Cross-sectional and longitudinal relation of IGF1 and IGF-binding protein 3 with lipid metabolism

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Abstract

Background: Previous intervention studies in patients with GH disorders suggested an impact of IGF1 and IGF-binding protein 3 (IGFBP3) on lipid metabolism, whereas population-based studies revealed conflicting results. Therefore, we aimed to assess the cross-sectional and longitudinal associations between IGF1 or IGFBP3 serum levels and lipids (total, LDL, or HDL cholesterol and triglycerides) in a large-scale study.

Methods: Data of 2935 subjects (1356 women) from the population-based Study of Health in Pomerania (SHIP) were used. ANOVA, quantile regression, and logistic regression models adjusted for age, waist circumference, physical activity, and alcohol consumption were performed.

Results: In cross-sectional analyses, we detected that IGF1 and IGFBP3 levels were positively related to total and LDL cholesterol and inversely related to HDL cholesterol in both sexes. Furthermore, IGFBP3 levels showed a positive relationship to triglycerides. In total, IGFBP3 levels were more strongly associated to lipids than IGF1. In longitudinal analysis, we found no influence of baseline IGF1 or IGFBP3 serum concentration on incidentally elevated or reduced lipid levels. However, the positive relationship between IGFBP3 and incidentally elevated triglycerides barely missed statistical significance in women.

Conclusion: The present study showed strong cross-sectional associations between IGF1 or IGFBP3 and lipids, whereas no longitudinal relationships were revealed. Therefore, our findings suggest IGF1 and IGFBP3 as a risk marker rather than a risk factor for alterations in lipid metabolism. Further studies are needed to elucidate the mechanisms underlying the association between the GH/IGF axis and lipid metabolism.

Introduction

Insulin-like growth factor 1 (IGF1), as the most important effector in the growth hormone (GH) system, influences physiological processes of metabolism and cell proliferation as well as pathological events (1). Circulating IGF1 is usually bound to IGF-binding proteins (IGFBPs), with IGFBP3 representing the major binding protein (2).

During the last decade, several studies reported associations between low IGF1 levels and cardiovascular diseases including congestive heart failure (3) or ischemic heart disease (IHD) (4), as well as between high levels of IGFBP3 and IHD (4). With respect to mortality, a meta-analysis using data of over 14 000 subjects showed that subjects with either low or high IGF1 levels had an increased all-cause and cardiovascular mortality risk (5).

An adverse lipid profile, demonstrated by increased total cholesterol, LDL cholesterol or triglycerides, and
decreased HDL cholesterol levels (6), represents a major risk factor for cardiovascular disease. In previous studies, IGF1 levels were linked to cardiovascular risk factors such as insulin resistance (7), metabolic syndrome (8, 9), and also single lipid levels (10, 11, 12, 13, 14, 15, 16, 17, 18, 19).

Most studies (16, 19, 20) investigating the association between the GH/IGF axis and lipid metabolism were done among individuals with pituitary diseases. Patients with GH deficiency (GHD) showed an adverse cardiovascular risk profile with a high prevalence of dyslipidemia (20). In detail, GHD patients exhibited higher triglyceride levels, while HDL levels were lower compared with healthy controls (19). These findings were partly confirmed by another study among GHD patients, showing an inverse association between LDL cholesterol and IGF1 levels, whereas no relation with HDL cholesterol and triglyceride was detected (16). Interestingly, GH replacement therapy leads to an improvement in lipid profile by increasing HDL as well as decreasing total and LDL cholesterol, and triglyceride levels in GHD patients (10, 17). An interruption of the therapy by administering placebo over 4 months, however, resulted in a subsequent increase in total, LDL, and HDL cholesterol, while triglycerides were decreasing (18). Beside GHD, also in acromegaly, characterized by an excess of GH and IGF1, a therapy with somatostatin analogs was linked to an improvement in lipid status by increasing HDL as well as decreasing total and LDL cholesterol, and triglyceride levels in GHD patients (10, 17). For cross-sectional analyses of the baseline cohort, subjects with missing serum data of IGF1 or lipids (n=274) were excluded from analyses. In addition, all subjects with one of the following conditions were excluded (overlap exists): subjects with type 2 diabetes mellitus (n=400), HMG-CoA reductase inhibitors (anatomical therapeutic chemical (ATC) classification: C10; n=320) medication, a creatinine clearance (CrCl) <30 ml/min (n=10), elevated thyrotropin (TSH) levels (n=125), and women taking oral contraceptives (ATC=G03A; n=375). Furthermore, all subjects with missing data for selected confounding factors (n=22) were excluded. Data from 2935 subjects, 1356 women and 1579 men, from SHIP-0 were available for cross-sectional analyses.

For longitudinal analyses, follow-up data for 2290 of the 2935 subjects were available. Seven subjects had incomplete follow-up lipid information. Furthermore, all subjects with one of the following conditions at follow-up were excluded (overlap exists): subjects with type 2 diabetes mellitus (n=122), HMG-CoA reductase inhibitors (n=206), CrCl <30 ml/min (n=6), elevated TSH levels (n=80), and women taking oral contraceptives (n=32). Of the remaining 1887 subjects, those with baseline increased or decreased lipid levels were excluded resulting in a different study population for incident adverse levels in total, HDL, LDL cholesterol, or triglycerides. The different study populations are presented in a flow diagram (Fig. 1).

Subjects and methods

Study population

The Study of Health in Pomerania (SHIP) is a population-based cohort study conducted in West Pomerania, a region in northeast Germany (24). Study sampling was carried out using the population registries, in which all German citizens are registered; the sampling protocol was published previously (24). The net sample, excluding subjects who migrated or died, consisted of 6267 eligible subjects. Of these, 4308 individuals aged 20–79 years participated in the baseline SHIP study (October 1997–March 2001, SHIP-0). The net sample at the first 5-year follow-up examination (March 2003–July 2006, SHIP-1) comprised 3300 subjects aged 25–85 years. All participants provided written informed consent. The study conformed to the principles of the Declaration of Helsinki as reflected by an a priori approval of the Ethics Committee of the University of Greifswald.

For cross-sectional analyses of the baseline cohort, subjects with missing serum data of IGF1 or lipids (n=274) were excluded from analyses. In addition, all subjects with one of the following conditions were excluded (overlap exists): subjects with type 2 diabetes mellitus (n=400), HMG-CoA reductase inhibitors (anatomical therapeutic chemical (ATC) classification: C10; n=320) medication, a creatinine clearance (CrCl) <30 ml/min (n=10), elevated thyrotropin (TSH) levels (n=125), and women taking oral contraceptives (ATC=G03A; n=375). Furthermore, all subjects with missing data for selected confounding factors (n=22) were excluded. Data from 2935 subjects, 1356 women and 1579 men, from SHIP-0 were available for cross-sectional analyses.

For longitudinal analyses, follow-up data for 2290 of the 2935 subjects were available. Seven subjects had incomplete follow-up lipid information. Furthermore, all subjects with one of the following conditions at follow-up were excluded (overlap exists): subjects with type 2 diabetes mellitus (n=122), HMG-CoA reductase inhibitors (n=206), CrCl <30 ml/min (n=6), elevated TSH levels (n=80), and women taking oral contraceptives (n=32). Of the remaining 1887 subjects, those with baseline increased or decreased lipid levels were excluded resulting in a different study population for incident adverse levels in total, HDL, LDL cholesterol, or triglycerides. The different study populations are presented in a flow diagram (Fig. 1).

Measurements

A computer-aided personal interview was used to collect information on medical history, behavioral, and
socio-demographic characteristics. Smoking status was assessed by self-report and categorized into current, former, and never-smokers. Participants who did not participate in physical training during summer or winter for at least 1 h a week were classified as being physically inactive. Alcohol drinking habits were evaluated as beverage-specific alcohol consumption (beer, wine, and distilled spirits) on the last weekend and last weekday preceding the examination. The mean daily alcohol consumption was calculated using beverage-specific pure ethanol volume proportions (25). Diabetes was defined as self-report based on the question of whether a physician had ever diagnosed diabetes or taking of antidiabetics (ATC code: A10). Waist circumference (WC) was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet. Liver diseases were defined based on self-reported and serum γ-glutamyl transferase, aspartate-amino transferase or alanine-amino transferase levels greater than the population mean + 2 S.D.

Exclusion criteria at baseline:
- Missing parameters
- Diabetes mellitus type 2, HMG-CoA reductase inhibitors elevated thyrotropin levels, women who taking oral contraceptives, creatinine clearance <30 ml/min

Exclusion criteria follow-up:
- Missing parameters
- Diabetes mellitus type 2, HMG-CoA reductase inhibitors elevated thyrotropin levels, women who taking oral contraceptives, creatinine clearance <30 ml/min

Exclusion of subjects without 5-year follow-up

Exclusion of subjects with adverse lipid levels at baseline
- Elevated total cholesterol
- Elevated LDL cholesterol
- Reduced HDL cholesterol
- Elevated triglycerides
- Dyslipidemia

Non-fasting blood samples were drawn from the cubital vein in the supine position. The samples were taken between 07:00 am and 04:00 pm, and serum aliquots were prepared for immediate analysis and for storage at −80 °C. For lipids, the measurements were immediately performed in fresh samples within 4 h. At baseline, triglycerides levels were determined enzymatically using reagents from Roche Diagnostics (Hitachi 717, Roche Diagnostics) and total cholesterol levels were measured photometrically (Hitachi 704, Roche). At follow-up, triglycerides and total cholesterol levels were measured enzymatically on a Dimension RxL automatic analyzer (Siemens Healthcare Diagnostics, Inc., Eschborn, Germany). HDL cholesterol was measured photometrically (Hitachi 704, Roche) at baseline and quantified by lipoprotein electrophoresis (HELENA SAS-3 system; Helena 7 BioSciences Europe, Tyne & Wear, UK) at follow-up. For total cholesterol or triglycerides, the inter-assay coefficients of variation (CV) were below 2.8 or 3.9% at the low level and 2.7 or 3.3% at high level respectively. For HDL cholesterol, the inter-assay CV was below 6.5% at the medium level. To ensure comparability, serum HDL levels (mg/l) at the follow-up examination were transformed by the equation: \( y = -80 + 1.158x \) (26). At both time points, LDL cholesterol were calculated by Friedewald’s formula (27): LDL cholesterol (mg/dl) = total cholesterol − HDL cholesterol − TGL/5 for subjects with TGL levels below 400 mg/dl. Altered lipid levels were defined based on cut-points found in the third report of the National Cholesterol


Figure 1
Flow diagram of the study population. *Missing parameters for the hormone and lipid levels used.
Education Program Adult Treatment Panel III (28) (total cholesterol, LDL, and HDL) or in the guidelines from the World Health Organization (triglycerides) (29): total cholesterol ≥239.75 mg/dl (6.2 mmol/l), LDL cholesterol >158.55 mg/dl (4.1 mmol/l), triglycerides ≥148.75 mg/dl (1.7 mmol/l), and HDL cholesterol <40.22 mg/dl (1.04 mmol/l). Subjects with elevated total cholesterol or LDL cholesterol or reduced HDL cholesterol were considered to be dyslipidemic.

Furthermore at baseline, serum creatinine levels were determined with the Jaffe’s method (Hitachi 717, Roche Diagnostics GmbH). CrCl (ml/min) was estimated using the Cockroft–Gault formula. Serum TSH levels were measured by immunochemiluminescent procedures (LIA-mat analyser, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany). The functional sensitivity of the TSH assay was 0.02 mIU/l. As recently established for the SHIP population (30), serum TSH exceeding the upper reference value of 2.12 mIU/ml was considered elevated. The interassay CV was 5.4%.

Serum IGF1 and IGFBP3 levels were determined by automated sandwich-type chemiluminescent immunoassay on the IDS-iSYS (Immunodiagnostic Systems, Boldon, UK). Two MABs raised against recombinant IGF1 were selected based on high specificity and affinity: one antibody directed against the N-terminal fragment is biotinylated, whereas a second anti-IGF1-antibody is coupled to an acrydinium ester derivate. According to the manufacturer, the limit of blank, limit of detection, and limit of quantitation were 1.9, 4.4, and 8.8 ng/ml for the IGF1 assay as well as 30, 50, and 80 ng/ml for the IGFBP3 assay respectively. The cross-reactivity of IGF1 assay with IGF2 <0.01%. The cross-reactivity of IGFBP3 assay with IGFBP1, IGFBP2, IGFBP4, IGFBP5, or IGFBP6 <0.1%. Precision of the assays was evaluated in accordance with a modified protocol based on CLSI EP-S2A, ‘Evaluation of Precision Performance of Quantitative Measurement Methods’. Five serum controls were assayed using three lots of reagents in duplicate twice per day for 20 days on one instrument. For the SHIP measurements, the CV varied between 6.0% (high level) and 9.8% (low level) for the IGF1 assay and between 7.9% (high level) and 15.5% (low level) for the IGFBP3 assay. The assay is calibrated against the new recombinant international standard 02/254.

Statistical analyses

Continuous data are expressed as mean (S.D.); nominal data are given as percentages. The Kruskal–Wallis test (continuous data) or χ²-test (nominal data) were used for comparisons between men and women. For cross-sectional analyses in a first step, adjusted mean lipid levels were calculated by ANOVA separately for men and women. For this, IGF1 and IGFBP3 values were categorized into three groups according to the age- and sex-specific tertiles. In a second step, the associations of continuous IGF1 or IGFBP3 with lipid levels were assessed with linear regression models by the following steps: i) the likelihood ratio test was used to compare the fit of linear models and models with restricted cubic splines with three knots to detected possible non-linear associations. Three knots were pre-specified, located at the 5th, 50th, and 95th percentiles as recommended by Stone & Koo (31), resulting in one component of the spline function: IGF1 or IGFBP3. ii) Furthermore, in case of significant models with restricted cubic splines, non-nested models with three and more knots were compared by Clarke testing (32). Only in men, the association between IGF1 levels and triglycerides were assessed by a model with restricted cubic splines with four knots pre-specified, located at the 5th, 35th, 65th, and 95th percentiles. In a third step, logistic regression was performed to investigate the relation between hormone levels and increased or decreased lipid levels. For longitudinal analyses, Poisson regression analyses were performed to investigate the relation of

Table 1: Baseline characteristics stratified by sex. Continuous data are expressed as mean (S.D.), nominal data are given as percentages.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men (n = 1579)</th>
<th>Women (n = 1356)</th>
<th>P *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.2 (16.2)</td>
<td>50.1 (14.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smokers</td>
<td>21.7</td>
<td>50.6</td>
<td></td>
</tr>
<tr>
<td>Former smokers</td>
<td>41.2</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>37.1</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>43.8</td>
<td>44.0</td>
<td>0.95</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>20.9 (23.9)</td>
<td>5.5 (8.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>94.4 (11.6)</td>
<td>83.3 (12.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.2 (4.0)</td>
<td>26.9 (5.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>224 (47)</td>
<td>227 (48)</td>
<td>0.20</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>139 (42)</td>
<td>139 (45)</td>
<td>0.95</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>51.5 (14.5)</td>
<td>61.9 (17.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>175 (117)</td>
<td>130 (76)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum IGF1 (ng/ml)</td>
<td>132 (51)</td>
<td>126 (50)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum IGFBP3 (ng/ml)</td>
<td>4123 (1003)</td>
<td>4176 (852)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

IGF1, insulin-like growth factor I; IGFBP3, IGF-binding protein 3; TGL, triglyceride. *χ²-test (nominal data) or Mann–Whitney U test (interval data) were performed.
baseline hormone levels with incident increased total cholesterol, LDL cholesterol, or triglycerides as well as decreased HDL cholesterol levels. Adjusted means, odd ratios (ORs), or relative risk and their 95% CI were calculated. All models were adjusted for age, WC, physical activity, and alcohol consumption. All statistical analyses were performed using SAS, version 9.2 (SAS Statistical Software, version 9.2, SAS Institute, Inc., Cary, NC, USA).

**Results**

The cross-sectional study population comprised 1356 women and 1579 men (Table 1). Women were older, more often never smokers, had a lower alcohol consumption, and lower WC than men. With respect to hormone levels, women exhibited lower IGF1 levels, whereas no difference for IGFBP3 levels became apparent. Concerning lipid levels, women showed a more favorable profile than men with higher levels of HDL cholesterol and lower levels of triglyceride.

**Cross-sectional analyses**

In multivariable ANOVA (Fig. 2), IGF1 was positively related to total and LDL cholesterol and inversely related to HDL cholesterol in men and/or women. In detail, the estimated mean of total and LDL cholesterol increased by up to 9 mg/dl (women) and 11 mg/dl (women), whereas HDL cholesterol decreases by 3 ng/ml (men) from the lowest to the highest IGF1 tertile respectively. These findings were confirmed by quantile regression analyses (Fig. 2 and Supplementary Table 1, see section on supplementary data given at the end of this article), even if the relation with total and LDL cholesterol seems to be inversely U-shaped. However, the detected decrease in lipid levels occurs only for relatively high IGF1 levels (>90th percentile). With respect to IGFBP3, the positive relation with total and LDL cholesterol, and triglycerides as well as the inverse association with HDL cholesterol detected by ANOVA and quantile regression was even stronger than those with IGF1 (Fig. 3 and Supplementary Table 1). In detail, total and LDL cholesterol, and triglycerides increased by up to 18 mg/dl (women), 14 mg/dl (women), and 52 ng/ml (men) from the lowest to the highest IGFBP3 tertile respectively.

In concordance with the results from ANOVA and quantile regression, logistic regression analyses confirmed the strong relation of IGFBP3 levels with an adverse lipid profile in men and women. Subjects in the highest IGFBP3 tertile have a 1.6- up to 2.4-fold higher odds of elevated

![Figure 2](https://example.com/fig2.png)

**Figure 2**

Association between insulin-like growth factor 1 (IGF1), serum concentration, and level of total cholesterol, LDL, HDL cholesterol, and triglyceride among men and women. Left side of each lipid: linear regression with restricted cubic splines. Right side of each lipid: estimated mean levels with 95% CI by tertiles of IGF1. All models were adjusted for age, physical activity, waist circumference, and alcohol consumption.
total or LDL cholesterol, or triglycerides levels compared with subjects in the lowest tertile (Table 2). Also the odds of dyslipidemia were up to 1.9-fold higher in these subjects. With respect to IGF1, high levels were linked to higher odds of elevated total and LDL cholesterol among women (Table 2). The positive association with dyslipidemia barely missed statistical significance. In men, only a positive relation between IGF1 and elevated triglycerides became apparent. Sensitivity analyses were run using BMI instead of WC as confounder and after the exclusion of subjects with liver disease (65 women and 85 men). All these analyses confirmed the reported findings, with no substantial changes in the estimates (data not shown).

Longitudinal analyses

In a second step, the relation between IGF1 and IGFBP3 with incident elevated total, LDL cholesterol, or triglycerides and reduced HDL cholesterol were investigated in a disease-free population at baseline (Table 3). These analyses did not reveal any significant association. Only in women, a tendency to a positive relation between IGFBP3 and incident elevated triglycerides (per 2000 ng/ml increase OR 1.56 (95% CI 0.98; 2.47), \*P*=0.06) became apparent.

Discussion

While the influence of a pathological GH axis on lipid levels was analyzed in numerous clinical studies (10, 14, 16, 17, 18, 19, 20, 21, 22, 23, 33, 34, 35), observational studies in general population samples are scarce and longitudinal analysis is missing. To the best of our knowledge, the present study is the largest population-based study using an IGF1 and IGFBP3 measurement in line with recommendation of the Keswick consensus conference to close this gap. Our data showed positive cross-sectional associations between IGF1 and total cholesterol or LDL cholesterol and an inverse relation with HDL cholesterol in women and men. Furthermore, strong positive relation of IGFBP3 levels with total cholesterol, LDL cholesterol, and triglycerides were revealed in both sexes. However, no longitudinal relation of IGF1 and IGFBP3 with lipid levels became apparent.

With respect to IGF1, a previous study among elderly subjects confirmed our positive association between IGF1 and total cholesterol (15). However, also an inverse association between rising levels of IGF1 and total cholesterol was reported among 3977 adults (12). Further relevant studies have focused on subjects in disease states. Thus, the decrease of extremely high GH and IGF1 levels...
in acromegaly patients under therapy with somatostatin analogs leads to a benefit on total and LDL cholesterol values (12). This relationship is consistent with our results. Furthermore, GHD patients under GH therapy showed also beneficial effects by decrease in total and LDL cholesterol levels while IGF1 levels increased (10, 14, 35, 36, 37). The translation of these conflicting results in patients with GHD or acromegaly to the population-based approach however is questionable. Moreover, other smaller intervention studies indicated that GH, but not IGF1, lead to the development of abnormal lipid levels with an influence on cholesterol and triglycerides (34, 35).

In the present study, the revealed inverse relationship of IGF1 with HDL cholesterol is in concordance with results regarding total and LDL cholesterol and shows that subjects with the lowest IGF1 levels have the most beneficial lipid profile. Similar findings were reported in a population sample of adults (12) and obese young men (11). In contrast to our results, among 132 subjects aged 60–91 years, a positive correlation between IGF1 and HDL cholesterol was detected (15). The older age of these subjects might be a reason for the conflicting results and further a limiting factor for a general conclusion. With respect to patient studies, low and high IGF1 levels outside the reference range are associated with lower HDL cholesterol (10, 14, 19, 20, 21, 23, 33). An interesting observation was made among GHD patients who discontinued their GH replacement therapy. By applying placebo, the patients showed a decrease in HDL cholesterol levels (18). In contrast, GH replacement therapy leads to increasing HDL cholesterol levels (10, 14) or no significant change (20) in other studies. Therefore, our results are more consistent with studies on patients with acromegaly under therapy that show increasing levels of HDL while decreasing levels of IGF1 (21, 23). In general, the discrepancies between the studies regarding the effect of GH therapy on lipid levels suggest wide-ranging variability in individual treatment response (38). Recent studies have implied that GH treatment response in lipid profile might be influenced by polymorphisms in the APOB and PPARG genes (14).

The evaluation of existing publications confirmed our results about a missing association between IGF1 and triglycerides (12, 15, 18). From the population-based perspective only in obese young men, a parallel decrease...
became apparent (11). The adjustment was unfortunately just done for the BMI. Obesity of the subjects and the fact that physical activity was not taken into account as a confounder might explain the association with triglycerides. Obesity leads to metabolic alterations and might result in insulin resistance, which itself represents a reason for hypertriglyceridemia (39). A study using the NHANES III (Third National Health and Nutrition Examination Survey) revealed an association between a low IGF1:IGFBP3 ratio and higher triglyceride levels in USA adults, which is also in conflict with our findings (9). The results of patient studies are similarly contradictory. Patients with pathologically high IGF1 levels under therapy with somatostatin analogs also showed no significant relationship (21) or a decrease in triglyceride levels (23). Taking GHD into account, triglyceride levels are higher in patients without therapy (10, 19, 20). After the GH replacement therapy, different effects on triglycerides were observed, including no significant relations (14, 20), a decrease (10) or an increase (35) in triglyceride levels. Interestingly, an interruption of the therapy showed the positive effect of a decrease in triglyceride levels (18). There is no explicit explanation that can be deduced from the diverse results. Further investigations have to be done to further explain the link between IGF1 axis and triglycerides.

Whereas the above-discussed studies examined the effect of IGF1 and lipids, only few studies investigated IGFBP3 with conflicting results. Our detected positive association of IGFBP3 with triglycerides and an inverse association with HDL cholesterol are consistent with other studies (18). The population-based Framingham Heart Study (12) showed inconsistent results by revealing that increasing HDL cholesterol, as well as triglyceride levels, were related to increasing IGFBP3 levels (12). Also in an elderly population, IGFBP3 levels were positively related with HDL cholesterol (15). Ceda et al. (15) developed the hypothesis that decreasing GH in the elderly is a reason for the decrease in both IGFBP3 and HDL cholesterol. The context needs further investigations. A relationship between higher IGFBP3 levels and total and/or LDL cholesterol was not described before. Already Lam et al. (12) emphasized the importance of a longitudinal study to analyze the relationship between GH/IGF1 axis and lipids. However, the uniform and clear

<table>
<thead>
<tr>
<th></th>
<th>Elevated total cholesterol</th>
<th>Elevated LDL cholesterol</th>
<th>Reduced HDL cholesterol</th>
<th>Elevated triglyceride</th>
<th>Dyslipidemia</th>
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<td>RR (95% CI)</td>
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<td><strong>Men</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>n (cases)</td>
<td>698 (85)</td>
<td>681 (138)</td>
<td>800 (426)</td>
<td>551 (167)</td>
<td>526 (313)</td>
</tr>
<tr>
<td>IGF1 per 100 ng/mg increase</td>
<td></td>
<td></td>
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<tr>
<td>IGF1 (ref: I tertile)</td>
<td>0.90 (0.53; 1.53)</td>
<td>0.69 (0.45; 1.06)</td>
<td>1.11 (0.89; 1.40)</td>
<td>1.17 (0.83; 1.66)</td>
<td>1.10 (0.85; 1.42)</td>
</tr>
<tr>
<td>II tertile</td>
<td>1.05 (0.61; 1.78)</td>
<td>1.17 (0.79; 1.75)</td>
<td>1.05 (0.83; 1.34)</td>
<td>0.88 (0.59; 1.30)</td>
<td>1.12 (0.85; 1.49)</td>
</tr>
<tr>
<td>III tertile</td>
<td>1.14 (0.67; 1.95)</td>
<td>0.80 (0.52; 1.25)</td>
<td>1.10 (0.87; 1.40)</td>
<td>1.12 (0.77; 1.62)</td>
<td>1.11 (0.84; 1.48)</td>
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<td>IGFBP3 per 2000 ng/ml increase</td>
<td></td>
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<tr>
<td>IGFBP3 (ref: I tertile)</td>
<td>1.22 (0.73; 2.04)</td>
<td>0.89 (0.59; 1.34)</td>
<td>1.19 (0.95; 1.49)</td>
<td>1.30 (0.91; 1.87)</td>
<td>1.09 (0.84; 1.41)</td>
</tr>
<tr>
<td>II tertile</td>
<td>0.84 (0.49; 1.42)</td>
<td>0.95 (0.64; 1.41)</td>
<td>1.16 (0.91; 1.48)</td>
<td>1.25 (0.87; 1.80)</td>
<td>1.02 (0.78; 1.35)</td>
</tr>
<tr>
<td>III tertile</td>
<td>0.97 (0.57; 1.63)</td>
<td>0.81 (0.53; 1.25)</td>
<td>1.23 (0.96; 1.58)</td>
<td>1.20 (0.81; 1.78)</td>
<td>1.04 (0.79; 1.37)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (cases)</td>
<td>599 (109)</td>
<td>650 (145)</td>
<td>823 (197)</td>
<td>652 (99)</td>
<td>541 (212)</td>
</tr>
<tr>
<td>IGF1 per 100 ng/mg increase</td>
<td></td>
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</tr>
<tr>
<td>IGF1 (ref: I tertile)</td>
<td>0.76 (0.45; 1.28)</td>
<td>0.76 (0.48; 1.21)</td>
<td>1.02 (0.73; 1.42)</td>
<td>1.05 (0.64; 1.71)</td>
<td>0.89 (0.63; 1.26)</td>
</tr>
<tr>
<td>II tertile</td>
<td>1.09 (0.70; 1.69)</td>
<td>1.37 (0.92; 2.02)</td>
<td>0.87 (0.61; 1.23)</td>
<td>0.86 (0.53; 1.40)</td>
<td>0.99 (0.72; 1.36)</td>
</tr>
<tr>
<td>III tertile</td>
<td>0.89 (0.55; 1.45)</td>
<td>1.11 (0.73; 1.70)</td>
<td>0.97 (0.69; 1.35)</td>
<td>0.87 (0.54; 1.41)</td>
<td>0.87 (0.62; 1.22)</td>
</tr>
<tr>
<td>IGFBP3 per 2000 ng/ml increase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGFBP3 (ref: I tertile)</td>
<td>1.18 (0.75; 1.86)</td>
<td>0.98 (0.65; 1.48)</td>
<td>0.99 (0.71; 1.39)</td>
<td>1.56 (0.98; 2.47)</td>
<td>1.07 (0.77; 1.49)</td>
</tr>
<tr>
<td>II tertile</td>
<td>1.13 (0.72; 1.77)</td>
<td>1.11 (0.75; 1.64)</td>
<td>1.07 (0.75; 1.53)</td>
<td>0.90 (0.54; 1.50)</td>
<td>0.94 (0.67; 1.32)</td>
</tr>
<tr>
<td>III tertile</td>
<td>1.01 (0.63; 1.62)</td>
<td>0.98 (0.65; 1.47)</td>
<td>1.12 (0.80; 1.59)</td>
<td>1.45 (0.91; 2.33)</td>
<td>1.08 (0.78; 1.50)</td>
</tr>
</tbody>
</table>

IGF1, insulin-like growth factor 1; IGFBP3, IGF-binding protein 3; RR, relative risk.
results of the present study led to the conclusion that the incidence of abnormal lipid levels and dyslipidemia is not attributed to IGF1 or IGFBP3 5 years ago. Therefore, we hypothesize that the previous reported association between IGF1 and mortality (40) is not mediated by lipids. Furthermore, the missing correlation leads to the assumption that the influence of IGF1 or IGFBP3 might be characterized by short-term effects.

The strengths of the present study are the large sample size and the investigation of the cross-sectional as well as longitudinal association between IGF1 or IGFBP3 and lipids. Furthermore, the IGF1 and IGFBP3 were measured in line with the recommendation of the Keswick consensus conference. Limitations arise from the fact that we had non-fasting samples, which might influence triglyceride levels and no general information about nutritional habits. However, this corresponds to common clinical practice.

In general, it is difficult to draw a comparison between our population-based study and those undertaken in patients with GHD or acromegaly. In pituitary gland diseases, patients often suffered from multiple hormone deficits and up to now our replacement therapy is just approximating physiological values that might influence lipid status as well. Therefore, the only way to increase the insights for clinical decision making are independent randomized clinical trials and large-scale Mendelian randomization meta-analyses following the Keswick consensus for IGF1 and IGFBP3 analyses.

With our study of the cross-sectional and longitudinal relationship between IGF1 or IGFBP3, and lipids, we did not confirm a direct influence of IGF1 and/or IGFBP3 on lipid levels. The present longitudinal analyses did not detect any evidence for causal associations of either IGF1 or IGFBP3 levels with lipid values as cardiometabolic risk factor, suggesting that previously reported and now documented cross-sectional associations might result from residual confounding or reverse causation. In conclusion, we propose that IGFBP3 represents a biomarker, which is linked with dyslipidemia rather than a causal risk factor of an adverse lipid profile. However, IGFBP3 assessment might improve risk prediction, especially for future individualized treatment. Notwithstanding, the pathophysiological mechanism that leads to abnormal lipid levels with rising IGF1 and IGFBP3 levels needs further investigation.

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**Supplementary data**
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-13-1017.

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**Declaration of interest**
M-L Eggert, H Wallaschofski, A Grotevendt, M Nauck, H Völzke, S Samietz, and N Friedrich have nothing to declare.

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**Author contribution statement**
The authors have made the following declarations about their contributions: conception and design: M-L Eggert, N Friedrich, and H Wallaschofski. Data analysis: N Friedrich. Interpretation of data: all. Article drafting: M-L Eggert, N Friedrich, and H Wallaschofski. Final approval: all.

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**References**


Clinical Study

M-L Eggert, H Wallaschofski and others

IGF1 or IGFBP3 and lipid levels

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