CHAPTER

The association of serum insulin-like growth factor-1 with mortality, cardiovascular disease and cancer in the elderly: a population-based study

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**ABSTRACT**

**Context**
Numerous studies have investigated the effect of serum IGF-1 concentration on aging and different aging-related diseases, e.g. cardiovascular disease and cancer. Both decreased as well as increased levels have been reported to be associated with reduced life expectancy in humans.

**Objective**
This study investigates the association of serum IGF-1 concentration with all-cause and cause-specific mortality of community-dwelling older persons and the development of cardiovascular disease and cancer.

**Design, Setting and Participants**
Data were used from the Longitudinal Aging Study Amsterdam (LASA), an ongoing multidisciplinary cohort study in the general Dutch population of older persons (≥65 yr old) where serum IGF-1 was measured (n=1273). The mortality information was ascertained using the International Classification of Diseases, 10th revision, and presence or absence of CVD and cancer by self-reports with a follow-up of 11.6 yr.

**Main Outcome Measure**
We measured all-cause, CVD, and cancer mortality and non-fatal CVD and cancer.

**Results**
Fully adjusted Cox proportional hazards models demonstrated an increased risk of all-cause mortality for older persons with IGF-1 values in the lowest quintile as compared to the middle quintile (hazard ratio (HR) 1.28 (95% confidence interval (CI) 1.01-1.63)). A more than 2-fold increased risk of CVD mortality was revealed for both low-normal (HR 2.39 (95% CI 1.22-4.66)) and high-normal (HR 2.03 (95% CI 1.02-4.06)) IGF-1 values. Significant associations of serum IGF-1 with non-fatal CVD and fatal and non-fatal cancer were not observed.

**Conclusions**
Results suggest a U-shaped relationship between IGF-1 level and mortality, with fatal cardiovascular disease as the most critical outcome in community-dwelling older persons.
INTRODUCTION

Growth hormone (GH) secretion and serum insulin-like growth factor-1 (IGF-1) levels in healthy individuals gradually decline with age. This phenomenon of relative GH and IGF-1 deficiency during normal aging has been named the ‘somatopause’ and is often ascribed to the reduced activity of the hypothalamic-GH-IGF axis. IGFs and their associated binding proteins (IGFBPs) play important roles in normal development and growth. IGF-1 is a key regulator of cell proliferation and an inhibitor of cell apoptosis and necrosis. In the last decade, numerous studies have investigated the effect of IGF-1 concentration on aging and different aging-related diseases, e.g. cardiovascular disease (CVD) and cancer.

Abnormally high levels of IGF-1, seen in acromegaly, have been extensively investigated and reported to be associated with higher mortality and a higher prevalence of cancer and CVD. In panhypopituitarism, abnormally low levels of IGF-1 are hypothesized to be responsible for high all-cause and cardiovascular mortality. Associations of IGF-1 concentrations within the normal range with disease are less clear. IGF-1 has been suggested to be involved in the pathogenesis of atherosclerosis. Low-normal IGF-1 levels have been shown to be associated with development of ischemic heart disease and stroke. High levels of IGF-1 have been expected to activate survival pathways that would make programmed cell death of damaged cells slightly less probable. In population-based studies high-normal levels of IGF-1 have been reported to be associated with a moderately increased risk of cancer.

Studies in experimental organisms, ranging from nematodes to mice, have provided evidence that reduction in the activity of the GH-IGF axis is associated with longevity. In humans, data on IGF-1 activity and longevity are still conflicting and controversial. Both decreased as well as increased levels have been shown to be associated with reduced life expectancy. Some studies suggest a U-shaped relationship between IGF-1 and mortality. If low IGF-1 activity is associated with an increased risk of developing CVD and high IGF-1 activity with an increased risk of developing cancer there might be an optimal set point for the GH-IGF axis associated with increased longevity.

The aim of the present study is to investigate the relationship between serum IGF-1 concentration and all-cause and cause-specific mortality in a national representative sample of community-dwelling older persons. In addition we investigate the relationship between IGF-1 concentration and development of aging-related diseases, namely CVD and cancer.

METHODS

Study sample

Data were collected in the context of the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing multidisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older people in The Netherlands. Data collection and sampling have been explained in more detail elsewhere. Briefly, a sample of older men and women (aged 55-85 years at baseline), stratified by age, sex, urbanization grade, and expected 5-year mortality, was drawn from the population registers of 11 municipalities in three regions in The Netherlands, being a representative sample of the Dutch population. At baseline (1992/1993) and every 3 years thereafter, subjects participated in an interview performed by trained nurses at
the subject’s home. Informed consent was obtained from all respondents. The study was approved by the Medical Ethics Committee of the VU University Medical Center, in Amsterdam.

The current study was performed in a subgroup of the LASA population, including participants from the second cycle (1995/1996) because at this cycle IGF-1 measures from blood samples were available in participants aged 65 yr or older on January 1, 1996 (n=1319). Women using estrogens and subjects using recombinant GH (n=14) were excluded from the analysis. Subjects with decreased renal function (creatinine >200 µmol/l) and clinical hypothyroidism were also excluded (n=17). Subsequently, subjects with missing values on the confounders were excluded (n=15). The number of participants included in the analysis for all-cause mortality was 1273, of whom 643 were women and 630 were men. For the analysis of cause-specific mortality and the development of CVD and cancer, subjects with prevalent CVD or cancer at baseline were excluded as well. Thus, 804 participants included in the analysis of CVD and 1119 participants for cancer (figure 1).

**Figure 1.** Design of study sample
Measurements

Serum IGF-1

Blood samples were drawn in the morning after tea and plain toast, processed and centrifuged within 60 minutes. Samples were kept frozen until determination. IGF-1 levels were measured using an immunoradiometric assay after extraction (DSL, Webster, Texas, USA) with a detection limit of 1 nmol/l. Inter-assay coefficient of variation (CV) was <14%. The reference range (PS-P95) for IGF-1 values with the used method is 11-19 nmol/l for both men and women aged 60-70 years. These analyses were carried out at the Endocrine Laboratory of the VU University Medical Center, Amsterdam.

Mortality and morbidity

For respondents who died, the date of death was traced through death certificates from municipal registers through June 1, 2007. Survival was computed as the date of death minus the date of the blood sampling or the end of follow-up minus the date of blood sampling, whichever came first. Using death certificates from the Dutch Central Bureau of Statistics (The Netherlands), all cardiovascular and cancer deaths during follow-up were identified. All cardiovascular deaths were defined as International Classification of Disease, 10th Revision (ICD-10) codes I20-I79 and ischemic CVD as codes I20-I25 and I60-I79. Cancer deaths were defined as ICD-10 codes C00-C97.

The development of CVD and cancer was based on self-reported (symptoms of) CVDs or cancer at the second cycle (1995/1996) and subsequently every three years. Time of event was defined as halfway the interval between the study cycles where CVD or cancer was first reported and the previous cycle.

Potential confounders

Data on age and sex were derived from the population registries at baseline. Self-reported lifestyle variables included smoking (never, former, current), alcohol consumption (Garretsen alcohol index; none, light, moderate, excessive), and physical activity in the past 2 weeks using the LASA Physical Activity Questionnaire (LAPAQ) and was based on the following activities: walking outdoors, bicycling, light and heavy household activities, and a maximum of two sports activities. Total physical activity score was calculated as time spent on physical activity in minutes per day. This variable was divided into tertiles for analysis, with the first tertile representing the lowest activity and the third tertile the highest activity. Health status variables included presence of diabetes mellitus (DM) (based on information obtained from general practitioners, inspection of medicine bottles, and self-report), and body mass index (weight (kg)/height (m²)). Thyroid hormones were measured in frozen samples in 2001 at the Endocrine Laboratory of the VU University Medical Center, Amsterdam. When thyroid stimulating hormone (TSH) was below or above the reference range, T4 and/or T3 was measured. Serum albumin (as indicator for nutritional status) was measured in blood samples in three different laboratories in The Netherlands. The results were converted by use of a validated formula to make the data comparable.
Statistical analysis
Categorical data were expressed as number (percentage); continuous data were expressed as mean (SD) for normally distributed variables, or as median (interquartile range) for skewed variables. At baseline, continuous variables were compared by ANOVA or by Kruskal-Wallis Test, whereas categorical variables were compared by chi-square test. Spearman and Pearson correlation coefficients were calculated to examine multicollinearity. The individual variables were checked for linearity. Because of non-linearity IGF-1 levels were divided in quintiles (Q), using the first quintile representing the lowest IGF-1 levels and the fifth quintile representing the highest IGF-1 levels.

Cox proportional hazards analysis was used to examine the association between IGF-1 level and mortality. Two models were applied to adjust for potential confounders in the Cox regression analysis. First, adjustments were made for sex and age. The second model was a model fully adjusted for relevant confounders. Variables which after inclusion in the first model showed an important change (>10%) in the regression coefficient of the association between IGF-1 and the outcome variable, were included as relevant confounder in the final model. To examine the association between IGF-1 level and all-cause mortality and CVD (fatal and non-fatal) we included sex, age, BMI, smoking, alcohol-use, DM, physical activity and albumin. For the association with cancer (fatal and non-fatal) sex, age, BMI, smoking, alcohol-use and DM were included as confounder. Log minus log plots and interaction terms were used to check the proportional hazards model assumption, which was not violated in any of the models.

Two-sided P values 0.05 or less were considered significant. The statistical analyses were performed by the statistical software package SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS
Baseline characteristics
Among the 1273 participants, 643 (50.5%) were female and 630 (49.5%) were male. The median follow-up time for all subjects was 10.6 year (range 0.1-11.6). The median age at baseline was 75 year (range 64.8-88.8), 74.9 year for females and 75.3 year for males. The mean IGF-1 concentration was 13.8 (SD 5.2) nmol/l. There were some subjects with IGF-1 level below or above the reference range for people aged older than 60 years. No indications of incorrect sample treatment or storage problems were detected. As the reference range for age above 70 years was not defined, it can be assumed that these levels were at the lower or upper part of reference range. Table 1 describes the baseline characteristics of the total study population, stratified by quintiles of IGF-1 concentration (n=1273) as follows: Q1, 1.3-9.4 nmol/l; Q2, 9.5-12.3 nmol/l; Q3, 12.4-14.5 nmol/l; Q4, 14.6-17.6 nmol/l; Q5, 17.7-53.4 nmol/l. It shows a significant variation in age, sex, number of deaths, smoking habits and serum albumin concentration over the five quintiles of IGF-1 concentration. The subjects in the first quintile of IGF-1 concentration were the oldest (median age of 78.3 yr), mostly female, included fewer smokers and had the lowest serum albumin.

All-cause mortality
During 11.6 years of follow-up, 633 subjects (49.7%) died (268 females and 365 males) with a median survival of 5.6 year. During regression analysis positive regression coefficients were observed in both the lowest and the highest quintile when compared to the middle quintile. Hence, the middle
Table 1. Baseline characteristics of the study population for all-cause mortality stratified by quintiles (Q) of IGF-1 concentration

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>258</td>
<td>255</td>
<td>248</td>
<td>261</td>
<td>251</td>
<td></td>
</tr>
<tr>
<td>IGF-1 (nmol/l) †</td>
<td>7.3 (1.7)</td>
<td>11.0 (0.8)</td>
<td>13.5 (0.6)</td>
<td>16.0 (0.9)</td>
<td>21.4 (4.2)</td>
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<tr>
<td>Age (yr) *</td>
<td>78.3</td>
<td>77.2</td>
<td>74.3</td>
<td>72.8</td>
<td>72.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(65.4-88.8)</td>
<td>(65.5-88.4)</td>
<td>(65.4-88.4)</td>
<td>(64.8-88.3)</td>
<td>(64.9-87.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, Female</td>
<td>153 (59.3)</td>
<td>138 (54.1)</td>
<td>129 (52.0)</td>
<td>117 (44.8)</td>
<td>106 (42.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m2) †</td>
<td>26.5 (4.4)</td>
<td>26.8 (4.3)</td>
<td>26.8 (4.4)</td>
<td>26.9 (3.9)</td>
<td>27.1 (3.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>never</td>
<td>115 (44.6)</td>
<td>93 (36.5)</td>
<td>90 (36.3)</td>
<td>77 (29.5)</td>
<td>75 (29.9)</td>
<td></td>
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<tr>
<td>former</td>
<td>96 (37.2)</td>
<td>118 (46.3)</td>
<td>113 (45.6)</td>
<td>133 (51.0)</td>
<td>128 (51.0)</td>
<td></td>
</tr>
<tr>
<td>current</td>
<td>47 (18.2)</td>
<td>44 (17.3)</td>
<td>45 (18.1)</td>
<td>51 (19.5)</td>
<td>48 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
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<td></td>
<td></td>
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<td>0.15</td>
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<tr>
<td>none</td>
<td>75 (29.1)</td>
<td>55 (21.6)</td>
<td>60 (24.2)</td>
<td>58 (22.2)</td>
<td>55 (21.9)</td>
<td></td>
</tr>
<tr>
<td>light</td>
<td>129 (50.0)</td>
<td>137 (53.7)</td>
<td>123 (49.6)</td>
<td>126 (48.3)</td>
<td>131 (52.2)</td>
<td></td>
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<tr>
<td>moderate</td>
<td>44 (17.1)</td>
<td>52 (20.4)</td>
<td>52 (20.4)</td>
<td>48 (18.4)</td>
<td>51 (20.3)</td>
<td></td>
</tr>
<tr>
<td>excessive</td>
<td>10 (3.9)</td>
<td>11 (4.3)</td>
<td>13 (5.2)</td>
<td>29 (11.1)</td>
<td>14 (5.6)</td>
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</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.74</td>
</tr>
<tr>
<td>tertile 1</td>
<td>85 (32.9)</td>
<td>93 (36.5)</td>
<td>97 (39.1)</td>
<td>88 (33.7)</td>
<td>93 (37.1)</td>
<td></td>
</tr>
<tr>
<td>tertile 2</td>
<td>81 (31.4)</td>
<td>79 (31.0)</td>
<td>83 (33.5)</td>
<td>85 (32.6)</td>
<td>81 (32.3)</td>
<td></td>
</tr>
<tr>
<td>tertile 3</td>
<td>92 (35.7)</td>
<td>83 (32.5)</td>
<td>68 (27.4)</td>
<td>88 (33.7)</td>
<td>77 (30.7)</td>
<td></td>
</tr>
<tr>
<td>Prevalent diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>103 (39.9)</td>
<td>88 (34.5)</td>
<td>89 (35.9)</td>
<td>101 (38.7)</td>
<td>72 (28.7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cancer</td>
<td>25 (9.7)</td>
<td>28 (11.0)</td>
<td>38 (15.3)</td>
<td>31 (11.9)</td>
<td>32 (12.7)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>27 (10.5)</td>
<td>22 (8.6)</td>
<td>20 (8.1)</td>
<td>22 (8.4)</td>
<td>23 (9.2)</td>
<td>0.90</td>
</tr>
<tr>
<td>Albumin (g/l) †</td>
<td>43.9 (2.6)</td>
<td>44.0 (3.0)</td>
<td>44.5 (2.8)</td>
<td>44.6 (2.5)</td>
<td>45.0 (2.5)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean (SD) * for normally distributed variables or median (interquartile range) † for skewed variables; categorical variables are given as numbers (%). * Chi-square test is used for categorical variables; one-way analysis of variance for continuous variables.

quintile was used as reference. Older persons having serum IGF-1 values in the lowest quintile had a significantly higher risk of all-cause mortality as compared to persons with serum IGF-1 values in the middle quintile (hazard ratio (HR) 1.53 (95% confidence interval (CI) 1.21-1.94); p<0.01). After adjustments for relevant confounders (age, sex, BMI, smoking, alcohol-use, DM, physical activity and albumin) this relationship was only moderately attenuated (HR 1.28 (95% CI 1.01-1.63); p=0.04) (table 2). The risk of all-cause mortality for persons with serum IGF-1 values in the highest quintile was not different from that of persons in the middle quintile (HR 0.91 (95% CI 0.70-1.18); p=0.47). In the fully adjusted model the HR was 1.17 (95% CI 0.90-1.53; p=0.24). These results are visualised in a survival curve (figure 2A).

Fatal and non-fatal CVD

Of the 804 subjects without prevalent CVD, 331 subjects died of which 94 (28.4%) due to cardiovascular causes. Persons with serum IGF-1 values in the lowest and highest quintile had a significantly higher risk of CVD mortality as compared to persons with serum IGF-1 values in
Table 2. Hazard ratio of IGF-1 concentration stratified by quintiles (Q) for all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Q1 (n=258)</th>
<th>Q2 (n=255)</th>
<th>Q3 (n=248)</th>
<th>Q4 (n=261)</th>
<th>Q5 (n=251)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>162</td>
<td>133</td>
<td>118</td>
<td>111</td>
<td>109</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.53 **</td>
<td>(1.20-1.93)</td>
<td>1.15</td>
<td>Reference</td>
<td>0.85</td>
</tr>
<tr>
<td>Adjusted model</td>
<td>1.27</td>
<td>(1.00-1.61)</td>
<td>1.00</td>
<td>Reference</td>
<td>0.94</td>
</tr>
<tr>
<td>Fully adjusted model</td>
<td>1.28 *</td>
<td>(1.01-1.63)</td>
<td>1.01</td>
<td>Reference</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Adjusted: sex and age  
Fully adjusted: sex, age, BMI, smoking, alcohol-use, DM, physical activity and albumin  
** P < 0.01, * P < 0.05

the middle quintile with a HR of 2.82 (95% CI 1.47-5.41; p<0.01) and 1.80 (95% CI 0.91-3.57; p=0.09), respectively. After adjustment for relevant confounders (age, sex, BMI, smoking, alcohol-use, DM, physical activity and albumin) the risk of CVD mortality was still more than 2-fold. The HR was 2.39 (95% CI 1.22-4.66; p=0.01) for the lowest and 2.03 (95% CI 1.02-4.06; p=0.04) for the highest quintile as compared to the middle quintile (table 3). These results are visualised in a survival curve (figure 2B). When ischemic CVDs were studied as primary cause of death the risk increased for persons with serum IGF-1 values in the lowest and in the highest quintile as compared to persons with serum IGF-1 values in the middle quintile (table 3).

During follow-up 215 of 804 subjects developed non-fatal CVD. There was no increased risk of development of non-fatal CVD for the lowest and the highest quintile of IGF-1 concentration as compared to the middle quintile (table 3).

Fatal and non-fatal cancer

Of the 1119 subjects without prevalent cancer, 538 subjects died of which 88 (16.4%) from cancer.

When, following previous studies, 3,7,23-25 the quintile with the lowest serum IGF-1 values was used as the reference, there was no increased risk of cancer mortality between subjects with serum IGF-1 values in the highest quintile as compared to subjects with serum IGF-1 values in the lowest quintile (table 4). These results are visualised in a survival curve (figure 2C). Sensitivity analyses were run excluding subjects who died within the first 2 years of follow-up (n=82) and looking solely at specific forms of cancer (prostate, lung and colorectal cancer, as mentioned in literature 3,11,23 (n=47) but substantial changes in risk of cancer mortality were not observed in our population (data not shown).

During follow-up 112 of 1119 subjects developed non-fatal cancer. There was no increased risk of developing cancer for persons with serum IGF-1 values in the highest quintile as compared to subjects with serum IGF-1 values in the lowest quintile (table 4).

DISCUSSION

In the present study, low-normal serum IGF-1 concentration was associated with a higher risk of all-cause mortality in the community-dwelling older population in The Netherlands. Our results show that the association between IGF-1 levels and mortality is not linear. Serum IGF-1 concentrations
in the lowest and highest quintile were associated with a more than 2-fold increased risk of mortality from CVD as primary cause of death. Associations were not observed between serum IGF-1 concentration and non-fatal CVD or cancer. The results support a U-shaped relationship for serum IGF-1 concentration and mortality with fatal (ischemic) CVD as the most critical outcome.
The risk of all-cause mortality was highest in persons with the lowest concentration of IGF-1. This is in line with other population-based studies. Andreassen et al. found the highest all-cause mortality rates in the lowest and highest quartile of serum IGF-1 concentrations.\textsuperscript{4} Friedrich et al. showed in adjusted analyses that men with low IGF-1 levels had an almost 2-fold higher risk of all-cause mortality (HR 1.92 (95% CI 1.35-2.73)) compared with men with normal IGF-levels.\textsuperscript{6} Capolla et al. demonstrated that low IGF-1 in combination with signs of inflammation in older women was associated with an increased risk of all-cause mortality.\textsuperscript{5} Two large cohort studies (National Health and Nutrition Examination Survey and Rancho Bernardo Study) did not find a significant association between serum IGF-1 level and all-cause mortality.\textsuperscript{26,27} A possible explanation might be the difference in age range between these studies and the present study. They included subjects aged 17 or
years or older respectively, and we included subjects aged 65 years or older, and therefore had the highest percentage of deaths.

Acromegaly and GH deficiency are both known to increase the risk of CVD and premature mortality.\textsuperscript{3,14,28} In the present study the risk of CVD mortality is increased for both ends of the normal range of serum IGF-1. Several population-based prospective studies have suggested that low circulating levels of IGF-1 within the normal range may predict increased risk of ischemic heart disease,\textsuperscript{8,15,26,29} and ischemic stroke.\textsuperscript{9} On the other hand both low concentrations\textsuperscript{12} and high concentrations of IGF-1 are found to be associated with chronic heart failure.\textsuperscript{4} Because our definition for cardiovascular deaths included all CVD, both low and high concentrations of IGF-1 could be associated with a higher risk of CVD mortality. Nonetheless, when specifically examining ischemic CVDs as the reported primary cause of death, and thus excluding non-ischemic CVD from the previous analysis, we could not confirm this hypothesis and only observed the increased risk for both low-normal as well as high-normal IGF-1 values. In a recent study, Yeap et al. conducted a cross-sectional analysis of 3980 community-dwelling older men to examine the association between IGF-1 concentration and the metabolic syndrome. There was a U-shaped relationship, with the middle quintiles possessing the lowest odds ratios for metabolic syndrome.\textsuperscript{30} The presence of metabolic syndrome is associated with an increased incidence of cardiovascular events. This may explain part of the variation in associations of IGF-1 concentration with cardiovascular outcome in previous studies and the present study. However, we did not find an association with development of non-fatal CVD. This difference may be the consequence of the fact that collecting data on morbidity through self-report by questionnaires is less reliable, as opposed to other studies where outcome measurements were more objective.\textsuperscript{5,29} Nevertheless, it has been demonstrated that self-reports, compared to general practitioners’ information, regarding the presence or absence of specific chronic diseases is adequate in this population. Only for peripheral atherosclerotic disease the accuracy of self-reports was slightly lower.\textsuperscript{31} Our mortality data contradicts the idea that high and high-normal IGF-1 concentrations are protective for atherosclerotic-associated cardiovascular events. Endocrinologists prescribing GH should be aware of this finding as strict dosing is becoming even more important. Not only cancer as an other study\textsuperscript{25} has shown but also fatal CVD could be an adverse implication of high IGF-1 values. Further research will be needed to learn more about the pathophysiological mechanisms involved in the association of IGF-1 and CVD, and to fully understand the variation in study outcomes.

The important mitotic and anti-apoptotic properties of the IGF system suggest a possible role in carcinogenesis. The role of IGF-1 has been reviewed and increased expression of growth factors and their receptors were found in different malignancies.\textsuperscript{7,32} In the present study cancer does not seem to be an important determinant of the association of IGF-1 concentration with mortality. A recent study from Major et al. revealed that increasing levels of IGF-1 were associated with an increased risk of all-cancer mortality but not with all-cause mortality in older men.\textsuperscript{25} Some epidemiologic data regarding IGF-1 and the risk of cancer show that a high level of serum IGF-1 is associated with increased risk for several cancers, namely lung, prostate, colorectal, and premenopausal breast carcinoma.\textsuperscript{7,23,32} Because causes of death were identified by ICD-10 we were able to select only these forms of cancer. We did not find a significant association of IGF-1 concentration with specific cancer mortality, but the power unfortunately decreased because of fewer events. We excluded subjects with prevalent cancer at baseline. However, we cannot be certain that some individuals
did have asymptomatic or undiagnosed disease. Nevertheless, excluding those subjects who died of cancer within the first 2 years did not alter the outcome. The development of non-fatal cancer was not associated with IGF-1 concentration, but unfortunately data on specific forms of non-fatal cancer was not available.

Strengths of the present study include the nationally representative and large sample, a maximum follow-up of almost 12 years and accurate assessment of cause of death based on the International Classification of Diseases, 10th revision. Nonetheless, there are some limitations of this study. We measured total serum IGF-1 as an accepted measure of IGF-1 status. A recently reported bioassay based on activation of the IGF-1 specific kinase receptor may provide a means of assessing circulating bioactive IGF-1, but this method is not in general use at this moment. Furthermore, biologic effects and bioavailability of IGF-1 are modulated through IGFBPs, which control IGF-1 access to cell surface receptors. Unfortunately we did not have IGFBPs available and therefore our results do not fully represent biologically active IGF-1. There is sufficient evidence that the GH-IGF axis is involved in aging and aging-related diseases through complex mechanisms. It is possible that our results reflect a causal influence of IGF-1 concentration on mortality, although it can not be excluded that some unadjusted confounders might influence the association. Our cohort existed of community-dwelling elderly but it would also be interesting to investigate whether these associations can be found in a large cohort of younger adults where longer follow-up will be necessary.

In conclusion, these findings suggest that in community-dwelling older persons a low serum concentration of IGF-1, even within the normal range, is associated with an increased all-cause mortality risk. Low and high serum concentration of IGF-1 increase the risk of (ischemic) CVD mortality by more than a factor of two. In contrast, there was no association of serum IGF-1 with the development of non-fatal CVD. The risk of fatal or non-fatal cancer seemed not to be associated with IGF-1 concentration. A U-shaped relationship between IGF-1 levels and mortality is suggested, with fatal CVD as the most critical outcome. More research is needed to fully understand the mechanisms and to investigate the possibility of an optimal set point for IGF-1 concentration related to longevity and the influence on cardiovascular mortality.

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REFERENCES


