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The Association of Plasma IL-6 Levels With Functional Disability in Community-Dwelling Elderly

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Background. IL-6 is a multifunctional cytokine that has been shown to increase with age.

Methods. Plasma IL-6 was measured by ELISA in 1,727 community-dwelling elderly subjects whose blood was drawn during the third in-person survey of the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE). Demographics, functional status (disability), and disease states were determined. Correlations of these factors with IL-6 were analyzed with Spearman's Rho while differences between groups were assessed by Wilcoxon test.

Results. IL-6 levels were higher with age ($p = .0001$) even in this older population (>70 years). There was a positive correlation between IL-6 and functional disability for each of the functional status measures ($p = .0001$), as well as a correlation between self-rated health and IL-6. Significantly higher median levels of IL-6 were found in subjects reporting prevalent cancer, heart attack, and high blood pressure, but not diabetes or arthritis. The association between age and functional status with high IL-6 remained when all other variables were controlled, in multivariable analysis.

Conclusions. This association between increased plasma IL-6 levels and functional status suggests that dysregulation of IL-6 may be related to the functional disability seen with aging, and that IL-6 may be useful as a component of an overall marker of health.

THERE is a growing body of evidence that a network of cytokines plays an important role in the regulation of a variety of physiologic functions (1,2). IL-6 is one such cytokine that has been shown to be multifunctional in nature but whose main role appears to be the induction of the acute inflammatory response and the induction of B-lymphocyte proliferation and differentiation (3,4). It also appears to play a role in the regulation of protease inhibitors and modulation of bone resorption (5).

Under usual circumstances, in the absence of an inflammatory condition, expression of IL-6 appears to be tightly regulated, with very little IL-6 detectable in plasma. IL-6 has been reported to be elevated in a number of age-related diseases such as B-cell lymphoma, multiple myeloma, Alzheimer's disease, and osteoporosis (6). However, a number of studies have now demonstrated that, with increasing age in both animals and humans (7–14), IL-6 increased to measurable levels even in the absence of significant disease. This has led to the suggestion that IL-6 is "a cytokine for gerontologists" (15), which may be related to some of the manifestations of aging in addition to the emergence of some age-related diseases. These previous studies, however, involved small numbers of subjects and have precluded further exploration of possible factors associated with the emergence of detectable IL-6 in elderly individuals, or disorders caused by or resulting from it.

In this study, we had the opportunity to measure IL-6 levels in more than 1,700 subjects in a community-based population of diverse racial and gender composition, as part of the Duke Established Populations for Epidemiologic Studies of the Elderly (EPESE), concomitant with extensive collection of survey information on demographic, social, health, and functional conditions (16–18). This has allowed more detailed analysis of the relationship between the level of IL-6 with age, sex, race, self-reported medical conditions, and functional status in the largest community-based sample of this type. We confirm the finding that IL-6 continues to increase with age even in people over 70, and is associated with some specific disease states. We demonstrate for the first time a specific association with measures of functional status (i.e., personal self-care activities). These observations have implications for our understanding of the role of such cytokines in aging and the diseases of old age.

Methods

Subject Population

Our subjects were from the Duke component of the NIA-funded study of the Established Populations for Epidemiologic Studies of the Elderly. The populations of both the overall four-site study and the Duke study have been described in detail (16–19). Briefly, the Duke study enrolled 4,164 subjects aged 65 years and older at onset in 1986, selected on the basis of random household sampling in a five-county area, including and adjacent to Durham, North Carolina. The sample was selected specifically to allow for comparison by racial groups. The initial in-person survey included extensive information in many spheres in-

cluding: cognitive and functional status, nutrition, depression, life satisfaction, exercise, social interactions and functioning, presence of chronic health conditions, and drug and medical care use. In each following year, either a telephone or in-person follow-up survey was conducted. At the third in-person survey in 1992, or year 6 of the study, blood samples were drawn for a variety of routine hematologic and blood chemistry determinations. In addition, a separate sample was drawn for a substudy of inflammatory and coagulation factors. IL-6 measurements were performed from this sample. This survey collected information on the same spheres as the initial in-person survey, using several scales measuring functional health status, defined as the level at which a person performs the tasks and roles of daily life (20). Information from several scales indicating levels of functional status are reported because they measure different aspects of function, thus in aggregate providing a comprehensive view. The Katz ADL (activities of daily living) measures activities such as bathing, toileting, dressing, eating, and grooming; the Rosow-Breslau Scale measures doing heavy housework, walking up a flight of stairs, and walking one-half mile; and the Nagi Scale measures ability to extend arms above shoulder level, manipulate small objects, stoop, crouch or kneel, and push a large object (20). The Instrumental Activities of Daily Living Scale (IADL) assesses ability to do more integrative functions such as using the telephone, traveling, shopping, and doing housework (21). In addition, self-reports of disease status, and questions pertaining to life satisfaction and self-rated health were recorded as previously described in detail (19).

At the time of the blood draw, 2,569 interviews were conducted with the living members of the cohort (or their proxies), all of whom were at least 70 years of age. Among those interviewed, 67% had a successful blood draw (1,727) and are the subjects of this report. Those not having blood drawn were either unable to give consent, generally because of cognitive dysfunction (269), or refused to have blood drawn, were unavailable, or technically could not be drawn (573). There were significant differences ($p < .05$) among the three groups: blood drawn, unable to consent, and refusers respectively as follows (means): age (71.6, 77.0, 72.5), % female (65.0, 72.1, 78.0), % Black (52.3, 61.7, 57.8), Katz ADL (0.3, 3.1, 0.5), Rosow-Breslau (1.0, 2.6, 1.3), Nagi (1.8, 1.3, 2.0), life satisfaction (10.6, n/a, 17.8), self-rated health (2.4, n/a, 2.9), and % cognitively impaired (SPMSQ) (12.4, 78.8, 15.0). There were no differences in % urban (53.7, 52.4, 57.4), years of education (9.0, 7.0, 8.8), or % depressed (8.8, n/a, 10.2). Thus, those unable to give consent were significantly more functionally and cognitively impaired, whereas those not having blood drawn for other reasons were somewhat older, slightly more cognitively impaired, and more functionally impaired than the sample studied. This could have imposed some degree of a ceiling on the relationships reported here.

Laboratory Methods for Measurement of IL-6

Blood was collected in EDTA-containing vacutainer tubes, placed on ice and taken to the laboratory, where it was centrifuged immediately to separate the plasma, which was promptly frozen at –70 °C in 0.5 ml aliquots. Plasma IL-6 was measured by ELISA; the minimal detectable level was .35 pg/ml (Quantikine, R&D systems, Minneapolis, MN) (22). The laboratory performing the IL-6 assays was blinded to functional and health status of the subjects. We have previously used this assay to conduct a pilot study of the variability of plasma IL-6 over time in elderly subjects, and it showed a high degree of reliability and reproducibility (23). For example, that analysis demonstrated that the intraclass correlation coefficient (ICC) for one measurement of IL-6 in 8 blood samples from an individual over a period of 36 days was .87, indicating that a single sample from a subject is quite representative of that individual's IL-6 level over an extended period of time.

Statistical Analysis

The relationship of IL-6 with demographic variables, health behaviors, functioning, hypertension, depression, smoking, and self-report disease was assessed. In an initial analysis, those with a valid blood draw were compared with those unable to give consent and those who refused blood drawn or were unavailable across the demographic and functional variables as defined above. Differences between the three groups were tested by analysis of variance (ANOVA). All analyses were performed using the Statistical Analysis System (SAS).

In the next set of analyses, the relationship of IL-6 with the independent variables of interest was assessed. In this data set, IL-6 demonstrated a heavily right skewed distribution (mean = 2.98 pg/ml, *SD* = 7.2, 88.9% less than 5 pg/ml). To assess the significance, we therefore used methods not sensitive to outliers and skew: Spearman's Rho for continuous variables and Friedman's or Wilcoxon's test for discrete variables, and parametric techniques for the log of IL-6 (a linear transformation which brought about near normality of the IL-6 distribution). Discrete levels for each of the continuous indicators were defined. For each level of each of these independent variables, three statistics were calculated: percent above 5 pg/ml (approximately highest 10% and the approximate breakpoint in the cumulative distribution curves — see Figure 1), median, and mean log (IL-6). For the median val-

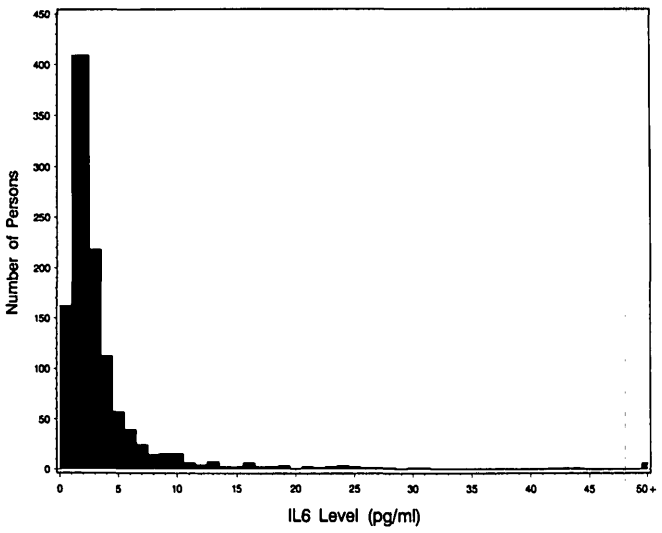

Figure 1. Distribution of IL-6 values.

ues presented, tests of significance were performed by the Wilcoxon or Friedman's test. Goodness-of-fit chi-square was used to assess the relationship of high IL-6 and group membership, and differences between log values between groups were assessed by ANOVA.

Based on these results, we derived multivariable estimates of the effect of health, function, and demographic variables on IL-6. Two models were tested. First, to assess which factors were related to extreme levels of IL-6 (IL-6 > 5 pg/ml), a forward stepwise logistic regression was performed relating extreme IL-6 to the predictors of interest. Second, since IL-6 showed such extreme skew, we analyzed the normalized IL-6 (log transformed) and related the log of IL-6 to the predictors of interest by a forward stepwise regression. In all models, the demographic variables age, sex, and race were forced into the final regression equation.

Results

Figure 1 demonstrates the distribution of Plasma IL-6 levels in the entire population studied. As can be seen, IL-6 was detectable in most subjects. The mean and median values for the entire population were 2.98 pg/ml and 1.7 pg/ml, respectively. The values are not uniformly distributed, with 88.9% under 5 pg/ml and 96.2% under 10 pg/ml. Values above 10 pg/ml ranged as high as 201 pg/ml in a few instances. Because the small number of subjects with extremely high values (or outliers) can disproportionately influence mean values, especially when relatively small numbers of subjects fall in a particular comparison group, median values are utilized for statistical comparisons between groups; and in order to normalize the distribution, a log transformation of IL-6 was performed.

There is no significant difference in IL-6 values among the various sex and racial groups. This is indicated in Table 1 where, regardless of whether assessing mean and median values or percentage levels > 5 pg/ml, non-Blacks and Blacks did not differ, nor did males differ from females. As this table shows, age was strongly correlated with IL-6 levels, both when assessing the median for the three age groups and the percentage of values > 5 pg/ml. In additional analyses, the Spearman correlation between age and IL-6 is .13 ($p = < .0001$). The age relationship holds for both males and females in this elderly subject sample ($p = < .0001$). Moreover, age correlates with increasing IL-6 levels for both racial groups of both sexes ($p = < .0001$) (Figure 2). The final demographic variable assessed, urban/rural status, was not associated with increasing IL-6 levels.

Table 1. Mean Log(IL-6), Median IL-6, and Percentage Above 5 (pg/ml) IL-6 With Demographic Variables

Value	*N* of Cases	Mean Log(IL-6) Level	Median IL-6 Level	% with IL-6 Level > 5
Race				
Non-Black	814	1.07	1.68	10.32
Black	913	1.09	1.72	11.94
		$p = .44$	$p = .49$	$p = .29$
Sex				
Male	605	1.09	1.73	12.40
Female	1122	1.08	1.68	10.52
		$p = .55$	$p = .53$	$p = .24$
Age				
70–79	1157	1.03	1.56	9.68
80–89	516	1.18	1.86	13.57
90–99+	54	1.23	2.20	20.37
		$p < .0001$	$p < .0001$	$p = .006$
Rural/Urban Status				
Rural	800	1.07	1.67	10.50
Urban	927	1.09	1.72	11.76
		$p = .50$	$p = .56$	$p = .48$

Table 2 shows the bivariate analysis of relationships between IL-6 and the measures of health status. The strongest bivariate correlations were with the measures of functional status. Regardless of whether functional status was assessed by the Katz ADL, Rosow-Breslau Scale, or Nagi Scale, or by measure of instrumental ADLs, poor functional status was associated with progressively increasing IL-6 levels ($p = < .0001$). Assessing general measures of health status, IL-6 levels were correlated with self-rated health, rising progressively from the best rated health states through the poorest assessed health. There was also an association, but a much weaker one, with life satisfaction.

Among the health conditions that were assessed in the EPESE (Table 3), a history of cancer overall was not associated with high IL-6 values, though the number with levels > 5 pg/ml was higher. This relationship may be clouded by the fact that this represents a history of cancer at any time and thus the activity of the cancer is uncertain. No individual cancer type was associated with elevated levels of IL-6, although in several, the number of cases is quite small ($p >$ 0.4 in all cases). On the other hand, a history of current cigarette smoking was associated with elevated IL-6 levels as was a history of heart attack. A history of high blood pressure was associated while stroke and diabetes were not. Interestingly, a history of arthritis was not associated with elevated IL-6 levels nor was a history of broken bone. A history of a broken hip was weakly associated. In order to address the issue of active vs inactive disease, the relationship of IL-6 levels with the report of disease occurring

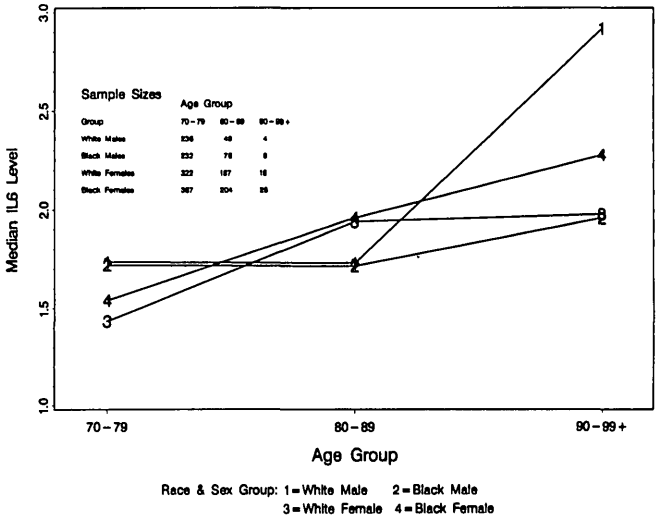

Figure 2. Distribution of median IL-6 levels by age group, race, and sex.

Table 2. Mean, Median, and Percentage Above 5 (pg/ml) IL-6 With Functional Status Variables

Variable Value*	N of Cases	Mean Log(IL-6) Level	Median IL-6 Level	% With IL-6 Level > 5	Spearman Correlation†
Katz ADL					
0	1490	1.05	1.62	9.80	
1	92	1.19	1.90	14.13	
2	44	1.21	2.01	18.18	
3	36	1.32	1.98	19.44	
4	44	1.40	2.66	29.55	
5	17	1.72	3.99	35.29	0.102
		$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
Rosow-Breslau					
0	819	1.00	1.46	8.67	
1	333	1.07	1.71	9.62	
2	216	1.13	1.74	12.50	
3	305	1.28	2.17	19.67	0.134
		$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
Nagi					
0	766	1.01	1.52	8.88	
1	310	1.05	1.68	7.10	
2	187	1.12	1.86	12.30	
3	249	1.18	1.90	16.87	
4	107	1.18	2.15	10.28	
5	49	1.45	2.69	30.61	0.082
		$p < .0001$	$p < .0001$	$p < .0001$	$p = .0006$
IADL total					
0	1049	1.02	1.52	9.15	
1	271	1.11	1.87	10.33	
2	111	1.09	1.63	10.81	
3	72	1.12	2.00	8.33	
4	62	1.36	2.62	20.97	
5	47	1.43	2.78	31.91	
6	48	1.28	2.24	22.92	
7	50	1.30	2.72	20.00	0.130
		$p < .0001$	$p < .0001$	$p < .0001$	$p < .0001$
Life satisfaction					
1	979	1.04	1.62	9.19	
2	651	1.13	1.81	13.67	
3	50	1.21	2.00	10.00	
4	47	1.19	1.72	19.15	0.066
		$p = .015$	$p = .038$	$p = .012$	$p = .006$
Self-rated health					
1	270	1.00	1.42	8.15	
2	742	1.05	1.68	9.57	
3	515	1.09	1.73	10.68	
4	200	1.29	2.16	22.50	0.1000
		$p < .0001$	$p = .001$	$p = .001$	$p < .0001$

*For all measures, high values indicate poorer function or status.
†Adjusted for age group.

since the last survey was assessed (Table 4). Although the case numbers are smaller, there is again no relationship for cancer, stroke, and broken bones and only weak relationships for hip fracture and heart attack.

Table 5 shows the multivariate analysis for both IL-6 > 5 pg/ml and for IL-6 levels. When controlling for all other variables, age remains independently associated with increased IL-6 values in both analyses. Current cigarette smoking is consistently an independent predictor of elevated IL-6 as is functional status by both Nagi and Katz assessment. Cancer and high blood pressure show independent relationships, but these associations are weaker than those for age or functional status. In models for IL-6 values > 5 pg/ml, female sex was negatively associated with IL-6 despite not having been associated in the bivariate analyses. This occurred because age acted as a confounder. Thus women tended to have lower IL-6 levels but also tended to be older (associated with higher IL-6 levels). Only when age was controlled is the sex effect noted. The other demographic variables, race and rural status, are shown but were

Table 3. Mean, Median, and Percentage Above 5 (pg/ml) IL-6 With "Ever" Disease Variables

Variable	Value	*N* of Cases	Mean Log(IL-6) Level	Median IL-6 Level	% With IL-6 Level > 5
All cancer	No	1415	1.07	1.69	10.11
	Yes	312	1.13	1.73	16.03
			$p = .16$	$p = .50$	$p = .003$
Heart attack	No	1352	1.05	1.63	10.13
	Yes	375	1.18	1.90	14.93
			$p = .0006$	$p = .001$	$p = .009$
High blood pressure	No	520	1.02	1.59	7.88
	Yes	1207	1.11	1.74	12.59
			$p = .005$	$p = .034$	$p = .004$
Stroke	No	1523	1.07	1.68	10.11
	Yes	204	1.14	1.87	16.03
			$p = .12$	$p = .13$	$p = .88$
Diabetes	No	1320	1.07	1.68	10.23
	Yes	407	1.11	1.78	14.25
			$p = .29$	$p = .28$	$p = .024$
Broken hip	No	1647	1.08	1.68	11.11
	Yes	80	1.20	2.05	12.50
			$p = .08$	$p = .055$	$p = .70$
Broken bone	No	1214	1.08	1.69	11.28
	Yes	513	1.08	1.71	10.92
			$p = .99$	$p = .93$	$p = .82$
Arthritis	No	469	1.06	1.71	10.66
	Yes	1258	1.09	1.69	11.37
			$p = .39$	$p = .63$	$p = .68$
Current smoker	No	1517	1.06	1.66	10.43
	Yes	205	1.21	2.03	17.07
			$p = .0006$	$p = .0044$	$p = .034$

Table 4. Mean, Median, and Percentage Above 5 (pg/ml) IL-6 With "In the Last Year" Disease Variables

Variable	Value	*N* of Cases	Mean Log(IL-6) Level	Median IL-6 Level	% With IL-6 Level > 5
Cancer	No	1670	1.09	1.71	11.08
	Yes	57	1.00	1.62	14.04
			$p = .31$	$p = .22$	$p = .49$
Broken hip	No	1708	1.08	1.69	11.18
	Yes	19	1.30	2.57	10.53
			$p = .14$	$p = .02$	$p = .93$
Broken bone(s)	No	1668	1.08	1.70	11.39
	Yes	59	1.01	1.90	5.08
			$p = .39$	$p = .78$	$p = .13$
Heart attack	No	1670	1.08	1.69	10.84
	Yes	57	1.23	1.90	21.05
			$p = .08$	$p = .081$	$p = .016$
Stroke	No	1677	1.08	1.69	11.03
	Yes	50	1.24	1.94	16.00
			$p = .08$	$p = .16$	$p = .27$

not associated with IL-6, and other conditions assessed did not retain independent associations ($p > .05$).

Discussion

Utilizing a large number of subjects randomly selected from a community-based population, our study demonstrates that even in the over 70-year-old age group, age is associated with IL-6 production independent of selected disease states and disorders of aging. The consistency of this elevation for both sexes and across racial lines, and the consistency of the level of elevation with previous studies, suggest that a primary aberration in IL-6 production may play a prominent role in the increased values. This is consistent with recent work in mice where the administration of dehydroepiandrosterone (DHEA) or dietary restriction, resulting in enhanced longevity, also reversed the increase of IL-6 seen during aging (8,9).

Previous studies using small numbers of subjects have shown increased levels of IL-6 in elderly, compared with younger subjects, in whom IL-6 is generally not detectable (12–15). This increase in IL-6 with age has been shown both for plasma levels as well as mononuclear cell production, and in humans as well as mice and primates (8,9,15). This has led to suggestions that a dysregulation of IL-6 expression occurs with age, predisposing individuals to a number of age-associated diseases with which IL-6 activation may play a role. These include cancer, in particular B-cell neoplasms, and disorders of bone resorption (5,6). These studies, however, have involved too few subjects in the elderly age range to allow for robust analysis of such possible relationships and, in particular, to assess the independent relationship of age vs other disease states and disorders of aging in order to provide the clues to the nature of the IL-6 relationship. Our study, comprising a large number of older subjects, provides support for the concept that even in older age groups (> 70), IL-6 levels are associated with increasing age, even apart from a number of age-associated diseases and disorders.

We report for the first time a relationship of measures of function (as well as self-rated health) with elevated IL-6 levels. That these measures of function are related to IL-6 independently, and to a much greater degree than any of the individual diseases, suggests a primary dysregulation. This is, of course, limited by the fact that specific disease information is based on self-report only. Our findings suggest also that IL-6 and potentially related cytokine networks may play an important role in how older persons feel and function. It has been pointed out previously that some of the phenomena that IL-6 and related cytokines, such as IL-1, produce may include fatigue, mediated through effects on the pituitary/adrenal axis (24,25). This has led to the hypothesis that a variety of stressors (or in this case, aging per se) could trigger IL-1 or IL-6 production which could then produce fatigue — or even chronic fatigue syndrome (26). It would be reasonable to speculate that in older persons with increased IL-6 levels, feelings of fatigue or decreased energy could result in lower self-ratings of health and a lower sense of life satisfaction. This might perhaps also decrease their ability to perform functionally. The latter might be mediated by decreased motivation or by actual changes in hormonal and other biological factors that could directly reduce energy levels. In a subsequent study, we plan to assess the relationship of IL-6 and other inflammatory markers in this population with psychologic factors and other biochemical markers.

We had hypothesized that increased IL-6 would be associated with diseases common in old age as a marker of ongoing subclinical inflammation. Previous studies in several cancers had indicated increased IL-6 production by monocytes in head and neck cancer (27) and elevated serum IL-6 levels in Hodgkins disease and other malignancies (28). We were surprised, therefore, to see the relative lack of overall association with disorders such as cancer and arthritis which might logically have fallen into that category. Cancer, however, was associated with some of the very elevated values in the sample, suggesting that with active disease, the level may be increased and that the numbers of specific cancers, e.g. lymphomas, myeloma, head and neck, with which etiologic associations have been postulated, may simply have been too small to detect independent associations. The lack of a relationship with self-report of arthritis is also unexplained. Previous studies in arthritis have shown an increase (29) or normal levels (30) of serum IL-6. Our results are consistent with the latter report. However, our data are limited in that we did not have measures of the specific type or severity of disease. Thus, it is likely that most of the arthritis reported in our sample is osteoarthritis which, because of the age range of the subjects, may represent largely "burned out" disease which is not producing a major stimulus to the inflammatory response. Moreover, our data on specific diseases are limited in that they are obtained by self-report and may not as accurately represent disease status as a clinical exam.

There were positive associations with smoking and smoking-related disorders such as heart attack and hypertension, and to a lesser extent, stroke. It is possible that such relationships are mediated through the now generally

Table 5. Final Multivariable Estimates

A. Stepwise Logistic Regression Odds Ratios (IL-6 > 5 pg/ml)			
Variable	Odds	95% CI	*p*-value
Age (10 years)	1.61	1.21, 2.14	.001
Female	0.67	0.48, 0.95	.022
Black	1.11	0.81, 1.53	.520
Katz ADL (0–5)	1.22	1.05, 1.40	.008
Nagi (0–3)	1.19	1.02, 1.38	.029
Cancer ever	1.74	1.20, 2.51	.003
High blood pressure ever	1.70	1.16, 2.48	.006
Current smoker	2.11	1.38, 3.23	.001
B. Stepwise Regression Estimates Log (IL-6) (pg/ml)			
Variable	Estimate (β)		*p*-value
Age (10 years)	..26		.0001
Female	–.063		.0536
Black	–.012		.7031
Rosow-Breslau (0–3)	.041		.0109
Katz ADL (0–5)	.059		.0012
Heart attack ever	.078		.0351
High blood pressure	.080		.0180
Current smoker	.187		.0001

accepted relationship between the inflammatory processes and the coagulation process, which may lead to a state of increased peripheral coagulation (31,32). Such interactions may also play a role in affecting functional status. In a previous study of a subcohort drawn from the EPESE for the MacArthur study of successful aging, we demonstrated significant relationships between indicators of subclinical altered inflammatory and coagulation status (reduced A/G ratio and elevated D-dimer levels), and functional decline (measured by ADL and IADL), particularly in elderly Black women (32). In future analyses of the full EPESE cohort, we will be able to explore the relationship of functional decline and alterations of coagulation status as marked by levels of circulating fibrin D-dimers.

On the basis of studies in mice, it has been suggested that IL-6 is involved in bone resorption and thus might play a role in osteoporosis etiology. Recent human studies have confirmed elevated levels after menopause, but a lack of correlation with bone density (33). In that study, the authors also failed to find a relationship between age and IL-6 in the postmenopausal women. It is likely that this was due to the small sample size, as our study clearly shows a relationship of age with IL-6 even in women long post-menopausal. In another recent study, there was also a strong age relationship over the 20- through 90-year range with no specific influence of menopausal status (34). However, there was no correlation with markers of bone turnover and no correlation with osteoporosis (35). Consistent with these reports, we did not find an independent relationship of IL-6 with hip fracture or other fractures cross-sectionally. However, we did not have data on bone mineral density or estimates of osteoporosis diagnoses. Moreover, since plasma levels represent the sum of IL-6 produced from a wide range of sources, it is certainly possible that IL-6 levels are much higher in the microenvironment of bone in osteoporosis or arthritis, or neoplastic tissue in the case of cancer, and play important roles in the pathogenesis of such diseases without elevating the plasma IL-6.

This study has a number of limitations. It must be emphasized that this is a report of cross-sectional data. IL-6 levels and age, functional status and other variables were simultaneously determined. Thus, we cannot be certain of any cause-and-effect relationship between the associations noted. Moreover, while the independent associations reported are strongly statistically significant, the order of magnitude of the absolute differences in IL-6 with age or functional status is modest and must represent only a portion of the variance. The elevated levels of IL-6 reported are generally not at the levels seen in active clinical disease. In fact, as an epidemiologic study, the associations reported should be taken as suggesting clues to possible biological and physiologic relationships, with stronger evidence of causality to come from future longitudinal studies.

In summary, IL-6 levels appear to be associated independently with aging and functional status. This large-scale study of older persons identifies these associations and shows that the presence of proinflammatory cytokines can be demonstrated in a large proportion of this population. The pathophysiologic correlates of IL-6 activation and the consequences of that activation are being explored in man (2,6). Because functional status has been shown to correlate strongly with subsequent survival, it is possible that IL-6 may be a good marker of such outcomes as well (36). Subsequent follow-up of this population should allow us to assess this prospectively.

Our studies suggest that cytokines such as IL-6 may be playing an important role in mediating the aging process and relationships between that process and functional outcomes. Our demonstration of these associations suggests the potential of using IL-6 as an intermediate outcome marker in studies of interventions to alter age-related biologic function. The use of anti-IL-6 antibodies, and other approaches to inhibit the activity of this cytokine have been suggested for therapeutic use (37,38). It would be of great interest in future trials to determine if inhibition of this cytokine can slow or reverse the functional decline associated with aging and age-related diseases.

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