Inflammatory Markers and Incident Mobility Limitation in the Elderly

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OBJECTIVES: To examine the relationship between indicators of inflammation and the incidence of mobility limitation in older persons.

DESIGN: Prospective cohort study: the Health, Aging and Body Composition Study.

SETTING: Pittsburgh, Pennsylvania, and Memphis, Tennessee.

PARTICIPANTS: A total of 2,979 men and women, aged 70 to 79, without mobility limitation at baseline.

MEASUREMENTS: Serum levels of interleukin (IL)-6, tumor necrosis factor alpha (TNFα), and C-reactive protein (CRP) and soluble cytokine receptors (IL-2sR, IL-6sR, TNFsR1, TNFsR2) were measured. Mobility limitation was assessed and defined as reporting difficulty or inability to walk one-quarter of a mile or to climb 10 steps during two consecutive semiannual assessments over 30 months.

RESULTS: Of the 2,979 participants, 30.1% developed incident mobility limitation. After adjustment for confounders (demographics, prevalent conditions at baseline, body composition), the relative risk (RR) of incident mobility limitation per standard deviation (SD) increase was 1.19 (95% confidence interval (CI) = 1.10–1.28) for IL-6, 1.20 (95% CI = 1.12–1.29) for TNFα, and 1.40 (95% CI = 1.18–1.68) for CRP. The association between inflammation and incident mobility limitation was especially strong for the onset of more severe mobility limitation and when the levels of multiple inflammatory markers were high. When persons with baseline or incident cardiovascular disease events or persons who were hospitalized during study follow-up were excluded, findings remained similar. In a subset (n = 499), high levels of the soluble receptors IL2sR and TNFsR1 (per SD increase: RR = 1.23 (95% CI = 1.04–1.46) and RR = 1.28 (95% CI = 1.04–1.57), respectively) were also associated with incident mobility limitation.

CONCLUSION: Findings suggest that inflammation is prognostic for incident mobility limitation over 30 months, independent of cardiovascular disease events and incident severe illness. **J Am Geriatr Soc 52:1105–1113, 2004.**

Key words: inflammation; mobility limitation; older; IL-6; CRP

Inflammation is a necessary response of the immune system to different stimuli such as infection and injury, resulting in elevated production of cytokines and acute-phase proteins, but when inflammation is chronic, it appears to have detrimental effects. Increased levels of inflammatory markers, such as interleukin-6 (IL-6) and C-reactive protein (CRP), have been observed in the presence of acute and chronic conditions, including atherosclerosis,[1] cerebrovascular disease,[2–4] coronary heart disease,[5–7] congestive heart failure (CHF),[8] and arthritis.[9,10] In addition, cytokines may contribute to decreased skeletal muscle mass in old age.[11] Because of the link between cytokines and several disabling conditions, it has been hypothesized that an elevated inflammatory response could be the common root of the pathophysiological mechanism leading to an age-related decline in physical function. Indeed, evidence linking inflammation to function is growing. In a cross-sectional study, serum levels of IL-6 were positively correlated with disability independent of prevalent disease.[9] In a 4-year longitudinal examination of nondisabled older

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people, high levels of IL-6 predicted the onset of disability.[12] Although various inflammatory markers such as IL-6, CRP, and tumor necrosis factor alpha (TNFα) are correlated with each other, the relative importance of these markers as predictors of physical decline has not been established.

The soluble receptors of proinflammatory cytokines may also play an important role in the deleterious effects of the inflammation process. There is some evidence that stimuli causing cytokine levels to rise may also induce shedding of soluble cytokine receptors in an attempt to dampen the inflammatory response. Thus, elevated levels of soluble receptors may represent a more prolonged or severe underlying inflammatory state.[13,14] In addition, because soluble cytokine receptors are generally more stable in the circulation over time than cytokines,[15,16] they might be more reliable markers of chronic inflammation. Soluble cytokine receptors are elevated in the presence of various chronic conditions. For instance, circulating levels of TNFα soluble receptors (TNFsR1 and TNFsR2) are more strongly correlated with severity of CHF than TNFα,[17,18] with a high level of TNFsR1 being associated with a poorer prognosis of CHF.[19] In arthritis, serum levels of soluble interleukin-2 receptor (IL-2sR) are positively correlated with disease activity and functional status.[10] Despite this evidence, the relationship between soluble cytokine receptors and physical function in a general older population has not been explored.

The present study examines the association between several markers of inflammation, including CRP, IL-6, TNFα, and the soluble receptors IL-2sR, IL-6sR, TNFsR1, and TNFsR2 with the onset of mobility limitation in a large sample of well-functioning black and white older men and women. Mobility limitation is one of the main outcomes in the Health, Aging and Body Composition (Health ABC) Study because of the need to identify risk factors at a stage of age-related decline that would be amenable to preventive interventions. More severe impairment (e.g., defined by activity of daily living disability) has more often been examined in previous large studies, but although an important outcome, it represents a stage of decline that may be too far advanced to be amenable to intervention.

METHODS

Study Population

Data from the Health ABC Study, a prospective cohort study of the influence of changes in body composition and health conditions on physiological and functional changes, were used. Well-functioning participants, aged 70 to 79, were recruited from April 1997 to June 1998. Participants were drawn from a sample of Medicare beneficiaries residing in the areas around Pittsburgh, Pennsylvania, and Memphis, Tennessee. To be eligible, participants had to report no difficulty walking one-quarter of a mile, climbing 10 steps, or performing basic activities of daily living. Participants also had to be free of life-threatening illness and plan to remain in the geographic area for at least 3 years. A total of 3,075 men and women, of whom 42% were black, were included in the study. Data on inflammatory markers were missing for 31 participants, and 65 had missing outcome data, leaving 2,979 participants for the present analyses. All participants signed an informed written consent approved by the institutional review boards of the clinical sites.

Measurements

Baseline assessments consisted of a questionnaire administered at a home visit and a subsequent clinic visit. During this visit, blood samples were drawn in the morning after an overnight fast (median time was 9:19 a.m. interquartile range was from 8:49 a.m. to 9:52 a.m.). After processing, serum aliquots were placed in cryovials, and shipped frozen to the Health ABC Core Laboratory at the University of Vermont.

Inflammatory Markers

Levels of IL-6, TNFα, CRP, and soluble receptors of IL-6 (IL-6sR), IL-2 (IL-2sR), and TNFα (TNFsR1 and TNFsR2) were assessed. Serum levels of soluble receptors were only available for a randomly selected subcohort of 499 persons. Cytokines and soluble cytokine receptors levels were measured in duplicate using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN). The detectable limit for IL-6 (using HS600 Quantikine kit) was 0.10 pg/mL, for TNFα (using HSTA50 kit) was 0.18 pg/mL, for IL-6sR (using DR600 kit) was 6.5 pg/mL, for TNFsR1 (using DRT100 kit) was 3 pg/mL, for TNFsR2 (using DRT200 kit) was 1 pg/mL, and for IL-2sR (using DR2A00 kit) was 10 pg/mL. Serum levels of CRP were also measured in duplicate using enzyme-linked immunosorbent assay based on purified protein and polyclonal anti-CRP antibodies (Calbiochem, San Diego, CA). The CRP assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/mL. Assays of blind duplicates collected for 150 participants yielded an average interassay coefficient of variation of 10.3% for IL-6, 8.0% for CRP, and 15.8% for TNFα. Circulating IL-6 and CRP levels obtained from one time point have been shown to be reproducible and representative over extended time periods.[20]

Mobility Limitation

The occurrence of mobility limitation over the first 30 months of study follow-up was determined at the annual study assessment visits (12 and 24 months after baseline) or during telephone follow-up assessments (6, 18, and 30 months after baseline). During all assessments, participants were asked whether they experienced difficulty (no, a little, some, a lot, or inability) in walking one-quarter of a mile or in climbing 10 steps. Incident mobility limitation was considered to be present if a person reported any difficulty or inability to walk one-quarter of a mile or climb 10 steps at two consecutive semiannual follow-up assessments. The requirement that limitations needed to be present at two consecutive assessments selects more chronic and severe functional limitation, and therefore this outcome is a more reliable indicator of a clinically relevant change in functional status. A special Health ABC Study committee that considered additionally available information such as reason for missing a study contact (severe illness, in nursing home) and proxy information for those who died adjudicated the incidence of mobility limitation. In additional analyses, the effect of severity of mobility limitation was

explored by distinguishing (1) the incidence of moderate mobility limitation as defined by at least a little or some difficulty walking one-quarter of a mile or climbing 10 steps at two consecutive assessments and (2) severe mobility limitation as defined by a lot of difficulty or inability to walk one-quarter of a mile or climb 10 steps at two consecutive assessments. Subjects who developed moderate and severe mobility limitation during study follow-up were classified as having the severe outcome.

Covariates

Sociodemographics included age, race, education, and study site. Smoking status (yes/no) was assessed in the baseline interview. Total body fat mass was determined using dual energy x-ray absorptiometry (Hologic 4500 A, Hologic Inc., Waltham, MA). Even though participants reported no functional limitation at baseline, there was still likely to have been a range of physical capacity within the sample. To adjust for this, a performance score was included that summarizes, on a scale from 0 (poor) to 12 (good performance), a person's performance on a 6-meter walk test, a standing balance test, and five repetitions of chair rises.[21] The baseline presence of lung disease, heart disease (including myocardial infarction, angina pectoris, and CHF), stroke, diabetes mellitus, cancer, and osteoarthritis was adjudicated using standardized algorithms considering self-report, medication use, and some clinic assessments. All medications regularly taken in the previous 2 weeks were recorded and coded according to the Iowa Drug Information System code. Using this drug inventory, the daily use of nonsteroidal antiinflammatory drugs (NSAIDs) and systemic corticosteroids was assessed. Incident cardiovascular disease (CVD) events over the 30 months of follow-up were defined using conclusive evidence for myocardial infarction, stroke, CHF, or angina pectoris from hospitalization or death records that were adjudicated according to criteria decided on by the Health ABC death and disease adjudication committee. Finally, plasma levels of total cholesterol, creatinine, and albumin were measured using a Johnson and Johnson Vitros 950 analyzer (New Brunswick, NJ).

Statistical Analyses

Differences in proportions and means of covariates between persons with and without incident mobility limitation were assessed using chi-square and *t* test statistics, respectively. Because serum levels of inflammatory markers were not normally distributed (except for IL-6sR), median values with 25th to 75th percentile ranges were reported, and nonparametric Mann-Whitney *U* tests were used to compare serum levels across outcome groups. Subsequently, Cox proportional hazards regression models were used to evaluate the association between inflammatory markers and time to incident mobility limitation. Persons surviving with no evidence of incident mobility limitation were censored at the last study visit (approximately 30 months after baseline), those dying with no evidence of incident mobility limitation were censored at the time of their death, and those lost to follow-up were censored after their last interview. Relative risks (RRs) and 95% confidence intervals (CIs) were adjusted for the covariates found to be associated with incident mobility limitation status. Continuous levels (after log-transformation to normalize the distribution) and tertiles of inflammatory marker levels were used in the analyses. To facilitate results interpretation, risks were expressed per population standard deviation (SD) of the log value of the inflammatory markers.

Because high levels of two or more inflammatory markers likely represent a more specific indicator of systemic inflammation than a high level of just one inflammatory marker,[22,23] additional analyses were conducted with a composite inflammation index, calculated as the number of inflammatory marker levels within the highest tertile. Finally, to establish whether the effect of inflammatory markers on the incidence of mobility limitation could be due to incident CVD events or to more general serious health events, the analyses were repeated after exclusion of persons with baseline or incident CVD events or persons with a hospitalization during study follow-up.[24]

RESULTS

The mean age ± SD of the study sample was 73.6 ± 2.9; 51.8% were women, and 41.5% were black. Of the initial 2,979 participants, 898 (30.1%) had incident mobility limitation during the 30 months of follow-up. Of the persons with incident mobility limitation, 321 (35.7%) fulfilled the severe mobility limitation definition (a lot of difficulty or inability to walk one-quarter of a mile or climb 10 steps at two consecutive assessments), and 577 (64.3%) had moderate mobility limitation. Population characteristics according to incident mobility limitation status are reported in Table 1. Participants with incident mobility limitation were older and more likely to be female, black, and less educated than those who did not develop mobility limitation. In addition, these persons had more body fat and more diseases at study baseline, poorer Established Population for Epidemiologic Studies of the Elderly (EPESE) performance scores, lower albumin and higher creatinine levels, and higher usage of NSAIDs and corticosteroids than those without incident mobility limitation.

Spearman correlations between cytokines and soluble receptors were calculated. A stronger correlation existed between IL-6 and CRP ($r = 0.47$, $P < .001$) than between IL-6 and TNFα ($r = 0.27$, $P < .001$) or TNFα and CRP ($r = 0.13$, $P < .001$). In the subset of 499 persons who had soluble cytokine receptors measured, TNFsR1 and TNFsR2 showed a strong intercorrelation ($r = 0.84$), and both were also highly correlated with IL-2sR (TNFsR1, $r = 0.64$; and TNFsR2, $r = 0.66$) and TNFα (TNFsR1, $r = 0.58$; and TNFsR2, $r = 0.61$) (all $P < .001$). Overall, IL-6sR showed the lowest correlations with other cytokines and soluble cytokine receptors; the correlation between IL-6sR and IL-6 was only 0.07 ($P = .10$).

Persons who developed incident mobility limitation had significantly higher serum levels of IL-6, TNFα, and CRP at baseline (Table 1). For instance, the median IL-6 level was 1.70 mg/L for those without incident mobility limitation and 2.18 mg/L for those with incident mobility limitation. Within the subgroup of 499 persons for whom soluble cytokine receptors were assessed, the levels of IL-2sR, TNFsR1, and TNFsR2, but not IL-6sR, were

Table 1. Baseline Characteristics According to Incident Mobility Limitation Status

Characteristic	No Incident Mobility Limitation n = 2,081	Incident Mobility Limitation n = 898	*P*-value*
Age, mean ± SD	73.5 ± 2.9	73.9 ± 2.9	<.001
Female, %	48.0	60.7	<.001
Black, %	37.3	51.2	<.001
Memphis site, %	49.8	50.2	.85
Education, %			<.001
<High school	21.5	33.4	
High school	31.9	34.6	
Postsecondary education	46.6	32.0	
Smoker, %			
Past	48.8	47.6	.35
Current	11.6	13.5	
Total body fat, kg, mean ± SD	23.1 ± 7.8	27.1 ± 9.9	<.001
Established Population for Epidemiologic Studies of the Elderly performance score, mean ± SD	10.3 ± 1.4	9.4 ± 1.9	<.001
Lung disease, %	12.7	21.8	<.001
Cardiovascular disease, %	15.5	27.7	<.001
Stroke, %	5.7	10.2	<.001
Diabetes mellitus, %	12.2	21.2	<.001
Cancer, %	19.8	16.4	.03
Osteoarthritis, %	11.3	20.6	<.001
Albumin, mg/dL, mean ± SD	4.0 ± 0.3	3.9 ± 0.3	<.001
Total cholesterol, mean ± SD, mg/dL	202.4 ± 37.6	204.6 ± 40.6	<.001
Creatinine, mean ± SD, mg/dL	1.04 ± 0.3	1.11 ± 0.6	<.001
Use of nonsteroidal antiinflammatory drugs, %	63.2	70.3	<.001
Use of corticosteroids, %	2.8	4.6	.01
C-reactive protein, mg/L, median (IQR)	1.51 (0.94–2.73)	2.31 (1.18–4.00)	<.001
IL-6, pg/mL, median (IQR)	1.70 (1.17–2.56)	2.18 (1.50–3.38)	<.001
TNF-α, pg/mL, median (IQR)	3.10 (2.40–3.94)	3.36 (2.58–4.39)	<.001
IL-2sR, mg/ml, median (IQR)†	1.22 (0.91–1.56)	1.36 (1.05–1.73)	.004
IL-6sR, mg/ml, median (IQR)†	33.4 (28.8–40.5)	33.6 (28.7–39.8)	.97
TNFsR1, mg/ml, median (IQR)†	1.48 (1.29–1.79)	1.65 (1.40–2.09)	<.001
TNFsR2, mg/ml, median (IQR)†	3.36 (2.96–3.91)	3.68 (3.02–4.67)	.001

* Based on chi-square statistics for categorical variables and *t* test or nonparametric Mann-Whitney statistics for continuous variables.
† Soluble cytokine receptor information available only for a random sample of 499 persons.
IL = interleukin; TNF = tumor necrosis factor; IQR = interquartile range.

significantly higher in those who developed incident mobility limitation during follow-up.

Table 2 shows the results of the Cox proportional hazard analyses between inflammatory markers and incident mobility limitation, adjusting for variables that showed a significant univariate association with onset of mobility limitation (age, race, education, total fat mass, EPESE performance score, lung disease, heart disease, stroke, diabetes mellitus, cancer, osteoarthritis, NSAID use, corticosteroid use, albumin, and creatinine). In these adjusted analyses, higher levels of CRP, IL-6, and TNFα were all significantly associated with an increased risk of incident mobility limitation but appeared to be stronger for IL-6 and CRP than for TNFα. This increased risk was consistent for (log-transformed) continuous levels and for tertiles of the markers. Compared with the lowest tertile, the RR of incident mobility limitation for the highest tertile was 1.40 (95% CI = 1.18–1.68) for CRP, 1.65 (95% CI = 1.37–1.98) for IL-6, and 1.18 (095% CI = .99–1.41) for TNFα. When analyses were repeated separately for the incidence of moderate versus severe mobility limitation, markers of inflammation showed the strongest association (highest risk ratios) for the severe outcome of mobility limitation. For incident moderate mobility limitation, there was no association with TNFα.

Whether the associations between CRP, IL-6, and TNFα and incident mobility limitation were different for men and women and for blacks and whites was examined by entering interaction terms in the multivariate Cox proportional hazards analyses. None of the interaction terms for sex or race were statistically significant ($P > .10$), indicating that the association between inflammatory markers and incident mobility limitation was consistent for sex and racial groups.

It has been suggested that a composite index of inflammatory markers may increase the specificity for ongoing inflammation and better predict physical decline than high levels of a single inflammatory markers.[22,23] Some evidence for this suggestion was found when an interaction term for CRP by IL6 by TNFα was added along with the individual markers in a multivariate Cox

Table 2. Risk of Incident Mobility Limitation by Tertile According to Level of Inflammatory Markers

		Incident Mobility Limitation by Severity Level	
	Incident Mobility Limitation	Moderate	Severe
Inflammatory Marker/Tertile	Cumulative Incidence [Adjusted Risk Ratio*] (95% Confidence Interval)		
CRP, mg/L			
Per SD† increase	30.2 [1.19] (1.10–1.28)	19.4 [1.17] (1.06–1.29)	10.8 [1.23] (1. 09–1.39)
Low (<1.17)	22.2 [1]	15.6 [1]	6.7 [1]
Middle (1.17–2.54)	26.9 [1.05] (0.88–1.26)	17.2 [1.00] (0.80–1.24)	9.7 [1.22] (0.89–1.68)
High (>2.54)	41.4 [1.40] (1.18–1.68)	25.3 [1.33] (1.08–1.65)	16.1 [1.74] (1.28–2.38)
IL-6, pg/mL			
Per SD† increase	30.1 [1.20] (1.12–1.29)	19.3 [1.18] (1.08–1.29)	10.8 [1.24] (1.10–1.40)
Low (<1.43)	19.8 [1]	13.5 [1]	6.3 [1]
Middle (1.43–2.42)	30.6 [1.34] (1.11–1.62)	19.7 [1.33] (1.06–1.67)	10.9 [1.48] (1.07–2.05)
High (>2.42)	40.2 [1.65] (1.37–1.98)	24.8 [1.65] (1.31–2.07)	15.4 [1.82] (1.32–2.52)
TNF-α, pg/mL			
Per SD† increase	29.9 [1.09] (1.01–1.18)	19.4 [1.07] (0.98–1.18)	10.5 [1.16] (1.03–1.32)
Low (<2.69)	25.0 [1]	17.2 [1]	7.8 [1]
Middle (2.69–3.72)	28.7 [1.09] (0.91–1.30)	19.6 [1.10] (0.90–1.37)	9.1 [1.11] (0.80–1.53)
High (>3.72)	36.1 [1.18] (0.99–1.41)	21.6 [1.13] (0.91–1.41)	14.5 [1.40] (1.03–1.90)

Note: High is defined as upper tertile score.
* Adjusted for age, sex, race, education, total fat mass, Established Population for Epidemiologic Studies of the Elderly performance score, lung disease, heart disease, stroke, diabetes mellitus, cancer, arthritis, nonsteroidal antiinflammatory drug use, corticosteroid use, albumin, and creatinine.
† 0.98 for (log) C-reactive protein (CRP), 0.67 for (log) interleukin-6 (IL-6), and 0.42 for (log) tumor necrosis factor-α (TNFα).
SD = standard deviation.

proportional hazard analyses, and a statistically significant interaction between the inflammatory markers was found (coefficient = 0.087, $P = .001$). Consequently, the three inflammatory markers were combined into a composite index. The risk of incident mobility limitation was found to be especially high in persons who had multiple high levels (upper tertile) of inflammatory markers (*P*-trend for composite index < .001). Persons with one (n = 882, cumulative incidence of incident mobility disability (cum inc) = 30.6%) or two (n = 563, cum inc = 37.5%) high inflammatory markers showed greater risk of incident mobility limitation of 1.32 (95% CI = 1.10–1.59) and 1.37 (95% CI = 1.12–1.68), respectively, than those with no high levels (n = 1,045, cum inc = 20.7%), but for persons with a high serum level for all three markers (n = 222, cum inc = 51.8%), the risk of incident mobility limitation was 1.84 (95% CI = 1.44–2.53). A similar gradient of risk across the composite inflammation index was present for the incidence of moderate and severe mobility limitation but strongest for the severe form of mobility limitation (Figure 1). For this outcome, the risk was somewhat elevated—but not statistically significant—when one inflammatory marker level was high (RR = 1.38, 95% CI = 0.99–1.92) but was much elevated when two or three inflammatory marker levels were high (RR = 1.90, 95% CI = 1.35–2.67 and RR = 2.23, 95% CI = 1.48–3.36, respectively).

Because inflammatory markers are associated with the prevalence and onset of CVD events,[24] additional analyses were conducted to determine whether the occurrence of CVD events in the persons who developed mobility limitation could explain the findings. As expected, an incident CVD event during the 30 months of follow-up occurred more often in those with incident mobility limitation than in those without incident mobility limitation (13.0% vs 7.1%, $P < .001$), but when the persons who had baseline or incident CVD events (n = 841) were excluded, the risk of mobility limitation across levels of inflammatory markers remained similar to the risk described before and remained statistically significant (Table 3). To explore the effect of general serious health events, all 817 persons with incident hospitalization during the 30-month study follow-up (37.1% of those with incident mobility limitation vs 22.2% without incident mobility limitation, $P < .001$) were then excluded. Again, after excluding those who underwent hospitalizations, the association between inflammatory markers and the incidence of mobility limitation remained statistically significant (Table 3).

In the subset of 499 participants in whom soluble cytokine receptors were measured, higher levels of IL-2sR and TNFsR1 were significantly associated with an increased incidence of mobility limitation (Table 4). These associations were especially strong for the incidence of severe mobility limitation. Within the subset, TNFsR1 and TNFsR2 appeared to be better predictors of incident mobility limitation than TNFα, because the −2 log likelihood test showed more predictive value for the models with TNFsR1 ($\times 2 = 121.5$, $df = 14$) and TNFsR2 ($\times 2 = 116.9$, $df = 14$) than for the model with TNFα ($\times 2 = 111.6$, $df = 14$). Models with calculated ratios for TNFα with its soluble receptors did not improve the prediction of incident mobility limitation ($\times 2 = 111.8$, $df = 14$ for TNFα/TNFsR1 and $\times 2 = 115.2$, $df = 14$ for TNFα/TNFsR2) compared with the models containing just the TNFα receptors.

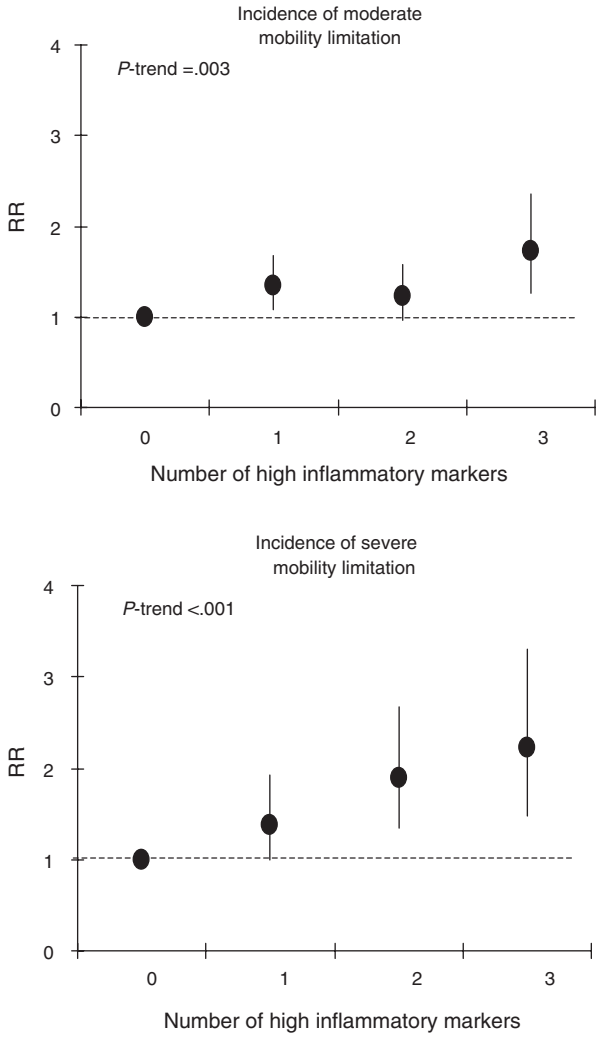

Figure 1. Adjusted (for age, race, education, total fat mass, Established Population for Epidemiologic Studies of the Elderly performance score, lung disease, heart disease, stroke, diabetes mellitus, cancer, arthritis, nonsteroidal anti-inflammatory drugs use, corticosteroid use, albumin, and creatinine) relative risk for incident moderate and severe mobility limitation according to the composite inflammation index counting the number of high levels (within highest tertile) of three inflammatory markers (C-reactive protein, interleukin-6, and tumor necrosis factor alpha). Dots indicate the adjusted relative risk; vertical lines indicate the 95% confidence intervals. RR = relative risk.

DISCUSSION

The study findings indicate that, in well-functioning older persons, high serum levels of the inflammatory markers CRP, IL-6, and TNFα predict an increased incidence of mobility limitation during a 30-month follow-up period. The relationships were stronger for the more severe mobility limitation (as defined by a lot of difficulty or inability to walk one-quarter of a mile or climb 10 steps at two consecutive semiannual assessments) than for moderate mobility limitation (those who reported at least a little difficulty at two consecutive assessments). The associations remained after excluding those persons with baseline or incident CVD or those persons who were hospitalized during follow-up, suggesting that CVD or the occurrence of general serious health events in those with high levels of inflammatory markers are not likely to explain the findings simply. In addition, persons who had high levels of all three markers (CRP, IL-6, and TNFα) showed the highest incidence of mobility limitation.

How could inflammation affect physical function over time? Despite good evidence that circulating levels of inflammatory markers are indicators of atherosclerosis[25,26] and CVD,[27] the analyses excluding persons who had a CVD event suggest that cardiovascular health is not the only pathway linking inflammation and physical decline. It could be that inflammatory markers are indicators of disease activity in conditions such as rheumatoid arthritis, systemic lupus erythematosus, or chronic infections, but because the participants were well-functioning, healthy individuals at baseline, it is again unlikely that these conditions fully explain the observed relationships in the study.

This epidemiological study confirmed an association between inflammatory markers and the onset of mobility limitation in older persons, but it does not permit for the determination of whether this association is causal. For example, it cannot be excluded that inflammation is a surrogate indicator for disease burden and consequently is associated with an increased risk of mobility limitation, but the literature shows some potentially causal mechanisms by which inflammation could lead to disability. Experiments in rodent models show that administration of IL-6 or TNFα increases skeletal muscle protein breakdown, decreases the rate of protein synthesis, reduces the total skeletal muscle amino acid concentration, and causes sarcopenia.[28–31] Consequently, inflammation has been hypothesized to cause loss of muscle mass and strength directly, which leads to mobility limitation.[32] Using cross-sectional data from the Health ABC Study, some investigators confirmed a relationship between IL-6 and TNFα and lower muscle mass and lower muscle strength.[33]

Another possibility is that elevated levels of inflammatory markers reflect an escape of the inflammatory process from normal biological regulation due to aging and therefore indicate biological frailty, which may directly affect (or simply reflect) physical function. Studies have shown that, with increasing age, levels of inflammatory markers rise into the measurable range.[9] Also, systemic inflammation has shown to be associated with lower hemoglobin levels,[34] which could also explain part of the link with physical decline. Anemia has shown to be a strong risk factor for physical decline,[34,35] even in those without disease, which may partly be due to its concurrent symptoms of fatigue or its physiological effects, such as loss of muscle strength through muscle deoxygenation.[36] Finally, high levels of inflammatory markers were recently associated with poorer pulmonary function in older persons.[37]

To the authors' knowledge, this study is the first to explore the association between serum levels of soluble cytokine receptors and incident mobility limitation. Despite the fact that information on soluble cytokine receptors was only available for 499 participants and analyses should be considered exploratory, significant results were observed. Higher serum levels of IL-2sR and TNFsR1 increased the risk of incident persistent mobility limitation, and a

Table 3. Risk of Incident Mobility Limitation without Cardiovascular Disease (CVD) Events or Hospitalizations During Follow-Up According to Levels of Inflammatory Markers

Inflammatory Marker	Excluding Persons with Baseline or Incident CVD Events	Excluding Persons with Any Incident Hospitalizations
	Adjusted* Relative Risk (95% Confidence Interval)	
C-reactive protein (CRP)		
Per SD increase in (log) CRP	1.15 (1.04–1.27)	1.31 (1.18–1.45)
Lowest tertile (<1.17)	1	1
Middle tertile (1.17–2.54)	0.93 (0.74–1.16)	1.09 (0.86–1.39)
Highest tertile (>2.54)	1.21 (0.98–1.51)	1.68 (1.34–2.11)
Interlukin-6 (IL-6)		
Per SD increase in (log)IL-6	1.23 (1.12–1.35)	1.25 (1.14–1.36)
Lowest tertile (<1.43)	1	1
Middle tertile (1.43–2.42)	1.23 (0.97–1.55)	1.46 (1.15–1.85)
Highest tertile (>2.42)	1.64 (1.30–2.08)	1.80 (1.42–2.29)
Tumor necrosis factor-α (TNF-α)		
Per SD increase in (log)TNF-α	1.09 (0.99–1.20)	1.13 (1.03–1.24)
Lowest tertile (<2.69)	1	1
Middle tertile (2.69–3.72)	1.06 (0.84–1.32)	1.23 (0.98–1.54)
Highest tertile (>3.72)	1.20 (0.95–1.51)	1.29 (1.03–1.63)
Composite inflammation index		
No high inflammatory markers	1	1
1 of 3 markers are high†	1.30 (1.03–1.64)	1.43 (1.13–1.81)
2 of 3 markers are high†	1.37 (1.06–1.76)	1.55 (1.19–2.01)
All 3 markers are high†	1.79 (1.29–2.48)	2.07 (1.51–2.85)

* Adjusted for age, sex, race, education, total fat mass, Established Population for Epidemiologic Studies of the Elderly performance score, lung disease, heart disease, stroke, diabetes mellitus, arthritis, nonsteroidal antiinflammatory drugs use, corticosteroid use, albumin, and creatinine.
† High level is defined as within highest tertile group.
IL = interleukin; CRP = C-reactive protein; TNF = tumor necrosis factor.
SD = standard deviation.

suggestive (but nonsignificant) trend was found for TNFsR2. For the soluble TNF receptors, this finding is not surprising, considering the strong intercorrelation between TNF soluble receptor levels and TNFα levels. High levels of soluble cytokine receptors may indicate the body's attempt to control inflammation and therefore reflect a more chronic, systemic state of inflammation. In addition, an advantage of the measurement of soluble TNFα receptors is that they are more stable in the circulation than TNFα and thus more accurately detected with a single blood draw.[15,16] This could indicate that the predictive value for incident mobility limitation may even be stronger for serum levels of soluble TNFα receptors than for TNFα levels, which these results support in part. In the subsample of 499 persons, better predictive values were found for incident mobility limitation for the models with soluble TNFα receptors than for the model with TNFα (see Results), and in line with this, RRs per SD increase were higher for the

Table 4. Adjusted* Risk of Incident Mobility Limitation According to Cytokine Receptor Levels in a Subcohort of 499 Persons

Soluble Cytokine Receptor, mg/mL	Incident Mobility Limitation	Incident Mobility Limitation by Severity Level	
		Moderate	Severe
	Relative Risk (95% Confidence Interval)		
IL-2sR per SD† increase in log(IL-2sR)	1.23 (1.04–1.46)	1.10 (0.87–1.39)	1.50 (1.14–1.96)
IL-6sR per SD† increase in IL-6sR	0.93 (0.78–1.11)	0.94 (0.75–1.18)	0.93 (0.68–1.27)
TNFsR1 per SD† increase in log(TNFsR1)	1.28 (1.04–1.57)	1.26 (0.93–1.70)	1.52 (1.11–2.10)
TNFsR2 per SD† increase in log(TNFsR2)	1.13 (0.95–1.35)	1.16 (0.90–1.51)	1.26 (0.93–1.72)

* Adjusted for age, sex, race, education, total fat mass, Established Population for Epidemiologic Studies of the Elderly performance score, lung disease, heart disease, stroke, diabetes mellitus, cancer, arthritis, nonsteroidal antiinflammatory drugs use, corticosteroid use, albumin, and creatinine.
† 0.42 for interleukin (IL)-2sR, 8.52 for IL-6sR, 0.30 for tumor necrosis factor soluble receptor (TNFsR) 1 and 0.46 for TNFsR2.
(IL)-2sR, soluble interleukin-2 receptor; IL-6sR a soluble interleukin-6 receptor; TNFsR2 tumor necrosis factor soluble receptor; and
SD = standard deviation.

soluble TNFα receptor levels (RR = 1.28 for TNFsR1 and RR = 1.13 for TNFsR2) than for TNFα level (RR = 1.10). This finding is consistent with findings that serum levels of soluble TNFα receptors were more strongly associated with certain disease processes, such as atherosclerosis[25] and CHF,[17] than TNFα levels.

The finding of a strong link between IL-2sR level and incident mobility limitation is also novel. High levels of IL-2sR are directly correlated with increased T and B cell and immune system activation,[38] and the current study showed a high correlation with TNFsR1 and TNFsR2 levels. In contrast, IL-6sR showed low correlations with other soluble cytokine receptors and with serum IL-6 levels and did not show an association with incident mobility limitation.

A composite measure of inflammation, combining information on CRP, IL-6, and TNFα, identified persons with a high incidence of future physical decline. About 19% of the well-functioning sample had high levels (upper tertile) on two, and 8% had high serum levels on three inflammatory markers. These persons had the highest risk for an increased incidence of (severe) mobility limitation. These findings are consistent with previous work showing an increased mortality risk if more than one inflammatory marker was elevated.[22,23] The use of a combined measure for inflammation likely increases the specificity for inflammation status, that is, the probability that persons with low levels of two or three inflammatory markers have no ongoing subclinical inflammation, and will reduce non-differential misclassification.

This study has several strengths. First, there was information on not just one but multiple markers of inflammation. Second, the sample consisted of a randomly selected community-based cohort in which loss to follow-up over time was limited. Third, the study was designed to study the transition to mobility limitation and used frequent contacts to assess changes in limitations, which increases the validity of functional change assessment.[39] Weaknesses of the study are that there was only limited information on the severity of baseline diseases and that inflammatory markers were only assessed once, which makes it impossible to explore the importance of change in inflammation before the onset of mobility limitation. Also, the main outcome was based on self-report, although comparable self-reported limitation outcomes have been shown to be reliable indicators of clinically relevant changes in health such as hospitalization, institutionalization, and death.[40–42]

In summary, this study supports the prognostic value of CRP, IL-6, TNFα, and the soluble receptors IL-2sR and TNFsR1 for incident mobility limitation in a relatively healthy cohort of older men and women. The analyses suggest that such a link is not purely due to CVD events or general serious health events but is likely to represent a general down-spiral pathway involving multiple pathophysiological mechanisms.

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