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Association of Inflammation With Loss Of Ability to Walk 400 Meters: Longitudinal Findings From the InChianti Study

Sarinnapha Vasunilashorn, PhD^{*}, Luigi Ferrucci, MD, PhD[†], Eileen M. Crimmins, PhD[‡], Stefania Bandinelli, MD[§], Jack M. Guralnik, MD, PhD^{||}, and Kushang V. Patel, PhD[#]

^{*}Office of Population Research, Princeton University, Princeton, New Jersey [†]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland [‡]Andrus Gerontology Center, University of Southern California [§]Geriatric Unit, Azienda Sanitaria Firenze, Italy ^{||}Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland [#]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, Washington

Abstract

Objectives—To examine relationships between eight markers of inflammation (interleukin [IL]-6, IL-6 receptor [R], C-reactive protein [CRP], tumor necrosis factor [TNF]- α , TNF receptor 1[R1], TNFR2, IL-1 receptor antagonist, IL-18) and incident loss of ability to walk 400 m.

Design—Prospective cohort study.

Setting—Older adults enrolled in the InvecchiareInChianti Study.

Participants—One thousand six community-dwelling participants aged 65+.

Measurements—The eight inflammatory markers were measured at baseline, and an inflammation score was calculated based on the number of inflammatory markers for which the participant was in the highest quartile. Incidence of mobility disability was determined among participants able to walk 400 m at baseline. Logistic regression models were used to determine whether each of the inflammatory markers and the inflammation score predicts loss of the ability to walk 400 m at six-year follow-up.

Results—After adjusting for covariates, individuals with a TNFR1 level in each of the top 3 quartiles (Q2, 3, 4) were more likely to be unable to walk 400 m at follow-up compared to those with TNFR1 levels in Q1. When adjusting for the same covariates, participants with an inflammation score of 3 or 4 were more likely to become unable to complete the 400 m walk at follow-up compared to participants with a score of 0.

Conclusion—These results bring additional evidence to the notion that inflammation is implicated in the mechanisms that cause incident mobility disability and suggest that a combined measure of inflammatory markers may improve our prediction of functional prognosis.

Corresponding Author: Sarinnapha Vasunilashorn, Office of Population Research, Princeton University, 263 Wallace Hall, Princeton, NJ 08544. Office: 609-258-6971. Fax: 609-258-1039. svasunil@princeton.edu.

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Author Contributions:

Sarinnapha Vasunilashorn analyzed the data and wrote the paper. Luigi Ferrucci, Eileen Crimmins, Stefania Bandinelli, and Eileen Crimmins assisted in writing the paper. Kushang Patel assisted in data analysis and in writing the paper.

Keywords

inflammation; mobility; 400 m walk; functional limitation; aging

INTRODUCTION

Higher levels of proinflammatory markers have been associated with the onset of various age-associated diseases, including cardiovascular disease,¹ atherosclerosis,² chronic kidney disease,³ cancer,⁴ and dementia⁵ as well as mortality.⁶ However, the functional consequences of higher levels of inflammation have received less attention.⁷ Studies suggest that the proinflammatory state has catabolic effects on muscle,⁸ leading to sarcopenia,⁹ and subsequently resulting in mobility limitations and disability.¹⁰

Prior research has studied the cross-sectional relationship between inflammation and physical functioning,^{11,12} but few studies have examined their longitudinal associations.¹³ Many longitudinal studies have focused on one or two markers of inflammation, namely interleukin (IL)-6 and C-reactive protein (CRP),^{8,14} but fewer studies have examined the associations among multiple inflammatory markers and changes in functioning.¹⁵ Nonetheless, inflammation is a complex and integrative response to changes in homeostasis with cytokines (e.g., tumor necrosis factor [TNF]- and interleukins) systemically affecting multiple organ systems.¹⁶ Given this complexity, it is unlikely that any single marker represents the entire burden of inflammation.¹⁴ For instance, the number of elevated inflammatory markers is positively associated with erythropoietin in non-anemic older adults, suggesting a cumulative effect of proinflammatory markers on erythropoiesis.¹⁷ While some studies have investigated the association of functional decline with other proinflammatory markers besides IL-6,^{14,18} fewer studies have evaluated the combined effect of these markers.

The majority of these studies showed that high cytokine levels were associated with adverse outcomes; however, few studies have examined the inability to walk some distance. Among older adults, the ability to walk 400 m represents a major public health outcome and serves as an appropriate proxy for mobility within the community.¹⁹ The inability to walk 400 m is associated with increased risk of cardiovascular disease, mobility limitation, disability, and mortality.²⁰ The study presented here examines whether eight markers of inflammation (IL-6, IL-6 receptor(R), C-reactive protein [CRP], TNF- α , TNFR1, TNFR2, IL-1 receptor antagonist [RA], IL-18), some which have been previously linked to physical function (e.g., IL-6 and CRP) and others that have yet to be investigated, predict objectively measured loss of ability to walk 400 meters over a 6-year follow-up period among community-dwelling older adults.

METHODS

Study Population

The InCHIANTI (“Invecchiare in Chianti,” aging in the Chianti area) study is a longitudinal epidemiological study investigating factors that contribute to decline in mobility during later life. The study was designed by the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging (INRCA, Florence, Italy) in conjunction with the Laboratory of Epidemiology, Demography, and Biometry at the National Institute on Aging (NIA). Using a multistage stratified sampling method, participants were randomly selected from community-dwelling residents of Greve and Bagno a Ripoli, both towns located in Chianti, Italy. The InCHIANTI Study methodology and design have been previously published.²¹

For the current study, baseline, 3-year, and 6-year follow-up data were included. There were 1,026 participants age 65 and older who underwent medical and physical function evaluations at baseline. Among those people, 801 were able to complete the 400 m walk at baseline. Of these 801 participants, 643 had follow-up information for the 400 m walk test at either 3- or 6- year follow-up (if failed at 3 years and died or were lost to follow-up at 6 years, participants remained in the analysis). Among the 643 individuals, 621 were included and 22 were excluded from these analyses because they did not have data on one of the inflammatory measures.

Compared to the 621 participants included in the analyses, the 180 excluded individuals (97 were missing at 3-year and 139 were missing at 6-year follow-up) who were able to walk 400 m at baseline did not differ by gender ($p=0.98$) or years of education ($p=0.06$); however, the 180 excluded individuals were significantly older ($p<0.001$) and had a greater number of chronic conditions ($p=0.04$) compared to the 621 participants included in the analyses.

Outcome measures

Objectively measured ability to walk 400 m was examined. For the 400 m walk, participants were asked to walk 20 laps on a 20 m course as fast as possible at a steady pace. A maximum of two standing rests were allowed for two-minute intervals each. Classification criteria for the inability to complete the 400 m-walk test in the InCHIANTI Study have been previously reported.²² Briefly, participants were considered unable to complete the walk if they: attempted but failed the 400 m walk, had self-reported difficulty walking 8 m without help, difficulty keeping their balance with feet together side-by-side, severe dyspnea and dyspnea at rest, or were unable to complete a 4 m walk. Among individuals able to walk 400 m at baseline ($N=621$), 81 (13.0%) were unable to walk 400 m at 3-year follow-up, 79 (12.7%) were unable to walk 400 m at 6-year follow-up, and 130 were unable to walk 400 m at either 3- or 6- year follow-up (20.9%).

Laboratory measures

Venipuncture was completed in the morning after a 12-hour fast. During blood sampling, the participant remained sedentary in a seated or supine position for a minimum of 15 minutes. In transferring blood samples, mechanical disruption was minimized to prevent hemolysis or activation. Serum and plasma were separated using low-speed centrifugation and stored at -80°C . Enzyme-linked immunosorbent assay (ELISA) tests were performed at INRCA.

Serum IL-6, IL-6R, and IL-1RA were quantified using commercial ELISA kits (BioSourceCytoscreenUltraSensitive kits, BioSource International Inc., Camarillo, CA, USA). The lowest detectable concentration was 0.10pg/ml for IL-6, 8.00pg/mL for IL-6R, and 4.00 pg/mL for IL-1RA. The interassay coefficient of variation (CV) was 7% for IL-6 and <10% for IL-6R and IL-1RA. High-sensitivity CRP levels were determined using a particle-enhanced immunonephelometric assay and monoclonal antibodies to CRP (Dade Behring, Inc., Deerfield, IL, USA). The detection limit for CRP was 0.16 mg/dL, and the interassay CV ranged from 2.1–5.7%. IL-18 was measured using high sensitivity quantitative assays (Quantikine HS, R&D Systems, Minneapolis, MN). The minimum detectable concentration was 100 pg/mL, and the interassay CV range was 10–12%. Serum TNF- α was quantified using multiplex technology (Human Serum Adipokine Panel B LINCOplex kit; Linco Research, Inc., St. Charles, MO, USA), and TNFR1 and TNFR2 levels were determined using an ultra-sensitive quantitative sandwich enzyme-linked immunoassay (ELISA; Quantikine Human Immunoassay; R&D Systems, Inc., Minneapolis, MN, USA). The lowest detectable concentration was 0.64 pg/mL for TNF- α and approximately 78 pg/mL for TNFR1 and TNFR2. The interassay CV was <21% for TNF- α , 10% for TNFR1, and 8% for TNFR2.

All cytokine assays were completed in duplicate and were repeated only if the second measure was greater or less than 10% of the first measure. The average of the two measures from each sample was used in our analysis.

Other covariates

Additional covariates included in the analysis were age, sex, and years of education. Chronic medical conditions were ascertained through a combination of self-report and physician examination. The total number of chronic conditions was calculated based on the presence of cancer, hypertension, angina, myocardial infarction, congestive heart failure, stroke, Parkinson's disease, diabetes mellitus, chronic obstructive pulmonary disease, peripheral arterial disease, hip fracture, and arthritis in the hip or knee. A summary variable was created for the presence of 0, 1, 2, 3 or more chronic conditions. We also included body mass index (BMI) in the analysis.

Measurement of physiologic subsystems related to mobility function in the InCHIANTI Study has been previously published.²¹ The Mini Mental State Exam (MMSE) was used to assess cognitive functioning. Nerve conduction velocity (NCV), measured by electroenceurography in the right peroneal nerve, detected impairment in the peripheral nervous system. Muscle power, an indicator of physical strength, was measured using a leg extensor power rig device. Hemoglobin levels were a general measurement of energy impairment, while the ankle-brachial index (ABI) assessed peripheral arterial circulation.

Analysis

Logistic regression models fitted with generalized estimating equations were used to determine whether each of the eight proinflammatory markers predicted incident mobility disability, as measured by the 400 m walk test. An inflammation score was calculated for each participant based on the number of inflammatory markers with values in the highest quartile of the study population (similar to Ferrucci et al.¹⁷). For example, if a participant only had IL-6 and TNF- α levels in the highest quartile, that individual received an inflammation score of 2. If the participant did not have any of the eight inflammatory values in the highest quartile an inflammation score of 0 was assigned. The inflammation scores ranged from 0–4, although the possible range was 0–8. Cronbach's alpha for the eight inflammatory markers was 0.67.

A series of models were tested for each inflammatory marker predicting incident mobility disability. Separate models were performed for all 8 inflammatory markers as well as the inflammation score. Models I show the unadjusted bivariate results for each proinflammatory marker and for the inflammation score. Age and sex-adjusted models were then estimated (Models II). Models III additionally adjusted for education, BMI, and total number of medical conditions. Finally, Models IV added the physiological impairment variables, including MMSE, NCV, muscle power, hemoglobin concentration, and ABI. Statistical analyses were performed using SAS 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS

The 3- or 6-year incidence of failing the 400 m walk test was 20.9%. Participants unable to walk 400 m at follow-up were significantly more likely to be older, female, less educated, more cognitively impaired, have a greater number of medical conditions, lower SPPB scores, and more likely to have higher IL-6, TNFR1, and TNFR2 levels at baseline compared to those able to complete the walk (Table 1).

In unadjusted and age- and sex-adjusted models, participants in the highest quartile (Q4) of IL-6, TNFR1, and TNFR2 were significantly more likely to have objectively measured

incident mobility disability than those in the lowest quartiles (Table 2, Models I and II). Compared to participants in the lowest quartile, those in the highest quartile of IL-6, TNFR1, and TNFR2 were about 2 to 3 times as likely to have incident mobility disability (Model II). In the age- and sex-adjusted model, participants in the highest quartile of IL-6 had a higher risk of incident mobility disability compared to those in the lowest quartile (Model II). After further adjusting for BMI, education, and medical conditions, only TNFR1 was significantly associated with increased inability to complete the 400 m walk at 3- or 6-year follow-up (Model III). The addition of physiological impairment measures did not substantially change the magnitude or statistical significance of this association (Model IV).

The categorical grouping of the inflammation score was also associated with an increased risk of incident mobility disability (Table 3). In the unadjusted model, participants with scores of 3 or 4 were 4.2 times more likely to develop mobility disability compared to participants with a score of 0, and individuals with scores of 1 or 2 were nearly twice as likely to have incident mobility disability compared to the reference group (Model I). The addition of age and sex did not substantially attenuate the significance or magnitude of the inflammation score's association with the inability to walk 400 m at follow-up (Model II). Further adjustment for BMI, education, medical conditions, and physiologic measures indicated that participants with inflammation scores of 3 or 4 were 2.2 times as likely to develop mobility disability (Model IV). Controlling for regular physical activity did not alter the significance nor the magnitude of the relationship between inflammation and mobility disability (results not shown). To account for multiple comparisons, a Bonferroni correction underscored a significant relationship between the inability to complete the 400 m walk and: TNFR1, TNFR2, and the inflammation score.

DISCUSSION

This prospective study of older adults finds that a proinflammatory state, as indicated by TNFR1, TNFR2, and the inflammation score, is strongly associated with objectively measured loss of ability to walk 400 m over a 6-year follow-up period. The effect of elevated levels of TNFR1 was robust to adjustments for age-associated diseases and impairments that contribute to mobility decline in later years of life. Moreover, participants with 3 or more inflammatory markers in the highest quartile had greater odds of loss of ability to walk 400 m compared to those without elevated levels of inflammatory markers in the highest quartile. This suggests a potential cumulative effect of elevated levels of inflammatory markers on decline in physical function.

Our study demonstrates a stronger association of a cumulative inflammation measure with the onset of objectively measured mobility disability than individual inflammatory markers alone. This finding contributes to a greater understanding of the relationship between inflammation and incident mobility disability that may occur through both independent and cumulative effects of proinflammatory markers. We acknowledge that all statistical hypotheses have a probability of making type-I errors and have used Bonferroni correction as a more stringent test of identifying 'false positives.'

While several studies have examined the association of IL-6 and TNF- α on physical function, fewer studies have investigated how functioning relates to receptors of IL-6 and TNF- α . Hsu et al.¹² used principal components analysis to identify two inflammatory "components" from an array of inflammatory markers, and they examined the relationship of these components with physical function. They found that the first component (with TNF- α , soluble [s]TNFR1, sTNFR2, IL-6sR, and IL-2sR loading highest on this TNF- α related component) was associated with knee strength and a physical performance battery score, while the second component (with CRP, IL-6, and plasminogen activator inhibitor-1 loading

highest on this CRP related component) was not associated with either measure of function. Penninx et al.¹³ reported higher levels of TNFR1 and TNFR2 among older adults with knee osteoarthritis who scored low on the Western Ontario and McMaster University Osteoarthritis index (WOMAC) of physical function. Both of these studies align with our findings of an association between loss of ability to walk 400 m and TNF- receptors. Moreover, the half-life of circulating TNF- is longer than the other inflammatory markers examined, perhaps reflecting a greater cumulative pro-inflammatory load.

Interestingly, we found an association between incident mobility disability and levels of TNFR1 and TNFR2 but not to TNF- levels. This may be due to differences in expression and roles that the TNF superfamily members play with respect to cell differentiation, proliferation, apoptosis, and induction of inflammation.²³ TNF- induces a variety of effects based on cell type, and it acts by binding to its two receptors: TNFR1 and TNFR2. This may explain our association between incident mobility disability and TNFR1 and TNFR2, and lack of association to TNF-. TNFR1 is the major signalling receptor for TNF- and is expressed in all human tissue, while TNFR2 is predominantly expressed in immune cells and mediates a limited number of biological responses.²⁴ The major role of TNFR1 in cell function may in part explain why its association with mobility disability remained after adjusting for medical conditions and physiologic measures, while TNFR2 was no longer associated with loss of ability to walk 400 m in the fully adjusted model.

Although the prospective design of our study is a strength, the repeated mobility assessments were separated by 3 year intervals, which likely contributes to under-ascertainment of mobility disability. Additional prospective studies are needed to replicate the current study findings. Another study limitation is our modest sample size, which may not provide adequate statistical power to detect additional associations if they exist. In terms of effect size, the statistically significant effect sizes are moderately high (e.g., OR= 2.2 for individuals with inflammation scores of 3 or 4 relative to those with a score of 0; Model IV, Table 3). Although we find no evidence of an association between TNF- and CRP, for example, we acknowledge that there may be small effects that we are unable to detect.

Declines in inflammation have been associated with physical exercise,²⁵ highlighting a potential intervention for lowering inflammatory levels and preventing disability onset. Clinical trials that examine the efficiency of physical exercise or drug therapies on inflammatory markers and physical function may provide a better picture of the highly complex, but potentially modifiable effects of inflammation on physical functioning in older adults.

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Table 1

Baseline Characteristics of the Study Population by 400 m Walk Performance at 3- or 6-year Follow-Up

Characteristic	Completed	Failed/Unable	P-value
	(N=491)	(N=130)	
Age, M ($\pm$ SD)	71.3 ($\pm$ 4.8)	76.8 ($\pm$ 6.7)	<.01
Men, %	48.5	29.4	<.01
Education (years), M ($\pm$ SD)	6.1 ($\pm$ 3.3)	4.9 ($\pm$ 3.0)	<.01
Mini Mental State Exam score, M ($\pm$ SD)	26.3 ($\pm$ 2.5)	24.5 ($\pm$ 3.8)	<.01
Total number of medical conditions, %			
0	31.0	13.1	<.01
1	44.4	36.2	
2	19.4	34.4	
3+	5.2	16.3	
Body Mass Index (kg/m ²), M ($\pm$ SD)	27.2 ($\pm$ 3.6)	27.5 ($\pm$ 4.2)	0.77
Short Physical Performance Battery, M ($\pm$ SD)	11.3 ($\pm$ 1.1)	9.5 ($\pm$ 2.2)	<.01
IL-6 (pg/mL), M ($\pm$ SD)	3.2 ($\pm$ 2.1)	3.8 ($\pm$ 2.6)	<.01
Q1 (2.035), %	30.6	23.7	
Q2 (>2.035, 2.978), %	27.6	22.5	
Q3 (>2.978, 4.133), %	25.4	24.4	
Q4 (>4.133), %	16.4	29.4	
IL-6R (pg/mL), M ($\pm$ SD)	104.2 ($\pm$ 53.4)	99.8 ($\pm$ 44.9)	0.26
Q1 (69.152), %	26.1	21.9	
Q2 (>69.152, 93.379), %	23.2	26.2	
Q3 (>93.379, 125.723), %	23.7	33.8	
Q4 (>125.723)	27.0	18.1	
CRP (mg/L), M ($\pm$ SD)	3.8 ($\pm$ 4.7)	4.3 ($\pm$ 6.3)	0.24
Q1 (1.320), %	31.7	30.0	
Q2 (>1.320, 2.765), %	24.9	23.7	
Q3 (>2.765, 5.800), %	26.7	27.5	
Q4 (>5.800), %	16.7	18.8	
TNF- (pg/mL), M ($\pm$ SD)	6.9 ($\pm$ 51.1)	4.8 ($\pm$ 2.1)	0.23
Q1 (3.29), %	30.4	25.6	
Q2 (>3.29, 4.62), %	27.2	25.0	
Q3 (>4.62, 6.07), %	23.5	27.5	
Q4 (>6.07), %	18.9	21.9	
TNFR1 (pg/mL), M ($\pm$ SD)	1319.0 ($\pm$ 444.8)	1565.1 ($\pm$ 568.7)	<.01
Q1 (1100.00), %	35.0	13.1	
Q2 (>1100.00, 1351.05), %	28.1	29.4	
Q3 (>1351.05, 1724.60), %	23.9	29.4	
Q4 (>1724.60), %	13.0	28.1	
TNFR2 (pg/mL), M ($\pm$ SD)	2557.9 ($\pm$ 596.0)	2888.3 ($\pm$ 726.0)	<.01
Q1 (2287.0), %	33.1	18.7	

Characteristic	Completed	Failed/Unable	P-value
	(N=491)	(N=130)	
Q2 (>2287.0, 2651.8), %	31.1	26.3	0.32
Q3 (>2651.8, 3177.5), %	22.7	25.0	
Q4 (>3177.5), %	13.1	30.0	
IL-1RA (pg/mL), M (±SD)	142.3 (±87.7)	145.6 (±70.9)	
Q1 (≤96.590), %	28.3	26.9	0.14
Q2 (>96.590, ≤132.865), %	26.6	28.1	
Q3 (>132.865, ≤185.875), %	24.2	24.4	
Q4 (>185.875), %	20.9	20.6	
IL-18 (µg/mL), M (±SD)	386.6 (±139.3)	406.1 (±156.7)	0.14
Q1 (≤302.39), %	29.0	28.1	
Q2 (>302.39, ≤383.30), %	27.5	24.4	
Q3 (>383.30, ≤482.96), %	24.7	21.2	
Q4 (>482.96), %	18.8	26.3	<.01
Inflammation score, [†] M (±SD)	3.4 (±0.9)	2.9 (±1.2)	
0 (%)	60.6	41.2	
1 or 2 (%)	33.7	41.9	
3 or 4 (%)	5.7	16.9	

[†]Elevated = In the highest quartile for each cytokine

M = Mean; SD = standard deviation; SPPB = Short physical performance battery;

IL = interleukin; CRP = C-reactive protein; TNF = tumor necrosis factor;

R = receptor; RA = receptor antagonist

Note: Individuals included in Table 1 are not necessarily individuals analyzed in Table 2 and 3 due to missing values.

Table 2

Association of Inflammatory Markers with Incident Inability to Complete the 400 m Walk at Follow-Up

	Models I ^a		Models II ^b		Models III ^c		Models IV ^d	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
IL-6 (pg/mL)								
Q1 (2.034724)	Reference		Reference		Reference		Reference	
Q2 (>2.034724, 2.978014)	1.2	(0.7-2.1)	1.1	(0.6-1.9)	1.0	(0.6-1.8)	0.9	(0.5-1.7)
Q3 (>2.978014, 4.133125)	1.4	(0.8-2.4)	1.2	(0.7-2.1)	1.1	(0.6-1.9)	1.0	(0.5-1.8)
Q4 (>4.133125)	2.4	(1.4-4.3)	1.8	(1.0-3.3)	1.4	(0.8-2.7)	1.3	(0.7-2.7)
<i>p</i> for trend	<i>p</i> < .01		<i>p</i> = 0.06		<i>p</i> = 0.29		<i>p</i> = 0.43	
IL-6R (pg/mL)								
Q1 (69.152)	Reference		Reference		Reference		Reference	
Q2 (>69.152, 93.379)	1.3	(0.7-2.2)	1.2	(0.7-2.3)	1.7	(0.9-3.0)	2.1	(1.1-4.0)
Q3 (>93.379, 125.723)	1.6	(0.9-2.7)	1.4	(0.8-2.5)	1.6	(0.8-2.9)	1.9	(1.0-3.8)
Q4 (>125.723)	0.8	(0.4-1.4)	0.8	(0.4-1.5)	1.0	(0.5-1.8)	1.1	(0.5-2.2)
<i>p</i> for trend	<i>p</i> = 0.60		<i>p</i> = 0.62		<i>p</i> = 0.93		<i>p</i> = 0.80	
CRP (mg/L)								
Q1 (1.320)	Reference		Reference		Reference		Reference	
Q2 (>1.320, 2.765)	1.0	(0.6-1.8)	0.9	(0.5-1.7)	0.8	(0.5-1.5)	0.8	(0.4-1.4)
Q3 (>2.765, 5.800)	1.2	(0.7-2.1)	1.3	(0.7-2.2)	1.0	(0.6-1.7)	1.0	(0.5-1.7)
Q4 (>5.800)	1.4	(0.8-2.5)	1.3	(0.7-2.4)	1.0	(0.5-1.9)	0.9	(0.4-1.8)
<i>p</i> for trend	<i>p</i> = 0.18		<i>p</i> = 0.29		<i>p</i> = 0.94		<i>p</i> = 0.82	
TNF- (pg/mL)								
Q1 (3.29)	Reference		Reference		Reference		Reference	
Q2 (>3.29, 4.62)	1.1	(0.6-1.9)	0.8	(0.5-1.5)	0.7	(0.4-1.3)	0.7	(0.4-1.4)
Q3 (>4.62, 6.07)	1.4	(0.9-2.5)	1.2	(0.7-2.2)	1	(0.6-1.9)	1.0	(0.5-1.8)
Q4 (>6.07)	1.4	(0.8-2.5)	1.0	(0.5-1.5)	0.8	(0.4-1.6)	0.8	(0.4-1.5)
<i>p</i> for trend	<i>p</i> = 0.14		<i>p</i> = 0.67		<i>p</i> = 0.89		<i>p</i> = 0.67	
TNFR1 (pg/mL)								
Q1 (1100.00)	Reference		Reference		Reference		Reference	
Q2 (>1100.00, 1351.05)	2.7	(1.4-4.9)	2.6	(1.4-4.8)	2.6	(1.4-5.1)	3.1	(1.5-6.4)

	Models I ^a		Models II ^b		Models III ^c		Models IV ^d	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Q3 (>1351.05, 1724.60)	3.0	(1.6–5.6)	2.2	(1.1–4.3)	2.0	(1.0–4.0)	2.4	(1.1–5.1)
Q4 (>1724.60)	5.1	(2.7–9.9)	3.1	(1.6–6.2)	2.4	(1.1–5.1)	2.8	(1.2–6.5)
<i>p</i> for trend	<i>p</i> < .01		<i>p</i> < .01		<i>p</i> = 0.05		<i>p</i> = 0.03	
TNFR2 (pg/mL)	Reference		Reference		Reference		Reference	
Q1 (2287.0)	1.4	(0.8–2.4)	1.2	(0.7–2.0)	1	(0.6–1.9)	1.3	(0.7–2.4)
Q2 (>2287.0, 2651.8)	1.8	(1.0–3.2)	1.4	(0.8–2.6)	1.4	(0.7–2.5)	1.4	(0.7–2.8)
Q3 (>2651.8, 3177.5)	3.7	(2.1–6.5)	1.9	(1.0–3.6)	1.5	(0.7–3.1)	1.5	(0.7–3.3)
Q4 (>3177.5)	<i>p</i> < .01		<i>p</i> = 0.05		<i>p</i> = 0.19		<i>p</i> = 0.26	
<i>p</i> for trend	<i>p</i> = 0.91		<i>p</i> = 0.76		<i>p</i> = 0.54		<i>p</i> = 0.28	
IL-18 (pg/mL)	Reference		Reference		Reference		Reference	
Q1 (96.590)	1.1	(0.7–1.9)	1.0	(0.6–1.7)	0.9	(0.5–1.5)	0.9	(0.5–1.5)
Q2 (>96.590, 132.865)	1.0	(0.6–1.7)	1.0	(0.5–1.7)	0.8	(0.4–1.5)	0.7	(0.3–1.3)
Q3 (>132.865, 185.875)	1.1	(0.6–1.9)	1.1	(0.6–2.0)	0.9	(0.5–1.5)	0.8	(0.4–1.5)
Q4 (>185.875)	<i>p</i> = 0.91		<i>p</i> = 0.76		<i>p</i> = 0.54		<i>p</i> = 0.28	
<i>p</i> for trend	<i>p</i> = 0.30		<i>p</i> = 0.14		<i>p</i> = 0.57		<i>p</i> = 0.96	
IL-18 (μg/mL)	Reference		Reference		Reference		Reference	
Q1 (302.39)	0.9	(0.6–1.6)	1.3	(0.7–2.2)	1.1	(0.6–2.0)	1.2	(0.6–2.3)
Q2 (>302.39, 383.30)	0.8	(0.5–1.4)	0.8	(0.4–1.5)	0.7	(0.4–1.3)	0.7	(0.4–1.4)
Q3 (>383.30, 482.96)	1.5	(0.9–2.5)	2.0	(1.1–3.7)	1.5	(0.8–2.9)	1.3	(0.6–2.7)
Q4 (>482.96)	<i>p</i> = 0.30		<i>p</i> = 0.14		<i>p</i> = 0.57		<i>p</i> = 0.96	
<i>p</i> for trend	<i>p</i> = 0.30		<i>p</i> = 0.14		<i>p</i> = 0.57		<i>p</i> = 0.96	

OR = Odds Ratio; CI = Confidence Interval

^aModels I = Unadjusted bivariate models

^bModels II = Age and sex adjusted models

^cModels III = Adjusted for Model II covariates as well as body mass index, education, total number of medical conditions (includes arthritis, cancer, coronary heart disease, chronic obstructive pulmonary disease, diabetes, hip fracture, peripheral arterial disease, stroke)

^dModels IV = Adjusted for Model III and the following physiologic measures: MMSE, nerve conduction velocity, leg muscle power, serum hemoglobin, ankle-brachial index

Models I–III are based on an analysis sample of 1006 observations representing 621 respondents

Models IV are based on an analysis sample of 941 observations representing 621 respondents

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Table 3

Association of Inflammation Score with Incident Inability to Complete the 400 m Walk at Follow-Up

	Models I ^a		Models II ^b		Models III ^c		Models IV ^d	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Inflammation score [‡]								
0		Reference		Reference		Reference		Reference
1 or 2	1.8	(1.2–2.8)	1.7	(1.9–2.8)	1.3	(0.8–2.3)	1.2	(0.7–2.1)
3 or 4	4.2	(2.2–7.9)	3.2	(1.6–6.4)	2.5	(1.2–5.0)	2.2	(1.0–5.0)
<i>p</i> for trend	<i>p</i> < 0.01		<i>p</i> < 0.01		<i>p</i> = 0.02		<i>p</i> = 0.09	

[‡]Elevated = In the highest quartile for each cytokine:

Q1 = Quartile 1, Q2 = Quartile 2, Q3 = Quartile 3, Q4 = Quartile 4

OR = Odds Ratio; CI = Confidence Interval

^aModels I = Unadjusted bivariate models

^bModels II = Age and sex adjusted models

^cModels III = Adjusted for Model II covariates as well as body mass index, education, total number of medical conditions (includes arthritis, cancer, coronary heart disease, chronic obstructive pulmonary disease, diabetes, hip fracture, peripheral arterial disease, stroke)

^dModels IV = Adjusted for Model III and the following physiologic measures: MMSE, nerve conduction velocity, leg muscle power, serum hemoglobin, ankle-brachial index

Models I–III are based on an analysis sample of 1006 observations representing 621 respondents

Models IV are based on an analysis sample of 941 observations representing 621 respondents

p < 0.05 (bolded)