Serum IGF1, metabolic syndrome, and incident cardiovascular disease in older people: a population-based study

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Abstract

Objective: High as well as low levels of IGF1 have been associated with cardiovascular diseases (CVD). The relationship of IGF1 with (components of) the metabolic syndrome could help to clarify this controversy. The aims of this study were: i) to investigate the association of IGF1 concentration with prevalent (components of) the metabolic syndrome; and ii) to examine the role of (components of) the metabolic syndrome in the relationship between IGF1 and incident CVD during 11 years of follow-up.

Methods: Data were used from the Longitudinal Aging Study Amsterdam, a cohort study in a representative sample of the Dutch older population (≥65 years). Data were available in 1258 subjects. Metabolic syndrome was determined using the definition of the US National Cholesterol Education Program Adult Treatment Panel III. CVD were ascertained by self-reports and mortality data.

Results: Levels of IGF1 in the fourth quintile were associated with prevalent metabolic syndrome compared with the lowest quintile (odds ratio: 1.59, 95% confidence interval (CI) 1.09–2.33). The middle up to the highest quintile of IGF1 was positively associated with high triglycerides in women. Metabolic syndrome was not a mediator in the U-shaped relationship of IGF1 with CVD. Both subjects without the metabolic syndrome and low IGF1 levels (hazard ratio (HR) 1.75, 95% CI 1.12–2.71) and subjects with the metabolic syndrome and high IGF1 levels (HR 2.28, 95% CI 1.21–4.28) demonstrated increased risks of CVD.

Conclusions: In older people, high-normal IGF1 levels are associated with prevalent metabolic syndrome and high triglycerides. Furthermore, this study suggests the presence of different pathomechanisms for both low and high IGF1 levels and incident CVD.

European Journal of Endocrinology 168 393–401

Introduction

IGFs and their associated binding proteins play important roles in normal development and growth. IGF1 is a key regulator of cell proliferation and an inhibitor of cell apoptosis and necrosis (1). In the cardiovascular system, IGF1 is postulated to protect against endothelial dysfunction, atherosclerotic plaque development, clinical instability, and ischemic myocardial damage (2). Aging is associated with a gradual decline of GH secretion and serum IGF1 concentration. Various studies have investigated the effect of serum IGF1 concentration on development of cardiovascular diseases (CVD) and mortality. Low-normal IGF1 levels have been associated with development of ischemic heart disease and stroke (3, 4, 5). The relationship of IGF1 with (cardiovascular) mortality is less clear. In a previous study in a Dutch cohort of older people, we have demonstrated a U-shaped relationship with mortality, with fatal CVD being the most critical outcome (6). One possible pathway of the relationship of IGF1 with cardiovascular outcomes is through the relationship of IGF1 with (components of) the metabolic syndrome. The metabolic syndrome is a cluster of cardiovascular risk factors, including hypertension, abdominal obesity, unfavorable lipid profile, and hyperglycemia. Older persons with metabolic syndrome are more likely to experience any CVD event than subjects without metabolic syndrome (7, 8). In two previous studies on the association of IGF1 with the metabolic syndrome in older populations, U-shaped relationships have been reported (9, 10). Others report low IGF1 values to be related to a greater metabolic burden (11, 12, 13, 14). These cohort studies only speculate about the role of this association in the development of CVD over time. Therefore, we investigated the relationship between serum total IGF1 concentration and (components of) metabolic syndrome and hypothesize to encounter a U-shaped relationship. Subsequently, we examine the role of (components of)
the metabolic syndrome in the relationship between IGF1 and incident CVD during 11 years of follow-up in a Dutch cohort of older persons.

Materials and 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 (15). Briefly, a sample of older men and women aged 55–85 years, predominantly Caucasian (>99%), 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.

This study was performed in a subgroup of the LASA population, selecting participants from the second cycle (1995/1996) aged 65 years or older on January 1st, 1996 (n = 1509). Women using estrogens and subjects using recombinant GH were excluded from the analysis (n = 14). Subjects with decreased renal function (creatinine > 200 μmol/l) and clinical hypothyroidism were also excluded (n = 17). Eventually, due to missing values, IGF1 values and metabolic syndrome could be determined in 1258 subjects. Subjects included in this study were significantly younger, smoked less, had higher alcohol use, and reported more physical activity per day (all P < 0.05) than the 251 subjects not included in this study.

Measurements

Serum IGF1 Blood samples were drawn in the morning after tea and plain toast, processed, and centrifuged within 60 min. Samples were kept frozen until determination. IGF1 levels were measured using an immunoradiometric assay after extraction (DSL, Webster, TX, USA) with a detection limit of 1 nmol/l. Interassay coefficient of variation (CV) was <14%. The reference range (P5–P95) for IGF1 values for this method is 11–19 nmol/l for both men and women aged 60–70 years. There were some subjects with an IGF1 level below or above the reference range for people aged >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 was assumed that these levels were at the lower or upper part of the reference range. These analyses were carried out at the Endocrine Laboratory of the VU University Medical Center, Amsterdam.

Metabolic syndrome Metabolic syndrome was defined as the presence of three or more of the following criteria: triglycerides ≥ 1.70 mmol/l (150 mg/dl), HDL-cholesterol < 1.00 mmol/l (40 mg/dl) for men and <1.30 mmol/l (50 mg/dl) for women, blood pressure ≥160/90 mmHg or antihypertensive medication, waist circumference > 102 cm for men and > 88 cm for women, and fructosamine ≥ 0.247 mmol/l or antidiabetic medication. This is the definition established by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (16), with an increased cutoff for blood pressure, adjusted for an older population (17). The cutoff of 0.247 mmol/l for fructosamine corresponds to 6.1 mmol/l for fasting plasma glucose (18).

Blood pressure was measured in sitting position using a standard mercury sphygmomanometer. Waist circumference was averaged over two readings measured midway between the lower rib margin and the iliac crest. Fructosamine was determined by a colorimetric test, and HDL-cholesterol and triglycerides were determined by an enzymatic colorimetric test (Roche Diagnostics). The interassay CV was <2.8% for fructosamine and triglycerides and <6.4% for HDL-cholesterol. All laboratory analyses were performed in EDTA-plasma samples stored at −80 °C at the Department of Clinical Chemistry of the VU University Medical Center in 2005. Prescription drugs taken in the previous 2 weeks were identified by container inspection.

Cardiovascular disease CVD include nonfatal and fatal cardiac, vascular, and cerebrovascular events. The development of nonfatal CVD was based on self-reported (symptoms of) CVD every 3 years in the preceding years. Time of event was defined as halfway the interval between the study cycles where CVD was first reported and the previous cycle. For respondents who died, the date of death was traced through death certificates from municipal registers through June 1st 2007. Using death certificates from the Dutch Central Bureau of Statistics (The Netherlands), all cardiovascular deaths during follow-up were identified. Cardiovascular deaths were defined as International Classification of Disease, 10th Revision (ICD-10) codes I20-179.

Potential confounders Data on age and sex were derived from the population registries at baseline. Self-reported lifestyle variables included smoking (never, former, and current), alcohol use (Garretsen alcohol index: none, light, moderate, and excessive) (19), and physical activity in the past 2 weeks using the LASA
Table 1  Baseline characteristics of the study population for metabolic syndrome stratified by quintiles (Q) of IGF1 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>251</td>
<td>253</td>
<td>248</td>
<td>257</td>
<td>249</td>
<td></td>
</tr>
<tr>
<td>IGF1 (nmol/l)</td>
<td>7.4 (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>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>77.8 (6.4)</td>
<td>76.9 (6.7)</td>
<td>75.2 (6.5)</td>
<td>74.2 (6.0)</td>
<td>73.3 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalent CVD</td>
<td>102 (40.6)</td>
<td>93 (36.8)</td>
<td>91 (36.7)</td>
<td>106 (41.2)</td>
<td>75 (30.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>No. of females</td>
<td>149 (59.4)</td>
<td>138 (54.5)</td>
<td>130 (52.4)</td>
<td>115 (44.7)</td>
<td>106 (42.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 (4.6)</td>
<td>26.8 (4.2)</td>
<td>26.7 (4.4)</td>
<td>26.9 (3.9)</td>
<td>27.0 (3.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>No. of females</td>
<td>113 (45.0)</td>
<td>92 (36.4)</td>
<td>91 (36.7)</td>
<td>74 (28.8)</td>
<td>73 (29.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Current</td>
<td>44 (17.5)</td>
<td>44 (17.4)</td>
<td>45 (18.1)</td>
<td>50 (19.5)</td>
<td>46 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>71 (28.3)</td>
<td>55 (21.7)</td>
<td>62 (25.1)</td>
<td>58 (22.6)</td>
<td>55 (22.1)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>128 (51.0)</td>
<td>135 (53.4)</td>
<td>120 (48.6)</td>
<td>125 (48.6)</td>
<td>129 (51.8)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>42 (16.7)</td>
<td>52 (20.6)</td>
<td>53 (21.5)</td>
<td>45 (17.5)</td>
<td>50 (20.1)</td>
<td></td>
</tr>
<tr>
<td>Excessive</td>
<td>10 (4.0)</td>
<td>11 (4.3)</td>
<td>12 (4.9)</td>
<td>29 (11.3)</td>
<td>15 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Physical activity (min/day)</td>
<td>80 (31.9)</td>
<td>88 (34.9)</td>
<td>91 (36.7)</td>
<td>83 (32.3)</td>
<td>80 (32.1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>78 (31.1)</td>
<td>79 (31.3)</td>
<td>84 (33.9)</td>
<td>82 (31.9)</td>
<td>92 (36.9)</td>
<td></td>
</tr>
<tr>
<td>Tertile 2</td>
<td>93 (37.1)</td>
<td>85 (33.7)</td>
<td>73 (29.4)</td>
<td>92 (35.8)</td>
<td>77 (30.9)</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43.9 (2.6)</td>
<td>44 (2.9)</td>
<td>44.5 (2.8)</td>
<td>44.5 (2.5)</td>
<td>44.9 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fructosamine (μmol/l)</td>
<td>227 (37)</td>
<td>226 (30)</td>
<td>226 (32)</td>
<td>230 (34)</td>
<td>229 (33)</td>
<td>0.35</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.20 (0.60)</td>
<td>1.30 (0.80)</td>
<td>1.30 (0.80)</td>
<td>1.30 (0.80)</td>
<td>1.40 (1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.36 (0.46)</td>
<td>1.35 (0.42)</td>
<td>1.36 (0.44)</td>
<td>1.31 (0.42)</td>
<td>1.31 (0.39)</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94 (12)</td>
<td>96 (12)</td>
<td>95 (11)</td>
<td>96 (10)</td>
<td>97 (11)</td>
<td>0.07</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>152 (29)</td>
<td>154 (25)</td>
<td>154 (25)</td>
<td>152 (25)</td>
<td>153 (26)</td>
<td>0.90</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81 (14)</td>
<td>83 (13)</td>
<td>83 (12)</td>
<td>83 (13)</td>
<td>85 (14)</td>
<td>0.01</td>
</tr>
<tr>
<td>Prevalent CVD</td>
<td>102 (40.6)</td>
<td>93 (36.8)</td>
<td>91 (36.7)</td>
<td>106 (41.2)</td>
<td>75 (30.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>66 (26.3)</td>
<td>67 (26.6)</td>
<td>71 (28.6)</td>
<td>81 (31.5)</td>
<td>55 (22.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>44 (17.5)</td>
<td>35 (13.9)</td>
<td>30 (12.1)</td>
<td>33 (12.8)</td>
<td>19 (7.6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>26 (10.4)</td>
<td>19 (7.5)</td>
<td>15 (6.0)</td>
<td>16 (6.2)</td>
<td>20 (8.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (9.6)</td>
<td>19 (7.5)</td>
<td>18 (7.3)</td>
<td>17 (6.6)</td>
<td>22 (8.8)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean (s.d.) for normally distributed variables or median (interquartile range) for skewed variables; categorical variables are given as numbers (%). $\chi^2$ test is used for categorical variables, one-way ANOVA for continuous variables, or Kruskal–Wallis test for skewed variables.

Statistical analysis

Categorical data were expressed as number (%); continuous data were expressed as mean (s.d.) 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 $\chi^2$ test. Spearman and Pearson correlation coefficients were calculated to examine multicollinearity. The individual variables were checked for linearity. Because of nonlinearity, IGF1 levels were divided into quintiles (Q), with the first quintile representing the lowest IGF1 levels. Logistic regression analyses were performed to study the association between IGF1 concentrations and the metabolic syndrome and the individual components. Two models were applied to adjust for potential confounders. First, adjustments were made for sex and age. Potential confounders that, after inclusion in the first model, showed an important change (> 10%) in the regression coefficient of the association between IGF1 and the outcome variable were included in the fully adjusted model. In addition, all analyses were repeated after exclusion of subjects with diabetes mellitus (n = 100) and lipid-lowering medication (n = 55). For the association of IGF1 with the components of the metabolic syndrome (except abdominal obesity), BMI was subsequently tested as a relevant confounder. Associations of IGF1 concentrations with components of the metabolic syndrome as continuous variables were analyzed with linear regression, both unadjusted and adjusted for relevant confounders. Subjects using lipid-lowering, antihypertensive, or antidiabetic medication were excluded for analysis via free access.
corresponding analyses. An interaction term with gender was tested in all models. For the longitudinal analyses, Cox proportional hazard model was used, both unadjusted and adjusted for age, gender, smoking habits, alcohol use, physical activity, and albumin. Subjects with a medical history of CVD or CVD present at baseline were excluded. To determine the role of metabolic syndrome in the association of IGF1 concentration with developing CVD, two options were explored. First, metabolic syndrome was studied as a potential mediator by testing the influence on the regression coefficient of entering the variable metabolic syndrome into the fully adjusted model of IGF1 and CVD. Secondly, an IGF1 concentration by metabolic syndrome interaction was tested in the regression model. Two-sided P values of 0.05 or less were considered significant, except for the interaction terms, for which 0.10 was tolerated (21). The statistical analyses were performed by the statistical software package SPSS version 15.0 (SPSS, Inc.).

Results

Baseline characteristics

Among the 1258 participants, 638 (50.7%) were female. The mean age at baseline was 75.5 (S.D. 6.5) years. The mean IGF1 concentration was 13.8 (S.D. 5.2) nmol/l. Age, sex, smoking habits, alcohol use, physical activity, and albumin. Subjects with a medical history of CVD or CVD present at baseline were excluded. To determine the role of metabolic syndrome in the association of IGF1 concentration with developing CVD, two options were explored. First, metabolic syndrome was studied as a potential mediator by testing the influence on the regression coefficient of entering the variable metabolic syndrome into the fully adjusted model of IGF1 and CVD. Secondly, an IGF1 concentration by metabolic syndrome interaction was tested in the regression model. Two-sided P values of 0.05 or less were considered significant, except for the interaction terms, for which 0.10 was tolerated (21). The statistical analyses were performed by the statistical software package SPSS version 15.0 (SPSS, Inc.).

Components of the metabolic syndrome

Blood pressure (66.1%) and abdominal obesity (51.4%) were the most prevalent components of the metabolic syndrome. The results of the logistic regression analyses are presented in Table 3, demonstrating only significantly increased ORs for the component of high triglycerides. An interaction with gender was demonstrated for the component of high triglycerides and this analysis was repeated stratified for gender (Fig. 2). Excluding subjects with prevalent diabetes mellitus or those using lipid-lowering medication did not substantially influence the outcomes. Subsequently, adding BMI as a confounder to the fully adjusted models did not change the outcomes. The different components of the metabolic syndrome were analyzed as continuous variables in a linear regression analysis. IGF1 was entered in the models as quintiles due to nonlinear associations with most of the components. To normalize

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Table 2 Odds ratios (ORs) for the presence of metabolic syndrome for IGF1 concentration, stratified by quintiles (Q). Data are expressed as ORs (95% CI). Adjusted for sex and age; fully adjusted for sex, age, smoking, alcohol use, physical activity, and albumin.

<table>
<thead>
<tr>
<th>Quintile</th>
<th>No. of subjects</th>
<th>No. of events</th>
<th>Unadjusted model</th>
<th>Adjusted model</th>
<th>Fully adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>251</td>
<td>86</td>
<td>Reference</td>
<td>1.02 (0.71–1.48)</td>
<td>1.07 (0.74–1.55)</td>
</tr>
<tr>
<td>Q2</td>
<td>253</td>
<td>88</td>
<td>1.13 (0.78–1.63)</td>
<td>1.24 (0.85–1.80)</td>
<td>1.16 (0.79–1.70)</td>
</tr>
<tr>
<td>Q3</td>
<td>248</td>
<td>92</td>
<td>1.37 (0.96–1.96)</td>
<td>1.60 (1.10–2.32)*</td>
<td>1.59 (1.09–2.33)*</td>
</tr>
<tr>
<td>Q4</td>
<td>257</td>
<td>107</td>
<td>1.16 (0.81–1.68)</td>
<td>1.39 (0.95–2.04)</td>
<td>1.30 (0.88–1.92)</td>
</tr>
<tr>
<td>Q5</td>
<td>249</td>
<td>94</td>
<td>1.11 (0.74–1.66)</td>
<td>1.20 (0.80–1.81)</td>
<td>1.32 (0.87–2.01)</td>
</tr>
</tbody>
</table>

*P < 0.05.
distributions of the residues, both lipids and systolic blood pressure variables were log transformed. In the fully adjusted models (age, gender, smoking habits, alcohol use, physical activity, and albumin), an IGF1 concentration in the highest quintile was positively associated with waist circumference and diastolic blood pressure compared with the lowest quintile (β = 2.12, s.e.m. 1.02, P = 0.04, and β = 4.24, s.e.m. 1.58, P = 0.01 respectively). An interaction with gender was observed for triglycerides, HDL-cholesterol, and systolic blood pressure. For men, an IGF1 concentration in the middle quintile was negatively associated with triglycerides compared with the lowest quintile (ln β = −0.13, s.e.m. 0.06, P = 0.04), and for women, the middle up to the highest quintile was positively associated compared with the lowest quintile with a maximum ln β of 0.25 (s.e.m. 0.06, P < 0.001). Again, including BMI as a confounder did not substantially alter the outcomes.

Cardiovascular diseases

After exclusion of prevalent CVD, 790 subjects remained (55.6% female, mean age 74.6 (s.d. 6.3) years). Metabolic syndrome was present in 31.6% of this cohort. The maximum follow-up was 11.6 (median 10.8) years. IGF1 demonstrated a U-shaped relationship with CVD (Q1: hazard ratio (HR) 1.51, 95% CI 1.04–2.19, Q3: reference, Q5: HR 1.46, 95% CI 1.02–2.09). Adding metabolic syndrome to the fully adjusted model did not significantly influence the regression coefficients. The interaction term of IGF1 and metabolic syndrome was significant with a P value of 0.07. The analysis of the association of IGF1 with CVD was repeated after stratification for the prevalence of metabolic syndrome. In subjects without the metabolic syndrome, CVD occurred in 36.9%, and in subjects with metabolic syndrome, this was 41.2% (P = 0.24).

In subjects without the metabolic syndrome, IGF1 concentrations in the lowest quintile demonstrated a significantly increased risk (HR 1.75, 95% CI 1.12–2.71) compared with the middle quintile (Fig. 3A). Subjects with the metabolic syndrome at baseline demonstrated an increased risk for developing CVD when having an IGF1 concentration in the highest quintile (HR 2.28, 95% CI 1.21–4.28) compared with the middle quintile (Fig. 3B).

Discussion

This population-based study among older persons demonstrated that subjects with higher IGF1 concentrations have an increased probability of prevalent metabolic syndrome, especially concentrations within the fourth quintile. IGF1 levels showed the same positive association with high triglycerides in women but not in men. The relationship of IGF1 and the metabolic syndrome.
syndrome did not directly reflect into the U-shaped relationship of IGF1 with incident CVD. But the relationship of IGF1 with incident CVD did depend on the presence of the metabolic syndrome.

In cohorts with younger subjects investigating the relationship of IGF1 with the metabolic syndrome, the common finding is an association of low IGF1 concentrations and the metabolic syndrome (12, 22, 23). In cohorts with older subjects, the findings are more heterogeneous. A small study in older people showed an association of low IGF1 concentrations with the metabolic syndrome (24), although an Italian cohort demonstrated no significant associations in older women, and a trend toward higher IGF1 values in men with the metabolic syndrome (25, 26). Most recently, Yeap et al. (10) studied a cohort of men of 70 years and older and found a U-shaped relationship, with increased risks for metabolic syndrome at the lower and upper end of IGF1 concentrations. However, there appears to be a difference in the association of IGF1 and metabolic syndrome in young and older persons. Chosen cutoff values for components of the metabolic syndrome have been established in predominantly middle-aged populations. This limitation is notable when the different cardiovascular risk factors are subsequently analyzed as continuous variables. In addition to triglycerides, waist circumference and (diastolic) blood pressure showed associations with IGF1, which was not the case for the dichotomous variables based on the general applied cutoff values.

Individually, the different components of the metabolic syndrome have most often been shown to be associated with low IGF1 values (27, 28, 29, 30, 31, 32, 33). In this study, when investigated as dichotomous variables, only the component of high triglycerides was associated with IGF1 concentrations. Subjects with the highest IGF1 values had an increased risk of high triglycerides compared with the lowest IGF1 values. Yeap et al. (10) describe this same phenomenon in an Australian cohort, with older men who have high triglycerides demonstrating higher IGF1 values than men without high triglycerides. Maison et al. (34) also conclude that IGF1 has a strong positive correlation with the lipid factor of metabolic syndrome. In adults with GH deficiency (GHD), alterations in the lipoprotein metabolism are often demonstrated. High levels of triglycerides are measured compared with healthy controls (35), but in other studies, only total cholesterol or HDL-cholesterol seems to be abnormal (36). On the other hand, in acromegaly, the same metabolic state is described. Here, triglyceride levels are elevated due to increased levels of plasma free fatty acids (FFA) attributed to lipolytic activity of GH (37).

Gender was demonstrated to be an effect modifier in the association of IGF1 with triglycerides. In women, the association was demonstrated to be positive. In men, only the linear regression analysis showed a decrease in triglycerides. When adjusted for age, gender, smoking habits, alcohol use, physical activity, and albumin, the odds ratio for high triglycerides was 3.5 (95% CI: 2.0-6.1) in men and 5.0 (95% CI: 3.2-7.8) in women.

Figure 2 Association of IGF1, divided into quintiles, with the presence of the component high triglycerides in older people, stratified for gender. Results are shown as odds ratio after adjustment for age, gender, smoking habits, alcohol use, physical activity, and albumin. Bars refer to 95% CIs.

Figure 3 Association of IGF1, divided into quintiles, with developing cardiovascular diseases in older people, stratified for the presence of metabolic syndrome. A) Subjects without metabolic syndrome; B) subjects with metabolic syndrome. Results are shown as hazard ratio after adjustment for age, gender, smoking habits, alcohol use, physical activity, and albumin. Bars refer to 95% CI.
significant association, which was negative. A gender difference is often described in studies on GHD (38), effects of GH replacement therapy (39), or GH–IGF1 axis in healthy older people (40). Mostly, sex hormone levels or substitution are considered accountable for the gender differences (22). Nevertheless, when comparing men and postmenopausal women in, for example, responsiveness to GH replacement therapy in GHD, differences are also demonstrated (41). Munzer et al. (40) speculate about a sexually dimorphic response of triglycerides to GH in healthy older persons. Increased GH-binding proteins in older women may be a contributing factor (42).

The relationship of IGF1 concentration with CVD is controversial. Low levels of IGF1 are demonstrated to be associated with an increased risk for CVD (3, 5). High levels of IGF1 have demonstrated similar associations (43, 44). Subsequently, in a previous study within the LASA cohort, a U-shaped relationship of IGF1 with CVD mortality was demonstrated (6). As Yeap et al. (10) already suggested, the heterogeneous outcomes in the association of IGF1 levels and the metabolic syndrome could explain the variance demonstrated in the associations of IGF1 levels with the development of CVD. This study is the first to include the role of the metabolic syndrome in the relationship of IGF1 with CVD. A U-shaped relationship was demonstrated with all cardiovascular events. Metabolic syndrome was not found to be a mediator in this relationship. It is suggested that older persons with metabolic syndrome are more likely to experience any CVD event than subjects without metabolic syndrome (7, 8). Nevertheless, the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and the British Regional Heart Study (BRHS) showed negligible clinical association with incident vascular events in older people (45). In this study, a profound association of neither the metabolic syndrome nor the individual components, with incident CVD could be demonstrated. Excluding subjects with prevalent CVD at baseline in an elderly cohort could have led to an underestimation of the association due to a ‘healthy survivor’ bias. Metabolic syndrome was demonstrated to be an effect modifier in the relationship of IGF1 with CVD in this study. Subjects without the metabolic syndrome at baseline have an increased risk of developing CVD when they have an IGF1 concentration within the lowest quintile. Subjects with the metabolic syndrome present at baseline have increased risk of developing CVD when they have an IGF1 concentration in the highest quintile. This underlines the hypothesis that the increased risks for CVD for both low and high IGF1 levels, even within the normal range, should be explained by different mechanisms. In GHD or low-normal IGF1 levels, this mechanism of developing CVD remains unclear. In high-normal IGF1 levels, an important interaction with insulin resistance could contribute to the mechanism. The cross-sectional aspect of the study on IGF1 and metabolic syndrome might be a limitation. Repeated measurements of (components of) the metabolic syndrome could help to better understand these relationships.

Strengths of this study include the nationally representative and large sample, the accurate assessment of cardiovascular events (46), over a maximum follow-up of almost 12 years, and the possibility to adjust for a range of potential confounders. Nonetheless, there are limitations that we have to address. We measured total serum IGF1 as an accepted measure of IGF1 status. A recently reported bioassay based on activation of the IGF1-specific kinase receptor may provide a means of assessing circulating bioactive IGF1 (47), but this method is not in general use at this moment. Furthermore, biological effects and bioavailability of IGF1 are modulated through IGFBPs, which control IGF1 access to cell surface receptors (1). Unfortunately, we did not have IGFBPs available and therefore our results do not fully represent biologically active IGF1. Because the instructions before blood sampling allowed subjects to take tea and plain toast, but no dairy products, we could not guarantee fasting blood samples. Fructosamine is little affected by eating, unlike plasma glucose level. The cutoff used for fructosamine was shown to have maximal effectiveness in discriminating subjects with impaired glucose tolerance from subjects with normal glucose tolerance (18). We used fructosamine as a proxy for plasma glucose as plasma glucose levels were not available. The possibility of a nonfasting state might also have affected our findings for triglycerides and to a lesser extent HDL-cholesterol. However, it has been demonstrated that lipid profiles change minimally in response to normal food intake (HDL-cholesterol $-$0.1 mmol/l; triglycerides 0.2 mmol/l), and nonfasting levels still predict cardiovascular events (48). For the longitudinal analysis, assigning halfway of the interval between follow-up for timing might reduce the accuracy for time-to-event in the Cox proportional hazard model.

In conclusion, in this sample of older people, high-normal levels of IGF1 are associated with a higher probability of prevalent metabolic syndrome and high triglycerides, the latter especially in women. Metabolic syndrome is not a mediator in the U-shaped relationship of IGF1 concentration with incident CVD. Subjects without the metabolic syndrome and low IGF1 levels and subjects with the metabolic syndrome and high IGF1 levels have an increased risk of developing CVD. This study suggests the presence of different pathomechanisms for both low and high IGF1 levels and developing CVD. Clarifications of these underlying mechanisms are essential for, in the end, optimal cardiovascular risk assessment for the older patients in clinical practice.
Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
The Longitudinal Aging Study Amsterdam is largely supported by a grant from The Netherlands Ministry of Health Welfare and Sports, Directorate of Long-term Care.

Acknowledgements
The authors would like to thank Jan Poppelrears for his assistance in providing the data.

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Received 6 September 2012
Revised version received 9 December 2012
Accepted 11 December 2012