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Association of IGF-I Levels with Muscle Strength and Mobility in Older Women

ANNE R. CAPPOLA, KAREN BANDEEN-ROCHE, GARY S. WAND, STEFANO VOLPATO, AND LINDA P. FRIED

Department of Medicine, The Johns Hopkins Medical Institutions (A.R.C., G.S.W., L.P.F.), and Department of Biostatistics, Johns Hopkins School of Hygiene and Public Health (K.B.-R.), Baltimore, Maryland 21205; Epidemiology, Demography, and Biometry Program, National Institute on Aging, National Institutes of Health (S.V.), Bethesda, Maryland 20892

The functional consequences of the age-associated decline in IGF-I are unknown. We hypothesized that low IGF-I levels in older women would be associated with poor muscle strength and mobility. We assessed this question in a population representative of the full spectrum of health in the community, obtaining serum IGF-I levels from women aged 70–79 yr, enrolled in the Women's Health and Aging Study I or II. Cross-sectional analyses were performed using 617 women with IGF-I levels drawn within 90 d of measurement of outcomes. After adjustment for age, there was an association between IGF-I and knee extensor strength ($P = 0.004$), but not anthropometry or other strength measures. We found a positive relationship between IGF-I levels and walking speed for IGF-I levels below 50 μg/liter ($P < 0.001$), but no relationship above this threshold. A decline in IGF-I level was associated with self-reported difficulty in mobility tasks. All findings were attenuated after multivariate adjustment.

In summary, in a study population including frail and healthy older women, low IGF-I levels were associated with poor knee extensor muscle strength, slow walking speed, and self-reported difficulty with mobility tasks. These findings suggest a role for IGF-I in disability as well as a potential target population for interventions to raise IGF-I levels. (*J Clin Endocrinol Metab* 86: 4139–4146, 2001)

A DECLINE IN IGF-I levels has been found to occur with normal aging, based on cross-sectional studies that included healthy, community-dwelling older people (1–6). Such a decline in IGF-I levels may reflect declines in GH production with age (7). Additionally, IGF-I levels are affected by nutritional status, physical activity level, coexistent illness, alcohol intake, and liver function (3, 4, 7–12). These relationships are summarized in Fig. 1.

IGF-I is a potential mediator of alterations in muscle mass and strength, and thereby of distal outcomes of clinical importance in the elderly, such as objective performance on muscle-dependent tasks and mobility (Fig. 1). However, the functional significance of the IGF-I level in older individuals is unknown. Although biologically plausible, prior observational studies have been unable to detect a relationship between IGF-I and body composition or muscle strength after adjustment for age (2–6, 13). It is possible that these associations were missed due to selection bias from exclusion of disabled elderly individuals, narrowing the distribution of functional status available for analysis. Furthermore, few studies have attempted to assess the relationships between IGF-I levels and more distal outcomes, such as performance tasks and mobility (2, 13, 14). Using a population representative of the full spectrum of health in older women in the community, we tested the hypotheses that 1) IGF-I levels would have a greater range of values and a lower mean value than those obtained in studies in which subjects in poor health were not included; and 2) low IGF-I levels would be associated with low lean body mass, poor muscle strength, slow completion of performance measures, and difficulty with mobility tasks.

Abbreviations: BMI, Body mass index; HCFA, Health Care Financing Administration; WHAS, Women's Health and Aging Study.

Subjects and Methods

Study population

Study subjects were community-dwelling women, 70–79 yr of age, residing in Baltimore, MD, who were recruited into 2 longitudinal, population-based companion studies: Women's Health and Aging Study I (WHAS I) and Women's Health and Aging Study II (WHAS II). The overall objectives of the 2 studies were to determine the etiology of onset and/or the progression of physical disability. Sampling, recruitment, and study designs for each study have previously been described in detail (15, 16). For WHAS I, an age-stratified random sample was selected from the Health Care Financing Administration's (HCFA) Medicare enrollment file for the 32,538 women 65 yr or older residing in 12 contiguous zip codes in Baltimore, MD, yielding 6,521 women to screen for study eligibility. Exclusion criteria included nursing home residence or having moved outside the catchment area. A screening interview in the home, designed to identify the one third most disabled older women living in the community, was administered to 4,137 women who were eligible for and consented to screening. Physical disability was identified through self-reported difficulty in 4 domains: 1) mobility tasks, 2) upper extremity tasks, 3) household management tasks, and 4) basic self-care tasks. Women who reported difficulty in 2, 3, or 4 domains represented the one third most disabled community-dwelling older women and were eligible for inclusion into WHAS I. Women with Mini-Mental State Exam scores less than 18 were excluded. Of the 1,409 who met study eligibility criteria, 1,002 agreed to participate in the study in 1992. There were no major differences in sociodemographic or health characteristics between participants and eligible women who declined. Standardized questionnaires were administered in the participant's home by trained interviewers. Two weeks later, a trained registered nurse conducted an examination of each study participant in her home, using a standardized protocol that included performance-based measures. Approximately 75% of women also consented to phlebotomy in the home at a separate visit, performed by a trained phlebotomist who followed a standardized protocol.

WHAS II was designed to be a companion study to WHAS I and is

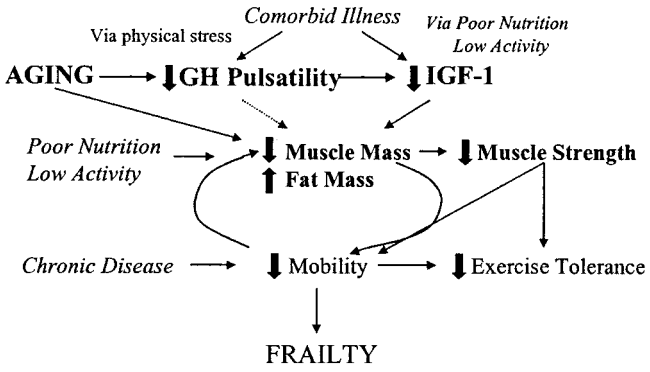

FIG. 1. Proposed causal pathway of the GH axis in frailty.

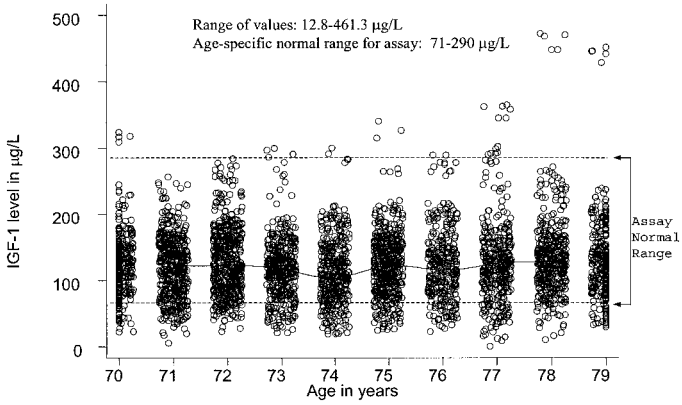

FIG. 2. Cross-sectional distribution of IGF-I levels by age, weighted to represent the original population sampled.

comprised of a cohort of women, aged 70–79 yr, who were selected to be representative of the two thirds least disabled older women living in the community. Potential participants were selected via age-stratified random samples from the same HCFA database as in WHAS I and were screened by telephone using the same 4 domains of physical function. Eligible women were asked to participate if they had difficulty in 0 or 1 domain of physical function and scored 24 or higher on a Mini Mental State Exam. In 1994, 880 women were found eligible for WHAS II, and 436 consented to participate (49.5%). Those agreeing to participate were more highly educated and had more diseases than those who refused to participate, but did not differ significantly in disability characteristics. An interview standardized to that performed in WHAS I was administered in The Johns Hopkins Functional Status Laboratory. In addition, trained technicians conducted an examination of each study participant, using a standardized protocol that included performance-based measures. Phlebotomy was performed in 93% of WHAS II participants by a trained phlebotomist following the same protocol as that used in WHAS I.

For comparability with the WHAS II cohort age range of 70–79 yr, we only included women from WHAS I if they were also in this age range. Of the 398 women in WHAS I and 436 women in WHAS II aged 70–79 yr, 325 women in WHAS I and 403 in WHAS II had IGF-I levels measured. These women are included in the descriptive graph in Fig. 2. For the regression analyses, participants who had samples obtained within 90 d of the baseline examinations were included (257 women in WHAS I and 360 women in WHAS II). Women included in either the descriptive or regression analyses reported slightly less disability in activities of daily living than those excluded, but did not differ significantly in other baseline characteristics or measured outcomes from women included in the original parent WHAS I or II studies.

Variables

The weekly level of leisure time physical activity was determined using the modified Minnesota Leisure Time Activities Questionnaire (17). A weighted score of kilocalories expended per wk was calculated from questions on frequency and duration of walking for exercise, dancing, bowling, performing moderately strenuous household and outdoor chores, and participating in any regular exercise program. The number of comorbid illnesses was based on self-report of prior physician diagnosis of myocardial infarction, angina, congestive heart failure, high blood pressure, other heart disease, diabetes, arthritis, stroke, cancer, hip fracture, Parkinson's disease, or lung disease. Self-assessed health was categorized as excellent, very good, good, fair, or poor by the participants and recoded as excellent-very good, good, and fair-poor. Physical function was ascertained with standardized questions regarding difficulty with specific aspects of mobility function, which began with "by yourself, that is without help from another person or special equipment, do you have any difficulty," and were completed with 1) "lifting or carrying something as heavy as 10 pounds, for example, a bag of groceries?" 2) "walking for a quarter of a mile, that is about 2–3 blocks?" 3) "walking up 10 steps without resting?" 4) "getting in and out of bed or chairs?" or 5) "doing heavy housework such as washing windows, walls, or floors?" Responses were categorized dichotomously as yes or no.

Height and weight were measured with the participant standing in stocking feet wearing light indoor clothing. The participant's head was positioned against a level doorway using a Frankfort plane, and height was measured to the nearest centimeter using a stadiometer. Weight was measured in kilograms using a digital scale. Triceps skinfold thickness was measured at the midpoint of the upper right arm with a Holtain skinfold calipers (Seritex, Carlstadt, NJ) to the nearest 0.2 mm in accordance with standard procedures (18). If the difference between the first and the second reading exceeded 2.0 mm, a third reading was performed. Skinfold thickness values represent the mean of all (two or three) measurements obtained. Arm circumference was measured with a measuring tape to the nearest 0.1 cm at the midpoint of the upper right arm. If the difference between the first and the second reading exceeded 0.8 cm, a third reading was performed. Arm circumference values represent the mean of all (two or three) measurements obtained. A calculated arm muscle area was obtained using the equation reported by Heymsfield *et al.* (19).

Blood samples were collected between 0900–1400 h in a nonfasting state, processed, frozen, and sent the same day to Quest Diagnostic Laboratories (Teeterboro, NJ). The serum IGF-I level was measured by RIA with ethanol extraction (Nichols Institute Diagnostics, San Juan Capistrano, CA). The overall coefficient of variation was less than 15%, and the assay sensitivity 0.1 μg/liter. Serum albumin was measured using a colorimetric assay.

Data on maximal grip strength were obtained using a JAMAR handheld dynamometer (model BK-7498, Fred Sammons, Inc., Burr Ridge, IL). Grip strength was measured 3 times with each hand. The best measure in the stronger hand is reported. Knee extensor (quadriceps) and hip flexor (iliopsoas) muscle strengths were determined using a Nicholas Manual Muscle Tester dynamometer (model BK-7454, Fred Sammons, Inc.). Tests were conducted with the participant seated comfortably in a hard chair and hips and knees flexed at 90 °. The dynamometer was placed a few inches above the right ankle between the medial and lateral malleolus for the knee extension test and immediately proximal to the femoral condyles at the distal thigh for the hip flexion test. Participants were instructed to push against the dynamometer as hard as they could, and the examiner then pushed hard enough to break the contraction. Each test was performed twice for each leg. The best measure for the stronger leg is reported. Interrater reliability of strength tests was assessed in a pilot study of 22 women: the intraclass correlation coefficient was 0.91 for knee extension and 0.93 for hip flexion (20).

The participant was timed walking over a 4-meter course. For a small group of women in WHAS I, adequate space was not available in the home, and a 3-meter course was used. Participants were instructed to stand with both feet at the starting line and to start walking after a specific verbal command. The subject could use a cane, a walker, or other walking aid, but not the aid of another person. The times to complete the first meter and the entire course were recorded at both a rapid and a usual pace. The length of the walk in meters divided by the time in seconds was used to calculate the walking speed. For the chair stand test, participants were asked to sit with their arms folded across their chests in a straight-backed chair placed against a wall and to stand and sit as quickly as possible five times in a row.

Data analysis

We first compared baseline characteristics between WHAS I and WHAS II; *t* tests were used for continuous variables, and χ^2 tests were used for categorical variables, to test differences between study populations. IGF-I levels were log-transformed for all analyses to normalize their skewed distribution. Two extreme outliers values above 400 μg/liter were included in analyses, as we were unable to confirm that these values were erroneous. The effect of inclusion of these individuals was minimized by log transformation of IGF-I, and their inclusion had neither a clinically nor a statistically significant impact on our analytic results. All categorical variables were coded as indicator variables.

Regression analyses were used to investigate associations between outcome variables and IGF-I, adjusting for age and other covariates. Linear regressions were fit to describe anthropometry, strength, and performance outcomes, and logistic regressions were fit to describe self-report of difficulty. Scatterplot matrixes and analyses by quintiles were performed to check for potential nonlinear associations between IGF-I and all outcomes. Spline terms (21) were fit if a nonlinear association was evident in plotting and quintile analyses and were maintained if they improved the F test of the overall model. These allowed different slopes *vs.* log IGF-I above *vs.* below a given threshold value of log IGF-I; separate models were fit using threshold values of IGF-I from 50–100 μg/liter in 10-U increments, and the model with the best fit (largest model F statistic) was selected. Data are presented with and without spline terms for all analyses in which splines were used. Partial residual plots (22) were used to display data from models with and without spline terms. Regression analysis residuals are the deviations between response data and their predicted values based on the regression model. Hence, if predictions accurately describe relationships between response variables and covariates, residuals should have no systematic relationship to covariate values. Lines displaying the model term for log IGF-I and the 95% confidence band, centered at the spline breakpoint, were superimposed on the partial residual plot. All *P* values are two-tailed and are presented analyzing log-transformed IGF-I as a continuous predictor variable. To aid in interpretation of the data, anthropometry and muscle strength dynamometer results are displayed using the predicted response obtained by inserting the mean level for each covariate into the model. For logistic regression analyses we report odds ratios for a decline in IGF-I level of 50 μg/liter (1 SD) to provide clinically relevant estimates. No adjustment was made for multiple comparisons; findings were assessed for coherence and consistency with theory, rather than by focusing on isolated *P* values.

To appropriately reference inferences derived from the combined data back to the sampling population of community-dwelling women, aged 70–79 yr, study-specific probability weights were used. Construction of the weights has been detailed previously (16, 23). Probability weights were incorporated into all of our descriptive and regression analyses using the survey weighting capability provided by Stata statistical software (24), which weights each woman's data to count proportionately in the analysis for the number of women she represents in the sampling frame and generates SEs that correctly represent the resulting coefficient variability. No qualitative differences in results were obtained in analyses without the probability weights.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the 617 women, aged 70–79 yr, who participated in WHAS I or WHAS II and whose phlebotomy was within 90 d of measurement of all outcomes. The WHAS I cohort, which was designed to include the one third most disabled community dwelling women, had a lower percentage of Caucasians, fewer high school graduates, lower income, less daily activity, and more medical diagnoses than their WHAS II counterparts of the same age ($P < 0.01$). In addition, WHAS I women had worse self-reported health, greater difficulty with activities of daily living, and greater difficulty with mobility-related tasks than did WHAS II women ($P < 0.01$). These attributes are reflected in their strength and performance measurements; WHAS I women were weaker and slower than the women of WHAS II ($P < 0.01$).

IGF-I measurements and age

The range of IGF-I values in the 728 women who had IGF-I levels drawn at baseline in WHAS I or II was 12.8–461.3 μg/liter. Using probability weighting to adjust for sample design and differential nonresponse (25), we obtained an approximation of the population distribution of IGF-I levels in community-dwelling women between the ages of 70 and 79 yr (Fig. 2). The mean IGF-I value was 123.6 ± 51.8 (±SD) μg/liter. Over the 10-yr span represented, IGF-I levels did not change with age. Fourteen percent of the IGF-I levels were below the age-specific normal lower limit of the assay (71 μg/liter).

TABLE 1. Baseline characteristics of 70- to 79-yr-old women in WHAS I (moderately to severely disabled women) and WHAS II (not or mildly disabled)

Characteristic	WHAS I (n = 257)	WHAS II (n = 360)
Demographic		
Age (yr)	74.2 (2.7)[a]	74.0 (2.7)[b]
Race (% Caucasian)	70	83
Education (% high school grad)	36	74
Income (% <$10,000/yr)	46	26
Activity		
Kcal expended/wk	657 (1184)	1182 (1339)
Health status		
No. of medical diagnoses	3.0 (1.6)	1.9 (1.3)
Self-reported health (%)		
Excellent or very good	13	51
Good	34	39
Fair or poor	53	10
Difficulty in at least 1 ADL (%)	60	11
Biochemical measurements		
Serum albumin (g/liter)	40 (3)	43 (3)
Serum IGF-I (μg/liter)	119.2 (61.1)	122.4 (44.4)[b]
Physical characteristics		
Wt (kg)	72.2 (18.2)	68.1 (13.0)
Ht (cm)	157.1 (6.6)	160.4 (6.0)
BMI (kg/m^2)	29.2 (7.2)	26.5 (5.0)
Arm muscle area (cm^2)	45.8 (18.4)	38.8 (11.1)
Strength by dynamometer (kg)		
Grip	22.1 (5.2)	25.7 (4.9)
Knee extension	13.9 (5.4)	21.5 (5.8)
Hip flexion	11.3 (5.3)	18.9 (8.2)
Performance measures		
Walking speed (m/sec)		
Rapid pace 4-m walk	1.04 (0.43)	1.51 (0.39)
Usual pace 4-m walk	0.66 (0.28)	1.02 (0.27)
5 chair stand speed (stands/sec)	0.36 (0.08)	0.40 (0.09)
Self-reported difficulty in physical functions (%)		
Getting in/out of a chair	33	3
Walking up 10 steps	53	7
Lifting/carrying 10 lb	67	10
Walking 2–3 blocks	75	12
Heavy housework	79	20

ADL, Activities of daily living.
[a] Expressed as mean, with SD in *parentheses*.
[b] $P = 0.42$ for age, $P = 0.45$ for IGF-I, $P < 0.01$ for all other variables.

Relationship between IGF-I and anthropometry measures

Tables 2 and 3 show the age-adjusted and multivariate-adjusted means, respectively, for measures of anthropometry by quintile of IGF-I value. There was no statistically significant relationship between IGF-I levels and body mass index (BMI), triceps skinfold measurement, or arm muscle area calculation in age-adjusted or multivariate-adjusted analyses. These values reflect the expected impact that variation in IGF-I values has on each measure when holding constant each of the other covariates at the group mean. For example, for a woman of average age, the predicted BMI is 27.1 kg/m^2 given an IGF-I level in the first quintile; it is 27.6 kg/m^2 given an IGF-I level in the second quintile, an incremental difference of only 0.5 kg/m^2. The values of the log IGF-I coefficient and the *P* value for IGF-I as a continuous measure are also shown.

Relationship between IGF-I and muscle strength measures

Predicted mean values of each of the muscle strength measures at each quintile of IGF-I level are shown in Tables 2 and 3 for a woman with average values of each of the covariates included in the analyses. In age-adjusted analyses, the IGF-I level was associated with knee extensor strength of the dominant leg ($P = 0.004$), although not with grip or hip flexor strength (Table 2). As shown in Table 3, the association of IGF-I with knee extensor strength was attenuated after adjustment for markers of activity level, nutritional status, comorbid illness, and chronic disease ($P = 0.07$). No improvement in either age-adjusted or multivariate-adjusted models was seen with fitting spline terms.

Relationship between IGF-I and performance-based measures

The level of IGF-I was weakly associated with walking speed in the age-adjusted analyses, with slopes indicating slight improvements in walking speed with increases in the natural log of the IGF-I level (Table 4). This relationship lost statistical significance after adjustment for other covariates. Figure 3A displays a representative partial residual plot for the multivariate-adjusted rapid pace 4-meter walk. These data and the others for walking speed suggested that there was a potentially different relationship between IGF-I and walking speed in those with the lowest IGF-I values compared with the remainder of the women studied. When we fit a spline term at a natural log of 3.91, which corresponds to an IGF-I level of 50 μg/liter, we found a positive relationship between IGF-I and all measures of walking speed in the 35 women with levels below that threshold level, and no relationship for IGF-I levels above 50 μg/liter (Table 4). The partial residual plot for the rapid 4-meter walk allowing different relationships with IGF-I above and below 50 μg/liter is shown in Fig. 3B. To illustrate the clinical difference below and above the threshold point, an increase in IGF-I level from 20 to 50 μg/liter was associated with a 0.60 m/sec (1.3 SD) increase in walking speed on the 4-meter rapid walk, whereas no change in walking speed was seen for an anal-

TABLE 2. Age-adjusted relationships between anthropometry and muscle strength measures and IGF-I level

	IGF-I coefficient[a]	*P*[a]	Adjusted means[b] by IGF-I quintile				
			1 (12.5–79.9)	2 (89–107.9)	3 (108–129.9)	4 (130–157.9)	5 (158–461.3)
Anthropometry							
BMI (kg/m^2)	0.61	0.33	27.1	27.6	27.4	27.4	28.0
Triceps skinfold (mm)	0.15	0.06	22.2	23.0	24.3	23.0	24.5
Arm muscle area (cm^2)	−0.42	0.79	42.3	41.4	41.6	41.7	41.4
Muscle strength (kg)							
Grip	0.85	0.09	23.2	24.5	25.5	24.2	24.4
Knee extensor	1.80	0.004	17.2	18.8	19.5	18.9	19.9
Hip flexor	0.63	0.39	15.2	16.5	17.3	15.5	16.4

[a] From multiple linear regression of response variable on IGF-I, adjusting for age. The IGF-I coefficient estimates the value by which the average response varies per unit variation in log IGF-I, holding age constant.
[b] Estimated from regression model, holding age constant at the overall mean age.

TABLE 3. Multivariate-adjusted relationships between body composition and strength measures and IGF-I level

	IGF-I coefficient[a]	*P*[a]	Adjusted means[b] by IGF-I quintile				
			1 (12.5–79.9)	2 (89–107.9)	3 (108–129.9)	4 (130–157.9)	5 (158–461.3)
Body composition							
BMI (kg/m^2)	0.77	0.19	26.7	27.9	27.8	27.6	27.9
Triceps skinfold (mm)	0.11	0.19	22.4	23.3	24.3	22.9	24.1
Arm muscle area (cm^2)	−0.50	0.67	41.2	42.0	42.3	41.9	41.4
Muscle strength (kg)							
Grip	0.52	0.31	23.4	24.3	25.3	24.1	24.4
Knee extensor	1.10	0.07	17.8	18.7	19.1	18.6	19.7
Hip flexor	−0.04	0.96	15.7	16.4	17.0	15.4	16.3

[a] From multiple linear regression of response variable on IGF-I, adjusting for age, serum albumin level, activity level, number of comorbid illnesses, and self-assessed health. The IGF-I coefficient estimates the value by which the average response varies per unit variation in log IGF-I, holding adjustment variables constant.
[b] Estimated from regression model, holding each variable constant at the overall mean of the variable.

TABLE 4. Change in muscle performance measures per log unit IGF-I level

	Age-adjusted[a] model			Multivariate-adjusted[a] model		
	Across all IGF-I levels [β (95% CI)]	IGF-I below threshold [β (95% CI)][b]	IGF-I above threshold [β (95% CI)]	Across all IGF-I levels [β (95% CI)]	IGF-I below threshold [β (95% CI)][b]	IGF-I above threshold [β (95% CI)]
Walking speed (m/s)						
Rapid pace 4-meter walk						
Speed in 1st meter	0.05 (−0.004–0.10)	0.51 (0.29–0.73)[c]	0.001 (−0.05–0.05)	0.02 (−0.03–0.08)	0.43 (0.20–0.66)[c]	−0.02 (−0.07–0.03)
Speed at 4 meters	0.11 (0.02–0.20)	0.80 (0.47–1.12)[c]	0.04 (−0.07–0.14)	0.06 (−0.03–0.15)	0.65 (0.30–1.00)[c]	−0.002 (−0.10–0.10)
Usual pace 4-meter walk						
Speed in 1st meter	0.05 (0.006–0.09)	0.34 (0.17–0.51)[c]	0.01 (−0.03–0.06)	0.03 (−0.01–0.06)	0.26 (0.09–0.42)[d]	−0.001 (−0.04–0.04)
Speed at 4 meters	0.07 (−0.001–0.13)	0.48 (0.24–0.73)[c]	0.02 (−0.06–0.10)	0.04 (−0.03–0.10)	0.37 (0.12–0.62)[d]	0.001 (−0.07–0.07)
Chair stand speed (stands/sec)						
5-repetition chair stand	0.01 (0.005–0.03)	0.09 (0.05–0.14)[c]	−0.01 (−0.04–0.02)	0.001 (−0.002–0.005)	0.08 (0.03–0.13)[d]	−0.01 (−0.04–0.01)

[a] From multiple linear regression of response variable on IGF-I, adjusting for age (age-adjusted model) or age, serum albumin level, activity level, number of comorbid illnesses, and self-assessed health (multivariate-adjusted model). The IGF-I coefficient estimates the value by which the average response varies per unit variation in log IGF-I, holding adjustment variables constant.

[b] Threshold point ≤50 μg/liter for walking speed; ≤70 μg/liter for chair stand speed.

[c] $P < 0.001$.

[d] $P < 0.005$.

ogous increase in log units, from 50 to 125 μg/liter, using the multivariate-adjusted model. We found a similar relationship in analyses of IGF-I and chair stand speed in a five-repetition chair stand; here, the best fitting model was at a threshold IGF-I value of 70 μg/liter (Table 4), with 95 women with IGF-I values less than 70 μg/liter.

Relationship between IGF-I and self-report of difficulty in physical function

To explore the relationship between IGF-I and outcomes distal in our pathway, we examined the association between IGF-I levels and self-reported difficulty in physical function. Five questions on mobility tasks were used as dichotomous outcomes (difficulty or no difficulty) in age-adjusted and multivariate-adjusted logistic regression analyses. Table 5 presents the age- and multivariate-adjusted associations between IGF-I and difficulty in specific tasks. A 50-U decline in IGF-I levels from the mean value of 123.6 μg/liter was associated with a 12–59% increase in the odds of reporting difficulty in each of the tasks in the age-adjusted analyses. These values achieved statistical significance for getting in or out of a chair, difficulty walking up 10 steps, and performing heavy housework ($P < 0.05$). In the multivariate analyses, the associations were attenuated for all tasks. However, statistical significance persisted for 2 tasks, with a 42% increase in difficulty getting in or out of a chair ($P = 0.007$) and a 31% increase in the odds of reporting difficulty walking up 10 steps ($P = 0.05$).

Discussion

In this combined cohort spanning the full range of physical function in community-dwelling older women, we found a wider range of IGF-I values and a lower mean value than those reported in prior cohort studies (3, 4); the exception is 1 study of 77 women over the age of 65 yr with functional limitations, who had a mean level of 110.9 μg/liter (13). In addition, we are the first, to our knowledge, to find associations between IGF-I and knee extensor strength and between IGF-I and self-reported function on several mobility-related tasks over the entire range of IGF-I values. Finally, we described an association between IGF-I level and walking and chair stand speed specific to levels below the reported age-specific normal range. These findings were attenuated after adjustment for markers of activity level, nutritional status, comorbid illness, and chronic disease.

IGF-I levels have been reported to decline with age, based on cross-sectional data from several cohort studies of older individuals (1–6). We report a wide range of IGF-I levels in the older women studied here, with a significant percentage (14%) below the assay range of 71–290 μg/liter specified by Nichols. This assay range was originally determined based on 123 healthy men and women between the ages of 55 and 85 yr, using the levels of the middle 95% of values to define normal. Using the same criteria in the 728 women, aged 70–79 yr, in WHAS I and II, the normal range could be considered to be 47–203 μg/liter, considerably lower than the current range. However, this method of determining the normal range fails to account for the clinical significance of

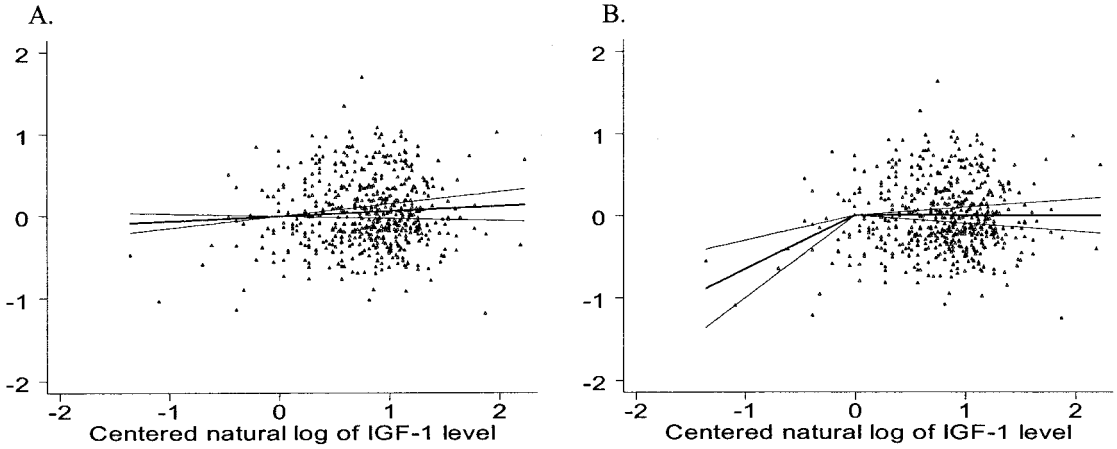

FIG. 3. Partial residual plots for rapid 4-m walking speed for models assuming linear (A) and spline (B) relationship with log IGF-I, respectively. The *y*-axis values are predicted walking speed, adjusting out contributions for all other covariates in the model and centered around predictions at log IGF-I = 3.91. The *darker solid line* plots model terms involving log IGF-I; the *small triangles* plot these terms plus model residuals. The *lighter solid lines* represent a 95% confidence band for predicted centered walking speed, adjusted for all other covariates in the model. A well fitting model should have plotted *triangles* distributed evenly around the *solid line*. In contrast, the *leftmost triangles* in A predominantly fall below the line, suggesting the need for the nonlinear model in B.

TABLE 5. Odds ratios of self-reported difficulty in physical function associated with a 50 μg/liter decline in IGF-I level from the mean

Task	Age-adjusted [OR (95% CI)]	Multivariate-adjusted [OR (95% CI)]
Getting in/out of a chair	1.59 (1.26–2.02)[a]	1.42 (1.10–1.83)[a]
Walking up 10 steps	1.41 (1.12–1.77)[a]	1.31 (1.00–1.70)[a]
Lifting/carrying 10 lb	1.21 (0.98–1.49)	0.99 (0.78–1.20)
Walking 2–3 blocks	1.12 (0.92–1.38)	0.92 (0.73–1.17)
Performing heavy housework	1.23 (1.01–1.50)[a]	1.09 (0.86–1.39)

[a] $P < 0.05$.

levels defined as abnormal and therefore may not be clinically appropriate or meaningful.

The clinical significance of an abnormal IGF-I level in an older individual is unknown. Because of the trophic effects of GH and IGF-I on muscle, it has been suggested that low IGF-I levels could result in adverse clinical consequences. Prior observational studies in large cohorts of elderly people have been unable to support relationships between the IGF-I level and measures of body composition or muscle strength after adjustment for age (2–6, 13). A potential explanation for this is the homogeneity of these outcomes in these relatively healthy older individuals. We were also unable to find an association in this present study between IGF-I levels and the anthropometry measures obtained in WHAS I and II: BMI, triceps skinfold, and arm muscle area. It is possible that other measurements that more precisely assess muscle and fat mass might make these relationships apparent. BMI is a poor marker for lean body mass, the skinfold measurement was performed using calipers at a single site, and the arm muscle area was calculated from triceps skinfold and arm circumference measurements using a formula that is not well validated in older individuals (19).

Our finding of a relationship between IGF-I levels and knee extensor strength suggests a role for IGF-I in the quadriceps muscle. However, we have difficulty explaining the lack of the consistency using other dynamometer measures of grip and iliopsoas strength, so that the isolated strength finding must be interpreted with caution. It is possible that the effects of arthritis diminished the validity of dynamometer testing of muscle strength, an insurmountable problem in testing older individuals. However, after exclusion of participants who reported pain in the joint with strength testing, the reported relationships were unchanged (data not shown).

Because of the large number of women available for our analyses, we were able to examine associations between IGF-I and mobility outcomes in women with low IGF-I levels. Clinical trials of GH therapy in older individuals have found modest improvements in the percentage of muscle mass or muscle strength using small numbers of healthy volunteers (26–29). Our analyses support the potential for a threshold of IGF-I values, below which clinically significant effects would be obtained from modest improvements in IGF-I level, but above which such effects would be unapparent. The specific threshold values identified in this investigation represent the best estimates from our data and are imprecise secondary to a limited number of WHAS participants at low IGF-I levels. The difference in threshold level that we found between walking speed and chair stand speed may also reflect this limitation. However, although we cannot precisely identify the threshold point, in sensitivity analyses in which we removed the lowest values of IGF-I, the presence of a threshold effect was upheld.

No prior studies of IGF-I in older women have used a study population with as wide a spectrum of physical function as our cohort. WHAS II, which was designed to include the two thirds least disabled women living in the community, is comprised of a study population that is typical of healthy older women who are usually included in epidemiological studies. WHAS I, as a cohort designed to represent the one third most disabled women living in the community, is comprised of a group of women who are ordinarily difficult to access for research studies. The use of sampling from the HCFA database instead of volunteer recruitment mecha-

nisms as well as home visits instead of travel to a study clinic enabled us to enroll women who ordinarily exclude themselves from research studies. Our findings were not present if we performed our analyses in WHAS II alone, but required the broader range of IGF-I values and function resulting from inclusion of both WHAS I and II. In addition, using information in the HCFA database, we were able to extrapolate back to the original population eligible for enrollment using weighting procedures to account for missing women. However, because our study sample was limited to women between the ages of 70–79 yr, our findings may not be generalizable to women outside this age range or to men.

There is considerable controversy regarding the use of the IGF-I level as a measure of GH status. Multiple GH-independent factors have been reported to affect IGF-I levels, including nutritional status, comorbid illness, liver function, and alcohol intake (3, 4, 7–12). We attempted to account for these confounding influences in our multivariate analyses by controlling for albumin level, a calculated activity level based on self-reported function, the number of physician-diagnosed illnesses, and self-reported health. Additional analyses in which we excluded those with abnormal transaminase levels or alcohol intake above 14 drinks/wk did not alter our findings (data not shown). The magnitude of the IGF-I effect was attenuated in all analyses after multivariate adjustment, and in several analyses, associations seen after adjustment for age alone lost statistical significance. These findings suggest that the IGF-I level is an aggregate marker for poor nutrition, low activity, and comorbid illness. For other relationships, in which the statistically significant association persisted after multivariate adjustment, two possibilities exist: there is an independent association of IGF-I with strength, muscle performance, and mobility; or residual confounding remains due to the crudity of measurement of our covariates or from other, unknown covariates not included in our model.

To our knowledge, we are the first to report an association between a decline in IGF-I levels and difficulty in strength and mobility-related functional outcomes. Although biologically plausible, a causal relationship between IGF-I and our outcomes cannot be proven from this study due to its cross-sectional design. Should these preliminary findings be confirmed in longitudinal analyses, other observational studies, and clinical trials, this would suggest a potential impact of raising IGF-I levels on the quality of life of older individuals. There has been appropriate caution regarding the administration of GH to older people, including concern over deleterious side-effects, promotion of growth of underlying malignancies, inconvenience of administration, and prohibitive cost. Moreover, the value of r^2 was less than 3% for all unadjusted models, which demonstrates that the IGF-I level predicts little of the variance in muscle measures. This finding reflects the multiple factors that are important in determination of muscle strength and function and suggests that current knowledge is insufficient to identify a target group in whom administration of GH could be expected to consistently improve strength outcomes. Although this finding cautions against the present utility of IGF-I for diagnosing or predicting functional outcomes clinically, it does not diminish the validity of our findings of population level trends in strength and function with IGF-I levels. At the population level, the confidence intervals about estimated spline functions strongly supported a substantial decline in average walking speed and chair stands in association with sufficiently low thresholds of IGF-I. Hence, the potential exists for identifying target groups who could benefit from interventions that raise IGF-I levels. Newer GH secretagogues show promise as more acceptable therapies for intervention (30). Continued investigation for an appropriate target group of older individuals for interventions to improve mobility is warranted in parallel with development of new hormonal pharmacological therapies.

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Address all correspondence and requests for reprints to: Anne R. Cappola, M.D., Sc.M., Division of Endocrinology, Diabetes, and Nutrition, University of Maryland School of Medicine, 660 West Redwood Street, Room 495A, Baltimore, Maryland 21201. E-mail: acappola@medicine.umaryland.edu.

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