

# Serum Insulin-like Growth Factor (IGF)-I and IGF-Binding Protein-1 in Elderly People: Relationships with Cardiovascular Risk Factors, Body Composition, Size at Birth, and Childhood Growth

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The IGF system is important in regulation of fetal and childhood growth. In later life, IGF-I and IGF-binding protein-1 (IGFBP-1) have been implicated in the pathogenesis of arteriosclerosis. They are, thus, potential candidates in explaining the link between early growth and adult cardiovascular disease. We measured fasting serum IGF-I and IGFBP-1 concentrations in 394 men and women from a cohort of 7086 individuals, born between 1924 and 1933 in Helsinki, Finland, whose weight and height were recorded at birth and from 7 to 15 yr of age. They also underwent clinical examination, including measurement of body fat using bioimpedance, blood pressure, glucose tolerance, and plasma insulin and fibrinogen concentrations. Serum IGF-I was positively correlated with fasting glucose ( $r = 0.10$ ,  $P = 0.06$ ) and fibrinogen ( $r = 0.19$ ,  $P = 0.0001$ ) concentrations and blood pressure (systolic and diastolic  $r = 0.10$ ,  $P \leq 0.05$ ) and inversely with percentage body fat ( $r = -0.13$ ,  $P = 0.01$ ) and waist circumference ( $r = -0.11$ ,  $P = 0.03$ ). IGFBP-1 was inversely correlated with adult body mass index (BMI) ( $r = -0.46$ ,  $P < 0.0001$ ), fasting glucose and insulin concentrations, and blood pressure. There were correlations between the adult level of IGFBP-1 and birth weight ( $r = 0.11$ ,  $P = 0.03$ ) and ponderal index (weight/length<sup>3</sup>) at birth ( $r = 0.13$ ,  $P = 0.01$ ), but IGF-I was not related to birth measurements.

There were interactive effects between childhood height or BMI and adult BMI on IGF-I and IGFBP-1 in adulthood. Tall height and high BMI at 7 yr were associated with low IGF-I ( $P = 0.03$  for height and  $P = 0.003$  for BMI) and high IGFBP-1 ( $P = 0.02$  and  $P = 0.06$ ) in adulthood but only in those subjects whose current BMI was below median. On further analysis these interactive effects were particularly strong for height in childhood and adult lean BMI (lean body mass/height<sup>2</sup>). Among men and women of below-average lean BMI, tall height at 7 yr was associated with low adult IGF-I ( $P = 0.007$ ) and high IGFBP-1 ( $P = 0.0004$ ) concentrations [interaction (7-yr height  $\times$  adult lean BMI);  $P = 0.008$  for IGF-I and 0.001 for IGFBP-1].

There is no evidence that reduced fetal growth programs IGF-I concentrations in old age. An association between small size at birth and low IGFBP-1 concentrations may in part reflect fetal programming effects on insulin resistance. Given the anabolic effects of the GH-IGF-I axis, subjects with tall height in childhood but low adult lean body mass may be at risk of late-life GH-IGF-I axis dysfunction. Prospective studies should address whether this group is susceptible to type 2 diabetes, coronary heart disease, and osteoporosis. (*J Clin Endocrinol Metab* 88: 1059–1065, 2003)

RECENT STUDIES HAVE suggested that several common diseases of adult life, including cardiovascular disease, type 2 diabetes, and osteoporosis, may have their origins during childhood or *in utero*. The original observations, linking adult cardiovascular disease with small size at birth (1), have been replicated in epidemiological studies in different populations. These and concurrent animal studies have introduced the concept of fetal programming of adult disease. New data from cohorts in Finland, for whom childhood growth data were recorded in addition to birth measurements, have expanded the concept to encompass programming effects of childhood growth (2–4). Translation of the concept of programming into measures to prevent disease will require insight into the pathophysiological mechanisms involved.

Abbreviations: BMI, Body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; IGFBP, IGF-binding protein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein.

The IGF system encompasses two IGFs, IGF-I and IGF-II, and at least six IGF-binding proteins (IGFBPs). A large body of evidence, ranging from studies in genetically engineered mice (5, 6) and human IGF-I gene mutations (7) to clinical studies in infants (8–10) and children (11), links the IGF system with both fetal and childhood growth. In adult life, IGF-I is an important anabolic hormone, required for the maintenance of bone integrity and lean body mass (12). Both pre- and postnatally IGF-I secretion is regulated by nutritional status, mainly through the stimulatory effect of insulin (13). After late infancy, the main regulator is pituitary GH (13). Circulating IGFBP-1 in nonpregnant adults is mostly inhibitory on IGF-I action (14). Although the regulation of IGFBP-1 is complex, insulin has a major inhibitory effect (15).

IGF-I and IGFBP-1 have been implicated in the pathogenesis of cardiovascular disease. Hypopituitarism is associated with increased cardiovascular mortality (16) and low IGF-I concentrations, possibly reflecting relative insufficiency of

the GH-IGF-I axis and predates impaired glucose tolerance (17) and is associated with coronary heart disease (18–20). That the relationship with coronary heart disease may be causal is supported by a recent study in middle-aged men and women showing low IGF-I to predict ischemic heart disease over a follow-up of 16 yr (21). Low IGFBP-1 is associated with impaired glucose tolerance, elevated blood pressure, and obesity (19, 20, 22). However, these relationships are not entirely uniform. High IGF-I has been shown to predict coronary artery disease progression after myocardial infarction (23), and high IGFBP-1 is associated with increased cardiovascular and overall mortality in elderly men (24).

It has been proposed that programming of the IGF axis *in utero* or childhood could contribute to increased cardiovascular risk in adulthood. The evidence is limited to studies of children and young adults. Low birth weight has been associated with reduced serum IGFBP-1 in girls with precocious pubarche (25), elevated urinary IGF-I excretion in children with catch-up growth (26), and elevated serum IGF-I concentrations in prepubertal children (27, 28) and young adult women (29). No data have been reported for older adults. We set out to study how serum IGF-I and IGFBP-1 concentrations are related to cardiovascular risk factors and fetal and childhood growth in a well-characterized cohort of men and women aged 65–75 yr.

## Subjects and Methods

### Subjects

The original study cohort comprised 7086 men and women born as singletons during 1924–1933 at Helsinki University Central Hospital, who went to school in the city of Helsinki and were resident in Finland in 1971. They have detailed birth records (2, 3), which include birth weight, length, placental weight, head circumference, and gestational age at birth, and school health cards with an average of 10 (SD 4) measurements of height and weight between the ages of 7 and 15 yr. The study protocol was approved by the Ethics Committee of the National Public Health Institute, and written informed consent was obtained from all subjects.

### Design

From the original study cohort, 421 subjects born at term (37 wk gestation or more) attended a clinic after an overnight fast between 0830 and 1000 h (4). Of these, 27 were on medication for type 2 diabetes and were excluded from the study because their medication could have altered their IGF-I and IGFBP-1 concentrations. To assess parameters of cardiovascular risk, we chose to perform a 75-g oral glucose tolerance test and measure body mass index (BMI), waist circumference, body fat content, and blood pressure as well as serum cholesterol [total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL)], triglyceride, and fibrinogen concentrations. Anthropometric and blood pressure measurements were performed as described (4). Body fat mass was determined based on bioelectric impedance analysis (Omron BF 300 body fat monitor, Omron, Tokyo, Japan), and lean mass was calculated as total body weight – fat mass. To express the lean and fat masses in units adjusted for height, we calculated lean BMI as lean mass (kilograms)/[height (meters)]<sup>2</sup> and fat BMI as fat mass (kilograms)/[height (meters)]<sup>2</sup>. The oral glucose tolerance test included glucose and insulin measurements from samples drawn at baseline and at 30 and 120 min. Measurements of plasma glucose concentration and serum insulin, proinsulin and 32–33 split proinsulin, total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride concentrations were performed by standard methods (4). Serum fibrinogen concentration was measured using an ACL autoanalyzer (Advanced Instrumental Laboratories, Milan, Italy). IGF-I concentration was measured by an IGF-I ELISA kit

(DSL-10–5600; Diagnostic Systems Laboratories, Inc., Webster, TX). IGFBP-1 concentrations were measured as described (30).

### Statistical analysis

IGF-I, IGFBP-1, glucose, insulin, proinsulin, HDL cholesterol, and triglyceride concentrations were log transformed to normality. Multiple linear regression and partial correlation analysis were used to assess associations between variables. Regression and correlation analyses were adjusted for sex, age, and adult BMI (unless lean or fat BMI was already included in the model). Height, weight, and BMI for each birthday between 7 and 15 yr were derived by first converting each measurement to a Z-score using the method of Royston (31). Successive Z-scores were interpolated with a piecewise linear function to obtain Z-scores separately for both sexes for each birthday. The Z-scores were back transformed to obtain corresponding height, weight, and BMI at these ages. A Z-score was not assigned if the child had not been measured within 2 yr of that age. Because findings were similar for all ages, we chose to present the 7-yr data to minimize confounding effects of individual variation in the timing of puberty.

## Results

### Birth and childhood measurements and results of the clinical examination

The subjects' birth and childhood data and adult clinical characteristics are summarized in Table 1. Compared with present-day standards, the mean birth weight corresponds to –0.5 SD at 40 wk gestation in both sexes (32), mean height at 7 yr to –0.6 SD in both sexes (33) and BMI at 7 yr to –0.3 SD in boys and –0.1 SD in girls (34). Fourteen subjects (3.6%) were born small for gestational age, defined as birth weight less than –2 SD (32). These subjects had similar IGF-I and IGFBP-1 concentrations, compared with the rest of the study population. Mean IGF-I concentrations were higher in men, whereas IGFBP-1 concentrations were higher in women. There was a negative correlation between IGF-I and IGFBP-1 concentrations ( $r = -0.33$ ;  $P < 0.0001$ ). Twenty percent of men and 13% of women had undiagnosed or diet-treated diabetes mellitus (DM), and 25% of men and 30% of women had impaired glucose tolerance (IGT), defined by 1998 World Health Organization criteria (35). Compared with subjects with normal glucose metabolism, those with IGT or DM had similar IGF-I concentrations (geometric mean 102.9  $\mu\text{g/liter}$  *vs.* normal subjects 98.1  $\mu\text{g/liter}$ ;  $P = 0.2$ ), lower IGFBP-1 concentrations (55.8  $\mu\text{g/liter}$  *vs.* 72.8  $\mu\text{g/liter}$ ;  $P = 0.004$ ), higher lean BMI (17.5  $\text{kg/m}^2$  *vs.* 16.7  $\text{kg/m}^2$ ;  $P < 0.0001$ ) and higher fat BMI (10.7 *vs.* 9.6  $\text{kg/m}^2$ ;  $P < 0.0001$ ). There were no significant differences between subjects with IGT and DM.

### IGF-I, IGFBP-1, and clinical examination

Table 2 shows correlations between IGF-I and IGFBP-1 concentrations and clinical measurements. IGF-I concentrations showed no correlation with current height or BMI but were negatively correlated with waist circumference ( $P = 0.03$ ) and percentage body fat ( $P = 0.01$ ). They were positively correlated with insulin and proinsulin variables, strongest with intact proinsulin and blood pressure and fibrinogen concentrations. IGFBP-1 concentrations showed strong negative correlations with adult total, lean, and fat BMI but no correlation with body fat percentage. Strong negative correlations were observed among IGFBP-1 concentration and glucose and insulin concentrations; total, intact, and

**TABLE 1.** Birth and childhood measurements and clinical data, expressed as mean  $\pm$  SD or geometric mean (25th–75th) percentile

	Males		Females	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD
<b>Birth data</b>				
Weight (g)	146	3504 $\pm$ 422	248	3342 $\pm$ 406
Length (cm)	146	50.5 $\pm$ 1.5	247	49.9 $\pm$ 1.6
Ponderal index (kg/m <sup>3</sup> )	146	27.2 $\pm$ 2.3	247	26.9 $\pm$ 2.2
Gestational age (wk)	146	279 $\pm$ 8	248	281 $\pm$ 10
Height at 7 yr (cm)	139	120.5 $\pm$ 4.7	236	118.8 $\pm$ 4.6
BMI at 7 yr (kg/m <sup>2</sup> )	139	15.5 $\pm$ 1.0	236	15.2 $\pm$ 1.3
Age (yr)	146	69.5 $\pm$ 3.1	248	69.4 $\pm$ 2.7
Height (cm)	146	174.6 $\pm$ 5.7	248	160.4 $\pm$ 5.3
BMI (kg/m <sup>2</sup> )	146	27.1 $\pm$ 3.9	248	27.3 $\pm$ 4.3
Waist circumference (cm)	143	100.4 $\pm$ 10.3	248	89.4 $\pm$ 10.4
Fat weight (kg)	143	25.0 $\pm$ 6.5	245	28.7 $\pm$ 7.2
Fat BMI (kg/m <sup>2</sup> )	143	8.2 $\pm$ 2.1	245	11.2 $\pm$ 2.8
Lean BMI (kg/m <sup>2</sup> )	143	18.8 $\pm$ 2.0	245	16.1 $\pm$ 1.6
Systolic blood pressure (mm Hg)	146	158 $\pm$ 22	248	158 $\pm$ 20
Diastolic blood pressure (mm Hg)	146	91 $\pm$ 11	248	88 $\pm$ 10
Fibrinogen (g/liter)	144	3.48 $\pm$ 0.75	248	3.55 $\pm$ 0.62
<b>Oral glucose tolerance test</b>				
Glucose at baseline (mmol/liter) <sup>a</sup>	146	5.7 (5.1–6.1)	248	5.4 (5.0–5.8)
Glucose at 120 min (mmol/liter) <sup>a</sup>	145	7.8 (6.2–10.0)	248	7.5 (6.1–9.1)
Insulin at baseline (IU/ml) <sup>a</sup>	145	9.9 (6.9–15.1)	247	9.5 (6.6–14.3)
Insulin at 120 min (IU/ml) <sup>a</sup>	144	71.3 (41.1–130.5)	246	74.1 (45.3–123.0)
Intact proinsulin (pmol/liter) <sup>a</sup>	145	3.3 (2.1–5.2)	246	2.8 (1.8–4.5)
32–33 split proinsulin (pmol/liter) <sup>a</sup>	145	8.5 (5.3–13.4)	246	7.5 (4.9–11.9)
Total cholesterol (mmol/liter)	146	5.9 $\pm$ 1.0	248	6.3 $\pm$ 1.1
HDL cholesterol (mmol/liter) <sup>a</sup>	146	1.30 (1.10–1.53)	248	1.56 (1.29–1.94)
LDL cholesterol (mmol/liter)	146	3.9 $\pm$ 0.9	248	3.9 $\pm$ 1.0
Triglycerides (mmol/liter) <sup>a</sup>	146	1.33 (1.00–1.80)	248	1.29 (1.05–1.70)
IGF-I ( $\mu$ g/liter) <sup>a</sup>	148	109.1 (90.6–139.7)	246	95.3 (74.5–124.6)
IGFBP-1 ( $\mu$ g/liter) <sup>a</sup>	148	56.0 (39.0–82.3)	246	70.8 (53.5–103.0)

<sup>a</sup> Geometric mean (25th–75th percentile).**TABLE 2.** Correlations between IGF-I, IGFBP-1, and clinical variables

	IGF-I	IGFBP-1
	r (P)	r (P)
Age <sup>a</sup>	0.02 (0.6)	0.08 (0.08)
Height	-0.08 (0.14)	0.03 (0.5)
BMI <sup>b</sup>	-0.03 (0.6)	-0.46 (<0.0001)
Waist circumference	-0.11 (0.03)	-0.05 (0.3)
Lean BMI <sup>b</sup>	0.04 (0.5)	-0.41 (<0.0001)
Fat BMI <sup>b</sup>	-0.06 (0.2)	-0.43 (<0.0001)
Fat percentage	-0.13 (0.01)	0.00 (1.0)
<b>Oral glucose tolerance test</b>		
Glucose at baseline	0.10 (0.06)	-0.09 (0.06)
Glucose at 120 min	0.04 (0.4)	-0.16 (0.001)
Insulin at baseline	0.08 (0.2)	-0.26 (<0.0001)
Insulin at 120 min	0.10 (0.05)	-0.37 (<0.0001)
Total proinsulin	0.13 (0.01)	-0.31 (<0.0001)
Intact proinsulin	0.15 (0.004)	-0.20 (<0.0001)
32–33 Split proinsulin	0.11 (0.04)	-0.29 (<0.0001)
Systolic blood pressure	0.10 (0.04)	-0.12 (0.02)
Diastolic blood pressure	0.10 (0.05)	-0.12 (0.02)
Fibrinogen	0.19 (0.0001)	-0.03 (0.6)

<sup>a</sup> Adjusted for sex and current BMI.<sup>b</sup> Adjusted for sex and current age.

All other correlations are adjusted for sex, current age, and BMI. There was no correlation with serum total, LDL, or HDL cholesterol, or triglyceride concentration.

32–33 split proinsulin concentrations; and blood pressure. IGF-I and IGFBP-1 did not, however, correlate with serum total cholesterol, HDL or LDL cholesterol, or triglyceride concentrations.

### IGF-I, IGFBP-1, and measurements at birth and in childhood

IGF-I concentrations were not related to birth weight (Fig. 1) or any of the other birth measurements. IGFBP-1 concentrations showed a weak positive correlation with birth weight ( $r = 0.11$ ;  $P = 0.03$ ; Fig. 1) and ponderal index at birth ( $r = 0.13$ ;  $P = 0.01$ ), which became nonsignificant when not adjusted for current BMI. The strength of these associations was weakened after adjustment for fasting insulin concentration (birth weight:  $r = 0.08$ ;  $P = 0.1$ ; ponderal index at birth:  $r = 0.12$ ;  $P = 0.02$ ). IGF-I concentration was not correlated with height or BMI at 7 yr. There was a positive correlation between IGFBP-1 concentration and BMI at 7 yr ( $r = 0.15$ ;  $P = 0.004$ ) but no relationship with height. There were no interactive effects on IGF-I or IGFBP-1 between birth measurements and measurements at 7 yr or between birth and adult measurements.

### Interactions between childhood and adult anthropometry

Height and BMI at the age of 7 yr were positively correlated ( $r = 0.21$ ;  $P < 0.0001$ ). Height at 7 yr was correlated with adult height ( $r = 0.70$ ;  $P < 0.0001$ ) but not with adult BMI or lean or fat BMI. BMI at 7 yr was correlated with adult total ( $r = 0.30$ ;  $P < 0.0001$ ), lean ( $r = 0.34$ ;  $P < 0.0001$ ), and fat ( $r = 0.27$ ;  $P < 0.0001$ ) BMI.

There were interactive effects on IGF-I and IGFBP-1 between childhood BMI or height and adult BMI (Table 3). In subjects with an adult BMI below the median, high BMI or tall height

FIG. 1. Correlation of birth weight with serum IGF-I and IGFBP-1 concentrations, adjusted for sex, current age, and BMI.

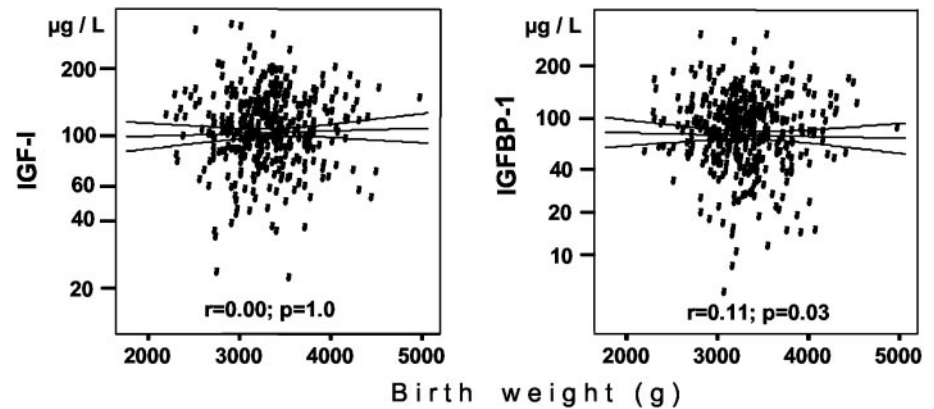


TABLE 3. IGF-I and IGFBP-1 according to current BMI and BMI or height at 7 yr

	IGF-I ( $\mu\text{g/liter}$ )			IGFBP-1 ( $\mu\text{g/liter}$ )		
	Current BMI below median	Current BMI over median	<i>P</i> for trend	Current BMI below median	Current BMI over median	<i>P</i> for trend
BMI at age 7 yr						
Lowest tertile	111.0 (85)	93.7 (40)	0.1	72.8	54.5	<0.0001
Middle tertile	92.9 (59)	95.3 (66)	0.7	79.7	56.3	<0.0001
Highest tertile	96.1 (45)	105.2 (80)	0.2	81.6	52.9	<0.0001
<i>P</i> for trend	0.003	0.5		0.06	0.6	
<i>P</i> for interaction		0.02			0.5	
Height at age 7 yr						
Lowest tertile	107.4 (62)	103.5 (61)	0.7	69.2	56.9	0.0001
Middle tertile	101.9 (69)	94.7 (62)	0.7	80.6	54.4	<0.0001
Highest tertile	94.8 (58)	99.2 (63)	0.4	81.0	52.2	<0.0001
<i>P</i> for trend	0.03	0.7		0.02	0.4	
<i>P</i> for interaction		0.12			0.008	

Numbers are geometric means. Numbers of cases are shown in parentheses in the IGF-I column, being equal for IGFBP-1 measurements. Medians and tertiles have been calculated for each sex separately. *P* values are based on regression models with BMI and height at 7 yr and current BMI as continuous variables, and are adjusted for age and sex.

at 7 yr was associated with low IGF-I and high IGFBP-1 concentrations. No associations were observed in subjects with above-median adult BMI. Because of the differing associations of IGF-I and IGFBP-1 with fat and lean body composition, we examined this further by dividing BMI into fat and lean components. The trends of IGF-I and IGFBP-1 with 7-yr height and BMI were accentuated in subjects of below-median lean BMI (Table 4A). No interactive effects were seen with adult fat BMI (Table 4B)<sup>6</sup>, percentage body fat, waist circumference, or height. There was also no any interactive effect between sex and any birth or childhood measurement.

### Discussion

We found clear correlations between IGF-I and IGFBP-1 concentrations and cardiovascular risk factors including blood pressure and glucose, insulin, and fibrinogen concentrations. In studying relationships between fetal and childhood growth and the adult IGF axis, we found that taller height or higher BMI at 7 yr was associated with lower circulating IGF-I and higher IGFBP-1 concentrations in adulthood. However, these relationships were dependent on adult body composition, being seen only in subjects with a low lean body mass. We found no associations between size at birth and circulating IGF-I concentrations. There were weak positive associations between birth weight and ponderal index at birth and IGFBP-1 concentrations.

IGF-I is a major endocrine and paracrine regulator of tissue growth and metabolism, with at least six binding proteins controlling its bioavailability. IGFBP-1 has both inhibitory and stimulatory effects on IGF-I, depending on the degree of phosphorylation. In nonpregnant adults, virtually all of the circulating IGFBP-1 is in the highly phosphorylated isoforms, which have a high affinity for, and are more inhibitory on, IGF-I (14). The strong associations we observed between low IGFBP-1 concentration and cardiovascular risk factors are in keeping with the known inhibition of IGFBP-1 synthesis by insulin (15) and clinical studies linking low IGFBP-1 with impaired glucose tolerance (19, 22), elevated blood pressure (22), and obesity (19, 22). The relationships between IGF-I concentration and cardiovascular risk factors were less straightforward to interpret, perhaps reflecting the dual regulation of IGF-I by insulin and GH. The association of high IGF-I with insulin resistance and blood pressure is consistent with the corresponding inverse associations with IGFBP-1 and is likely to reflect the differential regulation of IGF-I and IGFBP-1 synthesis by insulin. The strong association of IGF-I with fibrinogen may be related to the link between high circulating IGF-I and coronary artery disease progression (23). In contrast, high percentage body fat and waist circumference, well-established risk factors of atherosclerotic disease (36), were associated with low IGF-I concentrations. This could be a consequence of low GH activity, consistent with

**TABLE 4A.** IGF-I and IGFBP-1 according to current lean BMI and BMI or height at 7 yr

	IGF-I ( $\mu\text{g/liter}$ )			IGFBP-1 ( $\mu\text{g/liter}$ )		
	Lean BMI below median	Lean BMI over median	<i>P</i> for trend	Lean BMI below median	Lean BMI over median	<i>P</i> for trend
BMI at age 7 yr						
Lowest tertile	109.4 (92)	90.4 (30)	0.2	69.8	61.4	0.02
Middle tertile	92.2 (56)	95.8 (69)	0.2	79.1	57.5	<0.0001
Highest tertile	94.5 (42)	105.8 (80)	0.02	86.1	54.4	<0.0001
<i>P</i> for trend	0.001	0.16		0.01	0.9	
<i>P</i> for interaction		0.056			0.7	
Height at age 7 yr						
Lowest tertile	108.1 (65)	102.5 (55)	0.9	66.3	63.1	0.008
Middle tertile	102.4 (69)	94.1 (62)	0.8	77.0	57.2	<0.0001
Highest tertile	91.0 (56)	101.3 (62)	0.04	86.9	51.1	<0.0001
<i>P</i> for trend	0.007	0.9		0.0004	0.07	
<i>P</i> for interaction		0.008			0.001	

Numbers are geometric means. Numbers of cases are shown in *parentheses* in the IGF-I column, being equal for IGFBP-1 measurements. Medians and tertiles have been calculated for each sex separately. *P* values are based on regression models with BMI and height at 7 yr and current lean BMI as continuous variables, and are adjusted for age and sex. Note the strong trends in subjects with below median adult lean BMI.

**TABLE 4B.** IGF-I and IGFBP-1 according to current fat BMI and BMI or height at 7 yr

	IGF-I ( $\mu\text{g/liter}$ )			IGFBP-1 ( $\mu\text{g/liter}$ )		
	Fat BMI below median	Fat BMI over median	<i>P</i> for trend	Fat BMI below median	Fat BMI over median	<i>P</i> for trend
BMI at age 7 yr						
Lowest tertile	110.6 (78)	94.2 (44)	0.05	73.9	57.9	0.001
Middle tertile	96.5 (62)	91.8 (63)	0.8	77.7	56.8	<0.0001
Highest tertile	98.5 (47)	103.9 (75)	0.5	83.9	53.2	<0.0001
<i>P</i> for trend	0.03	0.7		0.03	0.9	
<i>P</i> for interaction		0.04			0.8	
Height at age 7 yr						
Lowest tertile	106.5 (61)	104.4 (59)	0.6	71.8	58.1	0.003
Middle tertile	103.6 (70)	92.8 (61)	0.3	80.4	54.2	<0.0001
Highest tertile	97.4 (56)	95.1 (62)	1.0	80.8	54.8	<0.0001
<i>P</i> for trend	0.12	0.2		0.02	0.6	
<i>P</i> for interaction		1.0			0.2	

Numbers are geometric means. Numbers of cases are shown in *parentheses* in the IGF-I column, being equal for IGFBP-1 measurements. Medians and tertiles have been calculated for each sex separately. *P* values are based on regression models with BMI and height at 7 yr and current fat BMI as continuous variables, and are adjusted for age and sex. The trends in the below median fat BMI group are considerably attenuated compared to those in the below median lean BMI group shown in Table 4A.

the fact that adult patients with frank GH deficiency have increased body fat (12), especially intra-abdominal fat (37) and higher mortality from cardiovascular disease (16). However, we cannot be sure because assessment of GH secretion is complex and highly impractical in population studies like ours. Nevertheless, these differing relationships of IGF-I with cardiovascular risk factors may in part explain why some studies associate cardiovascular disease with low (18–21) and some with high (23) IGF-I.

The key role of the IGF system in regulating growth is illustrated by mice with knockout of the IGF-I gene (5) or IGFBP-1 gene overexpression (6) as well as human IGF-I gene deletion (7). All these examples are characterized by severe pre- and postnatal growth retardation. In addition, numerous studies show low circulating IGF-I and high IGFBP-1 concentrations in fetuses with intrauterine growth restriction (8–10) and in children with decreased rates of growth (11). Studies on monozygotic and dizygotic adult twin pairs have shown that the proportion of variance attributable to genetic effects is 38% for the circulating IGF-I concentration, whereas no significant heritability is found for IGFBP-1 (38). Recently

preliminary evidence has suggested that a polymorphism in the promoter region of the IGF-I gene is associated with low birth weight, (39) low adult IGF-I concentration, and an increased risk of type 2 diabetes and myocardial infarction (40).

We found no relationship between IGF-I concentration and birth measurements and, thus, could not demonstrate any effect of fetal programming on circulating IGF-I in elderly people. This is at variance with studies in children who have linked low birth weight with elevated serum IGF-I (27, 28) or elevated urinary IGF-I excretion after catch-up growth (26). In young adults, some studies show a similar association (29), whereas others do not (41). Possible explanations include age-induced decline in the activity of the GH-IGF-I axis (42) or an existing association being obscured by the relatively high morbidity or selective survival of the study population. It is moreover of note that in a population study like ours, with only a small number of subjects born small for gestational age, possible programming effects of severe intrauterine growth restriction cannot be excluded.

The weak association we observed between low birth weight or thinness at birth and low IGFBP-1 concentration is

consistent with previous observations in young adults (41) and girls with precocious pubarche (25). This was attenuated after adjustment for insulin concentrations, suggesting that the effect may in part be mediated through insulin, which shows inverse associations with birth size in this cohort (4). Other possible mechanisms include conditions associated with chronic intrauterine hypoxia such as preeclampsia, in which IGFBP-1 secreted by the fetal liver is a key mediator of reduced fetal growth (43).

We found that low IGF-I and high IGFBP-1 concentrations were strongly associated with high 7-yr height or BMI but only in subjects of below median adult lean BMI. This was an unexpected finding, and we can only speculate about the possible mechanisms involved. Low adult lean BMI may reflect failure to gain lean body mass during childhood and puberty or subsequent excessive loss of lean body mass. It may therefore identify individuals with relative GH/IGF-I deficiency, or at least a low GH/IGF-I effect, either now or in the past. One possible scenario is that the group with tall height or high BMI in childhood and low lean BMI and IGF-I in adulthood could be a result of an advanced tempo of childhood growth, early puberty (44), and subsequent early cessation of growth with interrupted lean body mass acquisition. In general, only about 5% of lean mass is acquired after 20 yr (45). However, this scenario remains speculative because we do not have sufficient measurements to determine the timing of puberty in this cohort. An alternative explanation for low IGF-I in this group includes subsequent undernutrition, which in animal experiments has been shown to cause hepatic GH resistance (46). Finally, discordance between tall height in childhood and low adult lean body mass may indicate loss of lean body mass in adult life. This could result from disease or lifestyle, again factors that the present study was not designed to assess.

Although the exact mechanisms behind our observations remain to be elucidated, their importance is due to their putative health consequences. Low serum IGF-I is associated with subsequent development of type 2 diabetes (17), possibly in part because of reduced survival of pancreatic  $\beta$ -cells (47). This is of interest because previous observations in this cohort show that, although impaired glucose tolerance is associated with low childhood BMI (4), diabetes is predicted by tall height and high BMI in childhood (48). Correspondingly, coronary heart disease, which is similarly associated with low circulating IGF-I (18–21), is in this cohort associated with high childhood BMI in men (2) and tall height in women (3) who were small at birth. Further features of a low-IGF state include reduced bone mineral density (49). This is again consistent with epidemiological observations in our cohort that show an increase in the incidence of hip fracture in subjects with tall height at 7 yr and reduced height increment thereafter (50).

We conclude that, in elderly people, small size at birth is weakly related to low serum IGFBP-1 concentration but not associated with changes in IGF-I. Both IGF-I and IGFBP-1 are related to childhood growth in subjects who have low lean body mass as adults. This finding suggests that subjects with low adult lean body mass and tall height at 7 yr may be at risk of late-life relative GH-IGF-I insufficiency. Whether these subjects are also more susceptible for type 2 diabetes,

coronary heart disease, and osteoporosis remains the question that needs to be addressed in prospective studies.

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### References

- Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ 1989 Weight in infancy and death from ischaemic heart disease. *Lancet* 8663:577–580
- Eriksson JG, Forsén T, Tuomilehto J, Winter PD, Osmond C, Barker DJ 1999 Catch-up growth in childhood and death from coronary heart disease: longitudinal study. *BMJ* 318:427–431
- Forsén T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ 1999 Growth *in utero* and during childhood among women who develop coronary heart disease: longitudinal study. *BMJ* 319:1403–1407
- Eriksson JG, Forsén T, Tuomilehto J, Jaddoe VWV, Osmond C, Barker DJBP 2002 Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 45:342–348
- Liu JP, Baker J, Perkins AS, Robertson EJ, Efstratiadis A 1993 Mice carrying null mutations of the genes encoding insulin-like growth-factor I (Igf-1) and type 1 IGF receptor (Igf1r). *Cell* 75:73–82
- Rajkumar K, Barron D, Lewitt MS, Murphy LJ 1995 Growth retardation and hyperglycemia in insulin-like growth factor binding protein-1 transgenic mice. *Endocrinology* 136:4029–4034
- Woods KA, Camacho-Hubner C, Savage MO, Clark AJL 1996 Intrauterine growth retardation and postnatal growth failure associated with deletion of the insulin-like growth factor I gene. *N Engl J Med* 335:1363–1367
- Verhaeghe J, van Bree R, van Herck E, Laureys J, Bouillon R, van Assche FA 1993 C-peptide, insulin-like growth factors I and II, and insulin-like growth factor binding protein-1 in umbilical cord serum: correlations with birth weight. *Am J Obstet Gynecol* 169:89–97
- Giudice LC, De Zegher F, Gargosky SE, Dsupin BA, de las Fuentes L, Crystal RA, Hintz RL, Rosenfeld RG 1995 Insulin-like growth factors and their binding extremes of intrauterine growth. *J Clin Endocrinol Metab* 80:1548–1555
- Kajantie E, Hytinen T, Koistinen R, Risteli J, Rutanen EM, Seppälä M, Andersson S 2001 Markers of type I and type III collagen turnover, insulin-like growth factors and their binding proteins in cord plasma of small premature infants: relationships with fetal growth, gestational age, preeclampsia, and antenatal glucocorticoid treatment. *Pediatr Res* 49:481–489
- Juul A, Dalgaard P, Blum WF, Bang P, Hall K, Michaelsen KF, Müller J, Skakkebaek NE 1995 Serum levels of insulin-like growth factor (IGF)-binding protein-3 (IGFBP-3) in healthy infants, children, and adolescents: the relation to IGF-I, IGF-II, IGFBP-1, IGFBP-2, age, sex, body mass index, and pubertal maturation. *J Clin Endocrinol Metab* 80:2534–2542
- Attanasio AF, Howell S, Bates PC, Frewer P, Chipman J, Blum WF, Shalet SM 2002 Body composition, IGF-I and IGFBP-3 concentrations as outcome measures in severely GH-deficient (GHD) patients after childhood GH treatment: a comparison with adult onset GH patients. *J Clin Endocrinol Metab* 87:3368–3372
- Gluckman PD, Sizonenko SV, Bassett NS 1999 The transition from fetus to neonate: an endocrine perspective. *Acta Paediatr Suppl* 428:7–11
- Westwood M, Gibson MJ, White A 1997 Purification and characterization of the insulin-like growth factor-binding protein-1 phosphoform found in normal plasma. *Endocrinology* 138:1130–1136
- Suikkari AM, Koivisto VA, Rutanen EM, Yki-Jarvinen H, Karonen SL, Seppälä M 1988 Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. *J Clin Endocrinol Metab* 66:266–272
- Rosen T, Bengtsson BA 1990 Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 336:285–288
- Sandhu MS, Heald AH, Gibson JM, Cruickshank JK, Dunger DB, Wareham NJ 2002 Circulating concentrations of insulin-like growth factor-1 and devel-

- opment of glucose intolerance: a prospective observational study. *Lancet* 359:1740–1745
18. Spallarossa P, Brunelli C, Minuto F, Caruso D, Battistini M, Caponnetto S, Cordera R 1996 Insulin-like growth factor-I and angiographically documented coronary artery disease. *Am J Cardiol* 77:200–202
  19. Janssen JAMJL, Stolk RP, Pols HAP, Grobbee DE, Lamberts SWJ 1998 Serum total IGF-I, free IGF-I, and IGFBP-1 levels in an elderly population: relation to cardiovascular risk factors and disease. *Arterioscler Thromb Vasc Biol* 18:277–282
  20. Janssen JAMJL, Lamberts SWJ 2002 The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: is prevention possible? *Eur J Endocrinol* 146:467–477
  21. Juul A, Scheike T, Davidsen M, Gyllenberg J, Jørgensen T 2002 Low serum insulin-like growth factor 1 is associated with increased risk of ischemic heart disease. A population-based case-control study. *Circulation* 106:939–944
  22. Heald AH, Cruickshank JK, Riste LK, Cade JE, Anderson S, Greenhalgh A, Sampayo J, Taylor W, Fraser W, White A, Gibson JM 2001 Close relation of fasting insulin-like growth factor-1 with glucose tolerance and cardiovascular risk in two populations. *Diabetologia* 44:333–339
  23. Ruotolo G, Båvenholm P, Brismar K, Eféndic S, Ericsson CG, de Faire U, Nilsson J, Hamsten A 2000 Serum insulin-like growth factor-I level is independently associated with coronary artery disease progression in young male survivors of myocardial infarction: beneficial effects of bezafibrate treatment. *J Am Coll Cardiol* 35:647–654
  24. Harrela M, Qiao Q, Koistinen R, Tuomilehto J, Nissinen A, Seppälä M, Leinonen P 2002 High serum insulin-like growth factor binding protein-1 is associated with increased cardiovascular mortality in elderly men. *Horm Metab Res* 34:144–149
  25. Ibáñez L, Potau N, de Zegher F 1999 Precocious pubarche, dyslipidemia, and low IGF binding protein-1 in girls: relation to reduced prenatal growth. *Pediatr Res* 46:320–322
  26. Fall CH, Clark PM, Hindmarsh PC, Clayton PE, Shiell AW, Law CM 2000 Urinary GH and IGF-I excretion in nine year-old children: relation to sex, current size and size at birth. *Clin Endocrinol (Oxf)* 53:69–76
  27. Fall CH, Pandit AN, Law CM, Yajnik CS, Clark PM, Breier B, Osmond C, Shiell AW, Gluckman PD, Barker DJ 1995 Size at birth and plasma insulin-like growth factor-1 concentrations. *Arch Dis Child* 73:287–293
  28. Garnett S, Cowell CT, Bradford D, Lee J, Tao C, Petrauskas V, Fay R, Baur LA 1999 Effects of gender, body composition and birth size on IGF-I in 7- and 8-year-old children. *Horm Res* 52:221–229
  29. Jernström H, Olsson H 1998 Insulin-like growth factor-1 in relation to adult weight and birth weight in healthy nulliparous women. *Int J Gynaecol Obstet* 62:11–18
  30. Koistinen H, Koistinen R, Selenius L, Ylikorkala O, Seppälä M 1996 Effect of marathon run on serum IGF-I and IGFBP-1 levels. *J Appl Physiol* 80:760–764
  31. Royston P 1991 Constructing time specific reference ranges. *Stat Med* 10:675–690
  32. Pihkala J, Hakala T, Voutilainen P, Raivio K 1989 Uudet suomalaiset sikiön kasvukäyrät [New Finnish fetal growth curves]. *Duodecim* 105:1540–1546
  33. Sorva R, Lankinen S, Tolppanen EM, Perheentupa J 1990 Variation of growth in height and weight of children. II. After infancy. *Acta Paediatr Scand* 79:498–506
  34. Cole TJ, Freeman JV, Preece MA 1995 Body mass index reference curves for the UK, 1990. *Arch Dis Child* 73:25–29
  35. Alberti KGMM, Zimmet PZ for the WHO consultation 1998 Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabet Med* 15:539–553
  36. Després JP, Lemieux I, Prud'homme D 2001 Treatment of obesity: need to focus on high risk abdominally obese patients. *BMJ* 322:716–720
  37. Snel YEM, Brummer RJM, Doerga ME, Zelissen PM, Bakker CJ, Hendriks MJ, Kopperschaar HP 1995 Adipose tissue assessed by magnetic resonance imaging in growth hormone-deficient adults: the effect of growth hormone replacement and comparison with control subjects. *Am J Clin Nutr* 61:1290–1294
  38. Harrela M, Koistinen R, Kaprio J, Lehtovirta M, Tuomilehto J, Eriksson J, Toivanen L, Koskenvuo M, Leinonen P, Koistinen R, Seppälä M 1996 Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. *J Clin Invest* 98:2612–2615
  39. Vaessen N, Janssen JA, Heutink P, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM 2002 Association between genetic variation in the gene for insulin-like growth factor-I and low birthweight. *Lancet* 359:1036–1037
  40. Vaessen N, Heutink P, Janssen JA, Wittteman JC, Testers L, Hofman A, Lamberts SW, Oostra BA, Pols HA, van Duijn CM 2001 A polymorphism in the gene for IGF-I: functional properties and risk for type 2 diabetes and myocardial infarction. *Diabetes* 50:637–642
  41. Flanagan DEH, Holt RIG, Moore VM, Owens PC, Robinson JS, Phillips DIW 2001 The association between birthweight and IGF-I activity in young adults. *Pediatr Res* 50:40A
  42. Ho KKY, Hoffman DM 1993 Aging and growth hormone. *Horm Res* 40:80–86
  43. Popovici RM, Lu M, Bhatia S, Faessen GH, Giaccia AJ, Giudice LC 2001 Hypoxia regulates insulin-like growth factor-binding protein 1 in human fetal hepatocytes in primary culture: suggestive molecular mechanisms for *in utero* fetal growth restriction caused by uteroplacental insufficiency. *J Clin Endocrinol Metab* 86:2653–2659
  44. He Q, Karlberg J 2001 BMI in childhood and its association with height gain, timing of puberty, and final height. *Pediatr Res* 49:244–251
  45. Barlett HL, Puhl SM, Hodgson JL, Buskirk ER 1991 Fat-free mass in relation to stature: ratios of fat-free mass to height in children, adults, and elderly subjects. *Am J Clin Nutr* 53:1112–1116
  46. Thissen JP, Triest S, Moats-Staats BM, Underwood LE, Mauerhoff T, Maiter D, Ketelslegers JM 1991 Evidence that pretranslational and translational defects decrease serum insulin-like growth factor-I concentrations during dietary protein restriction. *Endocrinology* 129:429–435
  47. Withers DJ, Burks DJ, Towery HH, Altamuro SL, Flint CL, White MF 1999 IRS-2 coordinates IGF-I receptor-mediated beta-cell development and peripheral insulin signalling. *Nat Genet* 23:32–40
  48. Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D 2000 The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 133:176–182
  49. Fall C, Hindmarsh P, Dennison E, Kellingray S, Barker D, Cooper C 1998 Programming of growth hormone secretion and bone mineral density in elderly men: a hypothesis. *J Clin Endocrinol Metab* 83:135–139
  50. Cooper C, Eriksson JG, Forsén T, Osmond C, Tuomilehto J, Barker DJP 2001 Maternal height, childhood growth and risk of hip fracture in later life: a longitudinal study. *Osteoporos Int* 12:623–629