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Circulating Insulin-Like Growth Factor-1 and its Binding Protein-3: Metabolic and Genetic Correlates in the Community

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Abstract

Objectives—The metabolic and genetic correlates of circulating insulin-like growth factor-1 (IGF-1) and its main circulating carrier, IGF-1-binding-protein-3 (IGFBP-3), are unclear.

Methods and Results—We measured serum IGF-1 and IGFBP-3 concentrations in a sample of the Framingham Heart Study (N=3977, aged 40±9 years, 46% male), and evaluated their relations to cardiovascular risk factors using multivariable regression. Serum IGF-1 was inversely correlated with age, body mass index, total cholesterol, the presence of diabetes, alcohol consumption and glomerular filtration rate (all $p<0.01$); whereas the ratio of IGF-1:IGFBP-3 was lower in women and inversely related to age, triglycerides, high density lipoprotein cholesterol, systolic blood pressure and alcohol consumption (all $p<0.0001$). Circulating IGF-1 correlated negatively with insulin resistance (homeostatic model assessment) ($r=-0.1$; $p<0.0001$) and was lower in participants with more components of the metabolic syndrome (Adult Treatment Panel III criteria) ($p<0.0001$). Additive genetic factors (heritability) accounted for 43% and 39% of the variation of IGF-1 and IGFBP-3 respectively (both $p<10^{-27}$).

Conclusions—Our cross-sectional observations in a large community-based sample link lower circulating IGF-1 to greater metabolic risk burden, and underscore substantial genetic influences on IGF-1 concentrations. Prospective studies are warranted to elucidate if lower IGF-1 concentrations predict greater metabolic risk longitudinally.

Keywords

insulin-like growth factor; insulin resistance; metabolic syndrome; heritability

Insulin-like growth factor-1 (IGF-1) is a growth hormone that regulates cell metabolism, growth, proliferation and apoptosis in multiple organ systems.[1] It is abundant in the circulation, where it binds to insulin-like growth factor binding proteins (IGFBPs). IGFBP-3 is the major

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circulating carrier of IGF-1 and regulates the biological effects of IGF-1 by sequestering IGF-1 into a circulating reservoir, thereby reducing the free fraction of bioactive IGF-1 in the blood.[2]

In the cardiovascular system, the IGF axis is postulated to be an important mediator of cardiovascular risk and disease. Indeed, low IGF-1 concentrations have been shown to predict cardiovascular mortality among elderly participants of the Rancho Bernardo Study.[3] However, the associations of circulating IGF-1 concentrations with known cardiovascular risk factors and genetic influences remain unclear. Prior studies examining the clinical correlates of IGF-1 and IGFBP-3 have yielded mixed results. Studies relating IGF-1 concentrations to blood pressure have noted positive,[4] negative[5] and no[6] associations. Similarly, clinical reports have been inconsistent regarding the associations between IGF-1 or IGFBP-3 and diabetes mellitus (DM),[7, 8] dyslipidemia,[9, 10] or obesity.[5, 11–16] Most previous studies were limited to relatively small or highly selected samples, and data from large-scale community-based samples are still needed. Further, despite evidence of a significant genetic contribution to circulating IGF-1 concentrations from twin studies,[17–19] data are limited regarding the heritability of IGF-1 and IGFBP-3 in the general community.

Accordingly, we systematically assessed the clinical correlates, estimated the heritability and performed genome-wide linkage analyses of circulating IGF-1, IGFBP-3 and their ratio in a large community-based sample. Given the previously reported associations of IGF-1 and IGFBP-3 with individual components of the metabolic syndrome,[20] we hypothesized that these markers would reflect the burden of metabolic risk in the community. Specifically, we hypothesized that lower IGF-1 and higher IGFBP-3 circulating concentrations, possibly reflecting lower unbound (free) IGF, would be related to greater burden of metabolic risk. We further hypothesized that a significant proportion of the variability of circulating IGF-1 and IGFBP-3 in the general community would be attributable to additive genetic effects.

METHODS

Participants

The Framingham Heart Study[21] is an ongoing community-based cohort investigation of cardiovascular risk, first established in 1948, that is currently studying three generations of participants. The most contemporary generation of participants (Generation 3, recruited in 2002–2004) was included in the current study sample. We also included participants of the Omni generation 2 cohort, a minority cohort from Framingham similarly recruited in 2003–2005. All participants underwent detailed medical interviews, physical examinations and laboratory investigations according to standardized protocols. Of 4273 eligible participants, 296 were excluded due one of more of the following: prevalent cardiovascular disease (N=66) or renal impairment (serum creatinine > 2mg/dl; N=2), missing IGF-1/IGFBP-3 measurements (N=99) or missing covariates (N=162). A total of 3977 participants made up the final sample. All participants provided written informed consent and the study protocol was approved by the Institutional Review Board at the Boston University Medical Center.

Measurement of IGF-1 and IGFBP-3

Blood samples were collected according to rigorous protocol in the morning following overnight fast. Samples were centrifuged and aliquotted immediately for storage at −70 °C. Serum IGF-1 was measured by standard immunoassay (R&D Systems Quantikine Human IGF-I Cat#DG100, SG100 and PDG100; ELISA method) with a lower detection limit of 9.4 ng/ml. This assay involves pretreatment with an acid dissociation solution to eliminate IGFBP-3 interference. Serum IGFBP-3 was measured by standard immunoassay (R&D Systems Quantikine Human IGFBP-3 Cat#DGB300; ELISA method) with a lower detection limit of

75.99 ng/mL and an upper limit of 5000 ng/ml. Quality control measures included running duplicate samples and checking reproducibility according to strict protocol. The intra-assay coefficients of variation were 5.3% for the IGF-1 assay and 9.1% for the IGFBP-3 assay.

Statistical Analyses

Distribution of IGF-1 and IGFBP-3—Serum IGF-1 and IGFBP-3 concentrations were normally distributed, whereas the distribution of their ratio was skewed. Normal quantile transformation was used to normalize the distribution of the IGF-1:IGFBP-3 ratio.

Clinical correlates—The following clinical covariates were identified on the basis of published studies and biological plausibility:[6, 9–14, 22–24] age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), hypertension (SBP ≥140 mmHg and/or DBP ≥90 mmHg or the use of anti-hypertensive medications), DM (fasting blood sugar ≥126 mg/dl or the use of anti-diabetic medications), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, smoking status, alcohol consumption and estimated glomerular filtration rate (GFR, calculated using the MDRD equation).

To investigate the association of IGF-1, IGFBP-3 or the ratio of IGF-1:IGFBP-3 with clinical covariates, significant predictors were first identified for each biomarker using multivariable linear regression with stepwise forward selection ($P \leq 0.10$ for model entry). To account for relatedness among participants, generalized estimating equations (GEE; using Compound Symmetry Correlation Matrix) were then used to assess the association between each biomarker and the clinical covariates that were statistically significant in the initial regression analyses.

To assess the associations of IGF-1, IGFBP-3 and their ratio with insulin resistance and the metabolic syndrome, the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the equation HOMA-IR =(FPG × FPI)/22.5 where FPG =fasting plasma glucose in mmol/l and FPI =fasting plasma insulin in mU/l measured by ELISA (Linco Research, Millipore Bioscience Division, intra-assay coefficient of variation of 2.7%, with no cross-reactivity with human proinsulin at concentrations up to 100nM).[25] The presence of insulin resistance was defined as HOMA-IR ≥75th percentile in the sample. The updated Adult Treatment Panel III criteria were used to define the metabolic syndrome.[20] The diagnosis was met in the presence of ≥3 of: waist circumference ≥102 cm (≥40 inches) in men or ≥88 cm (≥35 inches) in women; triglycerides ≥150 mg/dL (1.7 mmol/L) or on drug treatment for elevated triglycerides; HDL <40 mg/dL (1.03 mmol/L) in men, <50 mg/dL (1.3 mmol/L) in women; SBP ≥130 mm Hg SBP or DBP ≥85 mm Hg or on antihypertensive drug treatment in a patient with a history of hypertension; and fasting blood glucose ≥100 mg/dL or on drug treatment for elevated glucose. We further related each biomarker with the number of components of the metabolic syndrome present using generalized linear models adjusting for age and sex.

Heritability estimates—Heritability was estimated from variance component models using Sequential Oligogenic Linkage Analysis Routines (SOLAR). Two heritability estimates were provided for IGF-1 and IGFBP-3: (i) adjusting for age and sex; and (ii) adjusting for all significantly associated clinical covariates.

Genetic Linkage—Multipoint quantitative trait linkage analyses were conducted with SOLAR on 687 autosomal microsatellite markers using the variance-components models adjusting for (i) age and sex; and (ii) all significantly associated clinical covariates. Linkage was assessed by comparing models that incorporated genetic marker information to models

that did not incorporate genetic information (i.e., identity by descent data). Results were expressed as the logarithm-of-the-odds (LOD) score from each model.

RESULTS

Sample characteristics

Our community-based sample consisted of predominantly young to middle-aged adults with low to moderate prevalence of known cardiovascular risk factors and a slight preponderance of women (Table 1). Age- and sex- stratified concentrations of IGF-1, IGFBP-3 and IGF-1:IGFBP-3 ratio are provided in the online Supplementary Table I.

Clinical correlates

In multivariable analysis (Table 2), IGF-1 concentrations were negatively associated with age, diabetes, total cholesterol, body mass index, alcohol consumption and renal function. IGFBP-3 concentrations were similarly negatively associated with age and body mass index, but were also lower in men and positively associated with SBP, HDL cholesterol and triglycerides in multivariable-adjusted models. The ratio of IGF-1:IGFBP-3 was higher in men and negatively associated with age, SBP, triglycerides, HDL cholesterol and alcohol consumption.

Adjusting for age and sex, HOMA-IR was inversely correlated with IGF-1 ($r=-0.096$; $p<0.0001$) and the IGF-1:IGFBP-3 ratio ($r=-0.056$; $p=0.0008$). The presence of insulin resistance, defined as HOMA-IR at or above the 75^{th} percentile of 1.25, was accordingly associated with reduced IGF-1 concentrations compared to those without insulin resistance, adjusting for age and sex (122±45 ng/ml vs 132±42 ng/ml; $p=0.0006$). There was also a strong association between reduced IGF-1 concentrations and the presence of the metabolic syndrome ($p<0.0001$, adjusted for age and sex). Similar findings were obtained with the IGF-1:IGFBP-3 ratio ($p=0.0004$) but not with IGFBP-3 concentrations alone ($p=0.95$). As shown in Figure 1, IGF-1 concentrations were lower in participants with more components of the metabolic syndrome (p for trend < 0.0001 adjusting for age and sex).

Genetic correlates

Both IGF-1 and IGFBP-3 were heritable, with estimates of 43% and 39%, respectively in adjusted analyses (Table 3). In linkage analyses adjusted for clinical covariates, none of the peak LOD scores reached the standard genome-wide significance threshold LOD score of 3. For IGF-1, the maximum LOD score was 2.41 (at chromosome 12, 8 cM) adjusting for age and sex; and 2.48 (at chromosome 1, 36 cM) adjusting for significantly associated clinical correlates. For IGFBP-3, the maximum LOD score was 1.94 (at chromosome 7, 70 cM) adjusting for age and sex; and 1.76 (at chromosome 8, 165 cM) adjusting for significantly associated clinical correlates.

DISCUSSION

Principal findings

Our study provides epidemiologic evidence for an association between the IGF-1 axis and metabolic risk burden, as well as the estimated contribution of genetic factors to circulating IGF-1 and its main binding protein IGFBP-3 in the general population. Among young to middle-aged adults in the community, reduced concentrations of circulating IGF-1 and its unbound fraction (IGF-1:IGFBP-3 ratio) are related to the metabolic syndrome and its components, adjusting for age and sex. After accounting for these clinical correlates, there was a significant contribution of heritable factors to the variability of IGF-1 and IGFBP-3 concentrations in the general community. These cross-sectional observations are consistent with the notion that the IGF-1 axis may be an important mediator of metabolic risk in the

community. Prospective studies are warranted to elucidate if lower IGF-1 concentrations predict increased risk of cardiovascular events longitudinally.

Clinical correlates of circulating IGF-1 & IGFBP-3

Age and sex—Numerous previous studies have reported a negative association between age and concentrations of IGF-1 or IGFBP-3.[13, 14, 22–24] This observation is consistent with the established role of the IGF axis in organ growth and the known parallel decline in growth hormone concentrations with age.[26] Many previous studies were limited to women[22–24] or men[16] alone. Nonetheless the current findings of similar IGF-1 concentrations in men and women, but higher IGFBP-3 in women are consistent with some[10, 27] but not all[12–14] previous studies. Of note, the latter studies[12–14] included predominantly post-menopausal women in whom exogenous hormone use may have led to suppression of circulating IGF-1 – a phenomenon consistently observed in previous studies[28] but occurring by unclear mechanisms. In contrast, our sample was comprised of predominantly premenopausal women.

Obesity—The relationship between obesity and concentrations of IGF-1 is complex. Increased body fat and decreased muscle mass has been associated with hyposecretion of growth hormone, a known regulator of hepatic IGF-1 production.[1] Thus, a negative association between IGF-1 and body mass index, as found in the current study and others,[11–13] may be expected. However, adipocytes can also produce IGF-1,[29] while obesity-related increases in insulin secretion may stimulate hepatic synthesis of IGF-1.[30]

Insulin resistance and diabetes mellitus—Given the known insulin-like effects of IGF-1 on glucose uptake[31] an association between lower IGF-1 concentrations and increasing insulin resistance may be expected. Our large sample size provided statistical power to detect this association, albeit a modest correlation and of uncertain clinical significance. However, similar modest associations ($r<0.2$) of known clinical importance include the correlation between severity or duration of systemic hypertension and degree of left ventricular hypertrophy.[32] The current results are also consistent with previous studies[33, 34] and are highly biologically plausible. Prospective studies have shown that reduced IGF-1 concentrations predict the development of impaired glucose tolerance and DM,[35] while exogenous IGF-1 administration reduces serum glucose concentrations in insulin resistance[36] and DM.[37, 38]

Lipids—The inverse association of IGF-1 with total cholesterol concentrations and, conversely, the positive association of IGFBP-3 with plasma lipids are consistent with the known role of IGF-1 in lipid metabolism,[38] the largely inhibitory effect of IGFBP-3 on IGF-1 bioactivity[2] and observations from previous cross-sectional studies.[9, 10] These observations are also corroborated by previous reports of increased risk of atherosclerosis among individuals with low IGF-1 and high IGFBP-3.[39]

Blood pressure—IGF-1 has been convincingly shown to favorably influence blood pressure via nitric oxide-dependent effects[40] and to play a critical role in vascular remodeling[41] in experimental studies. A direct association between IGFBP-3 and blood pressure found in the current study and others[6] supports the notion that alterations in the relative binding of IGF-1 to IGFBP-3 may be related to risk of hypertension and associated target organ damage.

Metabolic syndrome—The association between low IGF-1:IGFBP-3 ratio and the metabolic syndrome has recently been elegantly demonstrated in the multi-ethnic NHANES III population.[33] Our findings lend support to the authors' call for prospective studies to elucidate if lower IGF-1 or IGF-1:IGFBP-3 concentrations predict increased risk of cardiovascular events longitudinally. We further adjust for select lifestyle factors in the current study, and emphasize the genetic underpinnings to this association.

Genetic correlates of circulating IGF-1 & IGFBP-3

Heritability—Twin studies have estimated that genetic effects account for 38%[19] to >80% [17, 18] of the variation in serum IGF-1 and IGFBP-3 concentrations. Our current heritability estimates are consistent with these data and importantly extend the estimates to adults in the general population. The estimated heritability of IGF-1 and IGFBP-3 in the general community is comparable to that of common cardiovascular risk factors such as blood pressure, lipids and BMI.

Linkage—Genome-wide linkage analyses interestingly mapped to chromosomal regions other than that containing the known genes encoding IGF-1 (12q22–q23) and IGFBP-3 (7p13–p12) themselves. Thus, while genetic factors contribute to variation in circulating concentrations of these biomarkers, this genetic contribution does not appear to be related to variation in the IGF-1 or IGFBP-3 gene itself, but may instead be related to genes affecting the pathways through which these biomarkers are regulated. Supporting this concept, the most frequently investigated polymorphism relating to the IGF-1 gene -- a simple tandem repeat polymorphism lying 1kb 5' to the IGF-1 gene transcriptional start site -- has not been convincingly shown to affect circulating IGF-1 concentrations.[42] Intriguingly, the regions of suggestive linkage for IGF-1 identified in the current study (12p13 and 1p36) lie in quantitative trait loci known to be involved in blood pressure regulation and associated with hypertension (BP53_H and BP9_H respectively).[43, 44] These findings are hypothesis-generating but require confirmation in further studies.

Strengths and limitations

The strengths of the current investigation include the large, unselected community-based sample; systematic and complete ascertainment of clinical covariates, availability of extensive pedigrees and use of multivariable-adjusted analyses.

The cross-sectional design of our study precludes any causal inferences; prospective studies would be needed for that purpose. Since direct measurement of free (biologically active) IGF-1 was not available in our sample, we used the IGF-1:IGFBP-3 ratio as an estimate of free IGF-1, as previously suggested[45] and applied in several studies.[12, 13, 33, 46–48] However, this ratio does not account for IGF-II or proteolysis of IGFBP-3, and thus may not always reflect free IGF-1 concentrations.[49, 50] Our predominantly white, young to middle-aged sample limits the generalizability of findings to non-white and older populations. However, there was less potential for confounding by non-cardiovascular co-morbidities and concurrent medications in our sample.

Conclusions

Our cross-sectional observations in a large community-based sample link lower concentrations of circulating IGF-1 or its unbound fraction (IGF-1:IGFBP-3 ratio) to greater metabolic risk burden, and demonstrate substantial heritability for serum IGF-1 concentrations. These findings suggest that the IGF-1 axis may play an important role in predisposition to cardiometabolic disease in the community. Longitudinal studies are warranted to elucidate if lower IGF-1 concentrations predict risk of incident cardiovascular events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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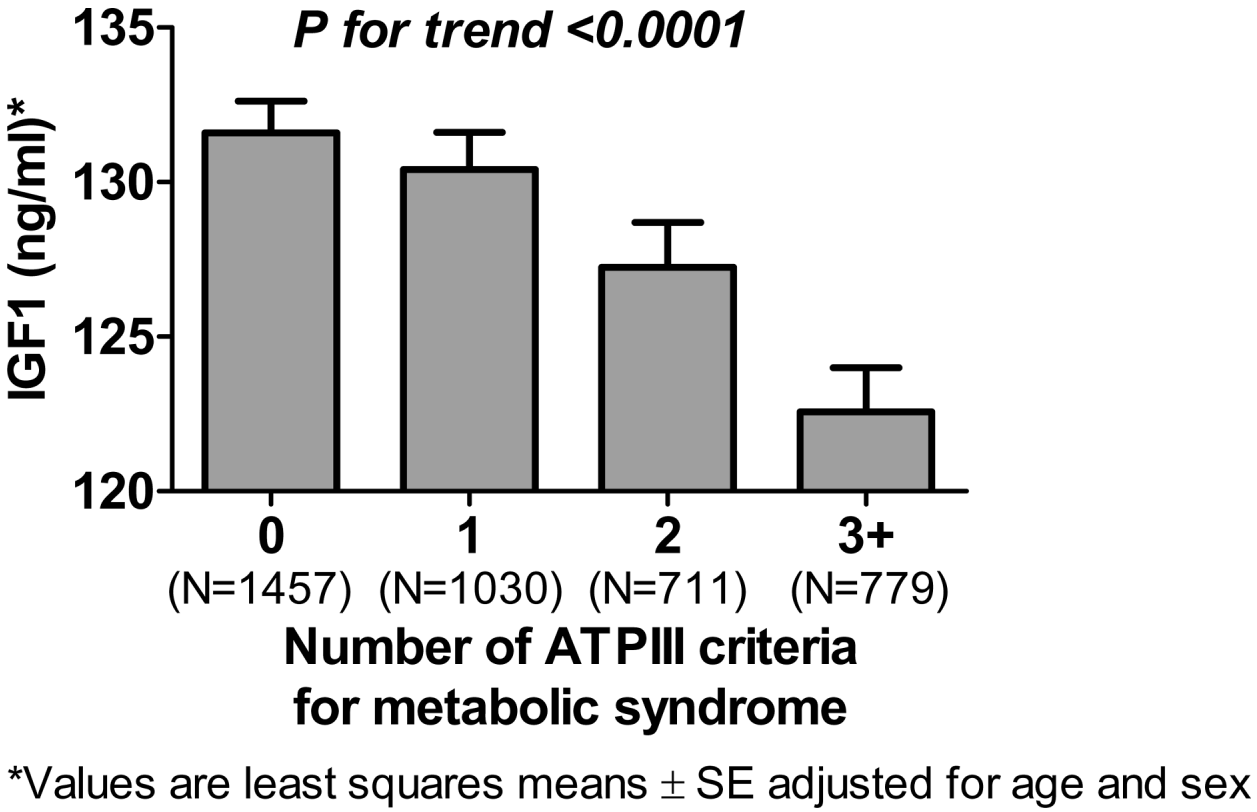

Figure 1. Association between circulating concentrations of insulin-like growth factor-1 (IGF-1) and the number of components of the metabolic syndrome

Bar graphs represent the least squares means ± SE of IGF-1 in ng/ml, adjusted for age and sex.

Table 1

Sample characteristics

Clinical variables	Men (N=1837)	Women (N=2140)
Age, years	40±9	40±9
Height, m	1.78±0.07	1.64±0.06
Weight, kg	88.1±15.8	69.5±16.4
Body mass index, kg/m^2	27.8±4.6	25.8±6.0
Systolic blood pressure, mmHg	121±13	113±14
Diastolic blood pressure, mmHg	78±9	73±9
Hypertension, %	20	12
Diabetes mellitus, %	3	2
Smoking, %	16	15
Alcohol consumption, ounces per month	13.6±18	5.9±8.0
Glomerular filtration rate, ml/min/1.73m^2	99.7±17.2	99.5±18.8
Total cholesterol, mg/dl	193±37	185±34
HDL cholesterol, mg/dl	47±12	61±16
LDL cholesterol, mg/dl	120±31	104±30
Triglycerides (median, 25th–75th percentile), mg/dl	107 (72–160)	80 (59–114)
HOMA-IR	1.20±1.02	0.97±0.75
Insulin resistance, %	31	20
IGF-1, ng/ml	128±39	129±45
IGFBP-3, ng/ml	2905±1079	3097±1096
IGF-1:IGFBP-3 ratio (median, 25th–75th percentile)	0.044 (0.034–0.057)	0.042 (0.032–0.054)

Values are mean±SD unless otherwise indicated.

HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance, calculated using the equation HOMA-IR = (FPI × FPG)/22.5 where FPI = fasting plasma insulin in mU/l and FPG = fasting plasma glucose in mmol/l[25]; The presence of insulin resistance was defined as HOMA-IR at or above the 75th percentile of 1.25; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IQR, interquartile range.

To calculate the molar ratio of IGF-1 to IGFBP-3 using molar weights of 7.65 kDa for IGF-1 and 30.5 kDa[45] for IGFBP-3, multiply ratio values by 3.987.

Table 2

Clinical correlates of insulin-like growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3) and their ratio

Dependent variable	Independent variable	Beta coefficient*	95% CI	P value
IGF-1, ng/ml	Age, per 1SD	−17.24	(−18.90, −15.58)	<0.0001
	Sex, men vs women	2.29	−0.57, 5.16	0.1160
	Diabetes, yes vs no	−10.95	(−18.27, −3.63)	0.0034
	Total cholesterol, per 1 SD	−2.10	(−3.60, −0.60)	0.0061
	HDL cholesterol, per 1SD	−1.56	(−3.08, −0.03)	0.0453
	Body mass index, per 1SD	−4.41	(−5.79, −3.03)	<0.0001
	Smoking, yes vs no	−3.19	(−6.54, 0.16)	0.0617
	Alcohol consumption, per 1SD	−3.79	(−4.84, −2.74)	<0.0001
	GFR, per 1SD	−2.69	(−4.10, −1.29)	0.0002
IGFBP-3, ng/ml	Age, per 1SD	−177.21	(−217.51, −136.92)	<0.0001
	Sex, men vs women	−190.61	(−270.35, −110.86)	<0.0001
	Systolic BP, per 1SD	54.30	(16.00, 92.59)	0.0055
	HDL cholesterol, per 1SD	75.59	(31.13, 120.06)	0.0009
	Triglycerides, per 1 SD	124.75	(72.68, 176.82)	<0.0001
	Body mass index, per 1SD	−86.44	(−127.49, −45.39)	<0.0001
	Alcohol consumption, per 1SD	32.12	(−7.65, 71.90)	0.1134
	GFR, per 1SD	−36.30	(−72.98, 0.37)	0.0524
IGF-1:IGFBP-3 ratio	Age, per 1SD	−0.1366	(−0.1720,−0.1012)	<0.0001
	Sex, men vs women	0.2571	(0.1828, 0.3315)	<0.0001
	Systolic BP, per 1SD	−0.0741	(−0.1094, −0.0388)	<0.0001
	Triglycerides, per 1SD	−0.1415	(−0/1971, −0.0860)	<0.0001
	HDL cholesterol, per 1SD	−0.1002	(−0.1414, −0.0591)	<0.0001
	Alcohol consumption, per 1SD	−0.1106	(−0/1468, 0.0744)	<0.0001

IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; GFR, glomerular filtration rate; BP, blood pressure; HDL, high density lipoprotein;

To calculate the molar ratio of IGF-1 to IGFBP-3 using molar weights of 7.65 kDa for IGF-1 and 30.5 kDa[45] for IGFBP-3, multiply ratio values by 3.987.

* Beta coefficients represent the expected change in mean IGF1, IGFBP3 or transformed ratio for each standard deviation increment of the indicated continuous variable (or each category of indicated discrete variable), adjusting for the other variables in the model.

Table 3

Heritability estimates for insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3)

Biomarker	Model	Heritability	95% CI	P value
IGF-1	Age- & sex- adjusted	0.43	(0.346,0.515)	1.6E-28
	Multivariable- adjusted	0.43	(0.346,0.515)	1.2E-27
IGFBP-3	Age- & sex- adjusted	0.39	(0.310,0.462)	6.6E-29
	Multivariable- adjusted	0.39	(0.315,0.471)	2.7E-30

IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3