Insulin-Like Growth Factor I and Interleukin-6 Contribute Synergistically to Disability and Mortality in Older Women

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The physiology of age-related functional decline is poorly understood, but may involve hormones and inflammation. We hypothesized that older women with both low IGF-I and high IL-6 levels are at high risk for disability and death. We assessed walking speed and disability in 718 women enrolled in the Women's Health and Aging Study I, a 3-yr cohort study with 5-yr mortality follow-up. Women with IGF-I levels in the lowest quartile and IL-6 levels in the highest quartile had significantly greater limitation in walking and disability in mobility tasks and instrumental activities of daily living than those with neither risk factor (adjusted odds ratios, 10.77, 5.14, and 3.66). Women with both risk factors were at greater risk for death (adjusted relative risk, 2.10) as well as incident walking limitation, mobility disability, and disability in activities of daily living compared with those with high IGF-I and low IL-6 levels.

The combination of low IGF-I and high IL-6 levels confers a high risk for progressive disability and death in older women, suggesting an aggregate effect of dysregulation in endocrine and immune systems. The joint effects of IGF-I and IL-6 may be important targets for treatments to prevent or minimize disability associated with aging. (*J Clin Endocrinol Metab* 88: 2019–2025, 2003)

G REATER NUMBERS OF individuals are living to older ages, with the prediction that by 2030, 20% of all Americans, 70 million in number, will be over the age of 65 yr (1). A major concern at the individual and population levels is how to live these years at a high functional level. Over one third of those over 65 yr and almost three fourths of those over the age of 80 yr report at least one severe disability (2). If we had physiological markers to identify those at risk for progressive functional decline and impending death, therapies could be targeted toward these individuals to prevent adverse outcomes.

Alterations in hormonal axes and inflammation pathways occur with age and have been proposed as critical, independent mediators of functional decline in older individuals. IGF-I has been found to decline with normal aging based on cross-sectional studies that included healthy, community-dwelling older people (3–9). Although the GH/IGF-I axis may mediate alterations in muscle mass and strength, the functional significance of the IGF-I level in older individuals is poorly understood. We have previously shown that low IGF-I levels are associated with slow walking speed and difficulty with mobility tasks (10), although others have not seen an association with poor physical function or disability (11, 12).

IL-6 is a proinflammatory cytokine with both immunological and nonimmunological roles. Although its production is tightly regulated at young ages, the serum concentration tends to increase with age, even in subjects free of acute or chronic inflammatory diseases (13). Several studies have shown cross-sectional and prospective associations of high IL-6 levels with functional disability and mortality (14–18). Furthermore, there is scientific evidence in model systems and in humans that high levels of IL-6 decrease IGF-I and that low levels of IGF-I stimulate IL-6, suggesting a biological link between IGF-I and IL-6 (19–21).

Given the prior work demonstrating individual detrimental effects and the plausibility of additive effects of dysregulation in multiple systems, we sought to examine the independent and combined effects of alterations of both IGF-I and IL-6 in a cohort of disabled women over the age of 65 yr. We hypothesized that women in the lowest quartile of IGF-I and the highest quartile of IL-6 levels at baseline in the Women's Health and Aging Study I (WHAS I) would be at the highest risk of disability and death compared with those with only one risk factor or neither.

Subjects and Methods

Study population

WHAS I is a study of the causes and course of disability among moderately to severely disabled older women living in the community. The study design was described in detail previously (22, 23). Briefly, a random sample of 6521 community-dwelling women 65 yr of age or older was selected from the Health Care Financing Administration's

Abbreviations: ADL, Activities of daily living; BMI, body mass index; CI, 95% confidence interval; IADL, instrumental activities of daily living; OR, odds ratio; RR, relative risk; WHAS I, Women's Health and Aging Study I.

Medicare eligibility list for Baltimore, Maryland. Women who reported difficulty with 1 or more tasks in 2 or more of 4 domains of functioning (mobility/exercise tolerance, upper extremity activities, basic self-care, and household management tasks) and who had a Mini Mental State score of 18 or greater were considered eligible for the study. Seventy-one percent (n = 1002) of those eligible (n = 1409) agreed to participate. The Johns Hopkins University institutional review board approved the study, and all participants gave informed consent.

Questionnaires and examinations were performed in the participant's home at 6-month intervals over 3 yr beginning in 1992, for a total of 7 visits. Baseline blood samples were obtained within 90 d of 1 of the first 3 examinations in 718 subjects, processed, placed on ice, and sent the same day to Quest Diagnostics, Inc. (Tetorboro, NJ). Samples were also processed to obtain aliquots of serum that were stored at −80 C. Participants who did not provide blood samples were older and had more disability in activities of daily living, but were not different in body mass index (BMI) or number of chronic diseases.

Assessment of biochemical measures

IGF-I was measured by RIA with ethanol extraction (Nichols Institute Diagnostics, San Juan Capistrano, CA) at the time of blood collection. The overall coefficient of variation was less than 15%, and the assay sensitivity was 0.1 μg/liter. IL-6 was measured in duplicate by ELISA (High Sensitivity Quantikine kit, R&D Systems, Inc., Minneapolis, MN) from the frozen specimens. The lower detection limit was 0.1 pg/ml, and the interassay coefficient of variation was 7%.

Assessment of functional outcomes

Physical function was assessed by self-reported disability and objective performance-based measures of lower extremity function. For the former, participants were asked to report the level of difficulty in performing specific tasks without help from another person or special equipment. Responses were coded as none, little, some, a lot, or unable to perform the task. Two mobility-related outcomes and two generalized disability outcomes were determined from the physical function data. Severe mobility disability was defined as a lot of difficulty or unable to walk one quarter of a mile and/or to climb stairs. Severe limitation in walking was defined as unable to walk or walking speed less than 0.4 m/sec (24, 25). Disability in activities of daily living (ADL) was defined as a lot of difficulty or inability in at least one of four tasks (bathing, transferring from bed to chair, using the toilet, and walking across a small room). Severe instrumental ADL (IADL) disability was defined as difficulty or unable to do three or more of four tasks (light housework, preparing meals, shopping, and managing money).

Mortality follow-up

Vital status was obtained through follow-up interviews with proxies, obituaries, and matching with the National Death Index over a 5-yr period.

Assessment of chronic diseases and other covariates

Seventeen chronic diseases were ascertained at baseline with disease-specific standardized algorithms (23). The algorithms used data from the baseline interview, the nurse's examination (including electrocardiogram, the ankle-brachial index, and spirometry), and the participant's current medication list. Medication use was determined by examination of medication containers. Additional information was collected from medical records, blood test results, and a questionnaire sent to each participant's primary care physician. Disease categories used in this analysis were congestive heart failure, diabetes mellitus, peripheral arterial disease, stroke, coronary heart disease (angina or myocardial infarction), chronic obstructive pulmonary disease, hip fracture, osteoarthritis, rheumatoid arthritis, and malignant neoplasms (excluding basal cell cancer). Sociodemographic characteristics included age, race, education, and smoking status. BMI (kilograms per square meter), computed from objective measures, was categorized as less than 21.5, 21.5–24.9, 25–29.9, and 30 or greater.

Statistical analysis

As we hypothesized that low IGF-I and high IL-6 levels represent adverse risk factors, we defined cut-points at the lowest quartile of IGF-I levels and the highest quartile of IL-6 levels as high risk groups for use in analyses. Under this paradigm, women with high IGF-I and low IL-6 levels represent the lowest risk group, women with low IGF-I and high IL-6 levels represent the highest risk group, and those with low IGF-I and low IL-6 or high IGF-I and high IL-6 represent intermediate risk groups. We selected the lowest quartile of IGF-I ($\leq$74.3 μg/liter) as our high risk IGF-I group based on prior work suggesting a threshold effect for mobility tasks at approximately this level (10). In addition, this level is near the age-specific normal range for this IGF-I assay (71–290 μg/liter). As there are no commonly used age-specific normal ranges for the IL-6 assay, we used the highest quartile of IL-6 ($\geq$3.7 pg/ml) as the cut-point for defining risk groups. This is congruent with other studies in which tertiles and quartiles of IL-6 were used to define risk categories for outcomes in older individuals (15, 16, 18).

Baseline characteristics were compared by category of IGF-I and IL-6, using the χ^2 test for binary outcomes and ANOVA for continuous outcomes. The χ^2 and ANOVA tests do not specify a reference group, and therefore are statistically significant when any group differs from the others. The t test was used to compare mean IGF-I and IL-6 levels by 5-yr mortality status. Kaplan-Meier analysis was used to study survival for the 4 risk categories of IGF-I and IL-6 across the 5 yr of follow-up. The log-rank test was used to compare survival curves, with a statistically significant result indicating that at least one of the curves differs from the others. Logistic regression models that account for intraperson correlation over time and interperson heterogeneity were used to assess longitudinal associations between IGF-I/IL-6 categories and functional outcomes (26). These models, which included all 718 women in our study population, account for cross-sectional associations over time and are primarily driven by prevalent effects. Four models were employed in all analyses: those with low IGF-I in the model, those with high IL-6 in the model, those with both low IGF-I and high IL-6 in the model, and those with low IGF-I, high IL-6, and an interaction term in the model. The interpretation of a model with both low IGF-I and high IL-6 that does not include an interaction term is that of the effect of one factor, *e.g.* IGF-I, after accounting for the effect of the other, *e.g.* IL-6. This model allows examination of the effect of IGF-I independently of IL-6 and *vice versa*, but does not allow for the possibility of synergy. Models with low IGF-I, high IL-6, and an interaction term for low IGF-I and high IL-6 allow detection of effect modification, that is, a different effect from high IL-6 in the presence of low IGF-I compared with high IL-6 in the presence of high IGF-I. This model is similar to using separate categories for each of the 4 combinations of IGF-I and IL-6, and thus is displayed in this manner in tabular form. All of the regression models included adjustment for age, education, race, smoking status, BMI, oral estrogen use, oral corticosteroid use, and chronic conditions (coronary heart disease, congestive heart failure, peripheral arterial disease, hip fracture, osteoarthritis, rheumatoid arthritis, diabetes mellitus, cancer, stroke, and chronic obstructive pulmonary disease). A nonparametric trend test across the four IGF-I/IL-6 categories was employed to compare incident disability in functional outcomes and mortality. Incident disability was defined as the new onset of disability during the course of the study in women without preexisting disability at baseline. Discrete-time Cox proportional hazard regression models were used to compare mortality risk across the IGF-I/IL-6 categories (27). These models were also adjusted for the covariates listed above. Analyses were performed using MIXNO (28) for logistic regressions and SPLUS, version 2000 (Insightful, Inc., Seattle, WA) for Cox proportional hazard models.

Results

Figure 1 displays a scatterplot of IGF-I and IL-6 levels in this cohort of disabled older women. The mean IGF-I level was 107.8 μg/liter, the median was 101.3 μg/liter, and the range was 12.8–281.3 μg/dl. The mean IL-6 level was 3.14 pg/ml, the median was 2.39 pg/ml, and the range was 0.4–10.1 pg/ml. IGF-I and IL-6 levels were not linearly correlated with each other, with a Spearman correlation coefficient of −0.011 ($P = 0.77$). IL-6 levels were similar in the low IGF-

I/high IL-6 and the high IGF-I/high IL-6 categories, with a median level of 6.23 and a mean level of 6.68 in the low IGF-I/high IL-6 category and a median level of 6.08 and a mean level of 6.47 in the high IGF-I/high IL-6 group ($P =$ 0.58, by t test for means).

The baseline characteristics of the study population are summarized in Table 1. The mean age of participants was 77.6 yr (range, 65–100 yr), with age varying slightly among the IGF-I/IL-6 categories. Educational level, race, current smoking, BMI, estrogen use, corticosteroid use, and prevalence of peripheral arterial disease, diabetes, and congestive heart failure varied by IGF-I/IL-6 category. Those in the low IGF-I and high IL-6 category had higher percentages of mo-
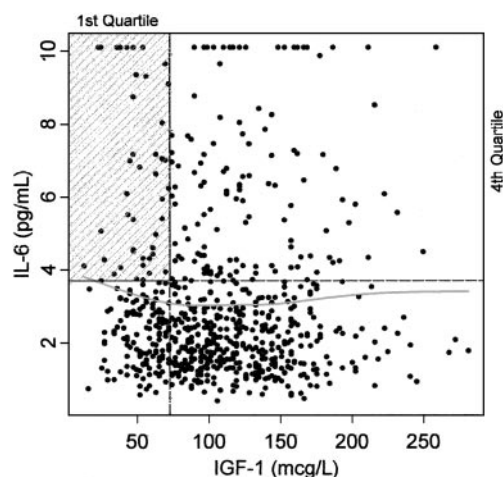

FIG. 1. Scatterplot showing the relationship between IGF-I and IL-6 serum levels in the study population. The *upper left quadrant* (*shaded*) identifies participants in the highest risk group, and the *lower right quadrant* shows those in the lowest risk group. A smooth spline (*solid line*) with 4 degrees of freedom is displayed, which reveals no systematic trend.

bility and ADL disability at baseline than those in other categories ($P < 0.05$ for trend).

Women with IGF-I levels in the bottom quartile were more likely to have walking limitation than women with IGF-I levels in the top three quartiles [odds ratio (OR), 2.54; 95% confidence interval (CI), 1.05–6.11; Table 2, model 1]. Those with IL-6 levels in the top quartile were significantly more likely to have walking limitation (OR, 4.99; CI, 1.95–12.80), mobility disability (OR, 1.79; CI, 1.00–3.19), and severe IADL disability (OR, 2.00; CI, 1.00–4.01) than those in the bottom three quartiles (Table 2, model 2). In models assessing the effects of IGF-I and IL-6 independently of each other, low IGF-I was not significantly associated with any of the functional outcomes (Table 2, model 3). However, high IL-6 was associated with walking limitation (OR, 4.55; CI, 1.78–11.62) and severe IADL disability (OR, 2.00; CI, 1.00–4.01) independently of low IGF-I. Then, using models examining each risk factor in the presence or absence of the other, women with both risk factors simultaneously were much more likely to be disabled than those with only one risk factor or neither (Table 2, model 4). Women with both low IGF-I and high IL-6 were more likely to have walking limitation (OR, 10.77; CI, 1.68–69.11), mobility disability (OR, 5.14; CI, 1.85–14.25), severe IADL disability (OR, 3.66: CI, 1.10–12.15), and ADL disability (OR, 2.47; CI, 0.96–6.32) than their counterparts without either of these risk factors. The ORs were smaller in magnitude for those in the intermediate risk categories (low IGF-I/low IL-6 or high IGF-I/high IL-6) than for those of the high risk category (low IGF-I/high IL-6). The results of model 4 are displayed graphically in Fig. 2.

We next examined the effects of IGF-I and IL-6 on incident disability (Table 3). Due to a high prevalence of disability in many tasks in this population, fewer women were available for analyses involving incident outcomes. Nevertheless, the incidence of new limitation in walking, mobility disability, and ADL disability over a 3-yr period was greatest in the low

TABLE 1. Demographic and health-related characteristics by category of IGF-I and IL-6

	High IGF-I and low IL-6 (n = 398)	Low IGF-I and low IL-6 (n = 142)	High IGF-I and high IL-6 (n = 128)	Low IGF-I and high IL-6 (n = 50)	Overall (n = 718)	P^a
Age (yr)	76.7 (7.7)	79.9 (8.0)	77.9 (7.6)	78.2 (8.0)	77.6 (7.9)	<0.01
Education (yr)	10.0 (3.7)	9.5 (3.8)	9.6 (3.7)	8.6 (2.9)	9.7 (3.7)	0.03
Black (%)	25.6	26.1	39.0	36.0	28.9	0.02
Current smoking (%)	11.1	4.9	18.0	22.0	12.0	<0.01
BMI (kg/m^2)	28.8	27.2	29.9	29.1	28.8	<0.01
Oral estrogen use (%)	5.8	16.2	3.1	10.0	7.7	<0.01
Oral corticosteroid use (%)	3.8	3.5	10.2	2.0	4.7	0.02
Chronic diseases (%)						
Osteoarthritis	57.0	52.8	53.1	54.0	55.3	0.77
CHD	31.9	31.0	34.4	26.0	31.8	0.75
PAD	16.6	17.6	32.8	22.0	20.1	0.001
Diabetes	14.6	7.7	25.8	22.0	15.7	<0.001
COPD	13.6	16.2	16.4	20.0	15.0	0.58
Cancer	11.1	11.3	10.9	18.0	11.6	0.53
CHF	8.8	7.7	12.5	22.0	10.2	0.02
Hip fracture	6.5	12.0	4.7	8.0	7.4	0.10
Stroke	5.8	4.9	5.5	8.0	5.7	0.88
Rheumatoid arthritis	2.3	2.8	4.7	6.0	3.1	0.32
Mobility disability (%)	44.9	45.0	50.8	65.3	47.4	0.04
ADL disability (%)	68.8	72.5	77.3	82.0	72.0	0.02

High IGF-I refers to IGF-I in the top 75% of the distribution of levels in WHAS (>74.3 μg/liter), low IGF-I to the bottom 25% ($\leq$74.3 μg/liter). Low IL-6 refers to the bottom 75% of the distribution of levels in WHAS (<3.7 pg/ml), high IL-6 to the top 25% ($\geq$3.7 pg/ml).
^{a} P value from χ^2 test for binary variables and ANOVA for continuous variables.

TABLE 2. Odds ratios of functional outcomes according to baseline levels of IGF-I and IL-6

	Model 1	Model 2	Model 3		Model 4			
	Low IGF-I	High IL-6	Low IGF-I	High IL-6	High IGF-I and Low IL-6	Low IGF-I and Low IL-6	High IGF-I and High IL-6	Low IGF-I and High IL-6
Walking limitation	2.54[a] (1.05–6.11)	4.99[a] (1.95–12.80)	1.77 (0.73–4.27)	4.55[a] (1.78–11.62)	1.0	1.38 (0.51–3.77)	3.38[a] (1.15–9.90)	10.77[a] (1.68–69.11)
Mobility disability	1.70 (0.86–2.51)	1.79[a] (1.00–3.19)	1.65 (0.94–2.90)	1.75 (0.98–3.12)	1.0	1.21 (0.64–2.30)	1.23 (0.64–2.40)	5.14[a] (1.85–14.25)
IADL disability	1.00 (0.49–2.04)	2.00[a] (1.00–4.01)	1.01 (0.51–2.03)	2.00[a] (1.00–4.01)	1.0	0.73 (0.32–1.63)	1.39 (0.62–3.10)	3.66[a] (1.10–12.15)
ADL disability	1.36 (0.81–2.29)	1.46 (0.86–2.46)	1.34 (0.80–2.25)	1.44 (0.85–2.43)	1.0	1.17 (0.65–2.09)	1.25 (0.69–2.25)	2.47 (0.96–6.32)

Model 1, Low IGF-I + covariates; model 2, high IL-6 + covariates; model 3, low IGF-I, high IL-6 + covariates; model 4, low IGF-I, high IL-6, interaction term for low IGF-I and high IL-6 + covariates. Covariate adjustment for all models includes age at first blood draw, education, race, smoking status, BMI, estrogen use, corticosteroid use, chronic conditions including CHD, CHF, PAD, hip fracture, OA hip and knee, RA, DM, cancer, stroke, COPD. High IGF-I refers to IGF-I in the top 75% of the distribution of levels in WHAS, low IGF-I to the bottom 25%. Low IL-6 refers to the bottom 75% of the distribution of levels in WHAS, high IL-6 to the top 25%.
[a] $P < 0.05$ *vs.* referent group.

IGF-I/high IL-6 group ($P = 0.11$, <0.001, and 0.09, respectively, for trend).

After 5 yr, 195 of 718 women had died. The Kaplan-Meier survival functions over the 5-yr period, stratified by category of IGF-I and IL-6, are shown in Fig. 3. Overall, there was a large difference in mortality between women with low and high IL-6 levels. In addition, within each group of IL-6 levels, those with low IGF-I levels tended to have higher mortality. At 5 yr, 46% of the low IGF-I/high IL-6 group were dead compared with 23% of the high IGF-I/low IL-6 group (Table 3). The mean baseline IGF-I level in those who survived for 5 yr was 110.1 μg/dl *vs.* 101.5 μg/dl for those who died within the 5-yr period ($P = 0.03$). The mean baseline IL-6 level for those who survived for 5 yr was 2.9 pg/ml *vs.* 3.8 pg/ml for those who did not ($P < 0.01$). In multivariate Cox proportional hazard models, high IL-6 was an independent predictor of mortality [relative risk (RR), 1.60; 95% CI, 1.17–2.19], whereas low IGF-I was not (RR, 1.29; CI, 0.94–1.78). However, the low IGF-I/high IL-6 group demonstrated the highest mortality risk of any of the IGF-I/IL-6 categories, with a 2-fold higher risk of mortality over a 5-yr period (RR, 2.10; CI, 1.29–3.41) than the reference group with high IGF-I/low IL-6.

Discussion

We report a combined effect of low IGF-I and high IL-6 in predicting mobility disability, walking limitation, ADL disability, severe IADL disability, and mortality in a cohort of disabled, community-dwelling older women. Other studies have shown independent effects of IGF-I and IL-6 on disability and mortality (10, 14–18). To our knowledge, we are the first to note a combined effect of circulating hormones and inflammatory markers on important health outcomes in an older population. Our findings provide evidence bridging two systems that undergo significant alterations with aging.

Our results suggest two interpretations: either that IGF-I and IL-6 are mediators of debilitating processes or that they are markers of poor health without any pathogenic effects of their own. Potential mechanisms for mediation effects from low levels of IGF-I include detrimental effects on muscle, bone, cardiac function, and cognition (29). As a proinflammatory cytokine, IL-6 has been implicated in the pathogenesis of muscle wasting, as well as of atherosclerosis, type 2 diabetes, osteoporosis, anemia, Alzheimer's disease, depression, rheumatological disease, and lymphoproliferative disorders (13, 18, 30–32). If IGF-I and IL-6 are biomediators, then interventions to raise IGF-I and lower IL-6 would be expected to result in beneficial effects on the clinical status of this group of patients that is at high risk for adverse and costly outcomes.

Substantial evidence in model systems and in humans suggests a mechanistic link between IGF-I and IL-6. In transgenic mice that overexpress IL-6, low levels of IGF-I are found relative to wild-type mice (19). Treatment of these transgenic mice with an IL-6 antibody or with an IL-6 receptor antagonist results in normalization of IGF-I levels (19, 33). Furthermore, treatment of wild-type mice with IL-6 results in lowering of IGF-I levels (19). In rat liver cells, the addition of IL-6 results in reduced IGF-I biosynthesis (34). Low IGF-I levels and stunted growth have been reported in inflammatory conditions that have high IL-6, such as systemic juvenile idiopathic arthritis (19). The lower IGF-I levels may be secondary to increased clearance of IGF-I in patients with this condition (35).

Additionally, low levels of IGF-I may induce IL-6 expression. A human model exists, that of patients with pituitary insufficiency who have GH deficiency. Adults with panhypopituitarism who are sufficiently replaced for all pituitary hormones except GH have been shown to have high levels of IL-6 (36). GH replacement therapy decreases serum IL-6 levels and IL-6 production by monocytes in these patients (20, 21). Additional support for a biological relationship between the GH/IGF-I pathway and cytokines is the finding that the GH receptor is a member of the cytokine-hemopoietin superfamily (37).

It could therefore be postulated that in some individuals, high IL-6 levels and low IGF-I levels could drive a vicious cycle, in which these levels are each driven to extremes. Why, then, are there individuals who have high IL-6 yet high IGF-I, and low IGF-I yet low IL-6? A possible explanation is that there are transient conditions that can produce high IL-6, such as infectious illnesses, that are not captured by our data. Other factors not examined, including other cytokines, cortisol, estrogens, and androgens, may also affect IL-6 produc-
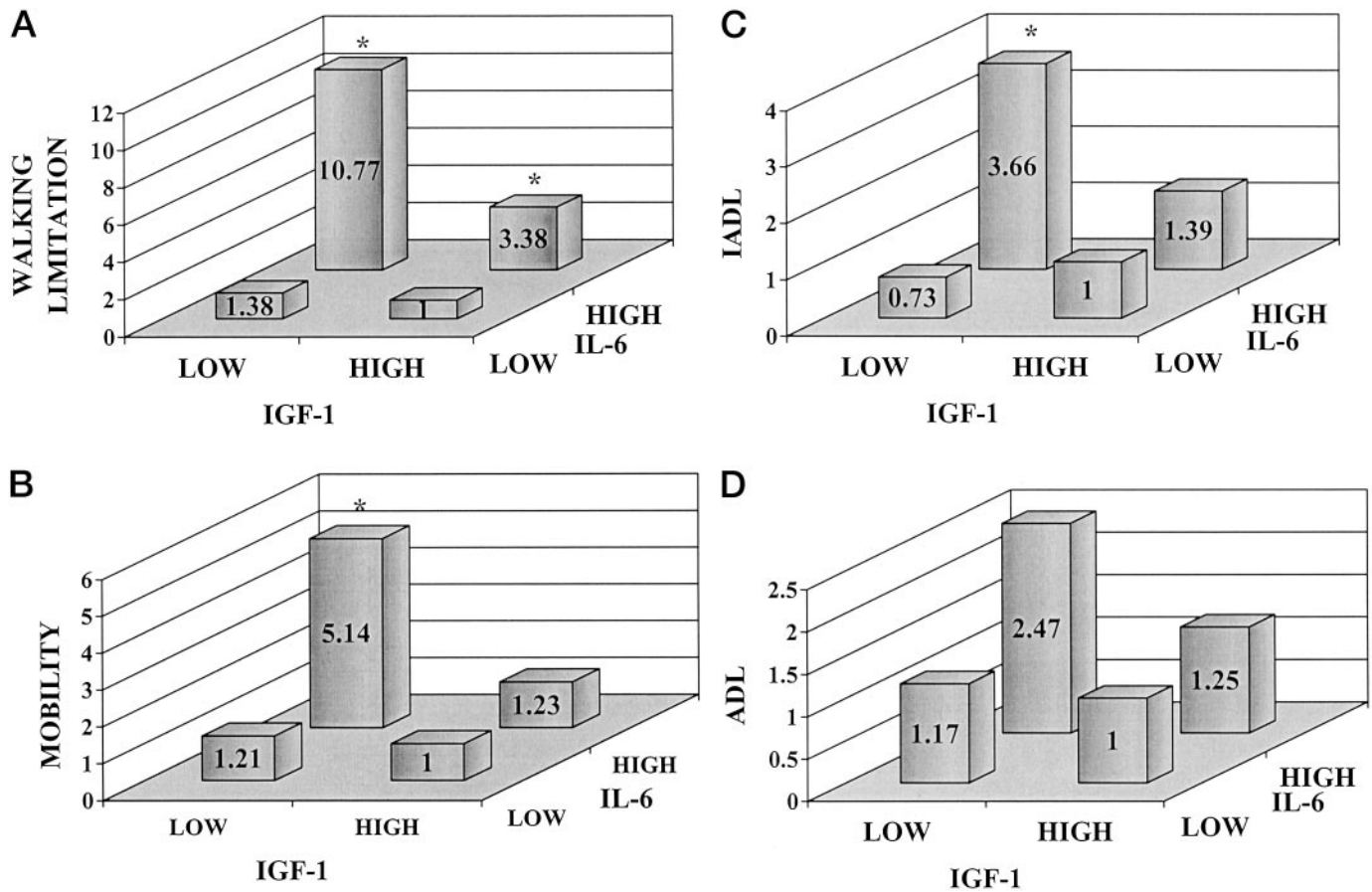
FIG. 2. Adjusted OR of functional outcomes according to baseline levels of IGF-I and IL-6. High IGF-I refers to the top 75% of study levels; low IGF-I refers to the bottom 25%. Low IL-6 refers to the bottom 75% of study levels; high IL-6 refers to the top 25%. Referent, High IGF-I and low IL-6. *, $P < 0.05$ *vs.* referent group.

tion (13). Likewise, multiple other factors may influence IGF-I levels besides GH status, including nutrition, exercise, and liver function (16, 38–40). Alternatively, some individuals predestined to become frail may be more susceptible to entry into this vicious cycle than others.

When the magnitude of an effect from two risk factors exceeds that which would be expected from merely combining their individual effects, synergy is present. The magnitudes of the effects seen in our high risk group suggest such synergy between IGF-I and IL-6. Biologically, this would mean that older women who have one risk factor (*e.g.* high IL-6) are at unexpectedly increased susceptibility to adverse events once they accumulate a second adverse risk factor (*e.g.* low IGF-I). In the presence of synergy, an intervention would need to target both risk factors to be maximally effective.

An alternative explanation is that IGF-I and IL-6 are not mediators of biological effects, but, rather, are markers for other processes. For example, IGF-I may be a marker of nutritional status or of other hormonal deficiencies. Levels of IGFBP-3, the major binding protein of IGF-I, are not available in our cohort. Conflicting reports exist regarding the impact that measurement of IGFBP-3 would have had on our results. It has been reported that both IGF-I and IGFBP-3 decline with age, although in one report the free IGF-I level was increased in those above 70 yr (41), whereas in another the molar ratio

of IGF-I to IGFBP-3 decreased with increasing age (42). IL-6 may be a marker for another biologically important mediator that is activated by the same process that stimulates IL-6 production. We adjusted for multiple potential confounders, including age, BMI, smoking, relevant medications, and certain chronic diseases, in an attempt to demonstrate a risk category independent of a specific disease state. Even if IGF-I and IL-6 are not directly in the causal pathway to disability and mortality, they have potential clinical utility in the identification of patients at high risk for these outcomes. It is often difficult to assess the clinical impact or severity of one or multiple conditions in an individual. Because multiple factors may lower IGF-I or raise IL-6, they may represent measures of global disease burden that identify the activation of detrimental pathways better than assessments of individual organ function.

WHAS I, as a cohort designed to represent the one third most disabled women living in the community, is comprised of women who represent the ideal group in which to examine the physiological dynamics underlying disability. The use of sampling from the Health Care Financing Administration database instead of a volunteer recruitment mechanism, home visits instead of travel to a study clinic, and visits every 6 months enabled us to enroll and closely follow a representative sample of women who ordinarily exclude them-

TABLE 3. Three-year incidence for functional outcomes and 5-yr incidence of death according to baseline levels of IGF-I and IL-6

	High IGF-I and low IL-6	Low IGF-I and low IL-6	High IGF-I and high IL-6	Low IGF-I and high IL-6	*P* value for trend
Walking limitation	22 (302)	27 (102)	28 (80)	32 (25)	0.11
Mobility disability	62 (214)	80 (76)	77 (60)	82 (17)	<0.001
ADL disability	59 (292)	62 (98)	68 (78)	70 (30)	0.09
Severe IADL disability	29 (354)	24 (124)	29 (101)	44 (39)	0.32
Death	23 (398)	26 (142)	35 (128)	46 (50)	<0.001

Data are expressed as percentage with event during 3-yr follow-up. Number at risk for event in *parentheses*. High IGF-I refers to IGF-I in the top 75% of the distribution of levels in WHAS, low IGF-I to the bottom 25%. Low IL-6 refers to the bottom 75% of the distribution of levels in WHAS, high IL-6 to the top 25%.
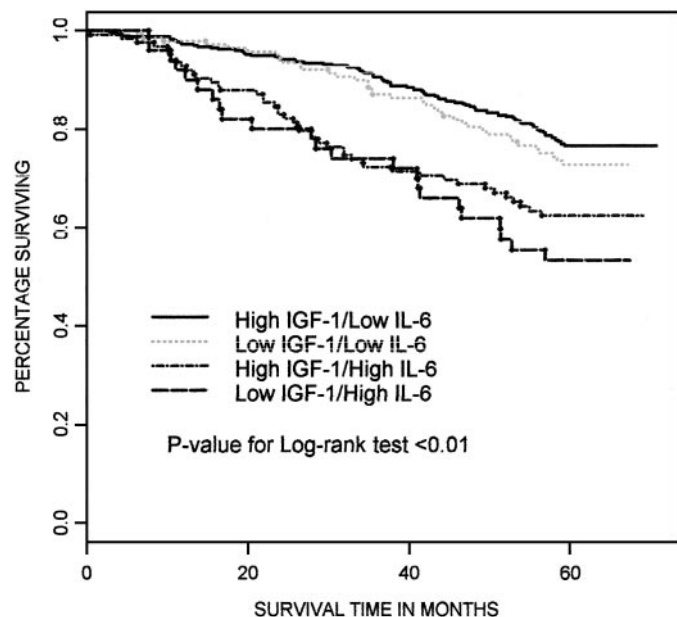

FIG. 3. Five-year survival categorized by baseline levels of IGF-I and IL-6.

selves or are excluded from research studies. Our cohort was large enough to achieve sufficient power to assess for joint effects. However, it is possible that our results are specific to frail older women and will not be generalizable to healthy older individuals or to men. In addition, precise threshold points cannot be determined from this study, although these data support the establishment of a lower limit for IGF-I and an upper limit for IL-6 that are linked to clinically significant outcomes in older individuals: disability and death. Although our findings support the hypothesis that those with low IGF-I and high IL-6 represent a high risk group for clinically meaningful adverse events, we have not elucidated specific targets through which IGF-I and IL-6 might mediate their effects. Additional studies are required to distinguish potential pathways, such as via muscle or cognition.

In conclusion, our work represents an initial step toward construction of a biological model for understanding how pathophysiological changes in the endocrine and inflammatory systems may have detrimental effects on health outcomes of aging. Further work is required to validate and extend our findings, so that appropriate target groups may be defined for interventions to prevent the progression of disabling conditions in older people.

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