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Associations of Childhood and Adulthood Height and the Components of Height with Insulin-Like Growth Factor Levels in Adulthood: A 65-Year Follow-Up of the Boyd Orr Cohort

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Context: Taller individuals with longer legs have a higher risk of cancer but a lower risk of coronary heart disease.

Objective: We investigated whether childhood height and its components are associated with the IGF system in adulthood.

Design and Participants: We analyzed data from 429 participants of the Boyd Orr cohort, for whom height measured in childhood (mean age, 7.4 yr) in 1937–1939 could be related to levels of IGF-I, IGF-II, IGF binding protein (IGFBP)-2, and IGFBP-3 in adulthood (mean age, 71.1 yr). In 385 participants, measured height in adulthood could be related to IGF levels.

Results: In fully adjusted models (controlling for age, sex, socioeconomic factors, lifestyle, and body mass index), childhood height and its components were not associated with adult circulating IGF-I, IGF-II, or IGFBP-2 levels. IGFBP-3 was 85.5 ng/ml higher (95% confidence interval, −11.6 to 182.5; $P = 0.08$) per SD increase in childhood trunk length and 83.6 ng/ml lower (95% confidence interval, −10.3 to 177.5; $P = 0.08$) per SD increase in childhood leg/trunk ratio. Height in adulthood was not associated with IGF-I, IGF-II, or IGFBP-3 and was inversely associated with IGFBP-2 ($P = 0.05$) after additionally controlling for childhood height.

Conclusion: There was no evidence that associations of childhood height with cancer and coronary heart disease risk are mediated by IGF-I in adulthood. The anthropometric associations with IGFBP-2 and IGFBP-3 could be chance findings but warrant additional investigation. IGF levels in childhood may be more important determinants of long-term disease risk than adult levels. **(*J Clin Endocrinol Metab* 91: 1382–1389, 2006)**

OBSERVATIONAL EVIDENCE POINTS toward positive associations of height with risk of some cancers (*e.g.* prostate, breast, and colon) (1) and inverse associations with insulin resistance and coronary heart disease (CHD) (2, 3). Although the biology underlying these observations is unclear, indirect evidence suggests that IGFs may underlie associations between height and these disease outcomes (4–6). The IGF system comprises IGF-I and IGF-II, which are mainly synthesized in the liver in response to GH, and six binding proteins, IGF binding protein (IGFBP)-1 to IGFBP-6, which regulate the biological activity of circulating IGFs. The GH-IGF axis plays a key role in controlling prepubertal growth (7). IGF-I is associated positively with childhood height (5, 8) and cancer risk (9–11) and inversely with insulin resistance (12) and CHD risk (13). IGFBP-3 controls IGF-I bioavailability and is associated inversely with some cancers (14) and positively with CHD (13). IGF-II has been positively associated with cancer (15) and atherosclerosis (16), and low levels of circulating IGFBP-2 may indicate insulin resistance, but their role in disease etiology is not well understood (17–19). IGFBP-1, IGFBP-4, IGFBP-5, and IGFBP-6 are difficult and expensive to measure, and these binding proteins are not studied in the current report.

Leg length is associated with socioeconomic conditions, nutrition, and energy intake in prepubertal children (20–22), whereas trunk length may be a marker for factors influencing pubertal growth (22). Because a greater proportion of prepubertal growth is attributable to an increase in leg rather than trunk length, leg length may act as a better indicator of exposures influencing prepubertal growth than total height (23–25). For this reason, it has been suggested that associations of stature with cancer and CHD may be stronger for leg length than for overall height (1, 3, 26, 27). Some (6, 28, 29), but not all (4, 30–32), cross-sectional studies indicate positive associations of height with IGF levels in adulthood, but there is no convincing evidence that leg length is more strongly associated than trunk length with IGF (4). In childhood, height (8, 33, 34) and both leg and trunk growth (Rogers, I., C. Metcalfe, D. Gunnell, P. Emmett, D. Dunger, J. Holly, and ALSPAC Study Team, submitted for publication) are positively associated with concurrently measured IGF-I. Few studies, however, have examined the association of childhood anthropometry, other than birth weight, with adult IGF levels (5, 35), and none have related childhood leg or trunk length with IGF levels in adulthood. Most reports are re-

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Abbreviations: BMI, Body mass index; CHD, coronary heart disease; CI, confidence interval; GP, general practitioner; HOMA, homeostasis model assessment; IGFBP, IGF binding protein.

stricted to investigating IGF-I and IGFBP-3 associations, although recent work suggests that IGFBP-2 may contribute to biological mechanisms underlying height-disease associations (4). A greater understanding of relationships between childhood stature and the IGF system in adulthood may help elucidate mechanisms linking nutrition and growth in early life with increased cancer and reduced CHD risks in adulthood. The Boyd Orr cohort has uniquely detailed records of measured childhood height, leg length, trunk length, and important dietary and socioeconomic confounding variables, among participants followed up for 65 yr. Adulthood follow-up data include measured height, leg length, trunk length, and circulating levels of IGF-I, IGF-II, IGFBP-2, and IGFBP-3. We report on relationships of height, leg length, and trunk length measured in childhood and adulthood with circulating IGF and IGFBP levels in adulthood in a cohort in which childhood height and leg length have been associated positively with cancer and inversely with CHD (36, 37). There have been too few follow-up events since blood sampling in 2002–2003 to directly relate IGFs with cancer and CHD risk.

Patients and Methods

The study is an historical cohort based on the Carnegie (Boyd Orr) Survey of Diet and Health in Pre-War Britain, 1937–1939 (38). A total of 4999 children from 1343 families were surveyed at 16 centers in England and Scotland. Detailed physical examination was performed on 3762 of the children (75%) from 14 centers. Of the original 4999 participants, 4397 (88%) have been traced and flagged using the National Health Service Central Register at Southport and its equivalent in Edinburgh.

Measures in childhood

Measurements of height and leg and trunk length taken on 2997 children aged 2 to 14 yr 9 months are available. Childhood standing height was measured to the nearest millimeter with a portable measuring stand (38). Childhood leg length was measured with a steel tape measure and recorded as the distance from the ground to the summit of the iliac crest (38). Trunk length was calculated by subtracting leg length from overall height.

Adult follow-up

Between 2002 and 2003, a total of 1295 surviving participants were invited to participate in a follow-up study, as described previously (39). Blood samples and measured adult height were obtained from 728 of 1295 (56%) potentially eligible subjects, either at a research clinic (n = 405) or by the general practitioner (GP) who sent the samples for analysis by mail in approved post office packaging (n = 323) (Fig. 1). GP- or clinic-measured adult heights in study members with complete data for multivariable analysis are available for 682 (53%) subjects. However, GPs measured height only, without any specific instruction on measurement techniques. In contrast, height and sitting height were measured in the research clinic by one of two trained researchers with a Harpenden stadiometer using a standardized protocol. Clinic-measured

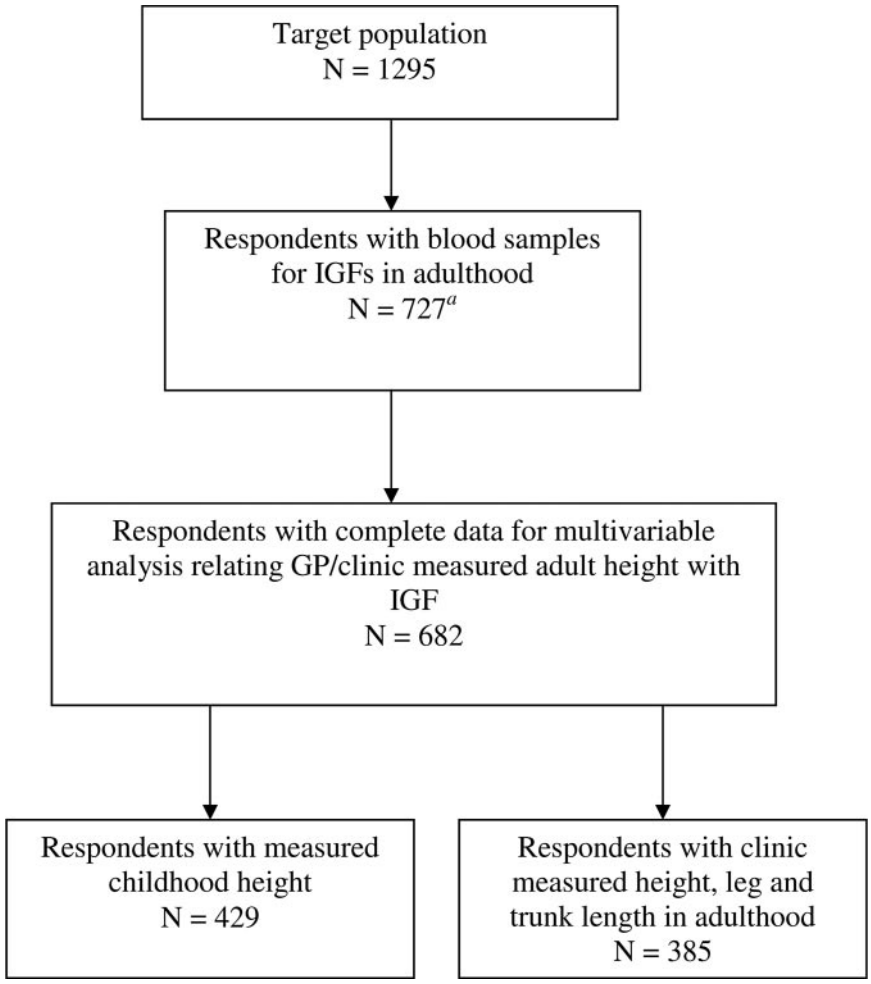

FIG. 1. Description of study numbers: target population, respondents with blood samples, numbers with measures of height and their components in childhood and adulthood, and numbers with complete data for multivariable analysis that were included in the final analyses. [a] One subject with a blood sample did not have enough serum for IGF measures.

adult height in study members with complete data for multivariable analysis are available for 385 (30%) of the subjects. We based our analysis relating adult height with IGFs, therefore, on the participants with clinic measures to reduce measurement error. In a sensitivity analysis, associations of IGF with adult height (measured by either the GP or in the research clinic) were repeated using all 682 respondents with complete data for multivariable analyses. The number of participants for whom childhood anthropometry was available was 429 (33%), and this is the subset of the cohort on which the main analyses relating childhood height with IGF levels in adulthood are undertaken.

Exposure variables in childhood and adulthood

As in previous analyses of this cohort relating childhood stature with cancer and CHD (36), internally derived age- and sex-standardized Z scores for height (n = 429), leg length (n = 418), trunk length (n = 418), and the leg/trunk ratio (n = 418) measured at one point in time in the children (aged between 2 and 14 yr 9 months) were the childhood exposure variables of interest. Internally age- and sex-standardized Z scores were computed using cubic polynomial regression for boys and girls separately within 6-month age and sex bands (21). SDs were modeled within 6-month age bands (21). Associations of the IGF system with anthropometry in adulthood were based on Z scores internally standardized for sex (n = 385). The magnitude of anthropometry-IGF associations in childhood are thus directly comparable with those in adulthood.

The leg/trunk ratio is an indicator of leg length in relation to total stature. An increased leg/trunk ratio suggests relatively long legs in relation to overall height, and associations of this ratio with IGFs would establish the importance of body proportion (leg relative to trunk length) in relation to the IGF system. During childhood, the leg/trunk ratio provides a measure of prepubertal growth that occurs more in the legs than the trunk (21, 25). In adults, it may also be a marker of delayed puberty, which leads to a prolonged period of leg growth.

IGF measurements

The IGF outcomes were IGF-I, IGF-II, IGFBP-2, IGFBP-3, and the molar ratio IGF-I/IGFBP-3 [a measure of free, biologically active IGF-I (29)]. Among the 727 subjects with IGF measurements, 405 blood samples were taken at research clinics, and 91% of these were obtained fasted for 6 h or more; bloods taken by the GPs were nonfasted (n = 322). The clinic samples were spun and frozen to −20 C within 1 h and then transferred within 3 wk to a −80 C freezer. Seventy-nine percent of bloods sent by mail arrived the next day, and only 1% took 5 d or more to arrive. Adjusting for age and sex, there is no evidence of any differences in mean levels of IGF-I, IGF-II, IGFBP-2, or IGFBP-3 between those that arrived the next day and those that took 2 or more days to arrive. The median (interquartile range) number of days that serum samples were stored before analysis (n = 727), in ascending order, were 355 (interquartile range, 291–442) for IGFBP-3, 409 (348–518) for IGFBP-2, 545 (429–655) for IGF-I, and 723 (562–833) for IGF-II. Adjusting for age and sex, there is no evidence of a linear trend in mean levels of IGF-I, IGFBP-2, or IGFBP-3 across quintiles of storage time, but IGF-II levels were higher in those samples that had been stored the longest. The median IGF-II levels in the shortest and longest quintiles of storage time were 481 and 669 ng/ml, respectively. This trend was not explained by age, sex, or any one of three conditions of sample measurement (whether fasted/not fasted, binary variable; laboratory technician undertaking the assay, indicator variables; or clinic *vs.* posted blood, binary variable). Hence, we repeated all IGF-II analyses to determine whether controlling for length of storage time made any difference to the results.

Serum IGF-I, IGF-II, and IGFBP-3 levels were measured using in-house double-antibody RIAs as described previously (40). Total levels of IGFBP-2 were measured by one-step sandwich ELISAs (DSL-10-7100; Diagnostic Systems Laboratories, Webster, TX). Results for IGF-I, IGF-II, and IGFBP-3 concentrations were based on the average of three measures and for IGFBP-2 on the average of two measures. The average coefficients of variation for intraassay variability for IGF-I, IGF-II, IGFBP-3, and IGFBP-2 were 6.7, 10, 3.9, and 5% and for interassay variation were 9.7, 14, 8.1, and 7.1%. Based on the molecular weight of IGF-I (7500) and IGFBP-3 (40,000, mean of glycosylated variants), we calculated the molar ratio of IGF-I/IGFBP-3 by multiplying the ratio by 5.33 (40,000:7500).

Statistical analyses

Relationships of childhood or adulthood height and its components with the IGF system in adulthood were assessed using multiple linear regression. The regression coefficients show the change in IGF and IGFBP levels per SD increase in stature. IGFBP-2 values were highly positively skewed and were $\log_e$ transformed; thus, the percentage change in IGFBP-2 per SD increase in stature is given.

Associations were adjusted for age (continuous variable), sex, clinic-obtained *vs.* posted blood sample, per capita household food expenditure in childhood [four categories: <£0.25 (equivalent 2002 monetary value, based on average earnings (41), <£36), £0.25 to £0.34 (£36-£49); £0.35 to £0.44 (£50-£65); and >£0.44 (>£65)], social class of head of household when a child in 1937–1939 (four categories: I/II, professional and managerial; III, skilled; IV/V, partly skilled and unskilled; other, unemployed and unclassifiable), social class in adulthood [three categories: I/II, III, IV/V/other (armed forces, unemployed, unclassifiable)], and lifestyle factors in adulthood [smoking (four categories based on pack-years), alcohol (three categories indicating frequency of consumption over the past 12 months: at least weekly, occasionally, and never), exercise (four-level score based on frequency and type of activity validated in the British Regional Heart Study (42), and measured adult body mass index (BMI) (continuous variable)]. We calculated robust SE values to account for lack of independence between observations within families (43). Additional models investigated the impact on observed associations of controlling for key components of diet previously associated with IGFs: milk intake in childhood [daily per capita total milk and milk products consumption (in grams)], dairy intake in adulthood [daily all dairy intake (in grams)], and total energy intake in adulthood [from all foods, including milk and alcohol (in kilocalories)]. We also investigated whether controlling for IGFBP-3 influenced associations of height and its components with IGF-I and IGF-II and whether the inclusion of homeostasis model assessment (HOMA) measures of insulin resistance (44) influenced anthropometry-IGF associations (45).

We performed likelihood ratio tests for interactions with sex and age [defined *a priori* as in previous analyses (21, 36) as <8 or ≥8 yr] at childhood measurement to investigate whether associations differed in those children who were prepubertal (<8 yr) compared with those who may have entered puberty (≥8 yr). We also controlled for childhood stature in models relating adult height with the IGF system to assess whether growth trajectory since childhood, independent of childhood height, was an important predictor of IGF in adulthood. All analyses were conducted using Stata 8 (Stata, College Station, TX).

Results

Mean age at childhood examination of the study participants was 7.4 yr, and mean age at time of blood sample was 71.1 yr (45.6% male). Males were taller than females, but the leg/trunk ratio was similar (Table 1). Mean IGF-I levels and the molar ratio IGF-I/IGFBP-3 were higher in men than women, but IGF-II and IGFBP-3 levels were lower in men than women.

Representativeness of the study population

There was no evidence that the 728 people who provided blood samples in the follow-up study differed from those eligible participants who did not (n = 567) in terms of sex, birth weight, childhood BMI, adult height, or adult BMI. However, those who provided blood samples were more likely to have been younger when originally surveyed (6.5 *vs.* 7.6 yr), to have fathers in social class I–III (33 *vs.* 24%), to have been taller in childhood (Z scores: 0.15 *vs.* −0.03 SDs), to be in social class I–II in adulthood (33 *vs.* 17%), to consume

TABLE 1. Characteristics of study participants

Participant characteristics	Values (mean or % as stated)		*P* value[b]
	Males[a]	Females	
Continuous variables [mean (5th to 95th percentile)]			
Age at childhood examination (yr) (n = 429)	6.9 (2.3 to 12.3)	7.7 (2.6 to 13.6)	0.006
Age at blood sample (yr) (n = 727[c])	71.3 (65.0 to 78.9)	71.0 (65.0 to 78.7)	0.77
Childhood			
Z score for height (n = 429)	0.2 (−1.4 to 2.0)	0.1 (−1.3 to 1.7)	0.81
Z score for leg length (n = 418)	0.2 (−1.5 to 1.8)	0.1 (−1.3 to 1.6)	0.90
Z score for trunk length (n = 418)	0.0 (−1.6 to 2.0)	0.0 (−1.6 to 1.6)	0.60
Z score for leg/trunk ratio (n = 418)	0.2 (−1.3 to 1.9)	0.1 (−1.4 to 1.5)	0.87
Adulthood			
Height (cm) (n = 385)	171.9 (161.4 to 184.4)	157.9 (148.7 to 167.8)	<0.001
Leg length (cm) (n = 385)	92.2 (84.8 to 100.6)	84.4 (78.3 to 91.4)	<0.001
Trunk length (cm) (n = 385)	79.7 (73.0 to 86.1)	73.5 (67.3 to 78.3)	<0.001
Leg/trunk ratio (n = 385)	1.16 (1.05 to 1.28)	1.15 (1.06 to 1.26)	0.22
IGF-I (ng/ml) (n = 727)	135.6 (74.4 to 211.8)	121.4 (64.4 to 186.9)	<0.001
IGF-II (ng/ml) (n = 726)	623.6 (299 to 1007)	708.0 (343 to 1140)	<0.001
IGFBP-2 (ng/ml) (n = 727)	484.2 (174.8 to 1020.8)	481.2 (159 to 1068)	0.42
IGFBP-3 (ng/ml) (n = 727)	3940 (2502 to 5510)	4270 (2628 to 6121)	<0.001
Molar ratio IGF-I/IGFBP-3 (n = 727)	0.18 (0.12 to 0.26)	0.15 (0.09 to 0.23)	<0.001
Categorical variables (%)			
Childhood			
Per capita household food expenditure ≤£0.25/week (n = 728)	43.1	48.2	0.16
Social class of head of household I and II (n = 728)	8.7	9.3	0.78
Adulthood			
Social class I and II (n = 727)	23.6	29.3	0.16
Never smoked (n = 728)	33.4	49.0	<0.001
Alcohol never consumed in last 12 months (n = 726)	7.3	18.5	<0.001
Exercise, never or infrequent and mild (n = 718)	13.2	13.0	0.97

[a] 332 of 728, 45.6% male.
[b] Unpaired *t* tests (assuming equal variances) were used to test for a difference between means, and Fisher's exact test was used to test for a difference between proportions. Because of a skewed distribution, IGFBP-2 was $\log_e$ transformed.
[c] One subject with a blood sample did not have enough serum for IGF measures.

alcohol at least weekly (52 *vs.* 43%), and to have never smoked (40 *vs.* 30%).

Height and components of height in childhood

Table 2 gives the regression coefficients for models assessing relationships of height and its components in childhood with IGF and IGFBP levels in adulthood, with three sequential levels of adjustment for potential confounding factors as shown. No associations were seen with IGF-I, IGF-II, or the molar ratio IGF-I/IGFBP-3. There was weak evidence that childhood trunk length was positively associated ($P = 0.08$) and that childhood leg/trunk ratio was inversely associated ($P = 0.08$) with adulthood levels of IGFBP-3. The association of IGFBP-3 with trunk length was similar after leg length was included in the fully adjusted model [coefficient, 91.7 ng/ml; 95% confidence interval (CI), −5.06 to 188.51; $P = 0.06$]. Neither HOMA insulin resistance nor dietary factors (milk intake in childhood and dairy and total energy intake in adulthood) confounded the above associations (data not shown). Associations of IGFBP-3 with childhood trunk length and leg/trunk ratio, however, were not independent of circulating IGF-I levels (fully adjusted coefficients additionally controlling for IGF-I were, for trunk length, 38.3 ng/ml; 95% CI, −31.8 to 108.4; $P = 0.28$; and for leg/trunk ratio, −42.9 ng/ml; −114.5 to 28.8; $P = 0.24$). When we additionally adjusted height-IGF-I and height-IGF-II associations for IGFBP-3, our conclusions did not change (data not shown). IGFBP-2 was weakly positively associated with height ($P = 0.07$) and leg length ($P = 0.06$) in simple models, but associations disappeared in models controlling for socioeconomic and lifestyle factors. Anthropometry-IGFBP-2 associations were similar when additionally adjusted for IGF-I. Height-IGF associations did not differ by sex (all *P* values for interaction >0.4, except for IGF-II, $P = 0.08$) or age (< 8 *vs.* ≥ 8 yr) at time of childhood examination (all *P* values for interaction > 0.35).

Height and components of height in adulthood

In fully adjusted models, neither measured adulthood height nor its components were associated with circulating IGF-I, IGF-II, IGFBP-2, or IGFBP-3 (Table 3). Analyses based on all 682 respondents with adult height, measured by either the GP or in the research clinic, were similar to those based only on those with clinic height. Among 243 participants with both childhood and clinic-measured adulthood heights, there was little evidence that change in height Z score between childhood and adulthood (to assess whether growth trajectory since childhood influences the IGF system in adulthood) was associated with circulating IGF-I, IGF-II, or IGFBP-3 (all correlation coefficients < 0.1). IGFBP-2 levels, however, were lower among those whose height Z score was greater in adulthood relative to the childhood measure (correlation coefficient between change in height Z score and (ln)IGFBP-2, −0.14; $P = 0.02$). Controlling for childhood stature in the fully adjusted model relating adult height with (ln)IGFBP-2, the regression coefficient implied a change of −7.2% per SD increase in adult height (95% CI, −14.0 to 0.0%; $P = 0.05$), and the association persisted after controlling for

TABLE 2. Associations of measured height and its components in childhood with IGFs and IGFBPs measured in adulthood

	Change (95% CI) in IGF levels per 1 SD increase in childhood height and its components[a], adjusted as shown[b]					
	Controlling for age, sex, and sample type	*P* value	As before + social class and food expenditure in childhood	*P* value	As before + social class in adulthood and lifestyle factors	*P* value
Levels of IGF-I						
Height	2.81 (−1.31,6.94)	0.18	1.94 (−2.68,6.56)	0.41	1.87 (−2.69,6.44)	0.42
Leg length	1.29 (−3.01,5.58)	0.56	0.44 (−4.32,5.19)	0.89	0.30 (−4.39,4.98)	0.90
Trunk length	3.58 (−0.38,7.53)	0.08	2.95 (−1.09,6.98)	0.15	2.98 (−1.14,7.09)	0.16
Leg/trunk ratio	−2.24 (−5.95,1.47)	0.24	−2.46 (−6.16,1.24)	0.19	−2.57 (−6.35,1.21)	0.18
Levels of IGFBP-3						
Height	38.0 (−57.8,133.8)	0.44	38.5 (−66.1,143.0)	0.47	39.5 (−65.2,144.1)	0.46
Leg length	−15.8 (−119.6,88.1)	0.77	−20.7 (−134.4,92.9)	0.72	−16.73 (−127.3,93.9)	0.77
Trunk length	85.2 (−6.3,176.6)	0.07	83.8 (−10.7,178.2)	0.08	85.5 (−11.6,182.5)	0.08
Leg/trunk ratio	−87.8 (−181.6,5.9	0.07	−86.9 (−181.6,7.7)	0.07	−83.6 (−177.5,10.3)	0.08
Levels of molar ratio IGF-I/IGFBP-3						
Height	0.0019 (−0.0020,0.0059)	0.35	0.0004 (−0.0040,0.0048)	0.85	0.0003 (−0.0041,0.0047)	0.89
Leg length	0.0019 (−0.0023,0.0062)	0.36	0.0007 (−0.0039,0.0053)	0.77	0.0005 (−0.0041,0.0051)	0.82
Trunk length	0.0013 (−0.0025,0.0052)	0.50	0.0004 (−0.0035,0.0043)	0.84	0.0002 (−0.0037,0.0042)	0.90
Leg/trunk ratio	0.0003 (−0.0036,0.0043)	0.87	−0.0001 (−0.0040,0.0038)	0.96	−0.0002 (−0.0041,0.0038)	0.94
Levels of IGF-II[c]						
Height	−7.78 (−28.79,13.23)	0.47	−7.68 (−30.16,14.80)	0.50	−9.37 (−31.40,12.66)	0.40
Leg length	−7.77 (−29.55,14.01)	0.48	−7.57 (−30.53,15.38)	0.52	−9.89 (−32.32,12.53)	0.39
Trunk length	3.09 (−16.98,23.16)	0.76	3.93 (−16.46,24.31)	0.71	3.43 (−16.36,23.22)	0.73
Leg/trunk ratio	−8.57 (−29.61,12.48)	0.42	−8.60 (−29.46,12.27)	0.42	−9.45 (−29.91,11.02)	0.36
Levels of IGFBP-2[d]						
Height	4.1% (−0.3,8.8)	0.07	2.2% (−2.5,7.2)	0.37	3.0% (−1.4,7.5)	0.19
Leg length	4.7% (−0.2,9.8)	0.06	3.0% (−2.0,8.2)	0.25	3.0% (−1.5,7.7)	0.19
Trunk length	2.5% (−1.9,7.0)	0.27	1.2% (−3.1,5.7)	0.59	1.9% (−2.0,6.0)	0.35
Leg/trunk ratio	2.0% (−2.8,7.2)	0.42	1.5% (−3.2,6.4)	0.55	1.0% (−3.3,5.5)	0.65

[a] Analyses were restricted to those for whom data on all confounding variables were available; n = 429 in the case of height and n = 418 in the case of leg and trunk length.

[b] Associations were adjusted for: 1) sex and age (as a continuous variable) and sample type (clinic or postal), 2) social class of head of household (four categories) and per capita household food expenditure (four categories) in childhood, 3) social class in adulthood (three categories), smoking (four categories), alcohol consumption (three categories), levels of exercise (four categories), and BMI in adulthood (as a continuous variable).

[c] Results for IGF-II are based on a total of one person less (*i.e.* n = 428 or 417) because a value for IGF-II was missing for one person as a result of insufficient blood volume.

[d] Because of a skewed distribution, IGFBP-2 result was $\log_e$ transformed. Thus, rather than difference in means, percentage increase per 1 SD increase in each of the anthropometry measures is reported.

HOMA insulin resistance. There was no evidence that adult height was associated with IGF-I, IGF-II, or IGFBP-3 in fully adjusted models additionally controlling for childhood stature (all *P* values > 0.2).

Associations for both childhood and adulthood anthropometry were little altered when controlled for −80 C freezer storage time.

Discussion

Contrary to our predictions, we found little evidence that either height or leg length, measured at one point in time in childhood or adulthood, was associated with circulating levels of IGF-I, IGF-II, or IGFBP-2 in adulthood. Nevertheless, there was weak evidence that IGFBP-3 was higher in participants who, as children, had longer trunks and a lower leg/trunk length ratio, an indicator of relatively long trunk length in relation to total stature. Height in adulthood was inversely associated with IGFBP-2 but only after additionally controlling for childhood height.

Implications

Previous analyses of the Boyd Orr cohort have documented that taller children, specifically those with longer legs, were at increased risk of dying from cancer and at reduced risk of CHD death (36, 37). Epidemiological studies also indicate that exposure to increased IGF-I levels is associated with greater cancer (9–11) and lower insulin resistance (12) and CHD (13) risk. We had speculated, therefore, that childhood height and leg length associations with chronic disease may be mediated by IGF-I, because circulating levels of this growth factor in early life influence childhood growth (1, 5, 8, 34, 35, 46). Our study indicates that associations of childhood height and leg length with later disease risk are not reflected strongly by associations of childhood anthropometry with adult levels of IGF-I. Two studies that have examined associations of childhood stature with adult IGF levels concur with our results (5, 35), although they did not specifically investigate the leg and trunk length components of height. In the Barry Caerphilly Growth study (5), no association was found between height measured at age 5 yr and IGF-I, IGFBP-3, and their molar ratio measured among men and women in their 20s, although a positive association between current IGF-I levels and adult height was found. Likewise, in a cohort of Finnish men and women in their 60s and 70s, height at 7 yr was not associated with IGF-I measured in old age (35). Others have found, however, that patterns of childhood growth in relation to birth weight (catch-up growth or rate of height gain) are associated with IGF-I levels

TABLE 3. Associations of measured height and its components in adulthood with current IGFs and IGFBPs

	Change (95% CI) in IGF levels per 1 SD increase in adult height and its components[a], adjusted as shown[b]					
	Controlling for age, sex, and sample type	*P* value	As before + social class and food expenditure in childhood	*P* value	As before + social class in adulthood and lifestyle factors	*P* value
Levels of IGF-I						
Height	2.33 (−2.06,6.72)	0.30	2.12 (−2.39,6.63)	0.36	1.66 (−2.85,6.17)	0.47
Leg length	2.17 (−1.82,6.15)	0.29	2.02 (−2.04,6.08)	0.33	1.71 (−2.38,5.81)	0.41
Trunk length	1.16 (−3.13,5.44)	0.60	0.92 (−3.30,5.14)	0.67	0.55 (−3.56,4.67)	0.79
Leg/trunk ratio	1.21 (−2.02,4.43)	0.46	1.19 (−1.97,4.35)	0.46	1.16 (−1.92,4.24)	0.46
Levels of IGFBP-3						
Height	48.8 (−64.7,162.3)	0.40	53.9 (−60.4,168.3)	0.35	54.1 (−60.8,169.0)	0.36
Leg length	78.7 (−41.9,199.2)	0.20	88.0 (−33.8,209.8)	0.16	85.5 (−38.0,209.0)	0.17
Trunk length	−10.1 (−140.2,120.1)	0.88	−13.8 (−143.2,115.5)	0.83	−9.9 (−135.2,115.5)	0.88
Leg/trunk ratio	69.4 (−48.3,187.2)	0.25	75.8 (−39.7,191.3)	0.20	69.7 (−45.2,184.5)	0.23
Levels of molar ratio IGF-I/IGFBP-3						
Height	0.0012 (−0.0037,0.0061)	0.63	0.0007 (−0.0044,0.0058)	0.78	0.0002 (−0.0049,0.0053)	0.93
Leg length	0.0000 (−0.0047,0.0046)	0.99	−0.0006 (−0.0055,0.0043)	0.82	−0.0008 (−0.0056,0.0041)	0.75
Trunk length	0.0018 (−0.0024,0.0060)	0.40	0.0016 (−0.0027,0.0059)	0.46	0.0010 (−0.0033,0.0053)	0.64
Leg/trunk ratio	−0.0009 (−0.0045,0.0028)	0.64	−0.0011 (−0.0049,0.0026)	0.56	−0.0009 (−0.0046,0.0028)	0.64
Levels of IGF-II						
Height	−6.64 (−29.31,16.04)	0.57	−12.59 (−35.97,10.79)	0.29	−12.09 (−35.29,11.10)	0.31
Leg length	−4.52 (−34.30,25.25)	0.77	−8.08 (−39.00,22.85)	0.61	−6.83 (−36.64,22.98)	0.65
Trunk length	−5.08 (−34.77,24.60)	0.74	−10.14 (−39.04,18.76)	0.49	−11.02 (−38.59,16.56)	0.43
Leg/trunk ratio	3.30 (−34.25,40.85)	0.86	4.02 (−32.96,41.00)	0.83	5.72 (−28.58,40.02)	0.74
Levels of IGFBP-2[c]						
Height	1.04% (−4.21,6.58)	0.70	0.93% (−4.63,6.82)	0.75	−0.79% (−5.66,4.33)	0.76
Leg length	3.81% (−2.34,10.34)	0.23	3.65% (−2.81,10.54)	0.28	0.28% (−5.04,5.91)	0.92
Trunk length	−2.65% (−8.54,3.62)	0.40	−2.62% (−8.72,3.90)	0.42	−1.68% (−7.31,4.29)	0.57
Leg/trunk ratio	4.76% (−4.08,14.43)	0.30	4.47% (−4.46,14.24)	0.34	1.15% (−48.09,97.11)	0.74

[a] Analyses were restricted to those for whom adult height measured at clinic and data on all confounding variables were available; n = 385 for height, leg length, and trunk length

[b] Associations were adjusted for: 1) sex and age (as a continuous variable) and sample type (clinic or postal), 2) social class of head of household (four categories) and per capita household food expenditure (four categories) in childhood, and 3) social class in adulthood (three categories), smoking (four categories), alcohol consumption (three categories), levels of exercise (four categories), and BMI in adulthood (as a continuous variable).

[c] Because of a skewed distribution, IGFBP-2 result was $\log_e$ transformed. Thus, rather than difference in means, percentage increase per 1 unit (centimeters or ratio) increase in each of the anthropometry measures is reported.

in childhood (8, 47, 48) and early adulthood (5). Downward centile crossing at any time in childhood was associated with lower levels of IGF-I in adulthood, and the highest levels of IGF-I were observed in young adults who were tall throughout early life (5). We could not investigate growth in childhood because childhood stature was measured only once in most members of our cohort, but we found little evidence that change in height between childhood and adulthood was associated with IGF-I, IGF-II, or IGFBP-3 in adulthood. The inverse association of height in adulthood with IGFBP-2 after controlling for childhood height could indicate that upward growth trajectory between the childhood measure and adulthood predicts lower adult IGFBP-2 levels, because the main determinant of adult height after controlling for the earlier childhood measure is likely to be a composite of the duration and rate of growth during puberty (5).

Mixed findings emerge from studies examining the association of adult stature with circulating growth factor levels. Some (6, 28, 29, 49), but not all (4, 30, 31), previous studies show positive associations of adult height with IGF-I and/or IGFBP-3, but few report on associations with the components of height. In keeping with the findings reported here and by others (30, 31), one study examining cross-sectional associations of both adult height and leg length with IGF-I found no evidence of any relationships, although it did show a weak inverse association between leg/trunk length ratio and IGFBP-3 ($P = 0.13$) and a positive association between leg/trunk ratio and the molar ratio IGF-I/IGFBP-3 ($P = 0.06$) (4). These findings are in line with our report, because they could indicate that relatively long trunk length in relation to total stature is associated with higher IGFBP-3 levels. Circulating levels of IGFBP-3 have been positively associated with height in childhood (29) and adulthood (50) and with prepubertal growth in height independent of serum IGF-I (Rogers, I., C. Metcalfe, D. Gunnell, P. Emmett, D. Dunger, J. Holly, and ALSPAC Study Team, submitted for publication). Our study, along with our previous investigation (4), provides limited evidence that differences in childhood body proportions (leg/trunk ratios) may act as indicators of levels of IGFBP-3 in adulthood and, speculatively, may thus be one mechanism linking childhood stature to adult chronic disease risk.

Although our findings do not support the hypothesis that childhood height, measured at one point in time, is a marker for adult IGF levels, it remains possible that childhood IGF levels, for which childhood stature is a marker (8, 47, 51), influence adult chronic disease, either by a direct effect on early pathophysiological processes underlying the later development of chronic disease (52) or via a long-term programming effect on the function of tissues and organs (53). Investigating associations of chronic disease outcomes with

IGF genetic polymorphisms that alter lifelong exposure to biologically active IGF and IGFBP levels could further our understanding of this issue (54). The duration and rate of growth in childhood, which influence final adult height, may be a better marker of IGF levels than height in childhood measured at one point in time (5, 46). We found no evidence, however, that height measured in adulthood was associated with circulating levels of IGF-I and IGFBP-3.

Strengths and limitations

A major strength of our study over previous cross-sectional analyses in adulthood (4) is that associations of childhood stature with IGF levels in adulthood will not be influenced by shrinkage, particularly in trunk length, accompanying age-related osteoporotic vertebral collapse (55). Shrinkage attributable to age and comorbidity does not affect stature measured in childhood. Our analysis is based on height, leg length, and trunk length measured in both childhood and 65 yr later in adulthood in a cohort in which childhood height-disease associations have been documented previously. Furthermore, we have detailed information on a range of possible confounding factors, again recorded in both childhood and adulthood, thereby decreasing the likelihood of residual confounding as an explanation for the observed associations. There are four main limitations to our analysis. First, our sample size is relatively small, limiting our power to detect relatively small but possibly biologically important associations. Second, associations of childhood height and its components with the IGF system may have been obscured by either the known age-induced decline in the activity of the GH-IGF axis (30), by coexisting morbidity in the study population, or because the study population was based on a selective sample of the survivors in the cohort. Third, there was an apparent positive association between storage time and levels of IGF-II, but associations were little altered when controlled for storage time. Finally, we tested multiple hypotheses, so observed associations could have arisen by chance. No formal statistical approaches to account for multiple hypothesis testing were used, but we have quoted exact rather than threshold *P* values.

Conclusions

As far as we are aware, this is the only study to date that relates measured childhood height, leg length, and trunk length to levels of IGF-I, IGF-II, IGFBP-2, and IGFBP-3 in old age. No studies to date have examined associations of the IGF system in childhood with adult cancer or CHD; studies have related IGF levels measured in adulthood with these outcomes. Our data suggest that neither a child's stature measured at one point in time and compared with his or her peers of the same age nor final height (a marker for the total duration and rate of growth) is strongly associated with the IGF system in adulthood. Levels of IGF in childhood may be more important determinants of long-term disease risk than adult levels. Additional studies should seek to elucidate the causal relationships between GHs, rate of childhood growth, and tumor generation, the origins of which may begin in early life (7).

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