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Serum IL-6 Level and the Development of Disability in Older Persons

[Clinical Investigation]

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For editorial comment, see p 755

Abstract

BACKGROUND: The serum concentration of interleukin 6 (IL-6), a cytokine that plays a central role in inflammation, increases with age. Because inflammation is a component of many age-associated chronic diseases, which often cause disability, high circulating levels of IL-6 may contribute to functional decline in old age. We tested the hypothesis that high levels of IL-6 predict future disability in older persons who are not disabled.

METHODS: Participants at the sixth annual follow-up of the Iowa site of the Established Populations for Epidemiologic Studies of the Elderly aged 71 years or older were considered eligible for this study if they had no disability in regard to mobility or in selected activities of daily living (ADL), and they were re-interviewed 4 years later. Incident cases of mobility-disability and of ADL-disability were identified based on responses at the follow-up interview. Measures of IL-6 were obtained from specimens collected at baseline from the 283 participants who developed any disability and from 350 participants selected randomly (46.9%) from those who continued to be non-disabled.

FINDINGS: Participants in the highest IL-6 tertile were 1.76 (95% CI, 1.17-2.64) times more likely to develop at least mobility-disability and 1.62 (95% CI, 1.02-2.60) times more likely to develop mobility plus ADL-disability compared with to the lowest IL-6 tertile. The strength of this association was almost unchanged after adjusting for multiple confounders. The increased risk of mobility-disability over the full spectrum of IL-6 concentration was nonlinear, with the risk rising rapidly beyond plasma levels of 2.5 pg/mL.

INTERPRETATION: Higher circulating levels of IL-6 predict disability onset in older persons. This

may be attributable to a direct effect of IL-6 on muscle atrophy and/or to the pathophysiologic role played by IL-6 in specific diseases.

The relationship between age and decline in physical function reported by many studies has been ascribed to the increased prevalence of major medical conditions,[1] changes in body composition,[2] and modification of physiologic parameters [3] that often parallel the aging process. However, the critical elements of the causal pathway connecting aging to deterioration of health and function have not been fully established.

Risk factors such as Apo-E,[4], cholesterol,[5] hypertension,[6] or obesity,[7] which are strongly associated with chronic diseases in adults, became less powerful predictors of health deterioration in old age and, especially, very old age. On the contrary, newly emerging risk factors such as chronic inflammation,[8] by contributing to the pathophysiology of multiple chronic conditions, may continue to be important markers of risk through very old age.

Inflammation is a biological response of the immune system to a number of different stimuli. Pathogens, chemicals, and physical trauma stimulate monocytes, macrophages, and a variety of different cells to produce intercellular signaling proteins, known as cytokines, that induce the inflammatory response.[9] Interleukin 6 (IL-6) plays a central role in this acute inflammatory response. In addition to its multiple effects at the site of inflammation, IL-6 also induces the synthesis of the hepatic acute-phase proteins, including C-reactive protein, haptoglobin, and fibrinogen, and inhibits the synthesis of others, such as albumin.[9]

The natural induction of cytokines during inflammation is probably beneficial. However, the overproduction of cytokines and the maintenance of the inflammatory state over a long period, which is observed in older persons, is probably detrimental. Thus, the substantial increases in IL-6 with age,[10] even through age 100,[11] may play a role in the exponential rise in disease rates in late life.

Interleukin 6 and C-reactive protein play an important role in the pathogenesis of many diseases that are highly prevalent and are major contributors to disability in the older population. These include diseases as different as coronary artery disease,[12-16] stroke,[13] congestive heart failure,[17] osteoporosis,[18] arthritis,[19,20] depression,[21] and dementia.[22] Some diseases that are characterized by chronic inflammation and high levels of Interleukin 6 cause an acceleration in the catabolism of proteins and consequent muscle wasting, a process of progressive reduction in the number of muscle fibers.[23,24] Muscle wasting shares many characteristics with sarcopenia, a reduction in muscle strength and in muscle mass that is often associated with physical disability in old and very old persons.[2] In sum, inflammation may be part of the common root of the pathophysiologic mechanism leading to a decline in physical function over the aging process. Higher levels of IL-6 are often found in older persons who are disabled in activities of daily living.[25] However, no information is available about whether high levels of IL-6 precede or follow the development of disability and, therefore, the direction of the relationship remains unknown.

In this paper, we tested the hypothesis that in older persons with no disability, high circulating

levels of IL-6 are the expression of a biological state which is predictive of future decline in physical function.

METHODS

Definition of the Eligible Population

The data presented here are from the Iowa site of the Established Populations for Epidemiologic Studies of the Elderly (EPESE), a longitudinal study of subjects aged 65 years and older, funded by the Epidemiology, Demography, and Biometry Program of the US National Institute on Aging.[26] The criteria used to define the eligible population are outlined in Figure 1. Between December 1981 and August 1983, 3673 persons living in two Iowa counties (80% of those eligible) were surveyed. Of the 2547 subjects re-interviewed at the sixth annual follow-up, 1939 (76.1%) gave informed consent to the blood sampling. Participants who refused the blood sampling were older, more often disabled and more likely to have been hospitalized in the last year. Inasmuch as the intended outcome of this study was the development of new disability, the 674 participants who, at the time of blood sampling, reported difficulty in mobility tasks (walking half a mile or climbing a flight of stairs)[27] or needed help in activities of daily living (ADLs) related to lower extremity function (walking across a small room, bathing, transferring from bed to chair, and using the toilet)[28] were excluded from the analysis. Also excluded were 236 persons who died or were lost to follow-up before the follow-up interview performed 4 years after the blood sampling. The eligible population after these exclusions comprised 1029 persons.

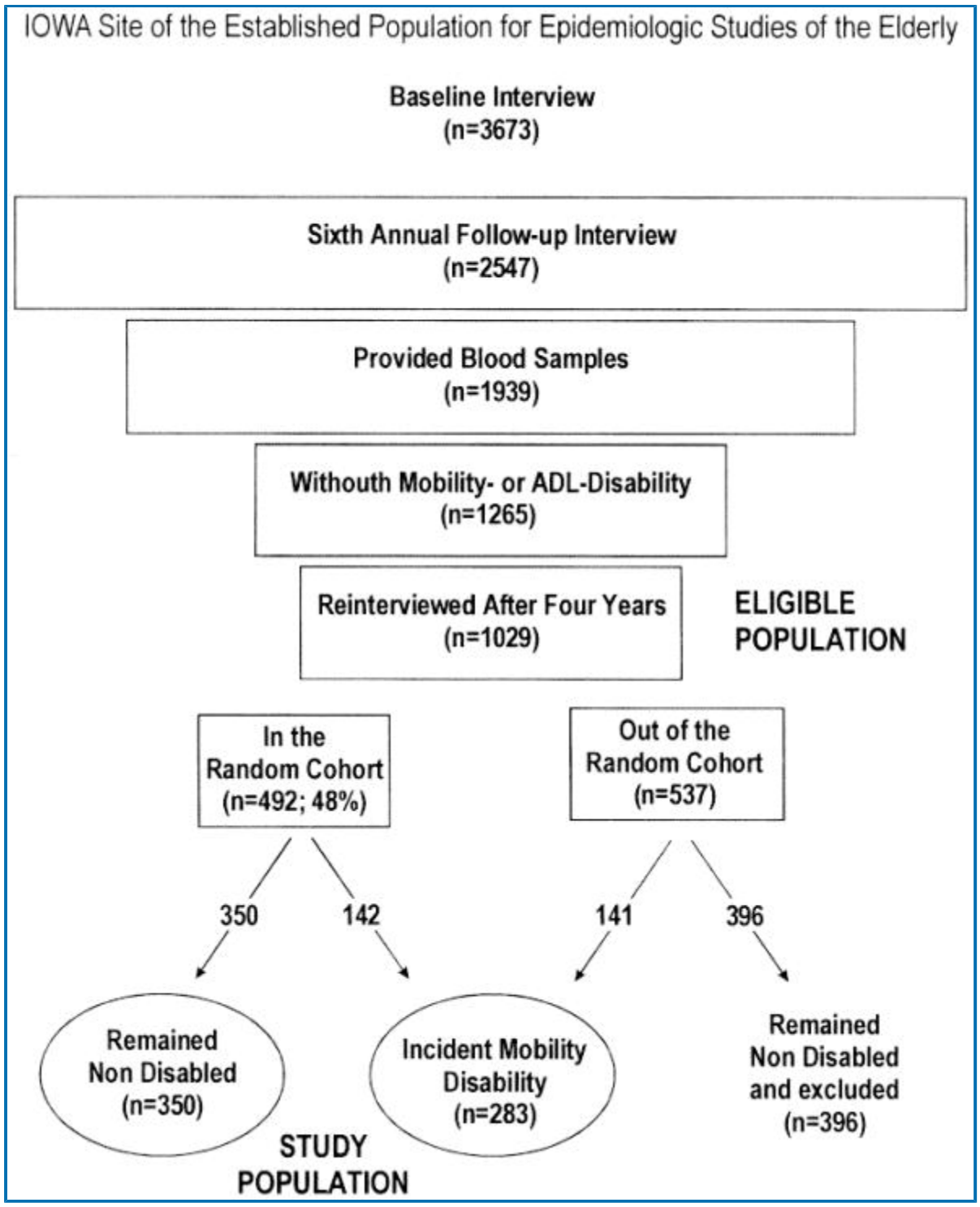

Figure 1. Selection of the eligible population and design of the mobility-disability analysis.

Outcome Measure

The two separate hierarchical definitions of incident disability used were based on responses to the follow-up interview performed 4 years after the blood sample collection. Eligible subjects who reported difficulty in mobility tasks (walking one-half mile or climbing a flight of stairs) were considered incident cases of mobility-disability, regardless of their responses to questions concerning activities of daily living (ADLs). Eligible subjects who reported difficulty in mobility activities and also needed help in performing at least one ADL (walking across a small room, bathing, transferring from bed to chair, and using the toilet) were defined as incident cases of

ADL-disability. The two definitions of disability used in this study represent different levels of severity of disability that are hierarchic. In fact, only a small number of participants (0.7%) reported disability in ADLs but no mobility-disability. These subjects were classified as incident cases of ADL-disability.

We hypothesized that inflammation is a risk factor for disability because of its role in the age-associated sarcopenia. We also hypothesized that sarcopenia would be implicated mainly in mobility-disability. Under these hypotheses, mobility-disability and ADL-disability were considered as two different outcomes and treated in separate analyses.

Measures of IL-6 and Assessment of Potential Confounders

Interleukin 6 was measured in duplicate by ELISA from frozen specimens, using a commercial kit (High Sensitivity Quantikine kit, R&D Systems, Minneapolis), and the average of the two measures was used in the analysis. Measurements obtained by this method are highly reproducible and representative of an individual's IL-6 level over an extended period of time.[29] The detectable limit for IL-6 was 0.10 pg/mL, and the inter-assay coefficient of variation for this study was 7%.

Factors shown in the literature to be related to IL-6 blood levels and potential predictors of major diseases and disability in older persons were considered to be potential confounders. Education was categorized into three groups: less than 9 years, 9 to 12 years, and more than 12 years of schooling. Cognitive function, scored from 0 to 8, was the number of correct answers to eight questions of Pfeiffer's Short Portable Mental Status Questionnaire (SPMSQ).[30] Smoking status was dichotomized as current or past smoker and never smoked, based on self-report. Prevalent cases of chronic lung disease (asthma, emphysema, and chronic bronchitis), arthritis, diabetes, stroke, heart attack, and cancer were identified by a self-report of a physician diagnosis at the time of blood sampling or in any of the previous six interviews.

Blood pressure was measured using the Hypertension Detection and Follow-up Program protocol,[31] and the average of two readings was used in the analysis. Body mass index was computed as weight (in kilograms) divided by the square of height (in meters).

White blood count (WBC) was obtained using a Coulter Counter. Hemoglobin, iron, albumin, creatinine, total cholesterol, and HDL-cholesterol concentrations were measured using standard methods with a sequential autoanalyzer. Participants were classified into three total cholesterol categories: less than 200 mg/dL, 200 to 239 mg/dL, and 240 mg/dL or higher; and three HDL-cholesterol categories: less than 35 mg/dL, 35 to 59 mg/dL, and 60 mg/dL or higher. The choice of the cut points follows the criteria set by the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.[32]

Study design

The study was conducted using a longitudinal case-based design.[33] To study mobility-disability, we obtained IL-6 measures for all of the 283 subjects who developed any disability (mobility-disability with or without ADL-disability) and for 350 subjects selected at random among those who remained non-disabled (47.0% of all the potential controls). The method used to identify these two groups is outlined in Figure 1. We started by selecting a 48% random cohort (n = 492)

from the entire eligible population. We then added all subjects who had developed mobility-disability but had not been previously selected in the random cohort (n = 141).

A similar approach was used when we considered incident ADL-disability as an alternative outcome. We identified the 46 subjects who had developed ADL-disability among the 492 participants originally included in the random cohort. The remaining 446 subjects who did not report ADL-disability at follow-up served as controls. Then, the 57 participants who had reported ADL-disability at follow-up but who had not previously been selected in the random cohort were added to the study population.

The main advantage of the case-based design is that the percentiles in the IL-6 distribution estimated from the random cohort are unbiased approximations of the analogous percentiles in the entire eligible population. Furthermore, since the fraction of the potential controls that is selected at random is known, we could estimate crude cumulative incidence rates of mobility- and ADL-disability according to IL-6 levels.

Data Analysis

Data from participants included in the random cohort were used to calculate deciles and tertiles in the IL-6 level distributions. The same approach was used in the analyses pertaining to mobility- and ADL-disability.

Differences in demographics and health-related characteristics between groups were tested by the Mantel-Haenszel chi-square tests for trend (ordinal or dichotomous variables) and general linear modes (continuous variables). The multivariate association of IL-6 level with the risk of incident disability after adjusting for potential confounders was estimated in logistic regression models. Results concerning mobility-disability are shown as odds-ratios (OR) and 95% confidence intervals (CI), comparing persons in the second and third tertiles of IL-6 with persons in the first tertile of IL-6. In the analysis concerning ADL-disability, the level of IL-6 was dichotomized, comparing persons in the top tertile (IL-6 >2.51 pg/L) with those in the first two tertiles. Finally, a generalized additive model was used to explore departures from linearity in the relationship between IL-6 level and incident mobility-disability [34] and to visualize the best threshold in the IL-6 distribution for discriminating the participants who remained non-disabled from those who developed mobility-disability after the follow-up.

RESULTS

Among those who were re-interviewed after 4 years, the cumulative incidence rate of mobility-disability was 27.5% (283/1029). The IL-6 distribution in the random cohort, which approximates the expected distribution in the full eligible population, was highly skewed (mean ± SD, 2.61 ± 2.68 pg/mL; median, 1.75 pg/mL). After a logarithmic transformation, the distribution became almost normal.

Figure 2 shows estimated incidence rates of mobility-disability according to decile of IL-6. Higher rates of incident mobility-disability were quite evident over the 60th percentile. Compared with controls, subjects who developed mobility-disability were older, had less education and lower SPMSQ scores, reported a history of stroke more frequently, and tended to have lower albumin

(Tables 1 and 2). Participants in the higher tertiles of IL-6 had less education and were more likely to be men, present or past smokers, and to report a history of stroke or heart attack. Furthermore, they tended to have higher BMI and WBC count and lower levels of albumin, iron, total-cholesterol and HDL-cholesterol (Tables 1 and 2). Variables with significantly different distribution between incident of mobility-disability and control and/or across IL-6 tertiles were considered as potential confounders of the association between IL-6 and incident mobility-disability.

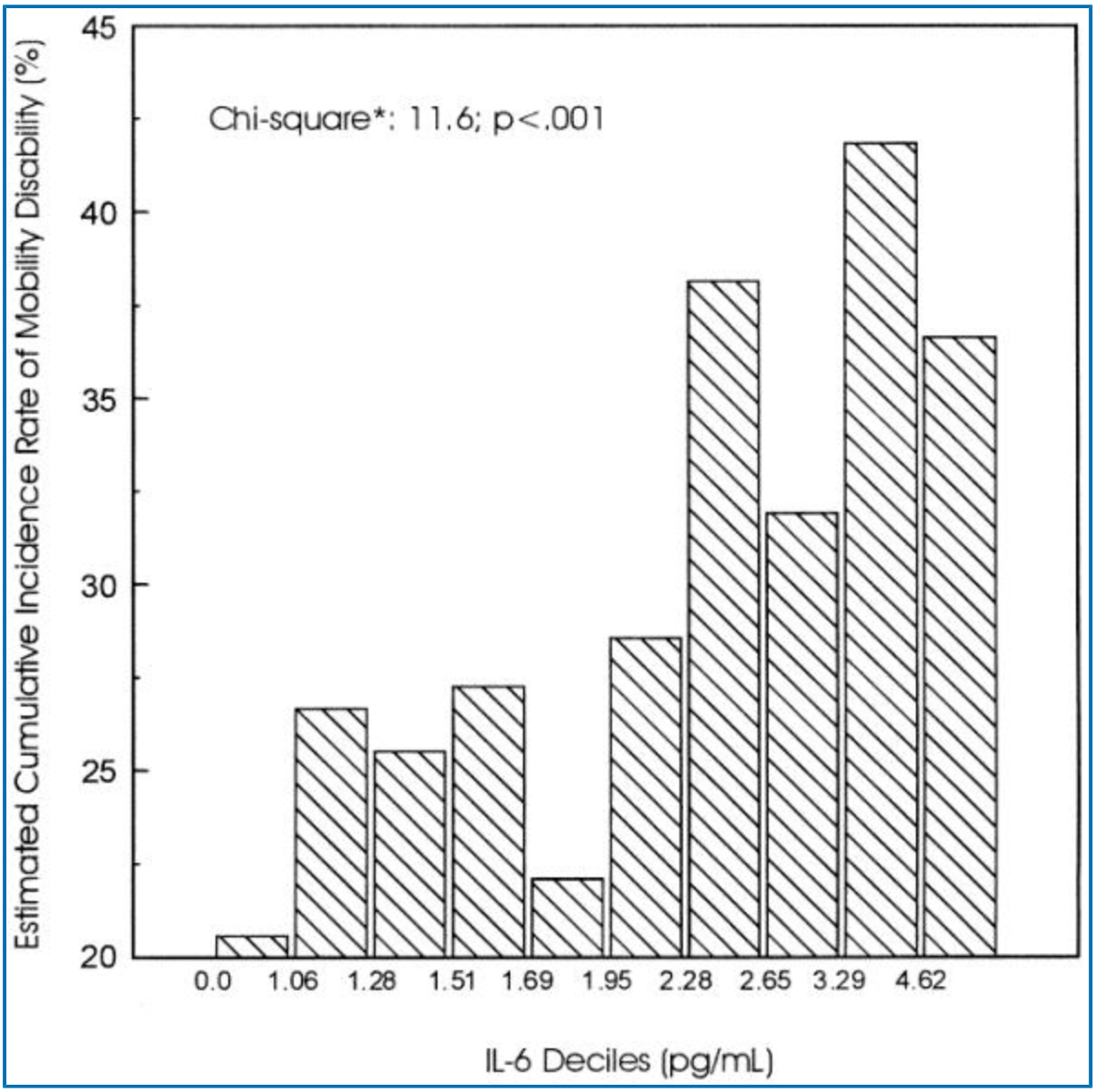

Figure 2. Incidence rates of mobility-disability over the 4-year follow-up according to deciles of IL-6 serum level. True cumulative incidence rates were estimated with the controls in each stratum representing 47% of all the potential controls and the cases all of the cases. The Mantel Haenszel chi-square analysis was performed on raw data.

Characteristics	Cases vs Controls		Distribution According to IL-6 Tertiles		
	Remained Nondisabled	Developed Mobility-Disability	<1.58 pg/mL	1.58–2.51 pg/mL	>2.51 pg/mL
N	283	350	205	201	227
Age (mean ± SE; years)	76.1 ± 0.2	79.4 ± 0.3**	76.8 ± 0.3	77.9 ± 0.4	77.8 ± 0.4
Sex (% females)	62.9	69.6	73.2	70.2	55.5‡
Education					
<9 yrs. (%)	30.8	38.2‡	29.2	33.2	39.2†
9–12 yrs. (%)	43.7	44.3	45.1	44.2	42.7
>12 yrs. (%)	25.6	17.5	25.7	22.6	18.1
Present/past smoker (%)	25.7	27.6	18.5	26.4	33.9‡
Cognitive function (SPMSQ Score) (mean ± SE)	7.1 ± 0.1	6.6 ± 0.1**	6.9 ± 0.1	6.9 ± 0.1	6.9 ± 0.1
Diastolic blood pressure (mean ± SE)	74.2 ± 0.5	74.1 ± 0.6	74.4 ± 0.7	74.2 ± 0.8	74.0 ± 0.7
Systolic blood pressure (mean ± SE)	137.9 ± 0.9	140.4 ± 1.1	138.9 ± 1.2	139.5 ± 1.3	138.8 ± 1.2
BMI (mean ± SE; Kg/m^2)	26.8 ± 0.3	26.7 ± 0.3	25.7 ± 0.3	27.0 ± 0.3	27.4 ± 0.3**
Chronic diseases					
Lung disease (%)	13.1	15.2	10.7	14.9	16.3
Arthritis (%)	46.5	52.3	48.3	47.8	41.1
Diabetes (%)	13.4	11.0	10.2	10.5	15.6
Stroke (%)	5.6	9.6†	6.0	4.6	11.2†
Heart attack (%)	8.0	11.0	4.9	10.0	12.8‡
Cancer (%)	16.0	14.5	12.7	16.9	16.3

Tertile threshold values were established using data from the subjects included in the random sample.
*$P < .05$; **$P < .01$ for difference between means tested by ANOVA.
†$P < .05$; ‡$P < .01$ for linear association tested by Mantel Haenszel chi-square test.

Table 1. Demographic and Other Characteristics of the Participants Who Developed Mobility-Disability and of Those Who Remained Nondisabled During the Follow-up and according to IL-6 Tertiles

Covariates	Cases vs Controls		Distribution According to IL-6 Tertiles		
	Remained Nondisabled	Developed Mobility-Disability	<1.58 pg/mL	1.58–2.51 pg/mL	>2.51 pg/mL
N	283	350	205	201	227
Hemoglobin (mean ± SE; g/dL)	14.4 ± 0.1	14.26 ± 0.1	14.2 ± 0.1	14.5 ± 0.1	14.3 ± 0.1
White blood cells (mean ± SE; 10^3/mm^3)	6.0 ± 0.1	6.1 ± 0.1	5.6 ± 0.1	5.9 ± 0.1	6.6 ± 0.1**
Albumin (g/L)					
<38 (%)	10.3	15.2†	8.8	13.9	14.5‡
38–41 (%)	38.6	39.9	38.5	34.8	43.6
41–43 (%)	27.7	26.9	27.3	28.9	26.0
>43 (%)	23.4	18.0	25.4	22.4	15.9
Iron (mean ± SE; μg/dL)	90.5 ± 1.6	88.4 ± 1.5	94.5 ± 2.2	90.0 ± 1.7	83.8 ± 1.8**
Creatinine (mean ± SE; mg/dL)	1.2 ± 0.1	1.1 ± 0.1	1.12 ± 0.02	1.18 ± 0.03	1.19 ± 0.02*
Total cholesterol (mg/dL)					
<200 (%)	28.6	31.5	21.5	25.9	41.0‡
200–239 (%)	41.1	37.1	40.5	39.8	37.9
≥240 (%)	30.3	31.5	38.0	34.3	21.2
HDL cholesterol (mg/dL)					
>60 (%)	27.4	20.5	30.2	24.9	18.5‡
35–59 (%)	60.3	68.6	60.5	66.2	65.2
<35 (%)	12.3	10.9	9.3	9.0	16.3

Tertile threshold values were established using data from the subjects included in the random sample.
*$P < .05$; **$P < .01$ for difference between means tested by ANOVA.
†$P < .05$; ‡$P < .01$ for linear association tested by Mantel Haenszel chi-square test.

Table 2. Blood Levels of Biological Markers in the Participants Who Developed Mobility-Disability and in Those Who Remained Nondisabled During the Follow-up, and according to IL-6 Tertiles

Adjusting for age and gender and compared with the lowest IL-6 tertile, participants in the highest IL-6 tertile were 1.76 (95% CI, 1.17-2.64) times more likely to have developed mobility-disability, whereas no difference was found comparing the intermediate and the lowest tertile (Table 3, model 1). The strength of this association was substantially unchanged when the potential confounders were included in the model as covariates (Table 3, model 2). Using a backward selection method, we removed the variables that were not independently associated with incident mobility-disability from the fully adjusted model. Age, gender, smoking, and cognitive function (SPMSQ score) remained significant in this final, most parsimonious model, and the

association between IL-6 and incident mobility disability was statistically significant (Table 3, model 3).

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3† OR (95% CI)
IL-6 (pg/L)			
<1.58	**Reference***	**Reference***	**Reference***
1.58–2.51	1.09 (0.72–1.65)	0.97 (0.62–1.52)	1.03 (0.67–1.57)
>2.51	1.76 (1.17–2.64)	1.51 (0.96–2.40)	1.62 (1.07–2.46)
Age (years)	1.14 (1.10–1.18)	1.14 (1.10–1.18)	1.14 (1.10–1.19)
Sex (Women vs Men)	1.27 (0.88–1.82)	2.16 (1.34–3.49)	1.67 (1.10–2.54)
Education (years)			
<9		**Reference***	**Reference***
9–12		1.00 (0.67–1.49)	0.99 (0.67–1.46)
>12		0.58 (0.35–0.94)	0.57 (0.36–0.92)
Present/past smoker		2.14 (1.34–3.42)	1.92 (1.23–3.00)
Cognitive function (SPMSQ)		0.79 (0.67–0.92)	0.78 (0.67–0.91)
BMI (Kg/m^2)		1.00 (0.96–1.04)	
History of stroke		1.62 (0.82–3.02)	
History of heart attack		1.00 (0.54–1.87)	
WBC (10^3/mm^3)		0.96 (0.87–1.06)	
Albumin (g/L)			
<38		**Reference**	
38–41		0.64 (0.36–1.12)	
41–43		0.64 (0.35–1.13)	
>43		0.54 (0.28–1.02)	
Iron (mean ± SE; μg/dL)		1.00 (0.99–1.01)	
Total cholesterol (mg/dL)			
<200		**Reference**	
200–239		0.98 (0.64–1.51)	
≥240		1.16 (0.72–1.87)	
HDL cholesterol (mg/dL)			
>60		**Reference**	
35–59		1.71 (1.09–2.68)	
<35		1.85 (0.92–3.71)	

†Best model after removing nonsignificant covariates by backward selection method.
*P < .001 in test for trend, using log(IL-6) and years of formal education as continuous variables in equivalent models.

Table 3. Logistic Regression Models Testing the Association Between IL-6 Serum Level and Incident Mobility-Disability, Adjusting for Potential Confounders

Further analyses were aimed at estimating the best critical threshold of IL-6, which identifies persons at higher risk of developing mobility-disability. Using a generalized additive model, we fitted a logistic regression model comparing cases and controls and including as predictors a smoothed spline function of log(IL-6) and all the covariates that had remained in the final most parsimonious model (Table 3, model 3). The addition of the smoothed term (a cubic spline) for log(IL-6) improved significantly the fit of the model (P = .043). Figure 3 shows the probability of developing mobility-disability as a function of the baseline log(IL-6) at the average of other covariates and correcting for the different sampling fraction ratio for cases and controls as suggested by Mantel.35 The overall shape of the curve suggests that the risk of incident mobility-disability starts rising for IL-6 levels above 2.5 pg/mL.

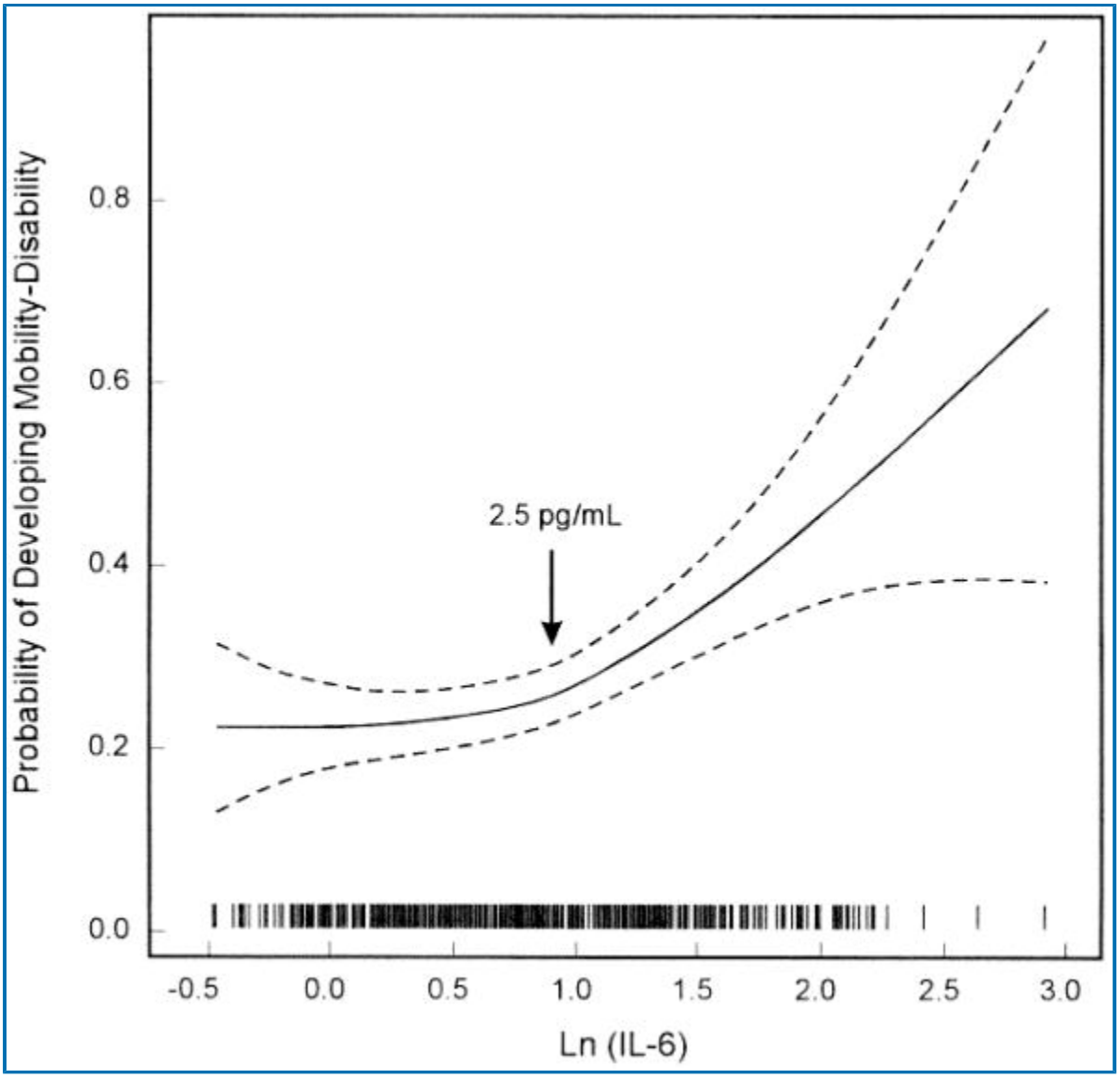

Figure 3. Probability of developing mobility-disability as function of the baseline log (IL-6), adjusting for age, gender, education, smoking status, and cognitive function (SPMSQ score) and taking into account the sampling fraction used to select the controls.[34] The vertical bars along the X-axis mark the observed IL-6 values.

The estimated cumulative incidence rate of ADL-disability was 10.0% (103/1029). Adjusting for age and gender, the odds-ratio for incident ADL-disability associated with IL-6 level above 2.51 pg/mL was 1.62 (95%CI, 1.03-2.56) and remained substantially unchanged (OR, 1.58; 95% CI, .96-2.06) when potential confounders were included as covariates in the model (Models 1-2, Table 4). After removal of nonsignificant effects by backward selection method, only age, gender, cognitive function (SPMSQ score), and IL-6 remained significantly associated with incident ADL-disability. In the final model, the odds-ratio for IL-6 above 2.51 pg/mL was 1.66 (95% CI, 1.04-2.64) (Model 3, Table 4).

	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3† OR (95% CI)
IL-6 (pg/L)			
≤2.51	**Reference**	**Reference**	**Reference**
>2.51	1.62 (1.03–2.56)	1.58 (0.96–2.61)	1.66 (1.04–2.64)
Age (years)	1.17 (1.12–1.22)	1.14 (1.09–1.20)	1.15 (1.10–1.20)
Sex (Women vs Men)	1.74 (1.08–2.80)	1.60 (0.87–2.93)	1.73 (1.07–2.79)
Education (years)			
<9		**Reference***	
9–12		1.00 (0.58–1.71)	
>12		1.19 (0.64–2.23)	
Present/past smoker		1.12 (0.61–2.04)	
Cognitive function (SPMSQ)		0.71 (0.59–0.85)	0.73 (0.62–0.87)
BMI (Kg/m^2)		0.98 (0.92–1.03)	
History of stroke		1.45 (0.65–3.22)	
History of heart attack		0.78 (0.35–1.73)	
WBC (10^3/mm^3)		1.06 (0.94–1.19)	
Albumin (g/L)			
<38		**Reference**	
38–41		0.87 (0.42–1.80)	
41–43		0.83 (0.38–1.80)	
>43		0.84 (0.36–1.96)	
Iron (mean ± SE; μg/dL)		1.00 (0.99–1.01)	
Total cholesterol (mg/dL)			
<200		**Reference**	
200–239		0.75 (0.42–1.32)	
≥240		0.94 (0.51–1.74)	
HDL cholesterol (mg/dL)			
>60		**Reference**	
35–59		1.06 (0.58–1.93)	
<35		0.88 (0.35–2.24)	

†Best model after removing nonsignificant covariates by backward selection method.
*P < .001 in test for trend, using years of formal education as continuous variables in an equivalent model.

Table 4. Logistic Regression Models Testing the Association Between IL-6 Serum Level (> 2.51 vs <=2.51 pg/L) and incident ADL-Disability, Adjusting for Potential Confounders

DISCUSSION

Using data from a large population-based prospective study, we found that older persons who are completely independent in ADLs and mobility and have circulating levels of IL-6 greater than 2.5 pg/mL are at higher risk of functional decline over the subsequent 4 years. Two possibly coexisting interpretations may be proposed to explain our findings: a direct causal role of cytokines in sarcopenia 36 and the role played by inflammation in medical conditions causing disability in older people.8

Sarcopenia,2 an age-associated reduction of muscular strength and mass, has features in common with the muscle wasting caused by the acceleration of protein breakdown that is often observed in cancer and chronic infections.23,24 In both sarcopenia and muscle wasting, the decline in muscle mass is attributable to a reduction in the number of fibers. It is not explained completely by reduced intake of calories or specific nutrients but is associated with a predominance of catabolic over anabolic processes, and, in contrast with starvation or malnutrition, it is associated with little change in adipose tissue. Many lines of research suggest that muscle wasting in cancer and chronic infections is caused by TNF-[alpha], IL-1, and IL-6 released from macrophages and endothelial cells, which activate the ubiquitin-protease pathway.24 Analogously, chronic high levels of IL-6, characteristic of old age, may contribute to sarcopenia.36 However, more research is required before this hypothesis can be confirmed.

Although sarcopenia remains the most likely explanation of the causal pathway between high IL-6 levels and excess risk of disability in old age, several alternative hypotheses should be

mentioned. The most important concerns atherosclerosis. Inflammation influences initiation, progression, and complications of atherosclerosis by, respectively, blocking the antioxidant effect of HDL on the LDL trapped in the endothelium,37 activating the endothelium, thereby causing it to become thrombogenic,38 and inducing the proliferation of muscle cells at the site of plaque rupture.39 Recent studies suggest that IL-6 is also important in a number of other age-related conditions 8 such as postmenopausal osteoporosis,40 congestive heart failure,17 major depression,21 rheumatoid arthritis,41 and dementia.22

In summary, IL-6 and other cytokines mediate changes in body composition that are typical of the aging process and are also implicated in a broad range of pathophysiologically unrelated diseases that are common in old age. These data suggest that IL-6 is a global marker of impending deterioration in health status in older persons. In this context, it is interesting to note that almost all the bio-markers tested in our analysis, including IL-6,25 albumin,42, iron,43 and total and HDL cholesterol,7 have all been related to negative health-related outcomes in older persons. In spite of this, IL-6 was the only one associated independently with subsequent disability in the multivariate analysis.

Supporting the hypothesis that IL-6 is a valid marker of inflammation and in accordance with the current literature, we found that higher levels of IL-6 were associated with smoking, positive history of stroke or heart attack, higher WBC count, and lower levels of albumin, iron, and total and HDL cholesterol (Tables 1 and 2).9,44 The direct association between BMI and IL-6 found in this study has not been reported previously, and it may be the result of the adipocytes of obese participants overproducing TNF, which is a potent inducer of IL-6.45

Two limitations of our analysis should be considered. First, whereas systemic inflammation may be envisioned as a state of interaction among cells, cytokines, acute phase reactive proteins, and hormones, IL-6 was the only measure of inflammation considered in our analysis. However, there is evidence that the three most important proinflammatory cytokines - IL-1, IL-6, and TNF-[alpha] - are strongly correlated and that acute phase reactive proteins are regulated primarily by IL-6.46 Second, although this study demonstrates a clear relationship between inflammation and the risk of disability, even after adjusting for prevalent chronic diseases at baseline, information on incident disease that may be in the causal pathway from inflammation to disability was not considered in the analysis. To translate our findings into clinical intervention, further research is needed to clarify whether the causal pathway from inflammation to disability involves specific diseases, the more global process of sarcopenia, or both.

A fundamental question in aging research is whether the exponential increase in the "force" or morbidity and disability with advancing age is intrinsic to aging or is caused by critical age-associated dysregulations of pathophysiologic mechanisms that are amenable to prevention and cure. The findings of this study support the view that the up-regulation of the inflammatory response may be one such mechanism.

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