Change in Muscle Strength Explains Accelerated Decline of Physical Function in Older Women With High Interleukin-6 Serum Levels

Luigi Ferrucci, MD, PhD,† Brenda W. J. H. Penninx, PhD,‡ Stefano Volpato, MD,† Tamara B. Harris, MD, PhD,† Karen Bandeen-Roche, PhD,§ Jennifer Balfour, MPH,† Suzanne G. Leveille, PhD,† Linda P. Fried, MD, PhD,‖ and Jack M. Guralnik MD, PhD†*

OBJECTIVES: To test whether accelerated sarcopenia in older persons with high interleukin (IL)-6 serum levels plays a role in the prospective association between inflammation and disability found in many studies.

DESIGN: Cohort study of older women with moderate to severe disability.

PARTICIPANTS: Six hundred twenty older women from the Women's Health and Aging Study in whom information on baseline IL-6 serum level was available.

MEASUREMENTS: Self-report of functional status, objective measures of walking performance, and knee extensor strength were assessed at baseline and over six semiannual follow-up visits. Potential confounders were baseline age, race, body mass index, smoking, depression, and medical conditions.

RESULTS: At baseline, women with high IL-6 were more often disabled and had lower walking speed. After adjusting for confounders, women in the highest IL-6 tertile (IL-6 >3.10 pg/mL) were at higher risk of developing incident mobility disability (risk ratio (RR) = 1.50, 95% confidence interval (CI) = 1.01–2.27), disability in activities of daily living (RR = 1.41, 95% CI = 1.01–1.98), and severe limitation in walking (RR = 1.61, 95% CI = 1.09–2.38) and experienced steeper declines in walking speed ($P < .001$) than women in the lowest IL-6 tertile (IL-6 ≤1.78 pg/mL). Decline in knee extensor strength was also steeper, but differences across IL-6 tertiles were not significant. After adjusting for change over time in knee extensor strength, the association between high IL-6 and accelerated decline of physical function was no longer statistically significant.

CONCLUSIONS: Older women with high IL-6 serum levels have a higher risk of developing physical disability and experience a steeper decline in walking ability than those with lower levels, which are partially explained by a parallel decline in muscle strength. **J Am Geriatr Soc 50: 1947–1954, 2002.**

Key words: IL-6; cytokines; disability; inflammation; aging; older women

High serum levels of markers of inflammation, such as interleukin (IL)-6 and C-reactive protein, are strong predictors of incident disability, independent of other known risk factors.[1] It has been suggested that chronically elevated levels of IL-6 cause an acceleration of muscle catabolism,[1 2] leading to sarcopenia, subsequent problems in walking, and, in turn, disability.[3–7] However, the only study that addressed the prospective relationship between IL-6 and disability[1] could not test this hypothesis because information on muscle strength was not available. Furthermore, because this previous study included mostly healthy older persons, its findings may not apply to the frail older population.

Using data from the Women's Health and Aging Study (WHAS),[8] the present study verified whether high IL-6 serum level is an independent risk factor for an accelerated decline in physical function and disability in older women. The analysis was adjusted further for change over time in muscle strength under the hypothesis that attenuation in the prospective association between IL-6 and disability, compared with the unadjusted analyses, could be

From the *Laboratory of Clinical Epidemiology, INRCA Geriatric Department, Florence, Italy; †Laboratory of Epidemiology, Demography and Biometry, National Institute of Aging, Bethesda, Maryland; ‡Sticht Center on Aging, Wake Forest University School of Medicine, Winston-Salem, North Carolina; §Department of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland; and ‖Center on Aging and Health, The John Hopkins Medical Institutions, Baltimore, Maryland.

This work was supported by Contract NO1-AG-0–2105 from the National Institute on Aging.

Address correspondence to Luigi Ferrucci, MD, PhD, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, 7201 Wisconsin Avenue, Gateway Building, Suite 3C-309, Bethesda, MD 20892. E-mail: ferrucci@dada.it

0002-8614/02/$15.00

interpreted as indicating that a decline in muscle strength mediated such a relationship. The WHAS is particularly suited for this purpose, because serial information on self-reported disability and objective measures of walking speed and muscle strength were collected in a representative sample of moderately to severely disabled older women every 6 months over a 3-year period.

METHODS

Study Population

The WHAS is an epidemiological study of the causes and course of disability among the one-third most disabled women aged 65 and older living in the community. The design of the WHAS and data collection methods have been described in detail elsewhere.[8] Briefly, of 5,316 community-dwelling women randomly sampled from Medicare beneficiaries in Baltimore, Maryland, 1,409 were eligible for the study because of a Mini-Mental State Examination[9] score of 18 or greater and difficulty performing one or more tasks in at least two of the following four domains of functioning: mobility/exercise tolerance, upper extremity abilities, basic self-care, and higher functioning tasks of independent living. One thousand two women (71% of those eligible) agreed to participate in the study.

Blood samples were obtained in 634 participants, and 620 of them were processed to obtain aliquots of serum or plasma that were stored at –80°C. Participants who did not provide blood samples were older and had more disability in activities of daily living (ADLs) but were not different in body mass index (BMI) or number of chronic diseases.

Measures

IL-6 was measured in duplicate by enzyme-linked immunosorbent assay from the frozen specimens (High-Sensitivity Quantikine Kit, R & D Systems, Minneapolis, MN), and the average of the two measures was used in the analysis.[10]

Disability was assessed at baseline and over six semiannual follow-up visits by asking participants to report level of difficulty in performing ADL and mobility-related tasks. Responses were coded as no difficulty, little difficulty, some difficulty, a lot of difficulty, or unable. Walking speed was assessed by having the participant walk at her usual pace over a 4-meter course. The average of two walks was used to compute a measure of walking speed (m/s). Three conditions were identified that mark critical thresholds in the disability spectrum: mobility disability, defined as self-report of a lot of difficulty or unable to walk one-quarter of a mile or to climb stairs; ADL disability, defined as self-report of a lot of difficulty or inability in at least one of the following mobility-related ADLs: transferring from bed to chair, walking across a small room, bathing, and using the toilet; and severe limitation in walking, defined as unable to walk or walking at a customary speed of 0.4 m/s or less. The threshold of 0.4 m/s identifies the lowest quartile of walking speed in the WHAS cohort, and many clinicians consider it an extreme reduction in walking ability. This definition of severe limitation in walking has been used in other analyses performed on the WHAS database and published in the geriatric literature.

Maximum isometric strength of the knee extensor muscles was assessed at each follow-up using a hand-held dynamometer (Nicholas Manual Muscle Tester; Model #BK-7454, Fred Sammons, Inc., Burr Ridge, IL). Participants, seated in a hard chair, were asked to extend the knee, pushing as hard as they could against the dynamometer, which was positioned on the tibial plate proximal to the ankle. Strength was measured as the peak force that the examiner had to apply to break the isometric contraction. The best performance of two trials was selected for each side, and the average of the left and right values, expressed as kilograms force per kilogram of body weight, was used in the analysis.[11]

BMI was computed as weight (in kilograms) divided by the square of height (in meters) using objective measures. Smoking status was coded as ever versus never smoked. Depressive symptoms were assessed using the Geriatric Depression Scale, which provides a score ranging from 0 to 30, higher scores indicating more depressive symptoms.[12]

Medical conditions were ascertained at baseline using standardized algorithms that incorporated information from the medical history, physical examination, medications, hospital records, and physicians' reports.[13] Disease categories used in this analysis were coronary heart disease ((CHD) angina pectoris or myocardial infarction), congestive heart failure (CHF), peripheral arterial disease (PAD), stroke, chronic obstructive pulmonary disease ((COPD) emphysema, asthma, or chronic bronchitis), diabetes mellitus, hip osteoarthritis (OA), knee OA, and hip fracture.

Complete data on vital status were collected over the 3-year follow-up through contacts with family members and by obtaining death certificates.

Statistical Analyses

Baseline variables were compared across tertiles of IL-6 ($<$1.78 pg/mL, n = 214; 1.79–3.10 pg/mL, n = 204; $>$3.10 pg/mL, n = 202) using age-adjusted linear or logistic regression models. Cox proportional hazards models were fitted to evaluate the effect of baseline serum level of IL-6 on time to onset of new disability. Those surviving with no new disability were censored at the date of the last follow-up; those dying with no new disability were censored at the time of their deaths. Risk ratios (RRs) and 95% confidence intervals (CIs) were used as measures of association. Subjects who were already disabled at baseline were excluded from the analysis. This same analysis was repeated using three definitions of disability that represent different degrees of severity across the disability spectrum. As a consequence, the number of women who were excluded from each of the three analytical models because they were already disabled at baseline varied according to the definition of disability used in that specific model. For example, because 331 women already had mobility disability at baseline, only 289 women could be used in the analyses concerning this specific outcome. All models were adjusted for initial level of functional limitation expressed as level of difficulty walking one-quarter of a mile. In parsimonious models, obtained by removing all variables that were not statistically associated with the

outcome, change in muscle strength was introduced over time as a time-dependent covariate. It was hypothesized that, if the independent, prospective association between high IL-6 and disability were reduced after adjusting the analyses for change over time in muscle strength, this finding would indicate that parallel decline in muscle strength mediated, at least in part, such an association.

The effect of IL-6 serum level on the magnitude of change over time in walking speed was tested using a regression model that takes into account the correlation between serial measures obtained in the same subjects (SAS Proc Mixed, SAS Institute, Inc., Cary, NC). Again, change over time in muscle strength was introduced as time-dependent variables in this parsimonious model to test the hypothesis that parallel decline in muscle strength mediated, at least in part, the association between baseline IL-6 serum level and the magnitude of change in walking speed over the follow-up.

RESULTS

Cross-Sectional Analyses

Women in the highest IL-6 tertiles were more likely to be black, to be smokers, and to have higher BMI. Higher IL-6 serum level tended to be associated with lower knee extensor strength, although the association was not statistically significant. Mobility disability, ADL disability, and severe limitation in walking were progressively more prevalent across tertiles of IL-6. Women in the middle and upper tertiles of IL-6 walked, respectively, 10% and 20% slower than women in the lowest tertile (0.64 and 0.58 m/s, respectively, vs 0.70 m/s). CHD, CHF, PAD, COPD, and diabetes mellitus were more prevalent in women with higher IL-6 serum levels, and a test for trend of increasing prevalence according to IL-6 tertile was statistically significant for all these conditions even when the analysis was age adjusted (see Table 1).

Change Over Time in Knee Extensor Strength

Overall, knee extensor strength declined slightly over time. On average, muscle strength declined 0.14 kg/y in women in the highest IL-6 tertile, whereas it remained substantially stable in women in the lowest IL-6 tertiles (+0.04 kg/y in women in the middle tertile, and +0.01 kg/y in women in upper tertile). As a consequence, differences in strength between women in the two lower and those in the upper IL-6 tertiles became more pronounced as time progressed. This same phenomenon is shown in Figure 1, in

Table 1. Health Characteristics According to Baseline Serum Levels of Interleukin-6 (IL-6)

Characteristic	Tertile of IL-6 at Baseline			*P*-value*
	<1.78	1.79–3.10	>3.10	
	pg/mL			
Measures of mobility/walking				
Mobility disability, n (%)†	94 (43.9)	116 (56.9)	121 (59.9)	<.005
Activities of daily living disability, n (%)‡	47 (22.0)	61 (29.9)	70 (35.7)	<.01
Severe limitation in walking, n (%)§	34 (16.0)	50 (24.6)	59 (29.5)	<.01
Walking speed, m/sec, mean ± SE‖	0.70 ± .02	0.64 ± .02	0.58 ± .02	<.001
Muscle strength/body weight				
Knee extensor, kg force/kg weight, mean ± SE	0.19 ± .01	0.19 ± .01	0.18 ± .01	.32
Potential confounders				
Age, mean ± SE	77.2 ± 0.2	78.1 ± 0.6	78.4 ± 0.5	.13
African American, n (%)	51 (23.8)	56 (27.5)	66 (32.7)	<.03
Body mass index, kg/m^2, mean ± SE	27.6 ± .4	29.1 ± .5	29.8 ± .5	<.001
Ever smoked, n (%)	79 (36.9)	100 (49.0)	114 (56.4)	<.001
Geriatric depression score, mean ± SE	7.2 ± .4	8.6 ± .4	8.2 ± .4	.08
Diseases, n (%)				
Coronary heart disease	50 (23.4)	79 (38.7)	80 (39.6)	<.001
Congestive heart failure	15 (7.0)	21 (10.3)	27 (13.4)	<.05
Peripheral artery disease	35 (16.4)	32 (15.7)	61 (30.2)	<.001
Stroke	10 (4.7)	14 (6.9)	14 (6.9)	.29
Chronic obstructive pulmonary disease	35 (16.4)	42 (20.6)	50 (24.8)	<.05
Diabetes mellitus	22 (10.3)	36 (17.7)	48 (23.8)	<.001
Hip osteoarthritis	25 (11.7)	18 (8.8)	11 (5.5)	<.05
Knee osteoarthritis	69 (32.2)	84 (41.2)	79 (39.1)	.10
Cancer	24 (11.2)	26 (12.8)	20 (9.9)	.70
Hip fracture	12 (5.6)	16 (7.8)	10 (5.0)	.60

*Tests for trend from age adjusted linear or logistic regression models.
†Considerable difficulty or unable to perform at least one of four activities of daily living.
‡Unable to walk or walking speed less than 0.4 m/sec.
§Considerable difficulty or unable to walk one-quarter of a mile or climb stairs.
‖Timed walk at usual pace on a 4-meter course.
SE = Standard error.

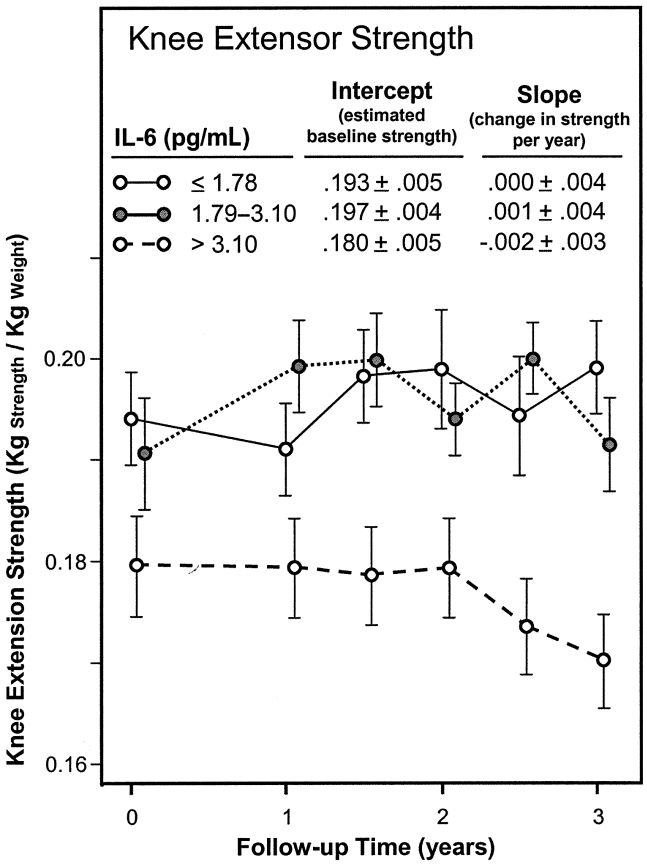

Figure 1. Change over time in knee extensor strength according to interleuken (IL)-6 tertiles. Means and standard errors are given for all participants with valid measures at each follow-up. The results of the random effect model estimating slopes of change over time in strength body weight, according to IL-6 tertiles, are reported on top.

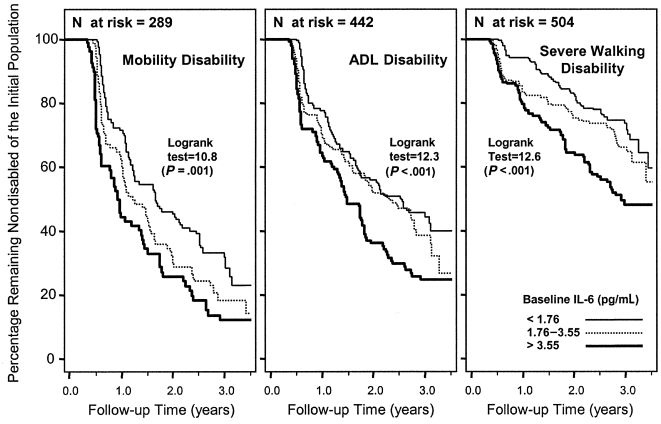

Figure 2. Kaplan-Mayer survival curves illustrating the association between interleuken (IL)-6 tertiles and percentage of the population remaining nondisabled in mobility disability, activity of daily living (ADL) disability, and walking disability. The number of women who were considered initially at risk is reported on top of each curve.

which average muscle strength per unit of body weight is reported for each follow-up according to IL-6 tertiles. In a random effect model testing the hypothesis that the average rate of decline in strength was higher in women with higher IL-6 serum levels, the interaction term between time and IL-6 tertile did not reach statistical significance ($P = .10$).

Effect of IL-6 and Change in Muscle Strength on Functional Decline

The rates of new mobility disability (left panel), ADL disability (middle panel), and severe limitation in walking (right panel) were consistently higher for women in the upper IL-6 tertile (Figure 2). In unadjusted proportional hazards models, women in the highest IL-6 tertiles had a relative risk (RR) of new disability of 1.98 (95% CI = 1.35–2.91) for mobility disability, 1.79 (95% CI = 1.30–2.47) for ADL disability, and 2.19 (95% CI = 1.44–3.33) for severe limitation in walking, compared with those in the lowest tertile. The size of these RRs remained almost unchanged after adjusting for age. When the analysis was adjusted for potential confounders, including residual difference in baseline functional status, expressed as level of difficulty walking one-quarter of a mile, the size of the RRs comparing the upper and the lower tertile of IL-6 serum level were reduced to 1.83 (95% CI = 1.24–2.72) for mobility disability, 1.47 (95% CI = 1.05–2.05) for ADL disability, and 1.71 (95% CI = 1.11–2.64) for severe limitation in walking. Table 2 shows adjusted parsimonious regression models obtained by removing all the independent variables that were not independent predictors of the outcome. In these models, the excess risks of new disability associated with the upper versus the lowest tertile of IL-6 all remained statistically significant (Table 2). Change over time in knee extension strength was introduced as a covariate in these final parsimonious models. For all three different outcomes, the size of the RRs of new disability comparing the lower with the upper tertile of IL-6 were substantially reduced compared with the previous unadjusted model, and their confidence intervals always included 1. For all three disability outcomes, change over time in muscle strength was a significant, independent predictor of new disability. These findings suggest that change in muscle strength is intrinsic to the causal pathway leading from high IL-6 to the development of new disability.

Overall, walking speed declined over the follow-up (Figure 3). A formal test for interaction between time and IL-6 tertile demonstrated that the magnitude of the decline in speed per year was larger in women with high IL-6 serum levels (Table 3). After adjusting for covariates (left column of Table 3), women in the upper IL-6 tertile experienced an average decline per year in walking speed nearly four times greater than the decline for women in the lowest tertile (0.040 vs 0.011 m/s/year), and the difference between the rates of decline was statistically significant. No substantial difference was found in the rate of decline comparing women in the middle and lowest IL-6 tertiles.

When knee extension strength was introduced as a time-dependent covariate in the parsimonious model (right set of columns (Table 3)), the magnitude of per-year decline in walking speed was substantially reduced, and the differences between women in the three tertiles of IL-6

Table 2. Cox Proportional Hazards Models Predicting Risk of Developing Mobility Disability, Activity of Daily Living (ADL) Disability, and Severe Limitation in Walking, According to Interleukin-6 (IL-6) Tertiles

	Mobility Disability* (n at Risk = 289)				ADL Disability† (n at Risk = 442)				Severe Limitation in Walking‡ (n at Risk = 445)			
	Most Parsimonious Model		Time-Dependent Knee Extensor Strength		Most Parsimonious Model		Time-Dependent Knee Extensor Strength		Most Parsimonious Model		Time-Dependent Knee Extensor Strength	
Independent Variables‖	Relative Risk (95% Confidence Interval)											
Serum IL-6 level, pg/mL												
≤1.78	—	Reference	—	Reference	—	Reference	—	Reference	—	Reference	—	Reference
1.79–3.10	1.07	(0.73–1.56)	1.09	(0.70–1.70)	1.05	(0.76–1.45)	0.98	(0.66–1.45)	0.82	(0.85–1.84)	0.97	(0.58–1.59)
>3.10	1.50	(1.01–2.27)	1.17	(0.72–1.90)	1.41	(1.01–1.98)	1.30	(0.86–1.95)	1.61	(1.09–2.38)	1.10	(0.82–1.96)
Potential confounders												
Age	1.05	(1.03–1.08)	1.05	(1.02–1.08)	1.04	(1.03–1.06)	1.05	(1.03–1.08)	1.06	(1.03–1.09)	1.08	(1.05–1.12)
Body mass index, kg/m²	‖		‖		1.03	(1.01–1.05)	1.03	(1.00–1.06)	‖		‖	
Geriatric depression score	1.05	(1.01–1.08)	1.05	(1.01–1.09)	‖		‖		‖		‖	
Level of difficulty walking 1/4 mile	1.31	(1.23–1.84)	1.48	(1.17–1.88)	1.36	(1.23–1.50)	1.38	(1.21–1.56)	1.40	(1.23–1.59)	1.24	(1.06–1.44)
Congestive heart failure	‖		‖		1.65	(1.04–2.63)	1.49	(0.84–2.63)	1.77	(1.00–3.15)	1.23	(0.60–2.54)
Diabetes mellitus	2.01	(1.24–3.28)	2.47	(1.42–4.31)	‖		‖		1.64	(1.01–2.67)	2.19	(1.26–3.79)
Chronic obstructive pulmonary disease	‖		‖		‖		‖		1.52	(0.98–2.35)	1.50	(0.89–2.55)
Knee arthritis	1.43	(1.00–2.04)	1.56	(1.04–2.36)	‖		‖		‖		‖	
Time-dependent covariate												
Knee extension strength¶			0.97	(0.94–0.99)			0.96	(0.93–0.99)			0.79	(0.75–0.82)

Note: Adjusted for potential confounders measured at baseline and then for knee extensor muscle strength as potential explanatory variable.

*Considerable difficulty or unable to walk one-quarter of a mile or climb stairs.

†Considerable difficulty or unable to perform at least one of four activities of daily living.

‡Unable to walk or walking speed less than 0.4 m/sec.

‖Coefficients are not presented if the corresponding variable had been removed from the final model using a backward selection method. Race, smoking, coronary heart disease, peripheral artery disease, stroke, chronic obstructive pulmonary disease, hip osteoarthritis, cancer, and hip fracture are not listed in the table because they were removed from all models.

¶Coefficient for knee extension strength introduced in the model as time-dependent covariate under the hypothesis that the effect of IL-6 on the risk of disability is mediated by the effect of IL-6 on muscle strength. Relative risks reported in the table are for difference of 1 kg strength per year for a woman weighing 68 kg (the average weight in the study population).

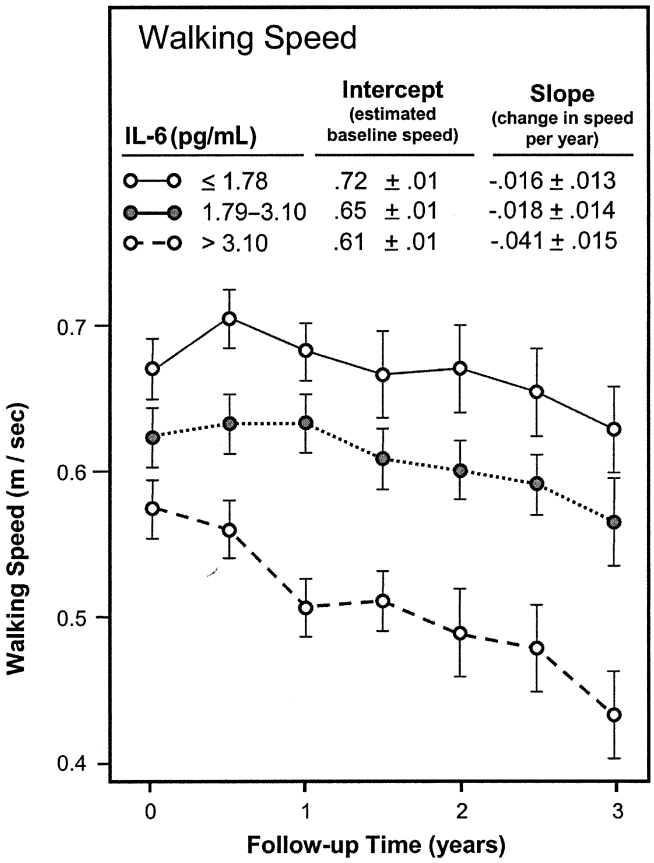

Figure 3. Change over time in walking speed according to interleuken (IL)-6 tertiles. Means and standard errors are given for all participants with valid measures at each follow-up. The results of a random effect model estimating slopes of change over time in walking speed according to IL-6 tertiles are reported on top.

were no longer statistically different. Again, in this model, change over time in knee extensor strength was a strong independent predictor of walking speed.

DISCUSSION

This study provides strong support for earlier reports suggesting that elevated IL-6 is an important risk factor for progression of disability[1] and breaks new ground in demonstrating evidence to support the hypothesis that a detrimental effect of IL-6 on muscles is intrinsic to the mechanism by which older persons with high IL-6 serum levels develop disability.

Inflammation plays an important role in a number of medical conditions that are highly prevalent and frequently cause disability in older persons. Therefore, the causal pathway leading from IL-6 to disability in old age is probably multifactorial. This study focused its analysis on the detrimental effect of IL-6 on muscle because a wide literature suggests this hypothesis. A reduction in the synthesis of muscle proteins, probably explained by a progressive withdrawal of a number of different anabolic stimuli, including neuronal activity, hormones, protein intake, and physical activity, causes sarcopenia, a decline in muscle mass and strength that is a universal phenomenon in aging humans. However, catabolic stimuli, such as the elevated levels of circulating cytokines, especially IL-6, that are often observed in older persons, can considerably accelerate the process leading to sarcopenia.[14] A number of studies support this hypothesis. In experimental animals, ciliary neurotrophic factor, a member of the IL-6 superfamily, produces loss of muscle mass.[15] Preclinical and clinical studies suggest that tumor necrosis factor alpha, IL-1 and IL-6 released from macrophages and endothelial cells, which activate the ubiquitin-protease pathway, promote muscle wasting in cancer and chronic infection.[16] Finally, recent data suggest that IL-6 inhibits production by the liver of insulin-like growth factor-1, which is an important anabolic stimulus for muscle. These data suggest that high levels of cytokines may contribute to an acceleration of sarcopenia and support the findings of our study.

Several epidemiological studies have reported that IL-6 serum level tends to increase with age.[17] Using data from the Framingham study, Rubenoff et al. also found that the production of IL-6 by peripheral blood mononuclear cells was higher in older than in younger nondisabled participants.[18] These findings can probably be ascribed to the overproduction of cytokines in chronic medical conditions that are highly prevalent in older persons, such as angina pectoris, myocardial infarction, CHF, diabetes mellitus, and cancer, but there is also some evidence of a primary dysregulation of the mechanism that modulates the cytokines response. Older patients produce higher levels of cytokines in response to acute infections and also show a more prolonged inflammatory reaction than younger controls, suggesting that the mechanism that modulates the cytokine response becomes defective in old age.[19] Although the mechanism by which some older persons develop high circulating levels of IL-6 is not fully understood, our results may have important implications for geriatric interventions. In this analysis, women across tertiles of IL-6 were compared because no standard threshold for normal serum concentration of IL-6 has been established for clinical use. However, it is interesting to note that only women in the upper and not those in the middle IL-6 tertile had higher risk of disability or accelerated decline in physical function, suggesting that the relationship between IL-6 serum concentration and disability is nonlinear. This finding is in accordance with the results of a previous study in which it was found that the risk of disability becomes higher only beyond a 2.5-pg/mL threshold of serum IL-6. Interestingly, this threshold value is close to the 3.1-pg/mL cutpoint that defines the upper tertile of IL-6 distribution in WHAS. Thus, these studies provide preliminary data that can be used to start developing standards for IL-6 serum levels that can be used for reference in clinical practice.

Some limitations of this study should be discussed. The relationship between IL-6 serum level and change in muscle strength was not clear as expected. This result was interpreted considering that many different factors beyond IL-6 affect the rate of sarcopenia progression with aging. Thus, although the association showed a trend in the right direction, a formal test for interaction between time and IL-6 was not statistically significant ($P = .10$). The WHAS study population includes only women, and therefore these findings should be confirmed in men. Fi-

Table 3. Random Effect Models Testing the Effect of Interleukin-6 (IL-6) on Change Over Time per Year in Walking Speed After Adjusting for Baseline Potential Confounders

	Walking Speed (m/sec)								
	Full Model			Reduced Model			Change in Knee Extensor Strength		
Independent Variables	b	SE	*P*-value	b	SE	*P*-value	b	SE	*P*-value
IL-6 serum level, pg/mL									
<1.78									
Intercept	2.23	0.08		2.28	0.07		2.23	0.08	
Change over time per year	−0.01	0.01		−0.01	0.01		0.003	0.01	
1.79–3.10									
Intercept	2.25	0.07	.37*	2.30	0.07	.26*	2.24	0.08	.40*
Change over time per year	−0.02	0.01	.88**	−0.02	0.01	.88**	−0.001	0.01	.58**
>3.10	2.23	0.07	.97*	2.28	0.07	.83*	2.23	0.08	.90*
Intercept	−0.04	0.01	<.05**	−0.04	0.01	<.05**	−0.011	0.01	.18**
Change over time per year	−0.15	0.01	<.001	−0.15	0.01	<.001	−0.15	0.01	<.001
Age (10-year difference)	−0.15	0.01	<.001	−0.15	0.01	<.001	−0.15	0.01	<.001
African American	−0.02	0.01	<.001	−0.03	0.01	<.001	−0.02	0.01	<.001
Body mass index (kg/m^2)	0.02	0.01	.14						
Ever smoked	−0.01	0.001	<.001	−0.01	0.001	<.001	−0.01	0.001	<.001
Geriatric depression score	−0.07	0.004	<.001	−0.07	0.004	<.001	−0.06	0.004	<.001
Level of difficulty walking 1/4 mile	0.02	0.01	.09						
Coronary artery disease	−0.02	0.02	.18						
Congestive heart failure	−0.01	0.01	.71						
Peripheral artery disease	−0.23	0.02	<.001	−0.22	0.02	<.001	−0.25	0.02	<.001
Stroke	−0.04	0.01	<.005	−0.04	0.01	<.01	−0.03	0.01	<.001
Chronic obstructive pulmonary disease	−0.04	0.02	<.01	−0.04	0.02	<.05	−0.04	0.02	<.05
Diabetes mellitus	−0.03	0.02	.14						
Hip osteoarthritis	−0.02	0.01	<.05						
Knee osteoarthritis	−0.04	0.02	<.05	−0.04	0.02	<.05	−0.04	0.02	<.05
Cancer	−0.07	0.02	<.005	−0.08	0.02	<.001	−0.08	0.02	<.005
Hip fracture							0.006	0.001	<.001
Knee extensor strength***									

Note: Variables that were not independent predictors of the outcome were removed from the final models by backward selection method.
*p for the hypothesis that the baseline walking speed was the same as women in the lowest IL-6 tertile.
**p for the hypothesis the magnitude of change in walking speed per year was the same as women in the lowest IL-6 tertile.
***Coefficient for knee extension strength introduced in the model as time-dependent covariate under the hypothesis that the effect of IL-6 on the magnitude of per-year decline in walking speed was mediated by the effect of IL-6 on muscle strength. The coefficient reported in the table indicates the difference in speed associated with 1 kg. Difference in strength per year for a woman weighting 68 kg. (the average weight for the whole study population).
SE = standard error.

nally, using a traditional epidemiological approach, baseline IL-6 serum levels to predict subsequent disability was used. The findings could be strengthened if the data could demonstrate that, independent of baseline IL-6, women whose IL-6 increased over time did worse than women whose serum IL-6 declined. Unfortunately, serial measures of IL-6 were not available in WHAS, and this approach should be pursued by future studies.

Physical exercise is currently the only intervention that has been shown to effectively improve muscle strength in old and old-old persons. In the future, this intervention may be complemented with pharmacological treatments that interfere with the detrimental effect of cytokines on muscle. This is a promising direction of research, but, because of the many physiological roles played by cytokines, potential toxicity and side effects would have to be carefully evaluated before this approach could be proposed as a therapeutic intervention.

ACKNOWLEDGMENTS

We are thankful to Mrs. Carlotta Pini for typing and carefully editing this manuscript.

REFERENCES

1. Ferrucci L, Harris TB, Guralnik JM et al. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999;47:639–646.
2. Cannon G, St. Pierre A. Involvement of inflammatory cells and cytokines in failure to thrive. Age Nutrition 1996;7:78–81.
3. Harris T. Symposium. Sarcopenia. Diagnosis and mechanisms. Muscle mass and strength: Relation to function in population studies. J Nutr 1997;127: S1004–S1006.
4. Tisdale MJ. New cachexic factors. Curr Opin Clin Nutr Metab Care 1998;1: 253–256.
5. Cannon JG. Cytokines in aging and muscle homeostasis. J Gerontol A Biol Sci Med Sci 1995;50 Spec No:120–123. Review.

6. Cannon JG. Intrinsic and extrinsic factors in muscle aging. Ann N Y Acad Sci 1998;854:72–77.
7. Fielding RA, Meredith CN, O'Reilly KI et al. Enhanced protein breakdown after eccentric exercise in young and older men. J Appl Physiol 1991;71:674–679.
8. Kasper JD, Shapiro S, Guralnik JM et al. Designing a community study of moderately to severely disabled older women. The Women's Health Aging Study. Ann Epidemiol 1999;9:498–507.
9. Folstein MF, Folstein S, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12:189–198.
10. Rao KMK, Pieper CS, Currie MS et al. Variability of plasma IL-6 and crosslinked fibrin dimers over time in community dwelling elderly subjects. Am J Pathol 1994;102:802–805.
11. Bandinelli S, Benvenuti E, Del Lungo I et al. Measuring muscular strength of the lower limbs by hand-held dynamometer: A standard protocol. Aging Clin Exp Res 1999;11:287–293.
12. Brink TL, Yesavage JA, Lum O et al. Screening test for geriatric depression. Clin Gerontol 1982;1:37–44.
13. Guralnik JM, Fried LP, Simonsick EM et al, eds. The Women's Health and Aging Study: Health and Social Characteristics of Older Women with Disability (NIH Publication no. 95–4009). Bethesda, MD: National Institute on Aging, 1995. (Available at http://www.nih.gov/nia/health/pubs/whasbook/tablcont.htm Accessed August 14, 2002).
14. Roubenoff R, Hughes VA. Sarcopenia: Current concepts. J Gerontol A Biol Sci Med Sci 2000;55A:M716–M724.
15. Henderson JT, Mullen BJ, Roder JC. Physiological effects of CNTF-induced wasting. Cytokine 1996;8:784–793.
16. Mitch WE, Goldberg AL. Mechanism of muscle wasting. N Engl J Med 1996;335:1897–1904.
17. Hager K, Machein U, Krieger S et al. Interlukin-6 and selected plasma proteins in healthy persons of different ages. Neurobiol Aging 1994;15:771–772.
18. Roubenoff R, Harris TB, Abad LW et al. Monocyte cytokine production in an elderly population. Effect of age and inflammation. J Gerontol A Biol Sci Med Sci 1998;53A:M20–M26.
19. Bruunsgaard H, Skinhoj P, Qvist J et al. Elderly humans show prolonged in vivo inflammatory activity during pneumococcal infections. J Infect Dis 1999;180:551–554.