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Associations of Adiposity from Childhood into Adulthood with Insulin Resistance and the Insulin-Like Growth Factor System: 65-Year Follow-Up of the Boyd Orr Cohort

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Context: One metabolic pathway through which adiposity influences disease risk may be via alterations in insulin and IGF metabolism.

Objective: Our objective was to investigate associations of adiposity at different stages of life with insulin and the IGF system.

Design, Setting, and Participants: The study was a 65-yr follow-up of 728 Boyd Orr cohort participants (mean age, 71 yr) originally surveyed between 1937 and 1939.

Main Outcomes: Outcomes included homeostasis model assessment of insulin resistance, total IGF-I and IGF-II, IGF binding protein (IGFBP)-2, and IGFBP-3 in adulthood.

Results: Childhood body mass index (BMI) was weakly inversely related to adult IGF-I (coefficient per BMI SD, −3.4 ng/ml; 95% confidence interval, −7.3 to 0.5; $P = 0.09$). IGF-II (but not IGF-I) increased with higher current fat mass index (coefficient, 26.1 ng/ml; 95% confidence interval, 4.6 to 47.6; $P = 0.02$) and waist-hip ratio (30.0 ng/ml; 9.4 to 50.5; $P = 0.004$). IGFBP-2 decreased by 21.2% (17.2 to 24.9; $P < 0.001$), and homeostasis model assessment of insulin resistance increased by 38.8% (28.9 to 49.6; $P < 0.001$) per SD higher adult BMI. Among thin adults (BMI tertiles 1 and 2), IGFBP-2 was positively, and insulin resistance was inversely, associated with childhood BMI.

Conclusion: There was only weak evidence that associations of childhood BMI with chronic disease risk may be mediated by adult IGF-I levels. Circulating IGFBP-2 in adulthood, a marker for insulin sensitivity, was inversely associated with current adiposity, but overweight children who became relatively lean adults were more insulin sensitive than thinner children. The findings may indicate programming of later insulin sensitivity and consequently IGFBP-2 levels in response to childhood adiposity. The role of IGF-II in obesity-related chronic diseases warrants additional investigation. (***J Clin Endocrinol Metab* 91: 3287–3295, 2006**)

IN THE LAST 30 yr, the prevalence of overweight children has tripled to around 20% in the United States (1) and United Kingdom (2). The long-term metabolic consequences of childhood obesity are, therefore, of great interest. Although hyperinsulinemia and insulin resistance are known features of childhood adiposity (3, 4), the impact of adiposity on IGFs is unclear (5). In adulthood, positive (5–7), inverse (8–16), and null (17–25) IGF-I-adiposity associations have been described in cross-sectional studies, whereas this association is generally positive in children (26–30). We previously showed that IGF-binding protein (IGFBP)-2 was inversely associated with body mass index (BMI) in healthy middle-aged men (19), consistent with reports in disease-free women (13, 31–33) and healthy elderly men (25). Given its inverse relationship with insulin (13, 25, 34–36), this suggests that IGFBP-2 may index adiposity-related hyperinsulinemia across the population range of BMI (19, 35). Greater understanding of these associations is valuable to help determine the possible long-term consequences of rising levels of childhood obesity. This is particularly important in view of research suggesting that the insulin-IGF-I system may mediate the effect of energy balance on cancer risk (37). In contrast, high IGF-I levels may protect against metabolic syndrome (38) and cardiovascular disease (17).

Despite many cross-sectional studies (5–30), few reports assess associations of adiposity over the life course with the IGF system (11, 16). The Boyd Orr cohort has records of measured adiposity over 65 yr of follow-up. We investigated relationships of adiposity in childhood and old age with insulin resistance, IGF-I, IGF-II, IGFBP-2, and IGFBP-3 in adulthood, in a cohort in which positive associations of childhood BMI with cancer (40) and ischemic heart disease (41) have been demonstrated.

Subjects and Methods

The study is an historical cohort based on the Carnegie (Boyd Orr) Survey of Diet and Health in Pre-War Britain, 1937–39 (42). Altogether, 4999 children from 1343 families were surveyed at 16 centers in England and Scotland. Physical examinations were carried out on 3762 of the children. A total of 4397 participants (88%) have been traced and flagged using the National Health Service Central Register.

Childhood anthropometry

Measurements of height and weight measured at one point in time on 2997 children aged 2 yr to 14 yr 9 months are available. Childhood standing height was measured to the nearest millimeter with a portable measuring stand, and weight was measured with a W&T Avery standard model calibrated level balance (now known as Avery Berkel, Smethick, UK) to the nearest ounce (28.4 g).

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Abbreviations: BMI, Body mass index; GP, general practitioner; HOMA, homeostasis model assessment; IGFBP, IGF-binding protein.

Adult follow-up

Between 2002 and 2003, a total of 1295 surviving participants were invited to participate in a follow-up study (42, 43). Blood samples and measured adult heights and weights were obtained from 728 subjects, either at a research clinic (n = 405), where measurements were conducted using a standardized protocol, or by their general practitioner (GP) who posted blood samples for analysis in approved packaging (n = 323) (Fig. 1). Of these, 725 had adult BMI (weight/height; kg/m^2) and IGF measured, whereas 682 (53%) had complete data for multivariable analysis. Clinic-measured adult height and weight in study members with complete data for multivariable analysis are available for 385 (30%) of the subjects. As in previous publications of the adult anthropometric data (43), we based our analysis relating adult BMI with IGFs on the participants with clinic measures to reduce measurement error. In a sensitivity analysis, associations of IGF with adult BMI (measured by either the GP or in the research clinic) were repeated using all 682 respondents with complete data for multivariable analyses. In total, 456 participants with IGF measures in adulthood also had childhood BMI data, and 431 (33%) had complete data for multivariable analyses.

Additionally, the following adulthood measures of fat and lean mass and central adiposity were measured on 405 participants in the research clinic: body composition (percent body fat, fat mass, and lean mass) measured by leg-to-leg bioimpedance (Tanita TBF 300; Tanita Corp., Tokyo, Japan) and waist (midway between lower ribs and iliac crests in relaxed exhalation) and hip (point of maximum circumference) circumferences. Circumference values were based on the mean of two measures. Fat mass and lean mass indices were defined as fat mass/height (kg/m^2) and lean mass/height (kg/m^2), respectively. Overall, 385 (30%) participants with these adiposity measures had complete data for multivariable analyses.

IGF and insulin resistance measurements

The IGF outcomes were IGF-I, IGF-II, IGFBP-2, IGFBP-3, and the molar ratio IGF-I:IGFBP-3 (a measure of the biological availability of IGF-I). Full details of how the blood samples were processed and stored have been provided in a previous publication (43). As reported in detail previously, there was evidence that storage time was associated with mean levels of IGF-II (43), but controlling for length of storage time or restricting to the clinic samples made no material difference to the results for IGF-II for this, or previous (43), analyses. A total of 370 participants in the clinic follow-up provided blood samples after fasting for 6 h or more, whereas the 323 participants whose blood was sent by post were not asked to fast.

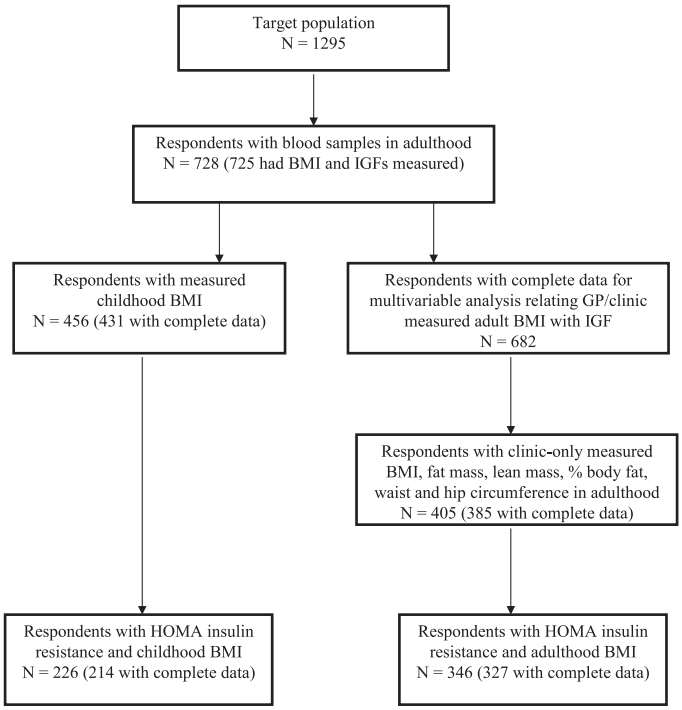

FIG. 1. Description of study numbers: target population, respondents with blood samples, numbers with measures of adiposity in childhood and adulthood, and numbers with complete data for multivariable analysis who were included in the final analyses.

Serum IGF-I, IGF-II, and IGFBP-3 levels were measured using in-house double-antibody RIAs as previously described (44). IGFBP-2 was measured by one-step sandwich ELISA (DSL-10–7100; Diagnostic Systems Laboratories, Webster, TX). 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 (40,000/7,500).

Among fasted clinic participants, insulin resistance was estimated according to the homeostasis model assessment (HOMA) as the product of fasting glucose (mmol/liter) and insulin (μU/ml) divided by the constant 22.5 (45). HOMA scores were not calculated for subjects with a fasting glucose of at least 7 mmol/liter or those with diagnosed diabetes because the results are inaccurate in these groups (45). Thus, 346 individuals were included in the adulthood BMI analysis and 226 in the childhood BMI analysis in relation to insulin resistance (327 and 214, respectively, in multivariable analyses) (Fig. 1).

Statistical analyses

Relationships of childhood or adulthood BMI with the insulin-IGF system in adulthood were assessed using multiple linear regression. We calculated robust SE to account for lack of independence between observations within families (46). Adiposity measures were expressed as z-scores, internally age and sex standardized for childhood BMI (40, 41) and sex standardized for our measures of adulthood adiposity (BMI, fat mass index, lean mass index, percent body fat, waist circumference, and waist-hip ratio). The regression coefficients show the change in IGF and IGFBP levels per SD increase in adiposity and are thus directly comparable. IGFBP-2 and HOMA insulin resistance values were highly positively skewed and were $\log_e$ transformed; thus, the compound percent change in IGFBP-2/HOMA insulin resistance per SD increase in adiposity measure is given.

Basic models control for age at adult examination, sex, and clinic-obtained *vs.* posted blood sample. The fully adjusted models control for the following variables, categorized as fully described in a previous publication (43): per capita household food expenditure in childhood, social class in childhood determined from the occupation of the head of the household, social class in adulthood, smoking, alcohol consumption, and exercise.

The impact of growth trajectory since childhood on IGF levels was demonstrated by computing mean IGF levels in a 3 × 3 matrix of childhood BMI tertiles by tertiles of adulthood BMI. Tests for trend across tertiles of adult BMI for each childhood BMI tertile (and vice versa) were based on fully adjusted regression models with tertiles of BMI in adulthood and in childhood, respectively, entered as continuous variables. We carried out likelihood ratio tests for interactions with sex, age at BMI measurement in childhood [defined *a priori* as in previous analyses (40, 43) as <8 (prepubertal) or ≥8 yr (may have entered puberty)] and for the interaction of childhood BMI tertiles with tertiles of adulthood BMI. All analyses were conducted using Stata 9.2 (Stata Corp., College Station, TX).

Results

The mean ages of the study participants were 6 yr at childhood measurement and 71 yr at follow-up (Table 1). There was no evidence that the 728 participants who provided blood samples differed from those eligible participants who did not (n = 567) in terms of childhood or adulthood BMI (43). Overall, BMI in childhood was not correlated with indices of fat mass in adulthood ($r < 0.05$) and was weakly correlated with adult lean mass and BMI (r = 0.18 and 0.12,

TABLE 1. Selected characteristics of the studied population by sex

Variable	Men		Women	
	n	Mean (SD)	n	Mean (SD)
Childhood measures				
Age at examination (yr)	332	6.6 (4.3)	396	6.3 (4.3)
z-score for BMI in childhood	196	0.022 (1.00)	260	−0.043 (1.00)
Adulthood measures				
Age at examination (yr)	332	71.3 (4.4)	396	71.0 (4.4)
Clinic-measured BMI in adulthood (kg/m^2)	182	27.3 (3.8)	223	27.6 (4.9)
GP-measured BMI in adulthood (kg/m^2)	148	26.7 (3.6)	173	27.7 (4.9)
Fat mass index (kg/m^2)	182	7.9 (2.7)	223	10.6 (3.2)
Fat-free mass index (kg/m^2)	182	19.5 (1.6)	223	16.9 (2.0)
Body fat (%)	182	27.9 (6.4)	223	37.8 (5.5)
Waist circumference (mm)	182	961.6 (117.5)	223	864.4 (122.0)
Waist-hip ratio	182	0.970 (0.076)	222	0.862 (0.076)
IGF-I (ng/ml)	332	135.7 (41.6)	395	121.4 (40.1)
IGF-II (ng/ml)	332	623.6 (222.0)	394	708.0 (232.3)
IGFBP-2 (ng/ml)[a]	332	484.2 (262.1)	395	481.2 (292.8)
IGFBP-3 (ng/ml)	332	3940.5 (950.6)	395	4270.2 (1063.1)
IGF-I/IGFBP-3 molar ratio	332	0.185 (0.042)	395	0.154 (0.042)
HOMA insulin resistance[a]	148	2.57 (1.82)	198	2.21 (1.56)

[a] Geometric mean and logged SD.

respectively) (Table 2), although correlations of BMI in children at least 8 yr of age with adulthood fat mass and waist circumference were stronger (r = 0.12). IGF-I was weakly positively correlated with HOMA insulin resistance scores (r = 0.16), waist circumference (r = 0.17), and waist-hip ratio (r = 0.22), whereas IGF-II was positively associated with percent body fat and fat mass index (r = 0.25 and 0.21, respectively). IGF-II was weakly positively associated with adult BMI (r = 0.13) but was weakly negatively associated with BMI measured in childhood (r = −0.13). IGFBP-2 was inversely related to adulthood measures of HOMA insulin resistance (r = −0.38), BMI (r = −0.43), percent body fat (r = −0.34), fat mass index (r = −0.41), lean mass index (r = −0.24), waist circumference (r = −0.42), and waist-hip ratio (r = −0.31). Adulthood IGFBP-2 was, however, weakly positively correlated with BMI measured in childhood (r = 0.10).

Age-, sex-, and sample-type-adjusted mean IGF measures across quartiles of BMI in childhood and in adulthood are given in Table 3. No associations of childhood BMI were seen with adulthood levels of IGF-I, IGF-II, IGFBP-3, the molar ratio IGF-I/IGFBP-3, or HOMA insulin resistance. IGFBP-2 was weakly positively associated with childhood BMI (*P* for linear trend = 0.12). In adulthood, there was no evidence of a linear association of BMI with IGF-I. IGFBP-2 was strongly and inversely associated with adult BMI (*P* for linear trend < 0.001), whereas HOMA insulin resistance was strongly and positively associated with adult BMI (*P* for linear trend < 0.001). IGF-II was positively associated with adult BMI (*P* for linear trend = 0.03). There was no evidence that adult BMI was associated with IGFBP-3 or the IGF-I/IGFBP-3 molar ratio.

In fully adjusted models, there was weak evidence that childhood BMI was inversely associated with adult levels of IGF-I (*P* for trend = 0.09) and IGFBP-3 (*P* for trend = 0.13) (Table 4). Inverse associations of childhood BMI with IGF-I (*P* for interaction = 0.07) and IGFBP-3 (*P* for interaction = 0.04) in adulthood were observed for BMI measured aged less than 8 yr but not aged 8 yr or more. In fully adjusted models, IGFBP-2 was weakly and positively associated with childhood BMI (*P* for trend = 0.16), but it was strongly and inversely associated with adulthood BMI (*P* < 0.001), even after additionally controlling for IGF-I or IGF-II. An inverse

TABLE 2. Pearson's correlations between the IGF system, HOMA insulin resistance, and measures of adiposity (n = 225 with all measures)

	IGF-I	IGF-II	IGFBP-2[a]	IGFBP-3	IGF-I/IGFBP-3	HOMA[a]	Child BMI	Adult BMI	% Fat	FMI	LMI	Waist circumference	WHR
IGF-I	1.00												
IGF-II	0.27	1.00											
IGFBP-2[a]	−0.22	−0.31	1.00										
IGFBP-3	0.49	0.53	−0.27	1.00									
IGF-I/IGFBP-3	0.73	−0.07	−0.04	−0.21	1.00								
HOMA[a]	0.16	0.14	−0.38	0.08	0.12	1.00							
Child BMI	0.03	−0.13	0.10	−0.06	0.10	−0.01	1.00						
Adult BMI	0.00	0.13	−0.43	0.07	−0.05	0.52	0.12	1.00					
% Fat	−0.11	0.25	−0.34	0.16	−0.23	0.22	−0.06	0.59	1.00				
FMI	−0.08	0.21	−0.41	0.12	−0.17	0.39	0.04	0.85	0.91	1.00			
LMI	0.12	−0.07	−0.24	−0.03	0.16	0.43	0.18	0.68	−0.19	0.19	1.00		
Waist circumference	0.17	0.05	−0.42	0.01	0.17	0.57	0.04	0.77	0.25	0.52	0.72	1.00	
WHR	0.22	−0.01	−0.31	−0.05	0.27	0.47	−0.03	0.42	−0.06	0.15	0.59	0.86	1.00

FMI, Fat mass index; LMI, lean mass index; WHR, waist-hip ratio.
[a] Based on log-transformed values.

TABLE 3. Levels of IGF-I, IGF-II, IGFBP-2, IGFBP-3, and HOMA insulin resistance in relation to quartiles of BMI in childhood and adulthood

	Quartiles of BMI z-scores				Per 1 SD increase (95% CI)	*P* linear trend
	1 (low)	2	3	4 (high)		
Childhood BMI (n = 456)						
IGF-I (ng/ml)	128.4	126.3	125.1	125.2	−1.3 (−5.2 to 2.6)	0.5
IGF-II[a] (ng/ml)	668.1	654.8	678.7	639.9	−11.6 (−28.9 to 5.7)	0.2
IGFBP-2[b] (ng/ml)	423.3	398.7	425.6	457.3	3.8% (−1.0 to 8.7%)	0.12
IGFBP-3 (ng/ml)	4123.9	4099.7	4012.0	4044.2	−58.0 (−152.6 to 36.7)	0.2
IGF-I/IGFBP-3 molar ratio	0.168	0.164	0.169	0.167	0.0011 (−0.0030 to 0.0051)	0.6
HOMA insulin resistance[b,c]	1.90	1.90	1.90	1.74	−4.5% (−11.3 to 2.8%)	0.2
Adulthood BMI (n = 405)						
IGF-I (ng/ml)	130.9	131.9	135.6	127.1	−2.2 (−6.0 to 1.7)	0.3
IGF-II (ng/ml)	687.8	749.3	772.0	776.8	23.1 (1.8 to 44.4)	0.03
IGFBP-2[b] (ng/ml)	588.1	445.4	352.1	309.8	−19.9% (−23.9 to −15.7%)	<0.001
IGFBP-3 (ng/ml)	3959.6	4175.5	4323.8	4093.6	15.0 (−86.7 to 116.6)	0.8
IGF-I/IGFBP-3 molar ratio	0.178	0.170	0.169	0.171	−0.0026 (−0.0076 to 0.0024)	0.3
HOMA insulin resistance[b,c]	1.34	1.60	2.21	3.06	32.3% (24.5 to 40.5%)	<0.001

All values are standardized for age, sex, and sample type. Confidence intervals (95% CI) are based on robust SE because of the hierarchical data structure.

[a] n = 455 for childhood BMI analysis because of insufficient blood volume in one sample.

[b] Geometric means in each quartile and compound percentage increase per 1 SD increase in IGFBP-2/HOMA is reported.

[c] n = 226 for childhood BMI and 346 for adulthood BMI analyses, based only on those who attended the research clinic and were both fasted and not diabetic.

association of childhood BMI with HOMA insulin resistance was strengthened (*P* for trend = 0.045), whereas the strong positive association of BMI in adulthood with insulin resistance ($P < 0.001$) was not altered in the fully adjusted models.

Among 327 participants with data on BMI in adulthood, and levels of both IGFBP-2 and HOMA insulin resistance, the association of BMI in adulthood with IGFBP-2 was attenuated by 33% (coefficients changed from −22.1 to −14.9%) but remained statistically significant ($P < 0.001$) when HOMA insulin resistance was added to the fully adjusted model. The association of BMI in adulthood with HOMA insulin resistance was attenuated by 31% (coefficients changed from −38.8 to 26.9%) but remained statistically significant ($P < 0.001$) in a model additionally controlling for IGFBP-2.

There was little evidence that childhood or adulthood BMI associations with any of the measured components of the IGF system differed by sex (*P* for interaction > 0.10). Effect estimates based on all 682 respondents with adult BMI, measured by either the GP or in the research clinic, were similar to those based only on those with clinic measures.

Table 5 shows associations of fat mass, lean mass, waist-hip ratio, and waist circumference in adulthood with the insulin-IGF system among 385 participants with available data for multivariable analysis. There was no evidence that IGF-I was associated with fat mass or central adiposity, although there was an inverse association with lean mass in fully adjusted models ($P = 0.03$). IGF-II was strongly and positively associated with fat mass and central adiposity

TABLE 4. Change in measure of the IGF system and HOMA insulin resistance (95% CI) per SD change in BMI in childhood and adulthood

	Change (95% CI) in growth factor levels per 1 SD increase in BMI					
	Basic model	*P* linear trend	*P* nonlinearity	Fully adjusted model	*P* linear trend	*P* nonlinearity
Childhood (n = 431)						
IGF-I (ng/ml)	−2.9 (−6.6 to 0.9)	0.14	0.9	−3.4 (−7.3 to 0.5)	0.09	0.9
IGF-II (ng/ml)[a]	−14.0 (−32.0 to 4.1)	0.13	0.4	−12.4 (−30.5 to 5.7)	0.18	0.6
IGFBP-2[b] (ng/ml)	4.1% (−0.8% to 9.2%)	0.10	0.3	3.4% (−1.4% to 8.5%)	0.16	0.4
IGFBP-3 (ng/ml)	−83.6 (−180.0 to 12.7)	0.09	0.9	−75.1 (−172.1 to 21.9)	0.13	0.6
IGF-I/IGFBP-3 molar ratio	−0.0001 (−0.0042 to 0.0040)	0.9	0.6	−0.0009 (−0.0050 to 0.0032)	0.7	0.3
HOMA insulin resistance[b,c]	−5.5% (−12.3% to 1.9%)	0.14	0.8	−8.0% (−0.2% to −15.1%)	0.045	0.7
Adultdhood (n = 385)						
IGF-I (ng/ml)	−2.7 (−6.7 to 1.3)	0.18	0.3	−2.7 (−6.7 to 1.3)	0.19	0.4
IGF-II (ng/ml)	21.2 (−0.5 to 43.0)	0.06	0.5	17.6 (−3.7 to 38.9)	0.10	0.3
IGFBP-2[b] (ng/ml)	−20.1% (−24.1% to −15.9%)	<0.001	0.4	−21.2% (−24.9% to −17.2%)	<0.001	0.7
IGFBP-3 (ng/ml)	2.7 (−103.3 to 108.7)	0.9	0.07	27.6 (−79.9 to 135.1)	0.6	0.16
IGF-I/IGFBP-3 molar ratio	−0.0029 (−0.0080 to 0.0023)	0.3	0.6	−0.0037 (−0.0092 to 0.0018)	0.18	0.7
HOMA insulin resistance[b,c]	38.3% (28.6% to 48.8%)	<0.001	0.4	38.8% (28.9% to 49.6%)	<0.001	0.9

All values are standardized for age, sex, and sample type. Fully adjusted models control additionally for social class of head of household in childhood, social class in adulthood, smoking, alcohol consumption, and exercise. Confidence intervals (95% CI) are based on robust SE because of the hierarchical data structure.

[a] n = 430 because of insufficient blood volume.

[b] Coefficient is compound percent increase in BMI per 1 SD increase in IGFBP-2/HOMA.

[c] n = 214 in childhood and 327 in adulthood.

TABLE 5. Association of measures of fat mass, lean mass, and central adiposity in adulthood with IGF-I, IGF-II, IGFBP-2, IGFBP-3 (n = 385), and HOMA (n = 327)

	Change (95% CI[a]) in growth factor levels per SD increase in adiposity measure					
	IGF-I (ng/ml)	IGF-II (ng/ml)	IGFBP-2 (ng/ml)[b]	IGFBP-3 (ng/ml)	IGF-I/IGFBP-3 ratio	HOMA[b]
Fat mass index (g)						
Basic model	−1.7 (−5.7 to 2.4), $P = 0.4$	29.5 (7.2 to 51.9), $P = 0.01$	−21.1% (−25.0% to −17.0%), $P < 0.001$	17.4 (−94.7 to 129.5), $P = 0.8$	−0.002 (−0.007 to 0.003), $P = 0.4$	39.7% (29.9 to 50.1%), $P < 0.001$
Fully adjusted model	−1.4 (−5.5 to 2.8), $P = 0.5$	26.1 (4.6 to 47.6), $P = 0.02$	−22.5% (−26.2% to −18.6%), $P < 0.001$	43.9 (−72.0 to 159.8), $P = 0.5$	−0.003 (−0.008 to 0.003), $P = 0.4$	40.4% (30.4 to 51.1%), $P < 0.001$
Lean mass index (g)						
Basic model	−4.0 (−7.9 to −0.1), $P = 0.05$	4.4 (−18.2 to 27.0), $P = 0.7$	−14.5% (−18.9% to −9.8%), $P < 0.001$	−21.0 (−126.3 to 84.2), $P = 0.7$	−0.004 (−0.009 to 0.001), $P = 0.13$	28.6% (19.4 to 38.5%), $P < 0.001$
Fully adjusted model	−4.3 (−8.3 to −0.4), $P = 0.03$	0.5 (−22.0 to 22.9), $P = 0.9$	−14.9% (−19.2% to −10.4%), $P < 0.001$	−2.3 (−108.2 to 103.5), $P = 0.9$	−0.005 (−0.010 to 0.000), $P = 0.06$	28.0% (18.8 to 38.0%), $P < 0.001$
Body fat (%)						
Basic model	0.5 (−3.6 to 4.7), $P = 0.8$	39.0 (17.8 to 60.2), $P < 0.001$	−21.7% (−25.1% to −18.1%), $P < 0.001$	63.6 (−47.3 to 174.5), $P = 0.3$	−0.001 (−0.007 to 0.004), $P = 0.6$	34.7% (25.8 to 44.2%), $P < 0.001$
Fully adjusted model	1.0 (−3.4 to 5.4), $P = 0.7$	35.6 (14.8 to 56.3), $P = 0.001$	−22.8% (−26.2% to −19.3%), $P < 0.001$	82.1 (−33.2 to 197.3), $P = 0.16$	−0.001 (−0.007 to 0.005), $P = 0.6$	34.9% (25.9 to 44.6%), $P < 0.001$
Waist-hip ratio						
Basic model	1.4 (−2.6 to 5.4), $P = 0.5$	33.2 (13.7 to 52.7), $P = 0.001$	−21.1% (−24.9% to −17.0%), $P < 0.001$	85.3 (−5.4 to 176.1), $P = 0.07$	−0.001 (−0.006 to 0.004), $P = 0.7$	37.5% (28.7 to 46.8%), $P < 0.001$
Fully adjusted model	1.9 (−2.2 to 6.1), $P = 0.4$	30.0 (9.4 to 50.5), $P = 0.004$	−22.6% (−26.5% to −18.6%), $P < 0.001$	105.0 (6.3 to 203.7), $P = 0.04$	−0.001 (−0.006 to 0.004), $P = 0.7$	36.7% (27.6 to 46.5%), $P < 0.001$
Waist circumference (mm)						
Basic model	−1.0 (−5.2 to 3.2), $P = 0.6$	30.1 (8.3 to 52.0) $P = 0.007$	−21.9% (−25.6% to −18.0%), $P < 0.001$	41.0 (−65.4 to 147.5), $P = 0.4$	−0.002 (−0.007 to 0.003), $P = 0.4$	43.1% (33.6 to 53.3%), $P < 0.001$
Fully adjusted model	−0.7 (−5.0 to 3.6), $P = 0.7$	23.8 (1.8 to 45.8), $P = 0.03$	−23.2% (−26.7% to −19.6%), $P < 0.001$	65.1 (−44.7 to 174.9), $P = 0.2$	−0.003 (−0.008 to 0.003), $P = 0.4$	43.8% (34.1 to 54.1%), $P < 0.001$

Basic models control for age, sex, and sample type. Fully adjusted models control additionally for social class of head of household in childhood, social class in adulthood, smoking, alcohol consumption, and exercise.

[a] Confidence intervals (CI) are based on robust SE because of the hierarchical data structure.

[b] Coefficient is compound percent increase in adiposity measure per 1 SD increase in IGFBP-2/HOMA.

measures (all $P < 0.04$) but not lean mass ($P = 0.9$). IGFBP-2 was strongly inversely associated with fat mass, lean mass, and central adiposity measures ($P < 0.001$), although the magnitude of the lean mass association was about 35% less than the magnitude of the fat mass and central adiposity associations. There was weak evidence that IGFBP-3 was positively associated with waist-hip ratio ($P = 0.04$) and percent body fat ($P = 0.16$).

Table 6 demonstrates that current levels of adiposity had the largest impact on IGFBP-2 levels when compared with childhood adiposity. Irrespective of BMI in childhood, the heaviest adults had the lowest IGFBP-2 levels (P for linear trend all < 0.001). In contrast, for participants who were relatively lean as adults (*i.e.* the low and mid tertiles of adult BMI), the highest IGFBP-2 levels were among the heavier children (P trend = 0.02 and 0.01, respectively). The effect of childhood BMI on IGFBP-2 was attenuated among those who became the heaviest adults ($P = 0.2$), although there was little statistical evidence that child BMI-IGFBP-2 effect estimates differed by tertile of adulthood BMI (P for interaction = 0.3). The lowest levels of IGFBP-2 in adulthood were observed in those who were thinnest in childhood and were heaviest in adulthood (geometric mean = 323.2 ng/ml), whereas the highest levels were in those who were heaviest in childhood and were thinnest in adulthood (geometric mean = 646.9 ng/ml). The opposite pattern was seen with respect to HOMA insulin resistance, and here there was borderline evidence ($P = 0.09$) that associations of childhood BMI with HOMA differed according to adult BMI.

Discussion

Childhood BMI was weakly inversely associated with levels in adulthood of IGF-I, IGFBP-3, and insulin resistance. There was little evidence that BMI in childhood was related to IGF-II or the molar ratio IGF-I/IGFBP-3. Current levels of adiposity, particularly fat mass and central measures, were strongly inversely associated with IGFBP-2 and positively associated with HOMA insulin resistance. In contrast, the heaviest children had the highest levels of IGFBP-2 and lowest levels of insulin resistance in adulthood; these associations were particularly evident among lean adults, suggesting that the influence of becoming overweight or obese in adulthood overshadows the effects of childhood adiposity. As in previous reports, IGFBP-2 was inversely associated with insulin resistance (13, 25, 34–36, 47, 48). Mutual adjustment of adult BMI-IGFBP-2 associations for HOMA insulin resistance, and vice versa, attenuated effects estimates by around 30%, but they remained statistically significant. There were strong positive associations of IGF-II with measures of current fat mass and central adiposity, and again there were indications for opposite associations with BMI measured in childhood that were overshadowed by the dominant effect of concurrent adiposity in adulthood.

Previous analyses of the Boyd Orr cohort demonstrated positive associations of energy intake and obesity in childhood with cancer in adulthood (40, 50). Given that IGF-I levels are positively associated with overnutrition (5), childhood adiposity (26–30), and the later development of some cancers (51), we had speculated that raised IGF-I levels in adulthood could underlie associations of childhood adiposity and energy intake with cancer. In contrast, our results are in line with others indicating inverse associations of adiposity measured in childhood (11, 16) or early adulthood (8) with IGF-I or the molar ratio IGF-I/IGFBP-3 measured later in life. A decline in total IGF-I levels with increased adiposity is biologically plausible because GH levels decrease with increased BMI in healthy individuals (52) as well as being depressed in obesity states (5). In line with many others,

TABLE 6. IGF-I, IGF-II, IGFBP-2, IGFBP-3, and HOMA insulin resistance according to BMI in childhood and adulthood

BMI in childhood	Adult BMI			*P* for trend
	Lowest tertile	Mid tertile	Highest tertile	
IGF-I (ng/ml)				
Lowest tertile	121.8 (n = 70)	138.6 (n = 54)	125.1 (n = 28)	0.6
Mid tertile	115.3 (n = 42)	125.4 (n = 52)	127.3 (n = 56)	0.3
Highest tertile	121.9 (n = 39)	131.0 (n = 48)	127.2 (n = 65)	0.8
P for trend	0.3	0.4	0.5	
P for interaction[a]		0.8		
IGF-II (ng/ml)				
Lowest tertile	630.5 (n = 70)	680.5 (n = 54)	764.4 (n = 28)	0.19
Mid tertile	679.6 (n = 42)	664.8 (n = 52)	656.5 (n = 56)	0.8
Highest tertile	594.0 (n = 39)	665.7 (n = 48)	656.8 (n = 65)	0.16
P for trend	0.07	0.9	0.12	
P for interaction[a]		0.18		
IGFBP-2 (ng/ml)[b]				
Lowest tertile	531.6 (n = 70)	373.7 (n = 54)	323.2 (n = 28)	<0.001
Mid tertile	582.8 (n = 42)	358.0 (n = 52)	331.2 (n = 56)	<0.001
Highest tertile	646.9 (n = 39)	462.4 (n = 48)	355.4 (n = 65)	<0.001
P for trend	0.02	0.01	0.2	
P for interaction[a]		0.3		
IGFBP-3 (ng/ml)				
Lowest tertile	4067.7 (n = 70)	4171.6 (n = 54)	4198.1 (n = 28)	0.7
Mid tertile	3878.8 (n = 42)	4099.3 (n = 52)	4168.4 (n = 56)	0.10
Highest tertile	3756.9 (n = 39)	4147.6 (n = 48)	4099.0 (n = 65)	0.3
P for trend	0.03	0.8	0.6	
P for interaction[a]		0.8		
HOMA insulin resistance[b]				
Lowest tertile	1.49 (n = 31)	2.09 (n = 30)	2.60 (n = 17)	0.02
Mid tertile	1.16 (n = 22)	1.99 (n = 23)	3.25 (n = 23)	<0.001
Highest tertile	1.25 (n = 24)	1.47 (n = 29)	2.68 (n = 27)	<0.001
P for trend	0.2	<0.001	0.8	
P for interaction[a]		0.09		

Data in adulthood are based on both clinic- and GP-measured BMI because our sensitivity analysis showed that the main effects were similar with and without GP measures, but numbers by tertiles were too small if GP measures were excluded. Numbers are means. Numbers of cases are shown in *parentheses*. *P* values are based on fully adjusted regression models with tertiles of BMI in childhood and in adulthood as continuous variables.

[a] Tests hypothesis that associations of childhood BMI with IGF levels differ by tertiles of adult BMI.

[b] Geometric means.

however, we found no evidence that adiposity in adulthood was associated with current levels of IGF-I (17–25). Overall, our data do not support the hypothesis that positive associations of energy intake or obesity in childhood with cancer risk in adulthood are mediated by a long-term positive influence of childhood BMI on IGF-I levels.

IGFBP-2 is the second most abundant binding protein in serum (53), and is regulated differently from IGFBP-3 as indicated by a correlation coefficient between these two binding proteins in Boyd Orr adults of −0.27. It is well known that chronic dietary restriction (long-term fasting, anorexia, or protein-calorie malnutrition) increases circulating IGFBP-2 but decreases serum IGFBP-3 (5). Our data are in line with reports indicating inverse associations of IGFBP-2 with current adiposity (13, 19, 25, 31–33) and insulin levels (25, 34–36). Additionally, we demonstrated that the current adiposity-IGFBP-2 association remained after controlling for HOMA insulin resistance, although effect estimates were attenuated by 33%. Given likely measurement error, this model must be interpreted cautiously. Nevertheless, if IGFBP-2 partly reflects unmeasured insulin resistance, it could act as a useful additional parameter in the assessment of metabolic syndrome that is relatively stable to day-to-day fluctuations and does not require pretest fasting. Alternatively, there could be other obesity-related regulators of IGFBP-2, including IGF-I and IGF-II (both of which were inversely correlated with IGFBP-2; r = −0.22 and −0.31, respectively). Controlling BMI-IGFBP-2 associations for IGF-I or IGF-II, however, did not make any difference to effect estimates. Prospective studies would determine whether IGFBP-2 is associated with later disease independent of obesity or insulin resistance.

The positive associations of IGFBP-2 and insulin sensitivity with childhood BMI are counterintuitive because childhood adiposity is positively associated with insulin levels in adolescence and young adulthood (3, 4) and insulin is thought to inhibit the hepatic synthesis of IGFBP-2 (5, 54). In animal models, the GH-neuroendocrine axis can be altered by transient events in early life (55), and previous population-based reports by our group (including one randomized trial of milk-supplemented diets) (56) and others have shown that nutritional exposures in childhood that would be expected to increase (or decrease) circulating IGF-I levels in cross-section are associated with an opposite effect in adulthood (56–58) (Martin, R. M., J. Holly, N. Middleton, G. Davey Smith, D. Gunnell, submitted for publication). These studies are compatible with a nutritionally stimulated increase in hepatic IGF-I production, which then suppresses pituitary GH output with a long-term resetting of the GH-neuroen-

docrine axis resulting in lower IGF-I levels in adulthood (56–59).

The positive childhood BMI-IGFBP-2 and BMI-insulin sensitivity associations were seen only in lean adults. We speculatively propose that overweight children, during a sensitive window of development (60), may adapt to the metabolic effects of high levels of adiposity in anticipation of relative adiposity in adult life, such that they synthesize greater quantities of IGFBP-2 and are less insulin resistant in later life than adults who were leaner in childhood. Such an adaptation could theoretically occur by a long-term resetting of the pituitary threshold levels for secreting GH, because greater adiposity suppresses hepatic production of IGFBP-1 and IGFBP-2 (13, 19, 25, 31–33), increasing free, bioactive IGF-I (34), which feeds back to the hypothalamus to reduce GH secretion, in turn stimulating glucose uptake, increasing IGFBP-2 (54), and improving insulin sensitivity (24). Insulin resistance, however, eventually develops and then increases progressively over time if obesity persists for a prolonged period (24). Thus, this adaptation may not hold at very high levels of overweight persisting into adulthood because of the dominant effect of concurrent insulin resistance. Our hypothesis is analogous to a classic example of developmental plasticity in which rats fed high-fat, high-cholesterol postweaning diets had 60% lower serum cholesterol concentrations at 32 wk of age (61). This hypothesis might also explain the observations from this study, albeit of borderline statistical significance, and others of inverse relationships of childhood BMI with IGF-I and IGFBP-3 in adulthood (11, 16), which are a reversal of previously reported positive associations of childhood BMI with IGF-I and IGFBP-3 in cross-section (5, 26–30). It is possible that such programming effects may underlie inverse associations of childhood BMI with breast cancer risk observed in a Danish birth cohort (62) and with risk of proliferative benign breast disease in the Nurses Health Study II (63).

Our finding that IGF-II is positively associated with current fat mass and central adiposity is in line with previous cross-sectional studies (31, 64) and a recent report of positive associations of IGF-II with BMI and with the amount of fat in breast tissue, as assessed by the translucent area on mammography (65). In a cross-sectional study of normal children, although IGF-I levels correlated with height and fat-free mass, levels of IGF-II were more closely correlated with fat mass (28). However, in prospective studies, IGF-II has been inversely associated with obesity and weight gain (66, 67). Again, there was an indication that the association of adult IGF-II with measured BMI in childhood was in the opposite direction to its association with concurrent BMI measured in adulthood, although this association was overshadowed by a dominant effect of the latter. This may indicate that excess weight gain early in life (in people who are lean as adults) is associated with low IGF-II levels, but adiposity itself increases IGF-II levels, and sustained weight gain is therefore associated with high IGF-II levels. In contrast to IGF-I, however, very little is known regarding the regulation of IGF-II throughout adult life.

The findings could have implications for health. IGFBP-2 has been inversely associated with postmenopausal breast cancer (13) and colon cancer (68). Insulin resistance and IGF-II are associated with increased risk of some cancers (69, 70). Future studies should elucidate the relative roles of IGFBP-2, insulin resistance, and IGF-II in obesity-related chronic disease.

Strengths and limitations

The major strength of this study is the measurement of BMI in childhood that could be related prospectively to IGFs and IGFBPs 65 yr later. There are five main limitations. First, childhood BMI is only a proxy for adiposity, and in our study, childhood BMI was correlated more strongly with lean mass than fat mass in adulthood. Second, when the participants were children in the 1930s, their dietary patterns and activity levels would not have been comparable to those of children today and may have been further influenced by rationing during and after the Second World War. In Boyd Orr, only 4% of participants were categorized as overweight and 0.2% as obese in childhood, compared with more recent figures of around 10% overweight and 1% obese in British growth surveys using identical thresholds (49). Thus, the results for the childhood measures may not be generalizable to current childhood adiposity, although the adult data are contemporary. Third, it is possible that in older populations, adiposity-BMI associations are disrupted by the known age-related decline in IGF-I levels or are masked by other age-related confounding factors. Fourth, free IGF-I has been shown to be increased in obesity in the presence of low-normal total IGF-I (36, 64), but we did not directly measure free IGF-I. The interpretation of free IGF-I is limited because of the known ability of IGFBPs to enhance IGF actions in some situations. The molar ratio IGF-I/IGFBP-3 used here is considered a marker of the biological availability of IGF-I. Finally, the studied sample represented one third of the eligible population. However, those studied were representative of nonresponders in terms of BMI in both childhood and adulthood, effect estimates were the same in our sensitivity analyses using GP- as well as clinic-based adult measures of BMI, and it seems unlikely that adiposity-IGF associations would differ between those who did and did not participate.

Conclusion

There was only weak evidence that associations of childhood BMI with chronic disease risk may be mediated by adult IGF-I levels. Circulating IGFBP-2 in adulthood, a marker for insulin sensitivity, was inversely associated with current adiposity, but overweight children who became relatively lean adults were more insulin sensitive than thinner children. The findings may indicate predictive programming of later IGFBP-2 levels in response to the metabolic effects of childhood adiposity. This suggests that childhood adiposity may not impact on adult levels of insulin resistance to the extent predicted from cross-sectional associations with obesity in adulthood. Because IGFBP-2 is inversely associated with both adiposity and insulin resistance, this protein could offer a nonfasting assessment of the metabolic syndrome and hyperinsulinemia-related cardiovascular risk. Furthermore, IGFBP-2 may have an important role in obesity and insulin-related carcinogenesis. Studies are required on the prospec-

tive associations of IGFBP-2 with the metabolic syndrome, ischemic heart disease, and obesity-related cancer risk. The role of IGF-II in obesity-related chronic diseases also warrants additional investigation. Investigating associations of chronic disease outcomes with IGF genetic polymorphisms that alter lifelong exposure to biologically active IGF and IGFBP levels could increase our understanding of this issue (39).

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