The relationship between serum IGF-1, handgrip strength, physical performance and falls in elderly men and women

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Abstract

Objective: Human aging is accompanied by a decrease in growth hormone secretion and serum insulin-like growth factor (IGF)-1 levels. Also, loss of muscle mass and strength and impairment of physical performance, ending in a state of frailty, are seen in elderly. We aimed to investigate whether handgrip strength, physical performance and recurrent falls are related to serum IGF-1 levels in community-dwelling elderly.

Design: Observational cohort study (cross-sectional and prospective).

Methods: We studied the association between IGF-1 and handgrip strength, physical performance and falls in participants of the Longitudinal Aging Study Amsterdam. A total of 1292 participants were included (633 men, 659 women). Serum IGF-1 levels were divided into quartiles (IGF-1-Q1 to IGF-1-Q4). Data on falls were collected prospectively for a period of 3 years. All analyses were stratified for age and physical activity and adjusted for relevant confounders.

Results: Men with a low physical activity score in IGF-1-Q1 and IGF-1-Q2 of the younger age group had a lower handgrip strength compared to IGF-1-Q4. In younger more active males in IGF-1-Q2 physical performance was worse. Recurrent fallers were less prevalent in older, low active males with low IGF-1 levels. In females, recurrent fallers were more prevalent in older, more active females in IGF-1-Q2. IGF-1 quartile may predict changes in handgrip strength and physical performance in men and women.

Conclusions: Our results indicate that lower IGF-1 levels are associated with lower handgrip strength and worse physical performance, but less recurrent fallers especially in men. Associations were often more robust in IGF-1-Q2. Future studies on this topic are desirable.

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Introduction

Human aging is accompanied by a decrease in spontaneous growth hormone (GH) secretion and a decline in serum insulin-like growth factor (IGF)-1. The term ‘somatopause’ is frequently used to refer to this age-related decline in GH secretion (1, 2, 3, 4). Studies indicate a decrease in spontaneous GH secretion of 14% per decade in adults

between the third and eighth decade, resulting in a state comparable with functional growth hormone deficiency (GHD) in elderly men and women in the lower part of the distribution of GH secretion (1, 5, 6, 7, 8).

During normal aging, several other physiological processes take place such as loss of muscle mass and

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muscle strength and an impairment of mobility, balance and physical performance, ending in a state of frailty (9, 10). A decrease in muscle strength of 30–40% is reported between the ages of 30 till 80 years, and this decrease may even accelerate in later decades of life (5). Furthermore, the incidence of falls increases with ageing (11). Within the community-dwelling persons over the age of 65 years, about 30% falls at least once every year and about 15% even falls twice or more per year (12).

Falls can result in fractures (about 5%), soft tissue and head injuries causing considerable morbidity and loss of quality of life. Over 95% of hip fractures in elderly persons are caused by falls (13). On a yearly basis, it was estimated that over 300 000 older people were hospitalised as a result of these hip fractures in the United States (14). Hospitalisation and increased morbidity resulting from both falls and fractures all lead to a substantial financial burden for the health care system.

Some of the physiological changes during normal aging in healthy elderly men and women show similarities with symptoms described in GH-deficient adults. There are some studies of associations between serum IGF-1, handgrip strength and physical performance in elderly, however, only one of these reports briefly that serum IGF-1 levels were not significantly associated with falls (15, 16, 17, 18, 19).

Hence, the aim of this study was to investigate whether handgrip strength, physical performance and falls are related to serum IGF-1 levels in community-dwelling elderly. Furthermore, we studied the clinical utility of serum IGF-1 concentration to predict a decrease in handgrip strength and physical performance and increased risk of falls in the next 3 years.

Subjects and methods

Study population

For the present study, data were collected within the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary, longitudinal cohort study on the predictors and consequences of changes in physical, cognitive, emotional and social functioning in older men and women (20, 21, 22). From the population registers of 11 municipalities in three regions in the Netherlands, a random sample was drawn of over 3000 community-dwelling older men and women, 55–85 years of age, stratified by age and sex and weighted according to

expected 5-year mortality. This sample is considered to be a representative sample of the Dutch population. In the baseline study, performed in 1992/1993, 3107 participants were enrolled. Every 3 years, medical interviews, performed by intensively trained and supervised interviewers, were repeated as well as follow-up measurements. The study was approved by the Medical Ethics Review Committee of the VU University Medical Center and informed consent was obtained from all participants.

For the present study, we used a subgroup of the LASA cohort at the second data collection in 1995/1996 (LASA-C), including participants aged ≥ 65 years as of January 1, 1996, since IGF-1 measurements were performed on blood samples of these participants ($N=1319$). Participants treated with GH ($N=1$) or oestrogens ($N=14$) and subjects with serum creatinine levels $>200\mu\text{mol/L}$ ($N=12$) were excluded from the analyses. Accordingly, 1292 participants were included in the present analysis ($N=633$ males and $N=659$ females).

Three years later, in 1998/1999 (LASA-D), several outcome measurements were repeated. We used these data to study whether serum IGF-1 concentration at LASA-C could be used to predict a change in handgrip strength, physical performance and risk of falls 3 years later. For more information about LASA and the data collection, see also the LASA website (<http://www.lasa-vu.nl>).

Handgrip strength

Handgrip strength was recorded to the nearest of 1 kg using a calibrated strain-gauged dynamometer (Takei TKK 5001, Takei Scientific Instruments Co. Ltd, Tokyo, Japan), adjusted for hand size. All participants performed two maximum handgrip strength trials with each hand, standing with their arm along the body. The mean of the maximum scores of the left and right hand was used for analysis of handgrip strength. If handgrip strength measurements were missing for one hand, handgrip strength was calculated using the scores of the other hand if available. This procedure was performed within LASA-C and 3 years later in LASA-D. Change in handgrip strength (LASA-D corrected for LASA-C) was calculated as $((\text{handgrip strength LASA-D} - \text{handgrip strength LASA-C}) / \text{handgrip strength LASA-C}) \times 100\%$. A positive value of change thus represents an increase in handgrip strength and negative value, a decrease in handgrip strength.

Physical performance

Physical performance was measured in LASA-C and LASA-D with a short battery of tests, including a walking test, chair stand test and tandem stand test. The walking test was used for measuring walking speed and was tested by asking subjects to walk 3 m, turn around 180° and walk back 3 m as quickly as possible and measure the total time needed. The chair stand test was used for measuring leg strength by testing the ability to rise from a chair. The participants were asked to fold their arms across the chest and to stand up from a sitting position and sit down five times as quickly as possible while time was measured. For both tests the score ranged from 0 (unable to perform the test) to 4 (fastest quartile of time required doing the test). The tandem stand test was used to test standing balance and subjects were asked to attempt to maintain their feet in the tandem position (heel of one foot directly in front of the other foot) for at least 10 seconds (s). This score was categorised in three categories, namely category 1: unable (0 points), category 2: 3–9 s (2 points) and category 3: ≥ 10 s (4 points). The total score for physical performance was calculated by summing the three before mentioned scores to a final score (0–12 points), where a lower score indicated a poor physical performance (23). The change in physical performance between LASA-C and LASA-D (LASA-D corrected for LASA-C) was calculated by: $((\text{physical performance score at LASA-D} - \text{physical performance score at LASA-C}) / \text{physical performance score at LASA-C}) \times 100\%$. A positive value of change thus represents an increase in physical performance and a negative value a decrease. Subjects with functional limitations (wheelchair users or subjects not able to perform the tests) were excluded.

Falls

Between LASA-C and LASA-D, data on falls have been registered prospectively by a 3-year 'fall calendar'. Participants were asked to record fall events weekly (whether or not they had fallen in that week and to document whether a fall occurred inside or outside their home). Fall calendars were mailed to the institute at the end of every 3-month period and if not participants received a reminder and were contacted by telephone if they did not respond. A fall was defined by 'an unintentional change in position resulting in coming to rest at a lower level or on the ground' (24). A recurrent faller was defined as a subject who fell at least two times within a 6-month period during the 3-year fall follow-up,

and this variable was used for analysis of falls. Subjects with functional limitations (wheelchair users or subjects not able to walk) were excluded from the analysis.

Laboratory assays

Blood samples for IGF-1 measurements were obtained during LASA-C and were drawn in the morning after at most tea and plain toast, processed within 60 min and stored at -20°C until analysis in 1999. All samples were analysed together in one run to eliminate possible inter-assay variation. For IGF-1 levels, an immunoradiometric assay after extraction (DSL, Webster, TX, USA) was used, detection limit 1 nmol/L, intra-assay coefficient of variation (CV) less than 4%, inter-assay CV $<14\%$. For both men and women aged >60 years, the reference range for IGF-1 values with the used method is 11–19 nmol/L. For conversion of IGF-1 from nmol/L to $\mu\text{g/L}$: multiply by 7.65. Creatinine was measured using the Jaffe alkaline picrate reaction with a Hitachi 747 analyzer, reference range 60–110 $\mu\text{mol/L}$. Albumin concentrations were measured using two different methods, namely the bromocresol green (BCG) and the bromocresol purple (BCP) photometric assay. Measurements were made comparable using the following validated formula $\text{BCG} = \text{BCP} + 5.5$, reference range 34–50 g/L. Testosterone level was measured using a radioimmunoassay (Coat-A-Count, DPC LA, USA) with an inter-assay CV of 11, 7 and 6% at mean testosterone concentrations of 1.5, 5 and 30 nmol/L respectively. The detection limit was 1 nmol/L. For measurements of oestradiol a radioimmunoassay (Double antibody Diasorin Biomedica, Saluggia, Italy) was used with an inter-assay CV of 14% and 7% at mean oestradiol concentrations of 30 pmol/L and 100 pmol/L respectively. The detection limit was 18 pmol/L. Except for albumin, all analyses were performed at the Endocrine Laboratory of the VU University Medical Center.

Potential confounders

Potential confounders included BMI, smoking habits, alcohol consumption, chronic diseases, albumin, creatinine, testosterone (in males), oestradiol (in both males and females), educational level and physical activity. BMI was calculated as weight (kg) divided by square height (m^2). Weight was measured using a calibrated bathroom scale (Seca, model 100, Lameris, Utrecht) to the nearest 0.1 kg. Height was measured using a stadiometer to the nearest 0.1 cm. To minimize possible overestimation of BMI, that may occur as height tends to

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decline with aging, weight measured in 1995/1996 and height from the baseline study in 1992/1993 were used for BMI calculations. Self-reported height and weight were used when measurements were not possible or not performed. Lifestyle variables were assessed during the face-to-face medical interviews. Smoking status included never/former/current smoking. Alcohol consumption was categorised as no/light/moderate/excessive according to Garretsen index (25, 26). Also, self-reported chronic diseases, including asthma/COPD, cardiac disease, peripheral arterial disease, diabetes mellitus, CVA/stroke, osteoarthritis/rheumatoid arthritis and cancer, were assessed with detailed questionnaires and were used for analysis in the following categories: none, one, two or more chronic diseases. Physical activity was estimated for the previous 2 weeks by using the LASA physical activity questionnaire (LAPAQ), which is a validated, face-to-face questionnaire of daily physical activity (household, sport and leisure activities) in older people (27). A total physical activity score was calculated as time spent on physical activity in minutes per day during the previous 2 weeks.

Statistical analysis

All outcome measures and confounders were checked for normal distribution and when needed a logarithmic transformation was performed to approximate normal distribution.

Since IGF-1 levels differ in both sexes and may have different effect in each gender, we analysed all data separately for male and female subjects. IGF-1 levels were normally distributed. IGF-1 levels were divided in quartiles (Q), with IGF-1-Q1 as lowest IGF-1 quartile and IGF-1-Q4 as highest, which was also used as reference group.

Age and physical activity were considered to be potential effect modifiers. Indeed, we found significant interactions between IGF-1 and total physical activity score and between IGF-1 level and age for some of the outcome measurements in men. Therefore, all analyses were stratified for age and physical activity, and in all analyses, they were also included as potential confounders, to correct for differences in age and physical activity within the stratified groups. In men, median age was 75.4 years, in women 74.9 years. Median total physical activity score in men was 94.3 min/day and for women 155.7 min/day. The groups were accordingly dichotomised and analysed separately.

Linear regression analysis was used to examine the association between IGF-1 levels and handgrip strength and physical performance. In the first model, only the

four IGF-1 quartiles were included (unadjusted model). In the second model, we adjusted for all previously mentioned confounders (adjusted model). For analysis of a possible association between IGF-1 quartiles and falls, logistic regression analysis was used with the same models as mentioned earlier. Two-sided *P* values of <0.05 were considered statistically significant. All analyses were performed using the statistical software package SPSS, version 22 (SPSS). Values are presented as mean with s.d. or median with interquartile range (IQR), unless stated otherwise. For linear regression analyses, all data are presented as standardised beta. For logistic regression analyses, all data are presented as odds ratios (OR).

Results

In total, 1292 participants were included in the analyses, 633 males (49%) and 659 females (51%). Table 1 describes the baseline characteristics. Mean IGF-1 levels were 14.4 nmol/L and 13.2 nmol/L in males and females respectively. Within the male participants, the IGF-1 ranges were as follows: IGF-1-Q1: 3.1–11.0 nmol/L; IGF-1-Q2: 11.1–14.0 nmol/L; IGF-1-Q3: 14.1–17.3 nmol/L; IGF-1-Q4: 17.4–37.0 nmol/L. In the female participants, the IGF-1 ranges were IGF-1-Q1: 1.3–9.7 nmol/L; IGF-1-Q2: 9.8–13.0 nmol/L; IGF-1-Q3: 13.1–16.0 nmol/L; IGF-1-Q4: 16.1–53.4 nmol/L.

Table 2 Panel A displays the results of linear regression analysis between IGF-1 quartiles and handgrip strength and physical performance in men aged 75.4 years and younger. Men in the low physical activity group with IGF-1 levels in the lowest two quartiles had significantly lower handgrip strength at LASA-C compared to men with IGF-1 levels in the highest quartile in the fully adjusted model. We did not observe these differences in the high physical activity group. There were no significant associations between IGF-1 quartiles and change in handgrip strength (LASA-D corrected for LASA-C), neither in the low nor in the high physical activity group. In men in the second IGF-1 quartile in the high activity group, physical performance at LASA-C was worse when compared to the reference group, both in the unadjusted and the fully adjusted model. In the younger, less active men there was a significant trend for the association between IGF-1 quartiles and handgrip strength at LASA-C in the adjusted model (*P*=0.004).

Table 2 Panel B describes the results of the older men. In the low physical activity group, there was a higher handgrip strength at LASA-C in men in the

Table 1 Baseline characteristics of the total study population.

	Men (n=633)	Women (n=659)
Age (years) [†]	75.4 (11.5)	74.9 (10.6)
IGF-1 (nmol/L) [†]	14.4 (5.0)	13.2 (5.2)
Lowest quartile (IGF-1-Q1)	8.5 (1.9)	7.4 (1.9)
Second quartile (IGF-1-Q2)	12.6 (0.8)	11.4 (1.0)
Third quartile (IGF-1-Q3)	15.6 (0.9)	14.4 (0.8)
Highest quartile (IGF-1-Q4)	21.0 (3.6)	19.8 (4.5)
Physical activity (min/day) [‡]	94.3 (113.6)	155.7 (120.0)
BMI (kg/m ²) [†]	25.9 (3.4)	27.4 (4.6)
Smoking (%)		
Never	10.3	59.5
Former	64.6	28.7
Current	25.1	11.8
Alcohol use (%)		
None	14.1	33.7
Light	49.1	51.6
Moderate	26.9	12.3
Excessive	10.0	2.3
Chronic diseases (%)		
None	29.5	25.5
One	36.7	38.2
Two ore more	33.8	36.1
Albumin (g/L) [†]	44.5 (2.7)	44.3 (2.6)
Creatinine (μmol/L) [†]	102.1 (19.9)	84.2 (15.5)
Total testosterone (nmol/L) [†]	15.4 (5.0)	na
Total oestradiol (nmol/L) [†]	77.2 (25.3)	31.7 (13.9)
Educational level (%)		
Elementary not completed	5.4	13.7
Elementary education	23.5	40.1
Lower vocational education	24.6	14.6
General intermediate education	9.2	12.6
Intermediate vocational education	18.0	9.3
General secondary education	2.7	2.7
Higher vocational education	10.7	4.7
College education	1.3	0.8
University education	4.4	1.5
≥2 falls within 6 months (%)	(n=619)	(n=638)
Yes	26.0	26.5
No	74.0	73.5

Continuous variables are expressed as mean (s.d.) for normally distributed variables (†) and as median (IQR) for skewed variables (‡). Categorical variables are presented as number (%).
N.a., not applicable.

lowest IGF-1 quartile in the fully adjusted model, this was borderline significant in the second quartile. Men in the second IGF-1 quartile in the high activity group showed a higher, positive, change in handgrip strength between LASA-C and LASA-D when compared to men in the highest IGF-1 quartile in the fully adjusted model. This was nearly significant in the first and third IGF-1 quartile. In the adjusted model, there also was a significant trend for the association between IGF-1

quartiles and handgrip strength at LASA-C in the low activity group ($P=0.011$).

Table 3 Panel A represents the results of linear regression analysis of quartiles of IGF-1 with handgrip strength and physical performance in younger women. No consistent associations were found. In women with a high physical activity score, there was a significant trend for the association between IGF-1 quartiles and both change in handgrip strength (LASA-D corrected for LASA-C) and change in physical performance (LASA-D corrected for LASA-C) in the adjusted model ($P=0.035$ and $P=0.025$, respectively).

In **Table 3** Panel B the results of older women are displayed. In the low activity group, handgrip strength at LASA-C was lower in women in the first and second IGF-1 quartile when compared to the highest quartile, in the fully adjusted model this remained significant in women in the lowest IGF-1 quartile only. Physical performance at LASA-D was worse in women in the lowest three IGF-1 quartiles when compared to the highest IGF-1 quartile in the unadjusted model, which after adjustments only remained significant in the first IGF-1 quartile. In the low activity group, there was a significant trend for the association between IGF-1 quartiles and handgrip strength at LASA-C as well as between IGF-1 quartiles and physical performance at LASA D in the adjusted model ($P=0.002$ and $P=0.026$, respectively).

Table 4 shows the results of logistic regression analysis of quartiles of IGF-1 and recurrent fallers in both men and women. Recurrent fallers were significantly less prevalent in older men with a low physical activity score in the lowest two IGF-1 quartiles (fully adjusted model, OR: 0.28 and 0.23, respectively). This was just above the level of significance for IGF-1-Q3 ($P=0.059$), P for trend=0.062. In contrast, in women, recurrent fallers were significantly more prevalent in the second IGF-1 quartile in the high age group with a high physical activity score (fully adjusted model, OR 8.0).

Discussion

In this population-based study of community dwelling elderly aged 65–88 years, we investigated the relationship between serum IGF-1 concentration and handgrip strength, physical performance and recurrent fallers. We observed several significant associations. Men in the lowest two IGF-1 quartiles of the younger age, low

Table 2 Results of unadjusted and adjusted linear regression analysis of quartiles of IGF-1 (Q1–Q4) with handgrip strength and physical performance, stratified for physical activity (total activity score in min/day), in men aged 75.4 years and younger (Panel A) and in men aged over 75.4 years (Panel B).

	Total activity ≤ 94.3						Total activity > 94.3					
	Q1		Q2		Q3		Q1		Q2		Q3	
	β	P	β	P	β	P	β	P	β	P	β	P
Panel A												
Unadjusted												
Hand grip												
LASA-C	-0.336	0.000*	-0.200	0.036*	-0.055	0.569	-0.114	0.188	-0.029	0.735	-0.015	0.863
LASA-D	-0.204	0.049*	-0.255	0.018*	0.006	0.954	-0.075	0.418	-0.050	0.592	-0.035	0.709
LASA-D corrected for LASA-C	0.015	0.890	0.007	0.952	0.133	0.235	0.028	0.763	0.012	0.897	0.000	0.999
Physical performance												
LASA-C	0.044	0.647	-0.116	0.254	-0.094	0.357	-0.129	0.134	-0.183	0.034*	-0.123	0.159
LASA-D	-0.046	0.666	-0.004	0.971	-0.051	0.647	-0.047	0.616	-0.055	0.561	-0.116	0.227
LASA-D corrected for LASA-C	-0.053	0.617	0.213	0.054	0.052	0.639	0.014	0.882	0.004	0.965	0.078	0.419
Adjusted†												
Hand grip												
LASA-C	-0.237	0.014*	-0.195	0.049*	-0.012	0.903	-0.130	0.133	-0.056	0.510	-0.032	0.711
LASA-D	-0.113	0.298	-0.130	0.251	0.113	0.319	-0.077	0.396	-0.104	0.259	-0.070	0.445
LASA-D corrected for LASA-C	-0.014	0.909	0.058	0.644	0.179	0.106	0.016	0.863	-0.042	0.663	-0.032	0.734
Physical performance												
LASA-C	0.066	0.530	-0.135	0.224	-0.089	0.428	-0.105	0.206	-0.167	0.042*	-0.079	0.338
LASA-D	-0.008	0.945	0.108	0.369	0.007	0.954	0.014	0.883	-0.046	0.623	-0.074	0.428
LASA-D corrected for LASA-C	-0.070	0.550	0.250	0.047*	0.105	0.430	0.044	0.660	0.019	0.855	0.094	0.346
Panel B												
Unadjusted												
Hand grip												
LASA-C	0.124	0.272	0.127	0.272	0.063	0.560	-0.083	0.505	0.045	0.700	0.199	0.098
LASA-D	0.016	0.907	-0.062	0.655	0.171	0.193	0.082	0.545	0.216	0.101	0.340	0.010*
LASA-D corrected for LASA-C	0.001	0.993	-0.121	0.382	0.115	0.379	0.221	0.108	0.343	0.011*	0.240	0.069
Physical performance												
LASA-C	-0.024	0.835	0.165	0.166	0.102	0.359	-0.214	0.089	0.137	0.243	0.069	0.562
LASA-D	0.136	0.309	0.184	0.176	0.195	0.132	-0.197	0.143	0.112	0.390	0.165	0.205
LASA-D corrected for LASA-C	0.091	0.517	0.078	0.585	0.015	0.910	-0.018	0.897	0.018	0.894	0.047	0.731
Adjusted†												
Hand grip												
LASA-C	0.273	0.015*	0.219	0.054	0.112	0.281	0.119	0.365	0.061	0.595	0.242	0.044*
LASA-D	0.112	0.441	-0.022	0.882	0.198	0.158	0.243	0.083	0.261	0.044*	0.340	0.010*
LASA-D corrected for LASA-C	-0.013	0.928	0.232	0.121	0.060	0.669	0.297	0.051	0.351	0.013*	0.266	0.059
Physical performance												
LASA-C	0.029	0.810	0.165	0.187	0.092	0.430	-0.069	0.595	0.179	0.116	0.129	0.267
LASA-D	0.175	0.208	0.144	0.301	0.212	0.109	-0.081	0.562	0.054	0.668	0.127	0.323
LASA-D corrected for LASA-C	0.061	0.692	0.054	0.733	-0.004	0.979	0.010	0.949	-0.072	0.612	0.016	0.911

†Adjusted for body mass index, age, smoking status, alcohol intake, chronic diseases, albumin, creatinine, testosterone, oestradiol, level of education and physical activity score. *Two-sided P value <0.05.

LASA-C, data collection in 1995/1996; LASA-D, data collection in 1998/1999.

Table 3 Results of unadjusted and adjusted linear regression analysis of quartiles of IGF-1 (Q1–Q4) with handgrip strength and physical performance, stratified for physical activity (total activity score in min/day), in women aged 74.9 years and younger (Panel A) and in women aged over 74.9 years (Panel B).

	Total activity ≤ 155.7						Total activity > 155.7									
	Q1		Q2		Q3		Q4		Q1		Q2		Q3		Q4	
	β	P	β	P	β	P	β	P	β	P	β	P	β	P	β	P
Panel A																
Unadjusted																
Hand grip																
LASA-C																
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Physical performance																
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LASA-D corrected for LASA-C																

†Adjusted for body mass index, age, smoking status, alcohol intake, chronic diseases, albumin, creatinine, oestradiol, level of education and physical activity score. *Two-sided P value <0.05. LASA-C, data collection in 1995/1996; LASA-D, data collection in 1998/1999.

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Table 4 Results of adjusted logistic regression analysis of quartiles of IGF-1 (Q1–Q4) with recurrent fallers in men and women stratified for age and physical activity. Data are stratified for age (men median age 75.4, women median age 74.9 years) and physical activity score (men median physical activity score 94.3 min/day, women median physical activity score 155.7 min/day). Adjusted for body mass index, age, smoking status, alcohol intake, chronic diseases, albumin, creatinine, testosterone (in men only), estradiol, level of education and physical activity score.

	Men				Women			
	<i>n</i>	OR (95% CI)	<i>P</i>	ER (%)	<i>n</i>	OR (95% CI)	<i>P</i>	ER (%)
Low age, low activity group								
Q1	20	0.195 (0.026–1.453)	0.111	10.0	24	2.277 (0.541–9.577)	0.262	45.8
Q2	36	0.433 (0.098–1.915)	0.270	25.0	33	0.351 (0.078–1.580)	0.173	18.2
Q3	40	0.336 (0.084–1.343)	0.123	17.5	37	0.689 (0.193–2.464)	0.567	27.0
Q4	45	REF		20.0	36	REF		30.6
		<i>P</i> for trend	0.141			<i>P</i> for trend	0.510	
Low age, high activity group								
Q1	32	2.548 (0.659–9.843)	0.175	25.0	33	0.908 (0.273–3.015)	0.875	27.3
Q2	33	3.702 (0.949–12.449)	0.060	24.2	50	0.569 (0.192–1.682)	0.308	20.0
Q3	48	2.102 (0.553–7.989)	0.276	16.7	49	0.343 (0.097–1.209)	0.096	10.2
Q4	64	REF		12.5	61	REF		26.2
		<i>P</i> for trend	0.089			<i>P</i> for trend	0.790	
High age, low activity group								
Q1	50	0.280 (0.083–0.940)	0.039*	34.0	58	1.805 (0.629–5.174)	0.272	41.4
Q2	54	0.234 (0.070–0.783)	0.018*	25.9	47	1.006 (0.336–3.018)	0.991	36.2
Q3	36	0.282 (0.076–1.051)	0.059	30.6	42	0.602 (0.178–2.030)	0.413	21.4
Q4	29	REF		48.3	39	REF		33.3
		<i>P</i> for trend	0.062			<i>P</i> for trend	0.124	
High age, high activity group								
Q1	51	0.849 (0.223–3.242)	0.811	41.2	43	3.435 (0.594–19.853)	0.168	23.3
Q2	30	0.839 (0.207–3.407)	0.806	30.0	31	8.016 (1.247–51.510)	0.028*	25.8
Q3	29	0.540 (0.124–2.349)	0.412	24.1	32	2.188 (0.358–13.355)	0.396	21.9
Q4	22	REF		40.9	23	REF		13.0
		<i>P</i> for trend	0.897			<i>P</i> for trend	0.135	

*Two-sided *P* value <0.05.

CI, confidence interval; ER, event rate (%); OR, odds ratio.

physical activity group had a lower handgrip strength when compared to the highest IGF-1 quartile. With regard to physical performance tests, results are less consistent. Our data show that in younger more active males physical performance was worse in men in the second IGF-1 quartile when compared to the highest IGF-1 quartile at the first measurement. Recurrent fallers were less prevalent in older, low active males with low IGF-1 levels (IGF-1-Q1 and IGF-1-Q2). On the other hand, in females recurrent fallers were more prevalent in older, more active females with an IGF-1 level in the second quartile. Therefore, our results indicate that lower IGF-1 levels are associated with lower handgrip strength and worse physical performance, but less recurrent fallers, especially in older men who are less active. In women on the other hand, recurrent fallers were more prevalent in older, highly active women in the second IGF-1 quartile. This striking difference between men and women might be due to change as it cannot be explained by differences in number of participants or event rates. This difference stresses the need for further research to the association between IGF-1 and falls.

Our study has several strengths. In the first place, we investigated a large group of community-dwelling elderly. This sample is considered to be representative of the general Dutch elderly population. Most of the included participants completed the fall follow-up, and there were sufficient fall events for statistical analyses.

Since IGF-1 levels were only measured at LASA-C and not repeated at LASA-D, we were not able to investigate whether there could be an association between changes in IGF-1 concentration over time and handgrip strength, physical performance and recurrent falls. However, at high age, these changes in IGF-1 level over a 3-year period are not expected to be of great importance. From our data, no conclusions can be drawn about any causal relationship, only on existing associations.

A sedentary lifestyle or low levels of physical activity are known to be important determinants of muscle strength and physical performance (9). Muscle weakness and physical frailty in the very old can be counteracted by high-intensity resistance exercise training (28). We stratified and corrected our data for physical activity

score. In our population, most associations were found in the low activity groups. Therefore, it seems like IGF-1 only plays a minor role in physical performance, but when elderly are less active this effect might become relatively more important. On the other hand, it is known that physical activity stimulates GH secretion and can thereby increase levels of IGF-1.

The associations between serum IGF-1 levels and changes in handgrip strength and physical performance between LASA-C and LASA-D are not completely consistent; nevertheless, serum IGF-1 quartile might predict changes in handgrip strength and physical performance over time in elderly men and women. We cannot totally rule out that there is a learning effect in measurements of handgrip strength and physical performance tests, although we do not expect this effect to be of great importance with a 3-year interval between the tests.

Previous studies that investigated associations between the GH-IGF-1 axis and muscle strength, exercise capacity, physical performance or disability/frailty in older adults show somewhat conflicting results (15, 16, 18, 19, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42). However, comparison between these studies is difficult because of different study outlines (cross-sectional vs prospective) with inclusion of participants of different age groups with and without functional limitations, different outcome measurements and a rather heterogeneous correction for possible confounders. We found differences in associations between the younger and older age groups within the same gender in our study population, which might indicate that IGF-1 plays a different role with increasing age. This is also supported by findings in studies on the effects of GH treatment in GHD adults or healthy elderly at different ages. This could also be one of the contributing factors for the ambiguous results of other studies investigating the GH-IGF-1 axis, as mentioned earlier.

The exact underlying pathophysiological mechanism for different effects of IGF-1 at different ages is unclear. Serum levels of IGF-1 may not be a good reflection of local effects of IGF-1. Changes in tissue-specific GH or IGF-1 expression and activity, the presence of different IGF-1 isoforms in muscle, abnormal protein metabolism, an altered composition of type I and II muscle fibres and/or the loss of myofibrillar motor neurons could be involved (1, 10, 43, 44, 45). Furthermore, other anabolic hormones than IGF-1, for example testosterone and DHEAS, inflammatory markers (IL-6 and TNF- α) and several minerals such as magnesium, selenium and zinc, could be involved in a pathway leading to increased

frailty or disability with aging (46, 47). In our study, as mentioned before, we corrected for testosterone levels. We did not have information about DHEAS, IL-6, TNF- α or minerals in our study population; hence, we were not able to investigate any possible associations or confounding within this study. In our study, only total IGF-1 was measured and serum levels of binding proteins were not available.

Although there was a significant trend for IGF-1 quartiles for some of the studied associations, several of the significant associations we found were only seen in the second quartile of IGF-1 values. This might indicate that there is no linear relationship between IGF-1 levels and the studied outcome measurements, but more likely an (inversed) U-shape relationship. A number of previously performed studies investigating an association between the GH-IGF-1 axis and (cardiovascular) mortality, also suggested that there might be an (inversed) U-shape relationship instead of a linear relationship (1, 48, 49). Direct comparison of absolute serum IGF-1 concentrations of our participants with that reported in other studies is not possible since different immunoassays with specific reference ranges were used. However, one of the aforementioned studies was performed within the same participants of the Longitudinal Aging Study Amsterdam as our study and therefore serum IGF-1 concentrations were within the same range.

In adults with GH deficiency, long-term treatment with GH has positive effects on muscle mass and exercise capacity, but not on muscle strength (10, 44, 50, 51). Since the availability of recombinant human GH and the publication of positive effects of treatment with GH on muscle mass in GHD adults, a number of studies with GH or GHRH analogues in healthy elderly were performed. Although most studies reported an increase in lean body and muscle mass, there is no convincing evidence that this leads to an improvement in muscle strength or physical performance, but treatment was accompanied by several side effects (2, 5, 8, 10, 52, 53, 54, 55, 56, 57, 58). Therefore, treatment with GH or GHRH analogues in healthy elderly is not recommended. Some of these studies showed a difference in the effect of GHT on muscle strength in participants who underwent exercise training and those who did not. This could indicate that the GH-IGF-1 axis has different effects on muscle strength in active and non-active elderly, as we also found in our study and that these effects are not solely explained by an increase in LBM and muscle mass.

In our study, we also prospectively investigated the association between IGF-1 levels and recurrent fallers. It

seems that in older men being inactive is accompanied by less recurrent fallers, while in women being more active gives a higher risk on recurrent falls. It is not only of interest whether there is an association between IGF-1 levels and recurrent falls, but also whether this is associated with more fractures, burden of disease and costs. Previous studies show conflicting results. One study showed that fracture risk in older men with low IGF-1 levels is increased (17). A recent study also performed in participants of the Longitudinal Aging Study Amsterdam, reports that in older women, lower IGF-1 levels were associated with a greater decrease in BMD 3 years later and increased 10-years fracture risk and these associations were not found in men(59). Further long-term studies are needed to confirm these observations.

In conclusion, we investigated whether handgrip strength, physical performance and recurrent falls were related to serum IGF-1 levels in healthy elderly men and women. Furthermore, we studied the clinical utility of serum IGF-1 concentration to predict a decrease of handgrip strength, physical performance and increased risk of recurrent falls in the nearby future. Our results indicate that lower IGF-1 levels are associated with lower handgrip strength and worse physical performance but less frequent fallers especially in men, although we found differences between men and women and also between low and high activity groups. The associations we found, were often most robust in IGF-1-Q2. As was suggested by other studies, there might be an (inversed) U-shape relation between IGF-1 level and the investigated outcomes. Since life expectancy increases, frail or disabled older people will inevitably be more prevalent. The debate about the GH-IGF-1 axis and aging is still ongoing. Future studies are desirable, preferably prospective studies in large groups of community dwelling elderly, with special emphasis on the differences between sexes and IGF-1 quartiles. At this moment, we believe that the prevention of sarcopenia, frailty and falls remains the most important goal in elderly. There is no convincing evidence that treatment with GH or GH secretagogues is beneficial, it might even be harmful in community-dwelling elderly.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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