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CLINICAL STUDY

# Associations of age-dependent IGF-I SDS with cardiovascular diseases and risk conditions: cross-sectional study in 6773 primary care patients

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## Abstract

*Objective*: We aimed at investigating the association of age-dependent IGF-I SDS with diabetes, dyslipidemia, hypertension, and heart diseases, in a large patient sample.

*Background*: IGF-I has been suggested to be associated with several diseases and a prognostic marker for the development of cardiovascular diseases and risk factors. The findings, though, have been inconsistent possibly due to the methodological factors.

*Methods*: We studied 6773 consecutive primary care patients, aged 18+ years, in a cross-sectional, epidemiological study in primary care, Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment study. All patients underwent a standardized clinical diagnostic and laboratory assessment. IGF-I levels were measured with an automated chemiluminescence assay system. We calculated the odds ratios (OR) for diseases in quintiles of IGF-I, and additionally analyzed the association of age-dependent IGF-I SDS with these conditions.

*Results*: After multiple adjustments for confounders, we found increased ORs for coronary artery disease in patients with high IGF-I. Women, but not men, with low IGF-I also showed increased ORs for coronary artery disease. Dyslipidemia was positively associated with IGF-I. Type 2 diabetes showed a curvilinear association with IGF-I SDS.

*Conclusions*: The findings suggest the existence of multiple and complex interactions between IGF-I and several health conditions. The complex nature of disease- and subgroup-specific associations along with the methodological factors can be held responsible for divergent findings in previous studies.

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## Introduction

Insulin-like growth factor-I (IGF-I) possesses proliferative and anti-apoptotic properties, and is regulated by growth hormone (GH). Apart from being a marker for pathological GH over- and undersecretion (1–4), IGF-I variance in the normal range has been suggested to be causally related to the pathogenesis of several cardiovascular risk factors and diseases such as insulin insensitivity and diabetes (5, 6), coronary artery disease, and heart failure (7–12). However, possibly due to the methodological constraints (sampling, statistical analyses) of the available clinical studies, the relationship of IGF-I with these conditions and its pathogenic role remains partly inconclusive and contradictory. Both protective (7, 10, 11) and detrimental (8, 9, 12) effects of IGF-I on cardiovascular risk have been reported. Low IGF-I has been associated with the presence (7) and risk of developing coronary artery disease (10) and with cardiovascular mortality (11). In other studies, differing results were obtained. Thus, IGF-I has been found to be positively associated with progression of coronary artery stenosis and restenosis (8, 9) and coronary artery disease (12). Heart failure has been found to be associated with low IGF-I (13–16). In some studies on patients with heart failure, positive effects of GH or IGF-I on cardiac function have been found (17, 18), whereas these effects could not be reproduced in other studies (19, 20). A recent meta-analysis on 12 studies evaluating GH therapy in 195 patients with chronic heart failure has shown some beneficial effects on hemodynamics, but recommended further research with larger trials (21). The literature



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available on the associations of IGF-I with different health conditions has been extensively reviewed by Juul (22).

Patients with low IGF-I levels have been found to be at increased risk of developing glucose intolerance (6). Results from the Rotterdam Study suggest that a genetic polymorphism leading to lower levels of serum IGF-I confers a higher risk of diabetes and myocardial infarction (5).

States of pathological GH over and undersecretion, which lead to pathological IGF-I levels, are associated with specific systemic complications. In active acromegaly, and thus a state of high IGF-I concentrations, cardiac dysfunction with ventricular hypertrophy, hypertension, and type 2 diabetes can be found along with other complications (23). GH deficiency is associated with atherosclerosis, diastolic dysfunction, decreased left ventricular mass, type 2 diabetes, or dyslipidemia for example (24).

Both GH secretion and IGF-I levels decrease with age in adults. Recently, age-dependent reference values in a large cohort of normal weight healthy subjects have been published (25). These values were established using an automated immunoassay system (Nichols advantage) and showed a high grade of reproducibility in different laboratories. This allows calculation of age-dependent SDS of IGF-I and elimination of the effect of age-related decline.

We have previously shown that age-dependent IGF-I SDS show a curvilinear association with body mass index (BMI) (26), in a large patient sample in primary care. Based on this exploration, the present paper aims to clarify the role of IGF-I by examining the association of IGF-I with cardiovascular risk factors and diseases using the same dataset.

## Subjects and methods

### Subjects

The study was approved by the local ethics committee and all patients gave written informed consent. IGF-I was measured in 4013 women and 2760 men, a random sample from the Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment study, which was the representative of the total DETECT population.

DETECT is a large, multistage cross-sectional study of 55 518 unselected consecutive patients (59% women and 41% men; over 17 years) from 3188 primary care offices in Germany with a prospective 12-month component in a random subset of 7519 patients and 851 primary care settings. The initial physician response rate was 60.2%, and further adjustments for non-response, regional distribution, and attrition were performed. For all patients, a comprehensive standardized clinical evaluation (patients self-report and physicians' assessments) was conducted. Patients were additionally characterized by an extensive standardized laboratory program focusing on cardiovascular (CV) risk assessment. For technical reasons, IGF-I measurements were available only in 6773 patients. These patients constituted the sample studied here. Table 1 summarizes patient characteristics in detail. Further details are available at http://www.detect-studie.de. Design, methods, and patient baseline characteristics, as well as prevalences of health conditions and diseases have been published (27).

### Instruments and measures

The main target of the DETECT study was the assessment of cardiovascular risk. Therefore, physicians were asked to diagnose diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease (CAD) as definite, possible, or not present. CAD was defined as the history of myocardial infarction, coronary intervention, bypass surgery, or angiographically documented coronary atherosclerosis. Patients with unclear findings were excluded from the analysis for CAD ($N=160$). In the case of diabetes, type 1 or type 2 was indicated. Other diagnoses were assessed by checkboxes without further specifications. Current cardiovascular medication was recorded. Laboratory values, obtained from the central laboratory in Graz were additionally used for the diagnosis of dyslipidemia and diabetes. Doctors were instructed to measure the weight, height, and blood pressure according to a standardized protocol. Systolic and diastolic blood pressure was measured by indirect cuff sphygmomanometry after several minutes of rest in the sitting position.

For the assessment of diseases and risk factors, physician's diagnoses (definite diagnoses) in addition to the parameters described below were used. Patients with a possible physician's diagnosis, but no further laboratory or clinical finding confirming this diagnosis, were excluded from the evaluation of the respective diagnosis. For the following diagnoses, these additional criteria established or confirmed the diagnosis: dyslipidemia – levels above total cholesterol $>240$ mg/dl, low density lipoprotein (LDL) cholesterol $>160$ mg/dl or high density lipoprotein (HDL) cholesterol $<40$ mg/dl, or intake of lipid-lowering medication; hypertension – systolic blood pressure (SBP) $\geq 140$ mmHg or diastolic blood pressure (DBP) $\geq 90$ mmHg, or intake of antihypertensive medication (NHANES criteria); type 2 diabetes – fasting blood glucose level $\geq 126$ mg/dl or intake of oral antidiabetic drugs.

### IGF-I measurements

Blood samples were collected and shipped by courier at room temperature within 24 h to the central laboratory at the Medical University of Graz (Austria). Upon arrival, the samples were centrifuged immediately and serum was stored at $-20$ °C until further processing. IGF-I was determined with an automated chemiluminiscence system

**Table 1** Patients characteristics in the study sample.

| | **Total** ($N=6773$)[a] | | **Female** ($N=4013$) | | **Male** ($N=2760$) | |
|---|---|---|---|---|---|---|
| | *N* | % | *N* | % | *N* | % |
| **Total** | | | | | | |
| Age group, 18–44 years | 1429 | 21.1 | 958 | 23.9 | 471 | 17.1 |
| Age group, 45–65 years | 3050 | 45.0 | 1718 | 42.8 | 1332 | 48.3 |
| Age group, 66+ years | 2294 | 33.9 | 1337 | 33.3 | 957 | 34.7 |
| Smoker | 1380 | 21.1 | 773 | 20.0 | 607 | 22.8 |
| Ex-smoker | 1574 | 24.1 | 551 | 14.2 | 1023 | 38.5 |
| Non-smoker | 3580 | 54.8 | 2551 | 65.8 | 1029 | 38.7 |
| Age[b] | 57.7 (14.3) | | 57.0 (14.9) | | 58.8 (13.4) | |
| BMI[b] | 27.1 (4.9) | | 26.7 (5.2) | | 27.7 (4.3) | |
| IGF-I[b] | 132.2 (54.4) | | 130.7 (55.5) | | 134.2 (52.6) | |
| IGF-I SDS[b] | 0.0 (0.9) | | 0.1 (0.9) | | −0.1 (0.9) | |
| CAD | 939 | 14.2 | 384 | 9.8 | 555 | 20.6 |
| Myocardial infarction | 343 | 5.1 | 96 | 2.4 | 247 | 9.0 |
| Heart failure | 675 | 10.0 | 365 | 9.1 | 310 | 11.2 |
| Type 1 diabetes | 52 | 0.8 | 30 | 0.8 | 22 | 0.8 |
| Type 2 diabetes | 1021 | 15.1 | 505 | 12.6 | 516 | 18.7 |
| Hypertension | 4104 | 60.6 | 2255 | 56.2 | 1849 | 67.0 |
| Dyslipidemia | 4267 | 63.9 | 2296 | 58.1 | 1971 | 72.3 |
| **Age group, 18–44 years** | | | | | | |
| Age[b] | 37.2 (5.8) | | 37.1 (5.9) | | 37.6 (5.5) | |
| BMI[b] | 25.6 (5.2) | | 25.0 (5.5) | | 26.9 (4.5) | |
| IGF-I[b] | 163.6 (56.7) | | 162.2 (56.4) | | 166.3 (57.3) | |
| IGF-I SDS[b] | −0.2 (0.8) | | −0.2 (0.8) | | −0.2 (0.9) | |
| CAD | 20 | 1.4 | 5 | 0.5 | 15 | 3.3 |
| Myocardial infarction | 6 | 0.4 | 0 | 0.0 | 6 | 1.3 |
| Heart failure | 8 | 0.6 | 3 | 0.3 | 5 | 1.1 |
| Type 1 diabetes | 13 | 0.9 | 8 | 0.8 | 5 | 1.1 |
| Type 2 diabetes | 38 | 2.7 | 23 | 2.4 | 15 | 3.2 |
| Hypertension | 371 | 26.0 | 195 | 20.4 | 176 | 37.4 |
| Dyslipidemia | 584 | 41.3 | 300 | 31.7 | 284 | 60.9 |
| **Age group, 45–65 years** | | | | | | |
| Age[b] | 55.7 (6.4) | | 55.3 (6.4) | | 56.3 (6.3) | |
| BMI[b] | 27.4 (4.9) | | 27.0 (5.3) | | 28.1 (4.4) | |
| IGF-I[b] | 130.4 (50.4) | | 129.1 (52.1) | | 132.1 (48.0) | |
| IGF-I SDS[b] | −0.1 (0.9) | | 0.0 (0.8) | | −0.1 (0.9) | |
| CAD | 298 | 10.0 | 96 | 5.7 | 202 | 15.5 |
| Myocardial infarction | 129 | 4.2 | 27 | 1.6 | 102 | 7.7 |
| Heart failure | 171 | 5.6 | 63 | 3.7 | 108 | 8.1 |
| Type 1 diabetes | 23 | 0.8 | 11 | 0.6 | 12 | 0.9 |
| Type 2 diabetes | 383 | 12.6 | 154 | 9.0 | 229 | 17.2 |
| Hypertension | 1787 | 58.6 | 928 | 54.0 | 859 | 64.5 |
| Dyslipidemia | 1969 | 65.3 | 987 | 58.2 | 982 | 74.3 |
| **Age group 66+** | | | | | | |
| Age[b] | 73.1 (5.4) | | 73.5 (5.5) | | 72.6 (5.1) | |
| BMI[b] | 27.6 (4.3) | | 27.5 (4.6) | | 27.7 (3.8) | |
| IGF-I[b] | 114.9 (49.4) | | 110.3 (48.5) | | 121.3 (49.9) | |
| IGF-I SDS[b] | 0.3 (0.9) | | 0.4 (0.9) | | 0.1 (0.9) | |
| CAD | 621 | 28.2 | 283 | 22.1 | 338 | 36.5 |
| Myocardial infarction | 208 | 9.1 | 69 | 5.2 | 139 | 14.5 |
| Heart failure | 496 | 21.6 | 299 | 22.4 | 197 | 20.6 |
| Type 1 diabetes | 16 | 0.7 | 11 | 0.8 | 5 | 0.5 |
| Type 2 diabetes | 600 | 26.2 | 328 | 24.5 | 272 | 28.4 |
| Hypertension | 1946 | 84.8 | 1132 | 84.7 | 814 | 85.1 |
| Dyslipidemia | 1714 | 76.1 | 1009 | 76.9 | 705 | 74.9 |

[a]$N=6773$ valid IGF-I measurements.
[b]Data are expressed as mean (S.D.).

(Nichols Institute Diagnostics, San Clemente, CA, USA). The maximal intra- and inter-assay coefficients of variation were 5 and 7% respectively. Reagents and secondary standard were used as recommended by the manufacturer. IGF-I levels were transformed to age-dependent IGF-I SDS, according to Brabant *et al.* (25).

## *Statistical analyses*

We sought to determine the associations of IGF-I and IGF-I SDS with different potential confounders by calculating correlations and partial correlations or $\beta$ coefficients for different conditions. We divided the study sample scores

into quintiles. Odds ratios (OR) for these quintiles of IGF-I, adjusted for sex, BMI, age, aspartate aminotransferase (AST), glomerular filtration rate (GFR) and smoking were calculated for each clinical condition considered in this paper, using the 1st quintile representing the lowest and the 5th quintile representing the highest IGF-I levels. Adjustment for AST as a marker of liver disease was done because IGF-I levels are decreased in liver diseases. Also, AST correlated weakly with both IGF-I and IGF-I SDS in our population. Adjustment for GFR was done because we found a weak negative correlation of IGF-I SDS with GFR. To evaluate both linear and curvilinear effects, we performed analyses using both the 1st and 3rd quintile as references. We additionally analyzed the OR for CAD, myocardial infarction, and heart failure after additional adjustment for hypertension, diabetes, and dyslipidemia. All analyses were also performed in the subgroups of sex and age groups of 18–44, 45–65, and 66 years or older.

To evaluate the effects of abnormally high or low values, we also calculated the IGF-I SDS distribution and determined the OR in different S.D. ranges of IGF-I SDS. Even though the effect of age-related decline on IGF-I levels is excluded using IGF-I SDS, we have also adjusted for age because it was shown previously that there is an albeit weak, positive correlation between IGF-I SDS and age (26). All statistical analyses were conducted with the software package STATA 8 (Stata Corp, College Station, TX, USA).

## Results

The prevalence of the cardiovascular conditions studied were comparable in the laboratory sample ($N=7519$) and the sample studied here ($N=6773$, maximal difference in prevalence: 0.3%).

**Table 2** Odds ratio (OR) for health conditions in insulin-like growth factor-I (IGF-I) quintiles, using the 1st quintile as the reference.

| | **1st quintile** (<90) (Ref) | **2nd quintile** (90–113) | | **3rd quintile** (114–137) | | **4th quintile** (138–170) | | **5th quintile** (>170) | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| *Adjusted for age, gender, BMI, AST, GFR and smoking status* | | | | | | | | |
| Total | | | | | | | | |
| CAD | 1.0 | 0.8–1.3 | 0.8 | 0.6–1.0 | 1.1 | 0.8–1.4 | 1.2 | 0.9–1.6 |
| Myocardial infarction | 0.9 | 0.7–1.4 | 1.1 | 0.7–1.5 | 1.3 | 0.9–1.9 | 1.1 | 0.7–1.6 |
| Heart failure | 0.9 | 0.7–1.1 | 0.8 | 0.6–1.0 | 0.9 | 0.7–1.2 | 1.0 | 0.7–1.3 |
| Type 1 diabetes | 1.3 | 0.6–2.9 | 0.6 | 0.3–1.6 | 0.4 | 0.2–1.1 | **0.3** | 0.1–0.9 |
| Type 2 diabetes | 0.9 | 0.7–1.1 | 0.9 | 0.7–1.1 | 0.9 | 0.7–1.1 | 0.9 | 0.7–1.1 |
| Hypertension | 0.9 | 0.8–1.1 | 1.0 | 0.8–1.2 | 1.0 | 0.8–1.2 | 1.1 | 0.9–1.4 |
| Dyslipidemia | 1.1 | 0.9–1.3 | 1.1 | 0.9–1.3 | **1.2** | 1.0–1.4 | **1.3** | 1.1–1.5 |
| Female | | | | | | | | |
| CAD | 1.0 | 0.7–1.3 | **0.7** | 0.5–1.0 | 1.0 | 0.7–1.5 | 1.3 | 0.8–1.9 |
| Myocardial infarction | 0.9 | 0.5–1.8 | 1.1 | 0.6–2.2 | 1.3 | 0.7–2.5 | 1.5 | 0.7–3.1 |
| Heart failure | 1.1 | 0.8–1.5 | 0.8 | 0.6–1.2 | 0.9 | 0.6–1.3 | 0.9 | 0.5–1.4 |
| Type 1 diabetes | 1.4 | 0.6–3.7 | 0.6 | 0.2–1.9 | 0.3 | 0.1–1.1 | 0.3 | 0.1–1.6 |
| Type 2 diabetes | 1.0 | 0.7–1.3 | 0.9 | 0.7–1.3 | 1.0 | 0.7–1.4 | 1.1 | 0.7–1.6 |
| Hypertension | 0.9 | 0.7–1.2 | 0.9 | 0.7–1.2 | 0.8 | 0.7–1.1 | 1.0 | 0.8–1.4 |
| Dyslipidemia | 1.1 | 0.9–1.4 | 1.1 | 0.9–1.4 | 1.2 | 1.0–1.5 | **1.5** | 1.2–1.9 |
| Male | | | | | | | | |
| CAD | 1.1 | 0.8–1.6 | 0.9 | 0.7–1.3 | 1.1 | 0.8–1.6 | 1.2 | 0.8–1.7 |
| Myocardial infarction | 0.9 | 0.6–1.5 | 1.0 | 0.6–1.6 | 1.3 | 0.8–2.0 | 1.0 | 0.6–1.6 |
| Heart failure | 0.7 | 0.5–1.0 | 0.8 | 0.5–1.2 | 0.8 | 0.6–1.3 | 1.1 | 0.7–1.6 |
| Type 1 diabetes | 1.3 | 0.3–5.5 | 0.7 | 0.1–3.4 | 0.6 | 0.1–2.6 | 0.2 | 0.0–1.4 |
| Type 2 diabetes | 0.8 | 0.6–1.1 | 0.8 | 0.6–1.2 | 0.7 | 0.5–1.0 | 0.7 | 0.5–1.0 |
| Hypertension | 1.0 | 0.7–1.4 | 1.1 | 0.8–1.5 | 1.2 | 0.9–1.6 | 1.3 | 0.9–1.8 |
| Dyslipidemia | 1.0 | 0.7–1.3 | 1.2 | 0.9–1.6 | 1.2 | 0.9–1.6 | 1.0 | 0.8–1.4 |
| *Adjusted for age, gender, AST, GFR, BMI, diabetes, hypertension, dyslipidemia and smoking status* | | | | | | | | |
| Total | | | | | | | | |
| CAD | 1.0 | 0.8–1.3 | 0.8 | 0.6–1.0 | 1.0 | 0.8–1.3 | 1.2 | 0.9–1.6 |
| Myocardial infarction | 1.0 | 0.7–1.4 | 1.1 | 0.7–1.6 | 1.2 | 0.8–1.8 | 1.1 | 0.7–1.6 |
| Heart failure | 0.9 | 0.7–1.2 | 0.8 | 0.6–1.1 | 0.8 | 0.6–1.1 | 1.0 | 0.7–1.3 |
| Female | | | | | | | | |
| CAD | 1.0 | 0.7–1.3 | **0.7** | 0.5–1.0 | 1.0 | 0.7–1.4 | 1.2 | 0.8–1.8 |
| Myocardial infarction | 1.0 | 0.5–1.9 | 1.2 | 0.6–2.4 | 1.2 | 0.6–2.4 | 1.5 | 0.7–3.1 |
| Heart failure | 1.1 | 0.8–1.5 | 0.7 | 0.5–1.1 | 0.8 | 0.5–1.2 | 0.8 | 0.5–1.2 |
| Male | | | | | | | | |
| CAD | 1.1 | 0.8–1.6 | 0.9 | 0.7–1.3 | 1.1 | 0.8–1.5 | 1.2 | 0.8–1.7 |
| Myocardial infarction | 0.9 | 0.6–1.5 | 1.0 | 0.6–1.6 | 1.2 | 0.7–1.9 | 0.9 | 0.5–1.5 |
| Heart failure | 0.7 | 0.5–1.1 | 0.9 | 0.6–1.3 | 0.9 | 0.6–1.3 | 1.1 | 0.7–1.8 |

Bold highlighted OR are significant at the 5% level.

IGF-I showed negative and IGF-I SDS weakly positive correlation with age. After controlling for age, sex, and BMI (if applicable), there were weak negative correlations of both IGF-I and IGF-I SDS with BMI, GFR, HDL cholesterol, triglycerides, AST, and γ-glutamyl transferase, and weak positive correlations with creatinine and lipoprotein (a). There were no significant correlations with HbA1c, blood glucose, or blood pressure. We found diverging associations of smoking status, cancer, or postmenopausal hormone replacement therapy with IGF-I and IGF-I SDS. However, after controlling for age, sex, and BMI, the associations with cancer or hormone replacement therapy were no longer significant, and smoking was negatively associated with both IGF-I ($P=0.06$) and IGF-I SDS ($P<0.01$; data not shown).

Table 2 reports the IGF-I quintiles and their associations with clinical conditions using the 1st quintile as the reference. The OR for type 1 diabetes was decreased in the 5th quintile. The OR for dyslipidemia was increased in the 4th and 5th quintiles. Some findings remained significant only in women but not in men. We additionally examined these associations using the 3rd quintile as reference (Table 3). Here, the 4th and 5th quintiles were associated with CAD. These findings remained significant only in women. Additionally, in women, there were increased OR for CAD in the lowest quintile and for dyslipidemia in the highest quintile. The association with CAD remained significant after additional adjustment for hypertension, dyslipidemia, and diabetes.

Figure 1 shows the OR for CAD, after adjustment for sex, age, BMI, AST, GFR, and smoking in the total age

**Table 3** Odds ratio (OR) for health conditions in insulin-like growth factor-I (IGF-I) quintiles, using the 3rd quintile as the reference.

| | **1st quintile** (<90) | | **2nd quintile** (90–113) | | **3rd quintile** (114–137) | **4th quintile** (138–170) | | **5th quintile** (>170) | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | (Ref) | OR | 95% CI | OR | 95% CI |
| *Adjusted for age, gender, AST, GFR, BMI, diabetes, hypertension, dyslipidemia and smoking status* | | | | | | | | | |
| Total | | | | | | | | | |
| CAD | 1.2 | 1.0–1.6 | 1.3 | 1.0–1.6 | | **1.3** | 1.0–1.7 | **1.5** | 1.1–1.9 |
| Myocardial infarction | 1.0 | 0.7–1.4 | 0.9 | 0.6–1.3 | | 1.2 | 0.9–1.8 | 1.0 | 0.7–1.6 |
| Heart failure | 1.3 | 1.0–1.7 | 1.1 | 0.9–1.5 | | 1.1 | 0.8–1.5 | 1.2 | 0.9–1.7 |
| Type 1 diabetes | 1.6 | 0.6–3.9 | 2.1 | 0.9–4.8 | | 0.7 | 0.3–1.8 | 0.4 | 0.1–1.3 |
| Type 2 diabetes | 1.1 | 0.9–1.4 | 1.0 | 0.8–1.3 | | 1.0 | 0.8–1.2 | 1.0 | 0.8–1.3 |
| Hypertension | 1.0 | 0.8–1.2 | 0.9 | 0.8–1.1 | | 1.0 | 0.8–1.2 | 1.1 | 0.9–1.4 |
| Dyslipidemia | 0.9 | 0.8–1.1 | 1.0 | 0.8–1.1 | | 1.1 | 0.9–1.3 | 1.2 | 1.0–1.4 |
| Female | | | | | | | | | |
| CAD | **1.5** | 1.0–2.1 | 1.4 | 1.0–2.1 | | 1.5 | 1.0–2.3 | **1.8** | 1.2–2.9 |
| Myocardial infarction | 0.9 | 0.5–1.7 | 0.8 | 0.4–1.6 | | 1.1 | 0.6–2.3 | 1.3 | 0.6–2.8 |
| Heart failure | 1.3 | 0.9–1.8 | 1.3 | 0.9–2.0 | | 1.1 | 0.7–1.7 | 1.1 | 0.7–1.8 |
| Type 1 diabetes | 1.6 | 0.5–4.7 | 2.2 | 0.8–6.4 | | 0.4 | 0.1–2.0 | 0.5 | 0.1–2.5 |
| Type 2 diabetes | 1.1 | 0.8–1.5 | 1.1 | 0.8–1.5 | | 1.1 | 0.7–1.5 | 1.2 | 0.8–1.7 |
| Hypertension | 1.1 | 0.8–1.4 | 1.0 | 0.7–1.2 | | 0.9 | 0.7–1.1 | 1.1 | 0.9–1.4 |
| Dyslipidemia | 0.9 | 0.7–1.2 | 1.0 | 0.8–1.3 | | 1.1 | 0.9–1.4 | **1.4** | 1.1–1.7 |
| Male | | | | | | | | | |
| CAD | 1.1 | 0.8–1.5 | 1.2 | 0.9–1.7 | | 1.2 | 0.9–1.7 | 1.3 | 0.9–1.8 |
| Myocardial infarction | 1.0 | 0.6–1.5 | 0.9 | 0.6–1.5 | | 1.2 | 0.8–1.9 | 0.9 | 0.6–1.5 |
| Heart failure | 1.3 | 0.9–1.9 | 0.9 | 0.6–1.3 | | 1.1 | 0.7–1.6 | 1.3 | 0.9–2.1 |
| Type 1 diabetes | 1.5 | 0.3–7.6 | 2.0 | 0.5–7.5 | | 0.9 | 0.3–3.2 | 0.2 | 0.0–1.5 |
| Type 2 diabetes | 1.2 | 0.9–1.6 | 0.9 | 0.7–1.3 | | 0.9 | 0.6–1.2 | 0.9 | 0.6–1.2 |
| Hypertension | 0.9 | 0.7–1.2 | 0.9 | 0.7–1.2 | | 1.1 | 0.8–1.4 | 1.2 | 0.9–1.5 |
| Dyslipidemia | 0.9 | 0.6–1.2 | 0.9 | 0.6–1.1 | | 1.1 | 0.8–1.4 | 0.9 | 0.7–1.2 |
| *Adjusted for age, gender, BMI, AST, GFR and smoking status* | | | | | | | | | |
| Total | | | | | | | | | |
| CAD | 1.2 | 1.0–1.6 | 1.3 | 1.0–1.6 | | 1.3 | 1.0–1.6 | **1.5** | 1.1–1.9 |
| Myocardial infarction | 0.9 | 0.6–1.3 | 0.9 | 0.6–1.3 | | 1.1 | 0.8–1.7 | 1.0 | 0.7–1.5 |
| Heart failure | 1.3 | 1.0–1.6 | 1.1 | 0.9–1.5 | | 1.1 | 0.8–1.4 | 1.2 | 0.9–1.7 |
| Female | | | | | | | | | |
| CAD | **1.5** | 1.0–2.2 | 1.5 | 1.0–2.2 | | 1.4 | 0.9–2.2 | **1.8** | 1.1–2.9 |
| Myocardial infarction | 0.8 | 0.4–1.6 | 0.8 | 0.4–1.7 | | 1.0 | 0.5–2.1 | 1.2 | 0.6–2.6 |
| Heart failure | 1.3 | 0.9–2.0 | 1.4 | 1.0–2.1 | | 1.1 | 0.7–1.7 | 1.0 | 0.6–1.7 |
| Male | | | | | | | | | |
| CAD | 1.1 | 0.7–1.5 | 1.2 | 0.9–1.7 | | 1.1 | 0.8–1.6 | 1.2 | 0.9–1.8 |
| Myocardial infarction | 1.0 | 0.6–1.6 | 0.9 | 0.6–1.5 | | 1.2 | 0.8–1.8 | 0.9 | 0.6–1.5 |
| Heart failure | 1.1 | 0.8–1.7 | 0.8 | 0.6–1.3 | | 1.0 | 0.7–1.5 | 1.3 | 0.8–2.0 |

Bold highlighted OR are significant at the 5% level.

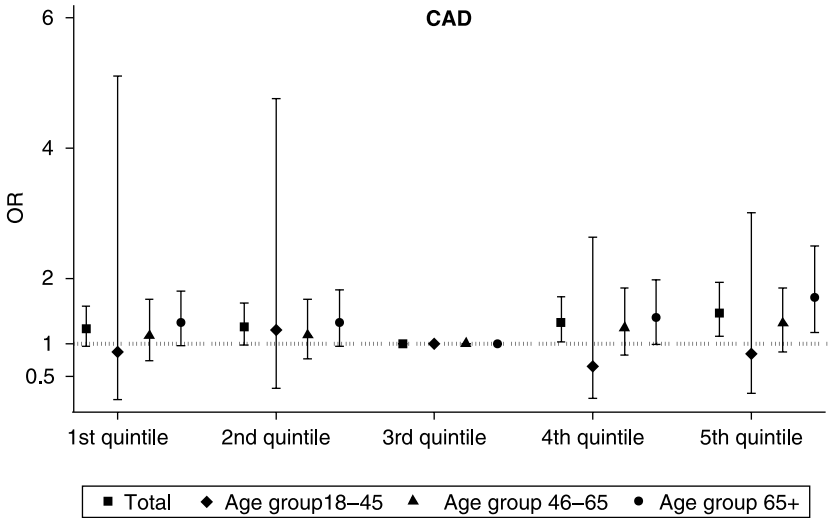


**Figure 1** IGF-I and coronary artery disease. Odds ratios and confidence intervals for the prevalence of coronary artery disease according to IGF-I quintiles in the total group and different age groups, adjusted for sex, age, BMI, AST, GFR, and smoking. Reference: 3rd quintile.

**Table 4** Odds ratios (OR) for health conditions in insulin-like growth factor-I (IGF-I) SDS groups, using −1 to 1 S.D. as reference.

| | **< −2 IGF-I SDS** (*N*=82) | | **−2 ≤ IGF-I SDS < −1** (*N*=667) | | **−1 ≤ IGF-I SDS ≤ 1** (*N*=5118) | **1 < IGF-I SDS ≤ 2** (*N*=781) | | **IGF-I SDS > 2** (*N*=125) | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | (Ref) | OR | 95% CI | OR | 95% CI |
| *Adjusted for age, gender, BMI, AST, GFR and smoking status* | | | | | | | | | |
| Total | | | | | | | | | |
| CAD | 0.3 | 0.1–1.0 | 1.2 | 0.9–1.6 | | **1.3** | 1.1–1.7 | 1.0 | 0.6–1.7 |
| Myocardial infarction | 0.3 | 0.0–2.1 | 1.2 | 0.8–1.9 | | 1.3 | 0.9–1.8 | 1.1 | 0.5–2.3 |
| Heart failure | 1.2 | 0.4–3.3 | **1.6** | 1.1–2.2 | | **1.4** | 1.1–1.7 | 1.1 | 0.6–1.9 |
| Type 1 diabetes | 3.4 | 0.7–16.5 | 1.2 | 0.5–2.8 | | 0.4 | 0.1–1.5 | 1.2 | 0.2–8.8 |
| Type 2 diabetes | **2.3** | 1.1–4.6 | **1.5** | 1.1–1.9 | | 1.1 | 0.9–1.4 | **2.2** | 1.3–3.6 |
| Hypertension | 1.1 | 0.6–2.1 | 1.1 | 0.9–1.3 | | **1.3** | 1.1–1.6 | 1.0 | 0.6–1.6 |
| Dyslipidemia | 0.8 | 0.5–1.4 | 1.0 | 0.8–1.2 | | **1.4** | 1.2–1.7 | 1.6 | 1.0–2.5 |
| Female | | | | | | | | | |
| CAD | | | 1.6 | 0.9–2.6 | | 1.3 | 1.0–1.8 | 0.9 | 0.5–1.8 |
| Myocardial infarction | | | 2.1 | 0.9–5.0 | | **1.8** | 1.1–3.0 | 0.7 | 0.2–3.2 |
| Heart failure | 1.4 | 0.1–13.5 | 1.6 | 0.9–2.7 | | 1.2 | 0.9–1.7 | 0.8 | 0.4–1.6 |
| Type 1 diabetes | 4.7 | 0.5–42.1 | 1.6 | 0.5–4.8 | | 0.3 | 0.0–2.1 | 1.8 | 0.2–13.7 |
| Type 2 diabetes | **4.4** | 1.1–17.7 | **1.7** | 1.2–2.5 | | 1.1 | 0.8–1.5 | **2.4** | 1.3–4.4 |
| Hypertension | 0.8 | 0.3–2.4 | **1.4** | 1.1–1.9 | | **1.3** | 1.0–1.7 | 0.8 | 0.5–1.5 |
| Dyslipidemia | 1.2 | 0.6–2.7 | 1.0 | 0.8–1.4 | | **1.4** | 1.1–1.8 | 1.6 | 0.9–2.9 |
| Male | | | | | | | | | |
| CAD | 0.4 | 0.1–1.2 | 1.1 | 0.8–1.5 | | 1.3 | 1.0–1.8 | 1.1 | 0.5–2.5 |
| Myocardial infarction | 0.3 | 0.0–2.5 | 1.1 | 0.7–1.7 | | 1.0 | 0.7–1.6 | 1.4 | 0.6–3.3 |
| Heart failure | 1.1 | 0.3–3.2 | **1.6** | 1.1–2.3 | | **1.5** | 1.0–2.2 | 1.8 | 0.7–4.1 |
| Type 1 diabetes | 3.9 | 0.5–33.7 | 0.9 | 0.2–4.0 | | 0.4 | 0.0–3.9 | | |
| Type 2 diabetes | 1.8 | 0.8–4.0 | 1.3 | 1.0–1.8 | | 1.0 | 0.7–1.5 | 1.8 | 0.7–4.6 |
| Hypertension | 1.3 | 0.6–3.0 | 0.9 | 0.6–1.1 | | 1.2 | 0.9–1.7 | 1.1 | 0.5–2.6 |
| Dyslipidemia | 0.8 | 0.4–1.6 | 1.1 | 0.8–1.4 | | 1.3 | 0.9–1.7 | 1.2 | 0.6–2.7 |
| *Adjusted for age, gender, AST, GFR, BMI, diabetes, hypertension, dyslipidemia and smoking status* | | | | | | | | | |
| Total | | | | | | | | | |
| CAD | **0.3** | 0.1–0.9 | 1.2 | 0.9–1.6 | | 1.2 | 1.0–1.5 | 0.9 | 0.6–1.6 |
| Myocardial infarction | 0.3 | 0.0–2.0 | 1.3 | 0.8–1.9 | | 1.2 | 0.9–1.7 | 1.0 | 0.5–2.1 |
| Heart failure | 1.1 | 0.4–3.1 | **1.5** | 1.1–2.1 | | 1.3 | 1.0–1.6 | 1.0 | 0.6–1.8 |
| Female | | | | | | | | | |
| CAD | | | 1.3 | 0.8–2.3 | | 1.2 | 0.9–1.6 | 0.8 | 0.4–1.6 |
| Myocardial infarction | | | 2.0 | 0.9–4.8 | | **1.7** | 1.0–2.8 | 0.6 | 0.1–2.7 |
| Heart failure | 1.1 | 0.1–11.2 | 1.5 | 0.8–2.6 | | 1.1 | 0.8–1.5 | 0.7 | 0.3–1.5 |
| Male | | | | | | | | | |
| CAD | 0.4 | 0.1–1.1 | 1.2 | 0.8–1.7 | | 1.3 | 0.9–1.8 | 1.1 | 0.5–2.4 |
| Myocardial infarction | 0.3 | 0.0–2.5 | 1.1 | 0.7–1.8 | | 1.0 | 0.6–1.5 | 1.3 | 0.5–3.2 |
| Heart failure | 1.0 | 0.4–3.1 | **1.6** | 1.0–2.3 | | **1.5** | 1.0–2.2 | 1.7 | 0.7–4.0 |

Bold highlighted OR are significant at the 5% level.

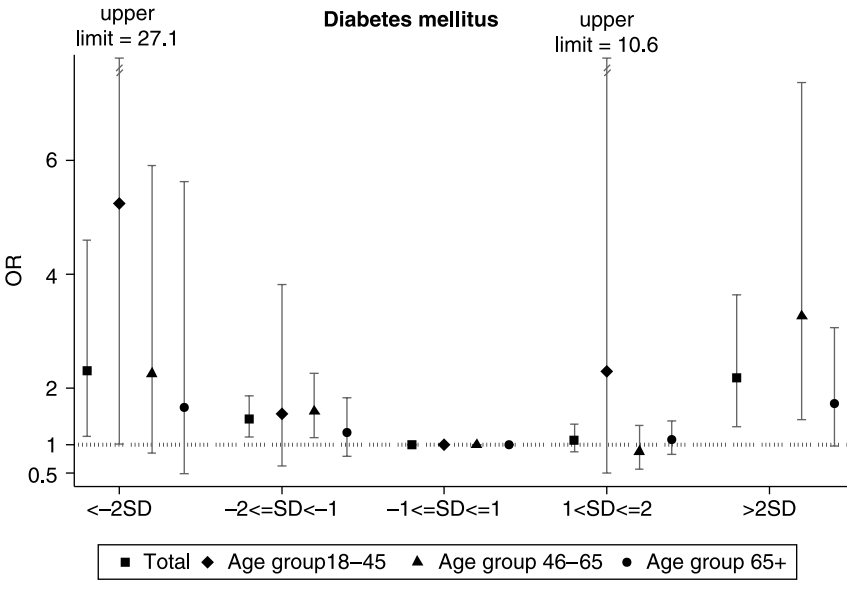


**Figure 2** IGF-I SDS and type 2 diabetes. Odds ratios and confidence intervals for the prevalence of type 2 diabetes according to IGF-I SDS groups in the total group and different age groups, adjusted for sex, age, BMI, AST, GFR, and smoking. Reference: IGF-I SDS, −1 to 1S.D.

groups and in three different age subgroups. There were significant findings in the 4th and 5th quintile. The findings in the 5th quintile remained significant in patients aged 66 years or more.

We further analyzed the ORs for different ranges of IGF-I SDS to examine the effect of elevated and decreased levels of IGF-I SDS in the normal and pathological range, as shown in Table 4. When compared with the IGF-I SDS range of −1 to 1, the OR for type 2 diabetes was increased both in patients with low (less than −2 SDS and −2 to −1 SDS) and abnormally elevated IGF-I SDS (>2 SDS). As shown in Fig. 2, this effect was more pronounced in patients aged 18–44 years but not significant in older subjects.

We found an increased OR for CAD, dyslipidemia, and hypertension in the high to normal IGF-I SDS ranges. Heart failure was more common both in patients with −2 to −1 SDS and 1 to 2 SDS. Sex-specific analyses revealed that the effects on type 2 diabetes (at IGF-I SDS >2), dyslipidemia, and hypertension were also present in women but not in men, whereas the effects on heart failure were only present in men but not in women.

## Discussion

To our knowledge, this is the largest study assessing the association of IGF-I with the prevalence of different cardiovascular diseases and risk factors, allowing re-examination of the controversial issue of IGF-I-associated health conditions. Age-dependent IGF-I SDS calculated from the largest published reference sample for IGF-I measurement (25) were used in addition to the IGF-I levels to analyze associations between IGF-I and various health conditions. Moreover, as we have previously shown, there is a significant curvilinear association of BMI with IGF-I SDS (26). So far, few studies on IGF-I and diseases have adjusted for BMI. This could possibly have confounded their results. Therefore, we have adjusted for BMI in our analyses in addition to other adjustments.

The key findings of our study are: a) no clear-cut linear increase or decline of any parameter with IGF-I, b) increased prevalences of CAD and dyslipidemia with high IGF-I, c) increased prevalence of CAD in women with low IGF-I, and d) curvilinear associations of IGF-I SDS with type 2 diabetes.

The presence of dyslipidemia was found to be increasing with higher IGF-I. This was also significant only in women. In acromegaly, dyslipidemia has also been found to be more common. Possibly, similar effects as in acromegaly play a role in this association. The prevalence of CAD was increased in patients with high IGF-I levels. This association was still present after adjustment for hypertension, dyslipidemia, and diabetes, indicating that this association is independent of the cardiovascular risk factors. This supports the findings of some authors who showed IGF-I to be associated with increased risk of CAD, possibly due to proliferative effects of IGF-I on the vascular intima and atherosclerosis (8). Interestingly, in women with low IGF-I, there were also increased OR for CAD. This curvilinear association in women might explain the diverging findings in the literature, which were mainly obtained from smaller samples. Our results, thus, also support the findings assuming a protective effect of IGF-I on CAD, though only in women (9–11).

Heart failure was more common in subjects with low IGF-I levels. Low IGF-I has been associated with heart failure and therapeutic approaches of GH or IGF-I in this field have been performed, but no clear benefit could be demonstrated in placebo-controlled trials (17–20).

The decrease of type 2 diabetes with increasing IGF-I SDS is in line with the previous observations that low IGF-I levels predispose to diabetes. It has been shown that

subjects with a genetic polymorphism causing lower IGF-I levels have increased prevalences of diabetes (5) and low IGF-I levels increase the future risk of glucose intolerance (6). Therefore, we can speculate that the increased prevalence of type 2 diabetes in our subjects with low IGF-I SDS is a consequence rather than a cause of IGF-I levels. However, the association was not linear, and in subjects with abnormally high IGF-I SDS the prevalence of type 2 diabetes was also increased. Type 2 diabetes is also more common in acromegaly that has been assumed to be due to the insulin antagonistic effects of GH (23). We have not assessed GH secretion in our study. Therefore, it is not clear whether higher GH secretion is the cause of high IGF-I levels and, possibly, increased risk of diabetes.

Taken together, our results show multiple interactions of IGF-I and several health conditions. Some limitations of our study need to be addressed. Due to the cross-sectional design of this study, we cannot prove whether the associations are causally related or due to a common, unknown third factor. Further prospective studies are needed to assess the causal associations of IGF-I with health conditions. With regard to cardiovascular risk prevalences, the laboratory sample was comparable with the total sample of the DETECT study (27), even though the prevalence of dyslipidemia was slightly higher in the laboratory sample. Even though a marginal selection bias cannot be ruled out with certainty, we have no reason to believe that this has a general effect on the associations of IGF-I with these conditions. The IGF-I assay we used is no longer available from the manufacturer, and we need to address whether these results are valid for other assays as well. Studies evaluating different IGF-I assays, including the one used here, have found high intercorrelations with all assays (28, 29); thus we think it is very likely that the associations found are independent of the assay used.

The large-scale approach allows detailed subgroup analyses. Our results demonstrate sex-specific associations of IGF-I with many health conditions and some effects are restricted only to certain age groups. These findings provide a possible explanation for the diverging results reported in the literature, which were derived from smaller samples.

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