in regularity over the previous 12 months; (c) late perimenopausal: no menstrual period within the past 3 months, but some menstrual bleeding within the past 12 months; (d) post-menopausal: no menstrual period within the past 12 months; (e) surgical menopausal: hysterectomy or bilateral oophorectomy; (f) indeterminate menopausal status: used hormone therapy before final menses or surgical menopause, thus, status could not be determined.

2.3 Data Analyses

The distributions of hs-CRP, PAI-1 and tPA-ag were skewed, and therefore log-transformed for analysis. Study population characteristics were summarized at SWAN follow-up visit 03 as frequencies (%) for categorical variables and means $\pm$ standard deviations (SD) or medians (interquartile range) for normally and non-normally distributed continuous variables, respectively.

For the time-lagged longitudinal analysis, physical functioning category at time t was modeled as a function of hs-CRP (in log-transformed standard deviation (SD) units), fibrinogen (in SD units), FVIIc (in SD units), PAI-1 (in log-transformed SD units), and tPA-ag (in log-transformed SD units), separately, at time $t-1$ using ordinal generalized estimating equation (GEE) using a cumulative logit link function since the proportional odds assumptions were met. Time-varying covariates were measured at time $t-1$. Initial models included age at visit 03, time between $t-1$ and t , race/ethnicity, ability to pay for basics and study site. We then evaluated models adjusted for additional covariates, first assessing BMI, then menopausal status, exogenous hormone use, and physical activity, and then disease conditions. Smoking status, marital status, aspirin use and education were initially included in multivariable analyses, and then excluded to achieve more parsimonious models as adding them to models did not change the main results and they were not significantly associated with PF limitation in the final models. Interactions of inflammatory and hemostatic markers with age, race/ethnicity, and BMI were evaluated.

Analyses were performed with SAS v9.2 (SAS Institute, Cary, NC). All models were 2-sided at $\alpha=0.05$.

3. Results

Women excluded from the analyses had a higher body mass index (BMI) (29.53 ± 7 vs. 28.36 ± 7), were less likely to have undetermined menopausal status (6% vs. 12%), and were less likely to be Japanese (3% vs. 11%), Chinese (2% vs. 10%), or African American (22% vs. 30%) than women included ($p < 0.01$). Compared with women eligible for this analysis, excluded women were more likely to have a higher hs-CRP (median(p25, p75): $2.3(0.9, 6.1)$ vs. $1.7(0.6, 4.8)$), fibrinogen (285.75 ± 56 vs. 276.57 ± 53), PAI-1 ($25.5(16.0, 42.7)$ vs. $17.9(9.6, 32.9)$), and tPA-ag ($7.9(5.9, 10.3)$ vs. $7.1(5.1, 9.6)$), and were more likely to report substantial limitations in physical functioning (17% vs. 10%) (all $p < 0.01$).

Participants at visit 03 ranged in age from 45 to 56 years; mean $\pm$ SD BMI was 28.36 ± 7.34 kg/m² (Table 1). Our sample was 49% Caucasian, 30% African American, 10% Chinese, and 11% Japanese, by design. Overall, 60% reported no limitation in physical function, 31% reported some limitations, and 10% reported substantial limitations in physical function at follow up visit 04.

Table 2 presents proportional odds ratios from generalized estimating equation models for the time-lagged longitudinal associations between inflammatory and hemostatic markers at time $t-1$ with physical functioning at time t . Independent of age, time between $t-1$ and t , site, race, and ability to pay for basics, higher levels of hs-CRP, PAI-1, tPA-ag, and FVIIc at time $t-1$ were significantly associated with greater odds of physical functioning limitation at time t . After additional adjustment for BMI, menopausal status, exogenous hormone use, and physical activity, the relationships between PAI-1 and FVIIc and subsequent physical function limitations were slightly attenuated and became marginally significant (OR=1.08, 95% CI=1.00, 1.17, $p=0.05$; OR=1.08, 95% CI=1.00, 1.17, $p=0.06$, respectively). However, higher levels of hs-CRP (OR=1.11, 95% CI=1.00, 1.22, $p=0.049$) and tPA-ag (OR=1.19, 95% CI=1.11, 1.29, $p < 0.0001$) remained significantly associated with greater subsequent

physical function limitation, even after adjustment for the aforementioned variables. The relationship between higher levels of hs-CRP and physical function limitations was similar in magnitude after additional adjustment for comorbidities, but precision was compromised (OR=1.08, 95%CI=0.98,1.19, $p=0.13$). The relationship between higher levels of tPA-ag and greater subsequent physical function limitations remained significant, even after adjustment for comorbid health conditions (OR=1.18, 95%CI=1.09,1.27, $p<0.0001$).

Interactions of inflammatory and hemostatic markers with age and BMI were not significant. However, we observed a marginally significant interaction between fibrinogen and ethnicity ($p=0.06$), therefore fibrinogen results are reported separately, stratified by race (Table 3). In fully adjusted models, the relationship between fibrinogen at time t-1 and limitations in physical function at time t was statistically significant (OR=1.30, 95%CI 1.13,1.50), $p=0.0004$) in African Americans only.

4. Discussion

This study is one of the first to examine the relationships between inflammation and hemostasis and subsequent physical functioning in midlife women. We found that higher levels of tPA-ag and hs-CRP at the previous follow-up visit were associated with reporting greater physical function limitations in an ethnically diverse sample of middle-aged women. In African American women, higher fibrinogen levels at the previous visit were also associated with reporting greater physical function limitations.

Our results are in agreement with previous studies conducted in older adults and extend the findings to a younger, multiethnic population of women at midlife. Inflammatory markers are consistently associated with age-related chronic diseases, functional limitations, and disability in elderly populations. In a prospective cohort study of men and women enrolled in the Health, Aging, and Body Composition Study, high CRP (>2.54 mg/L vs. <1.17 mg/L, $p<0.05$) was associated with incident mobility disability, defined as difficulty or inability to walk one-quarter of a mile or to climb ten steps, at 30 months follow-up (Penninx et al., 2004). Using data from the Cardiovascular Health Study All Stars, Jenny et al. recently reported that in persons who were on average 84.9 years, a doubling of CRP over nine years of follow-up was associated with increased impaired physical performance (Jenny et al., 2012). In addition, in a sample of 250 older adults (average age 63.8 years), poorer perceived physical functioning was associated with inflammation, as measured by interleukin-6 (IL-6) (Christian et al., 2011).

Although again limited to populations of older adults, hemostatic markers have been associated with declines in physical functioning and with limitations in a wide variety of functional domains, including independent activities of daily living and lower extremity function (McDermott et al., 2005). In the Women's Health Initiative, a prospective analysis among women aged 65 to 79 years at enrollment, higher t-PA levels were associated with increased risk of incident frailty (Reiner et al., 2009). Other markers of activated coagulation and fibrinolysis, including factor VII, D-dimer, and fibrinogen have been associated with functional decline (Cohen et al., 2003; Reiner et al., 2009).

A number of pathways have been suggested as mechanisms linking inflammatory and hemostatic markers to functional decline. Inflammatory markers, such as CRP, may be directly related to declines in physical functioning through deleterious effects of inflammation on muscle mass and strength (Cesari et al., 2004; Goodman 1991; Goodman 1994; Schaap et al., 2006). Hemostatic markers may impact functioning by modulating the actions of immunocytes to stimulate the release of mediators and cytokines, and by

modulating cell migration, vascular remodeling, and endothelial cell activation (Cohen et al., 2003).

Inflammation and hemostasis are mechanisms by which the menopausal transition may influence physical functioning during the mid-life. Changes in cytokine levels may be related to ovarian, as well as to chronological aging. During the menopausal transition, women experience an increase in inflammatory burden and alterations in hemostasis (Gebara et al., 1995; Pfeilschifter et al., 2002; Teede et al., 2000). The loss of estrogen's modulating influence on inflammatory T-cells may unleash unfavorable cytokine production, evidenced by numerous *in-vitro* and animal experiments (Pacifci 2012). E2 may be favorable for fibrinolysis (Sowers et al., 2005) and endogenous hormones (e.g., androgens) may modulate the relation of hemostatic and inflammatory factors to insulin resistance (Sowers et al., 2003). In addition, exogenous estrogen replacement therapy lowers PAI-1 levels (Teede et al., 2000), and PAI-1 is lower in premenopausal compared with postmenopausal women (Gebara et al., 1995). In a recent SWAN analysis, we report that women who are naturally or surgically postmenopausal show greater declines in perceived physical function over 8 years of follow up. Similarly, changes in endogenous sex hormones were associated with limitations in perceived physical function; women with greater declines in estradiol and testosterone reported greater limitations in physical function during follow up (El Khoudary et al., under review).

Changes in body composition that occur with menopause may accelerate inflammatory changes that are typical of the aging process. Obesity, accompanied by inflammation as measured by CRP, has been associated with poorer physical function and decreases in physical function over time (Sowers et al., 2009). Adipose tissue, once considered an energy storage depot, is a metabolically active organ with the capacity to secrete adipokines and pro-inflammatory cytokines (Fried et al., 1998; Kern et al., 1995). However, our results indicate that although adjustment for BMI substantially attenuated the associations between inflammatory and hemostatic markers and subsequent declines in physical function, statistical significance remained, providing additional evidence for a direct pathway.

Higher levels of fibrinogen were associated with subsequently greater PF limitations in African Americans only. In cross-sectional studies of older adults, racial/ethnic differences in hemostatic markers were related to age and functional status, with some suggestion of a racial association (Currie et al., 1994; Currie et al., 1990; Pieper et al., 2000). For example, Currie et al. (1994) reported that a marker of fibrinolytic activity, D-Dimer, was significantly higher in physically impaired subjects, but most prominently among black females (Currie et al., 1994). Compared to Caucasians, African Americans have higher mean values of fibrinogen (Folsom et al., 1992; Lutsey et al., 2006; Tracy et al., 1992). Differences in adiposity (Mertens and Van Gaal 2005; Rosito et al., 2004), lifestyle factors (Pieper et al., 2000), and/or genetic heterogeneity may contribute to the racial/ethnic difference in hemostatic factor levels (Lutsey et al., 2012).

Our study has some limitations. The sampling frequency was driven by the overall study design, rather than by biological considerations of how long the duration of exposure to each biomarker would be required to have an influence on physical functioning. However, in a sensitivity analysis, we observed that the relationships between the time-lagged measurements and physical functioning were stronger than for the concurrent measures. This paper is based on perceived physical function as performance measures (e.g., gait speed, grip strength, etc.) were not available. However, the SF-36 PF scale is a widely used scale with high reproducibility and validity measures (Ware 1992; Ware 1993). It has been reported that perceived physical functioning measurements and performance-based measurements provide information about related but distinct aspects of physical functioning

(Wittink et al., 2003). Due to our exclusion criteria, our results may not be generalizable to Hispanic women. Women were also excluded from the analysis when CRP values were ≥ 10 . In a sensitivity analysis, we observed similar results to those we reported in our final longitudinal models. Finally, it is important to note that we were unable to examine bidirectional relationships. Currently, there is no accepted standard to define the incidence of functional limitations, thus we could not determine which came first- the functional decline or elevated biomarkers.

Nonetheless this study has several strengths including the multi-ethnic sample of women, thorough assessment of time-varying covariates, excellent retention of women, and multiple measures of inflammatory and hemostatic makers and physical function limitation.

Given the public health burden of age-related declines in physical functioning, it is important to identify targets for early intervention for the prevention of functional decline. The assessment of inflammatory markers may represent a useful screening test and perhaps a potential target for intervention. Future prospective studies are warranted to replicate our findings and determine whether intervention in this area would be effective in reducing the rate of functional decline.

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References

- Achat H, Kawachi I, Spiro A 3rd, DeMolles DA, Sparrow D. Optimism and depression as predictors of physical and mental health functioning: the Normative Aging Study. *Annals of behavioral medicine* : a publication of the Society of Behavioral Medicine. 2000; 22:127–130. [PubMed: 10962705]

- Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *The American journal of clinical nutrition*. 1982; 36:936–942. [PubMed: 7137077]
- Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JD, Fried LP. Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Archives of internal medicine*. 2007; 167:635–641. [PubMed: 17420420]
- Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, Guralnik JM, Ferrucci L. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2004; 59:242–248.
- Christian LM, Glaser R, Porter K, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. Poorer self-rated health is associated with elevated inflammatory markers among older adults. *Psychoneuroendocrinology*. 2011; 36:1495–1504. [PubMed: 21601365]
- Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *The American journal of medicine*. 2003; 114:180–187. [PubMed: 12637131]
- Cohen HJ, Pieper CF, Harris T, Rao KM, Currie MS. The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *The journals of gerontology Series A, Biological sciences and medical sciences*. 1997; 52:M201–208.
- Currie MS, Rao MK, Blazer DG, Cohen HJ. Age and functional correlations of markers of coagulation and inflammation in the elderly: functional implications of elevated crosslinked fibrin degradation products (D-dimers). *Journal of the American Geriatrics Society*. 1994; 42:738–742. [PubMed: 8014349]
- Currie MS, Vala M, Pisetsky DS, Greenberg CS, Crawford J, Cohen HJ. Correlation between erythrocyte CR1 reduction and other blood proteinase markers in patients with malignant and inflammatory disorders. *Blood*. 1990; 75:1699–1704. [PubMed: 2158365]
- Ferrucci L, Penninx BW, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, Leveille SG, Fried LP, Md JM. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *Journal of the American Geriatrics Society*. 2002; 50:1947–1954. [PubMed: 12473005]
- Figaro MK, Kritchevsky SB, Resnick HE, Shorr RI, Butler J, Shintani A, Penninx BW, Simonsick EM, Goodpaster BH, Newman AB, Schwartz AV, Harris TB. Diabetes, inflammation, and functional decline in older adults: findings from the Health, Aging and Body Composition (ABC) study. *Diabetes care*. 2006; 29:2039–2045. [PubMed: 16936150]
- Folsom AR, Wu KK, Conlan MG, Finch A, Davis CE, Marcucci G, Sorlie PD, Szklo M. Distributions of hemostatic variables in blacks and whites: population reference values from the Atherosclerosis Risk in Communities (ARIC) Study. *Ethnicity & disease*. 1992; 2:35–46. [PubMed: 1458214]
- Freedman VA, Martin LG. Understanding trends in functional limitations among older Americans. *American journal of public health*. 1998; 88:1457–1462. [PubMed: 9772844]
- Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *The Journal of clinical endocrinology and metabolism*. 1998; 83:847–850. [PubMed: 9506738]
- Fried TR, Bradley EH, Williams CS, Tinetti ME. Functional disability and health care expenditures for older persons. *Archives of internal medicine*. 2001; 161:2602–2607. [PubMed: 11718592]
- Gebara OC, Mittleman MA, Sutherland P, Lipinska I, Matheney T, Xu P, Welty FK, Wilson PW, Levy D, Muller JE, et al. Association between increased estrogen status and increased fibrinolytic potential in the Framingham Offspring Study. *Circulation*. 1995; 91:1952–1958. [PubMed: 7895352]
- Goodman MN. Tumor necrosis factor induces skeletal muscle protein breakdown in rats. *The American journal of physiology*. 1991; 260:E727–730. [PubMed: 2035628]
- Goodman MN. Interleukin-6 induces skeletal muscle protein breakdown in rats. *Proc Soc Exp Biol Med*. 1994; 205:182–185. [PubMed: 8108469]
- Jenny NS, French B, Arnold AM, Strotmeyer ES, Cushman M, Chaves PH, Ding J, Fried LP, Kritchevsky SB, Rifkin DE, Sarnak MJ, Newman AB. Long-term Assessment of Inflammation

- and Healthy Aging in Late Life: The Cardiovascular Health Study All Stars. The journals of gerontology Series A, Biological sciences and medical sciences. 2012
- Kern PA, Saghizadeh M, Ong JM, Bosch RJ, Deem R, Simsolo RB. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. The Journal of clinical investigation. 1995; 95:2111–2119. [PubMed: 7738178]
- Lutsey PL, Cushman M, Steffen LM, Green D, Barr RG, Herrington D, Ouyang P, Folsom AR. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. Journal of thrombosis and haemostasis : JTH. 2006; 4:2629–2635. [PubMed: 17002663]
- Lutsey PL, Wassel CL, Cushman M, Sale MM, Divers J, Folsom AR. Genetic admixture is associated with plasma hemostatic factor levels in self-identified African Americans and Hispanics: the Multi-Ethnic Study of Atherosclerosis. Journal of thrombosis and haemostasis : JTH. 2012; 10:543–549. [PubMed: 22332961]
- Martin LG, Freedman VA, Schoeni RF, Andreski PM. Health and Functioning Among Baby Boomers Approaching 60. Journals of Gerontology Series B-Psychological Sciences and Social Sciences. 2009; 64:369–377.
- McDermott MM, Ferrucci L, Liu K, Criqui MH, Greenland P, Green D, Guralnik JM, Ridker PM, Taylor LM, Rifai N, Tian L, Zheng J, Pearce WH, Schneider JR, Vonesh E. D-dimer and inflammatory markers as predictors of functional decline in men and women with and without peripheral arterial disease. Journal of the American Geriatrics Society. 2005; 53:1688–1696. [PubMed: 16181167]
- Mertens I, Van Gaal LF. Visceral fat as a determinant of fibrinolysis and hemostasis. Seminars in vascular medicine. 2005; 5:48–55. [PubMed: 15968580]
- Michael YL, Colditz GA, Coakley E, Kawachi I. Health behaviors, social networks, and healthy aging: cross-sectional evidence from the Nurses' Health Study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 1999; 8:711–722.
- Pacifici R. Role of T cells in ovariectomy induced bone loss--revisited. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2012; 27:231–239. [PubMed: 22271394]
- Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, Nevitt M, Visser M, Harris T, Pahor M. Inflammatory markers and incident mobility limitation in the elderly. Journal of the American Geriatrics Society. 2004; 52:1105–1113. [PubMed: 15209648]
- Pfeilschifter J, Koditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. Endocrine reviews. 2002; 23:90–119. [PubMed: 11844745]
- Pieper CF, Rao KM, Currie MS, Harris TB, Cohen HJ. Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. The journals of gerontology Series A, Biological sciences and medical sciences. 2000; 55:M649–657.
- Pleis JR LJ. Summary health statistics for U.S. adults: National Health Interview Survey 2007. National Center for Health Statistics. Vital Health Stat. 2009; 10
- Pope SK, Sowers MR, Welch GW, Albrecht G. Functional limitations in women at midlife: The role of health conditions, behavioral and environmental factors. Womens Health Issues. 2001; 11:494–502. [PubMed: 11704470]
- Reiner AP, Aragaki AK, Gray SL, Wactawski-Wende J, Cauley JA, Cochrane BB, Kooperberg CL, Woods NF, LaCroix AZ. Inflammation and thrombosis biomarkers and incident frailty in postmenopausal women. The American journal of medicine. 2009; 122:947–954. [PubMed: 19682668]
- Rose MS, Koshman ML, Spreng S, Sheldon R. Statistical issues encountered in the comparison of health-related quality of life in diseased patients to published general population norms: problems and solutions. Journal of clinical epidemiology. 1999; 52:405–412. [PubMed: 10360335]
- Rosito GA, D'Agostino RB, Massaro J, Lipinska I, Mittleman MA, Sutherland P, Wilson PW, Levy D, Muller JE, Tofler GH. Association between obesity and a prothrombotic state: the Framingham Offspring Study. Thrombosis and haemostasis. 2004; 91:683–689. [PubMed: 15045128]
- Schaap LA, Pluijm SMF, Deeg DJH, Visser M. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. American Journal of Medicine. 2006; 119

- Sowers M, CS.; Sternfeld, B. SWAN: a multicenter, multiethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, KJ.; Marcus, R., editors. *Menopause: Biology and Pathology*. Academic Press; New York, NY: 2000.
- Sowers M, Derby C, Jannausch ML, Torrens JJ, Pasternak R. Insulin resistance, hemostatic factors, and hormone interactions in pre- and perimenopausal women: SWAN. *The Journal of clinical endocrinology and metabolism*. 2003; 88:4904–4910. [PubMed: 14557472]
- Sowers M, Karvonen-Gutierrez CA, Palmieri-Smith R, Jacobson JA, Jiang Y, Ashton-Miller JA. Knee osteoarthritis in obese women with cardiometabolic clustering. *Arthritis and rheumatism*. 2009; 61:1328–1336. [PubMed: 19790111]
- Sowers MR, Matthews KA, Jannausch M, Randolph JF, McConnell D, Sutton-Tyrrell K, Little R, Lasley B, Pasternak R. Hemostatic factors and estrogen during the menopausal transition. *The Journal of clinical endocrinology and metabolism*. 2005; 90:5942–5948. [PubMed: 16105968]
- Sternfeld B, Ainsworth BE, Quesenberry CP. Physical activity patterns in a diverse population of women. *Preventive medicine*. 1999; 28:313–323. [PubMed: 10072751]
- Stevens JA, Olson S. Reducing falls and resulting hip fractures among older women. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control*. 2000; 49:3–12. [PubMed: 15580729]
- Teede HJ, McGrath BP, Smolich JJ, Malan E, Kotsopoulos D, Liang YL, Peverill RE. Postmenopausal hormone replacement therapy increases coagulation activity and fibrinolysis. *Arteriosclerosis, thrombosis, and vascular biology*. 2000; 20:1404–1409.
- Tiainen K, Hurme M, Hervonen A, Luukkaala T, Jylha M. Inflammatory Markers and Physical Performance Among Nonagenarians. *Journals of Gerontology Series a-Biological Sciences and Medical Sciences*. 2010; 65:658–663.
- Tomey K, Sowers M, Zheng H, Jackson EA. Physical functioning related to C-reactive protein and fibrinogen levels in mid-life women. *Exp Gerontol*. 2009; 44:799–804. [PubMed: 19819323]
- Tracy RP, Bovill EG, Fried LP, Heiss G, Lee MH, Polak JF, Psaty BM, Savage PJ. The distribution of coagulation factors VII and VIII and fibrinogen in adults over 65 years. Results from the Cardiovascular Health Study. *Annals of epidemiology*. 1992; 2:509–519. [PubMed: 1342301]
- Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med*. 1994; 38:1–14. [PubMed: 8146699]
- Walston J, McBurnie MA, Newman A, Tracy RP, Kop WJ, Hirsch CH, Gottdiener J, Fried LP. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Archives of internal medicine*. 2002; 162:2333–2341. [PubMed: 12418947]
- Ware, J. Measures for a New Era of Health Assessment. In: WJ, SA., editor. *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach*. Duke University Press; Durham, NC: 1992.
- Ware, J. Manual and Interpretation Guide. The Health Institute, New England Medical Center; Boston, MA: 1993. SF-36 Health Survey.
- Wittink H, Rogers W, Sukiennik A, Carr DB. Physical functioning: self-report and performance measures are related but distinct. *Spine*. 2003; 28:2407–2413. [PubMed: 14560092]
- Wolinsky FD, Miller DK, Andresen EM, Malmstrom TK, Miller JP, Miller TR. Effect of subclinical status in functional limitation and disability on adverse health outcomes 3 years later. *The journals of gerontology Series A, Biological sciences and medical sciences*. 2007; 62:101–106.

Highlights

- Inflammatory markers may be related to physical functioning in mid-life women.
- Hemostatic markers may be related to physical functioning in mid-life women.
- Higher tPA-ag was related to subsequently greater physical functioning limitations.
- Higher fibrinogen was related to subsequently worse function in African Americans.

Table 1Visit 03 characteristics of women included in the analytic sample.^a

	n=2296
Age (years), Mean±SD	49.54±2.68
Body Mass Index, kg/m ² , Mean±SD	28.36±7.34
Physical activity score ^b , Mean±SD	7.72±1.70
Menopausal Status, n(%)	
Surgical Postmenopausal	61(3)
Natural Postmenopausal	236(12)
Late Perimenopausal	176(9)
Early Perimenopausal	1030(52)
Premenopausal	224(11)
Undetermined	246(12)
Hormone Users, n(%)	356(18)
Ethnicity, n(%)	
African American	683(30)
Caucasian	1131(49)
Chinese	229(10)
Japanese	253(11)
How Hard to Pay for Basics, n(%)	
Very Hard	160(7)
Somewhat	615(27)
Not Very	1513(66)
Education, n(%)	
High School	440(19)
Some college	752(33)
College Degree +	1092(48)
Current Smoker, n(%)	252(13)
Heart Condition, n(%)	664(34)
Diabetes, n(%)	120(6)
Arthritis, n(%)	715(36)
Depression, n(%)	480(24)
Thyroid Condition, n(%)	375(19)
Aspirin Use n(%)	224(10)
Time between V03 and V04, Years	0.95±0.17
High sensitivity-C-reactive protein, mg/dl, Median(Q1, Q3)	1.7(0.6,4.8)
Fibrinogen, mg/dl, Mean±SD	276.57±53.17
Factor VIIc, %, Mean±SD	120.57±24.72
PAI-1, ng/ml, Median(Q1,Q3)	17.9(9.6,32.9)
TPA Antigen, ng/ml, Median (Q1,Q3)	7.1(5.1,9.6)
Physical Function ^c (at V04), n(%)	

	n=2296
No limitation	1179(60)
Some limitation	607(31)
Substantial limitation	192(10)
<u>Specific limitations in physical function activities (at V04), n(%)</u>	
<u>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</u>	
<u>Not limited at all</u>	<u>728(37)</u>
<u>Limited a little</u>	<u>795(40)</u>
<u>Limited a lot</u>	<u>453(23)</u>
<u>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf</u>	
<u>Not limited at all</u>	<u>1542(78)</u>
<u>Limited a little</u>	<u>335(17)</u>
<u>Limited a lot</u>	<u>100(5)</u>
<u>Lifting or carrying groceries</u>	
<u>Not limited at all</u>	<u>1606(81)</u>
<u>Limited a little</u>	<u>298(15)</u>
<u>Limited a lot</u>	<u>74(4)</u>
<u>Climbing one flight of stairs</u>	
<u>Not limited at all</u>	<u>1697(86)</u>
<u>Limited a little</u>	<u>201(10)</u>
<u>Limited a lot</u>	<u>78(4)</u>
<u>Climbing several flights of stairs</u>	
<u>Not limited at all</u>	<u>1279(65)</u>
<u>Limited a little</u>	<u>504(26)</u>
<u>Limited a lot</u>	<u>191(10)</u>
<u>Bending, kneeling, or stooping</u>	
<u>Not limited at all</u>	<u>1281(65)</u>
<u>Limited a little</u>	<u>554(28)</u>
<u>Limited a lot</u>	<u>142(7)</u>
<u>Walking one block</u>	
<u>Not limited at all</u>	<u>1771(90)</u>
<u>Limited a little</u>	<u>133(7)</u>
<u>Limited a lot</u>	<u>72(4)</u>
<u>Walking several blocks</u>	
<u>Not limited at all</u>	<u>1640(83)</u>
<u>Limited a little</u>	<u>209(11)</u>
<u>Limited a lot</u>	<u>128(6)</u>
<u>Walking more than a mile</u>	
<u>Not limited at all</u>	<u>1400(71)</u>
<u>Limited a little</u>	<u>375(19)</u>
<u>Limited a lot</u>	<u>200(10)</u>
<u>Bathing or dressing yourself</u>	
<u>Not limited at all</u>	<u>1870(95)</u>

	n=2296
<u>Limited a little</u>	<u>61(3)</u>
<u>Limited a lot</u>	<u>47(2)</u>

SD, Standard Deviation; hs-CRP, high sensitivity-C-reactive protein

^aDenominators for percentages may vary based on missing data at visit 03.

^bPossible range: 3.25–13.20.

^cNo Limitation: Physical functioning score 86–100 points; Some Limitation: Physical Functioning score 51–85 points; Substantial Limitation: Physical Functioning score: 50 points.

Table 2

Longitudinal associations between Inflammatory and Hemostatic Markers at Time t-1 with Physical Functioning Limitation measured at Time t.

Physical Functioning Limitations at Time t	Inflammatory and Hemostatic Markers at Time t-1			
	hs-CRP ^e (SD units)	PAI-1 ^e (SD units)	tPA-ag ^e (SD units)	FVIIc (SD units)
Model 1 ^a				
Proportional Odds Ratio (95% CI)	1.44(1.32,1.57)	1.34(1.25,1.45)	1.45(1.34,1.56)	1.22(1.13,1.32)
P value	<0.0001	<0.0001	<0.0001	<0.0001
Model 2 ^c				
Proportional Odds Ratio (95% CI)	1.15(1.05,1.27)	1.11(1.03,1.20)	1.24(1.15,1.34)	1.10(1.02,1.19)
P value	0.005	0.007	<0.0001	0.02
Model 3 ^c				
Proportional Odds Ratio (95% CI)	1.11(1.00,1.22)	1.08(1.00,1.17)	1.19(1.11,1.29)	1.08(1.00,1.17)
P value	0.0490	0.05	<0.0001	0.06
Model 4 ^d				
Proportional Odds Ratio (95% CI)	1.08(0.98,1.19)	1.05(0.97,1.14)	1.18(1.09,1.27)	1.04(0.96,1.13)
P value	0.13	0.23	<0.0001	0.34

^a Model 1: Adjusted for age at visit 03, time between t-1 and t, site, race, and ability to pay for basics

^b Model 2: Model 1 additionally adjusted for BMI

^c Model 3: Model 2 additionally adjusted for menopausal status, exogenous hormone use, and physical activity

^d Model 4: Model 3 additionally adjusted for heart condition, diabetes, osteoarthritis, thyroid condition and depression

^e log transformed for analysis

Table 3

Longitudinal associations between Fibrinogen at Time t-1 with Physical Function Limitation measured at Time t stratified by race/ethnicity.

Physical Functioning Limitations at Time t	Fibrinogen (SD units) at Time t-1			
	Caucasian	African American	Chinese	Japanese
Model 1 ^a				
Proportional Odds Ratio (95% CI)	1.50(1.33,1.68)	1.44(1.26,1.66)	1.14(0.89,1.45)	1.01(0.78,1.31)
P value	<0.0001	<0.0001	0.30	0.95
Model 2 ^b				
Proportional Odds Ratio (95% CI)	1.17(1.03,1.33)	1.30(1.13,1.50)	1.07(0.86,1.34)	0.95(0.74,1.22)
P value	0.01	0.0004	0.53	0.70
Model 3 ^c				
Proportional Odds Ratio (95% CI)	1.11(0.97,1.26)	1.27(1.10,1.47)	1.04(0.82,1.31)	0.94(0.73,1.21)
P value	0.12	0.002	0.77	0.64
Model 4 ^d				
Proportional Odds Ratio (95% CI)	1.08(0.95,1.23)	1.30(1.13,1.50)	1.00(0.79,1.27)	0.98(0.75,1.27)
P value	0.23	0.0004	0.97	0.86

Final model sample sizes: Caucasian=972; African American=492; Chinese=214; Japanese=229

^a Model 1: Adjusted for age at visit 03, time between t-1 and t, and ability to pay for basics

^b Model 2: Model 1 additionally adjusted for BMI

^c Model 3: Model 2 additionally adjusted for menopausal status, exogenous hormone use, and physical activity

^d Model 4: Model 3 additionally adjusted for heart condition, diabetes, osteoarthritis, thyroid condition and depression