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ORIGINAL PAPER

The relation between adiposity throughout the life course and variation in IGFs and IGFBPs: evidence from the ProtecT (Prostate testing for cancer and Treatment) study

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Abstract
Objective Adiposity is positively associated with advanced, metastatic, and fatal prostate cancer. Obesity-related variations in insulin-like growth factors (IGF-I and -II) and their binding proteins (IGFBPs) could underlie these associations.
Methods We investigated associations of adiposity throughout the life course (determined retrospectively) with serum levels of IGF-I, IGF-II, IGFBP-2 and IGFBP-3 in a population-based study of 1,106 healthy men.
Results IGF-I and IGF-II showed inverted U-shaped associations with adult body mass index (BMI) (p quadratic model = 0.04 and 0.06, respectively), although differences between quartiles with the highest and lowest IGF-I levels were small (no more than 5 ng/ml). IGFBP-2 was strongly inversely related to adult BMI (−22% change per SD increase in BMI; 95% confidence interval (CI) −24% to −19%) and waist circumference (−18% change per SD increase in waist circumference; 95% CI −20% to −15%) ($p < 0.001$). IGFBP-3 was positively related to BMI (63.5 ng/ml increase per SD increase in BMI; 95% CI −2.69 to 129.8, $p = 0.06$). IGFBP-2 and IGFBP-3 were strongly related to body shape change from childhood to adulthood, with men who gained the most weight having the lowest IGFBP-2 (9% lower per category body shape change; 95% CI −11% to −7%, $p < 0.001$) and the highest IGFBP-3 (50 ng/ml increase per category; 95% CI 8 to 92, $p = 0.02$).
Conclusions We provide evidence that adiposity and change in body shape through the life course are related to the IGF system, with the largest effect of adiposity being to lower IGFBP-2, a possible marker of insulin resistance. The results suggest that circulating IGF-I levels may not be important mediators of the association of adiposity with aggressive prostate cancer, but the role of IGFBP-2 deserves further investigation.

Keywords Adiposity · Life course · Insulin-like growth factors

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Introduction

Although prostate cancer mortality is decreasing in industrialized countries [1, 2], it has been argued that obesity, a growing epidemic that has been linked to increased risk of several cancers in men (including prostate, colorectal, esophageal and renal cancers) [3–5], has obscured a greater decline in prostate cancer mortality [6]. This is because several studies have shown that adiposity in adulthood is associated with an increased risk of prostate cancer,

particularly advanced disease [7] and prostate cancer mortality [8–17]. The evidence for localized prostate cancer is less consistent, with studies showing positive, inverse, and null associations [4, 7].

The mechanisms underlying the possible link between obesity and prostate cancer progression are not fully understood, but obesity affects many hormones and metabolic factors that may be involved in carcinogenesis. One hormone system that is modified by obesity involves insulin-like growth factors (IGF-I and -II) and their binding proteins (IGFBPs) [18–25]. IGF-I and IGF-II stimulate cell proliferation and inhibit apoptosis, and IGF-I and possibly IGF-II are associated with increased prostate cancer risk [26–28]. IGFBP-3 has been associated with a small decreased risk of prostate cancer [27], although no relationship was observed in a collaborative analysis of twelve prospective studies after adjusting for IGF-I levels [26, 27].

Studies into the relationship of adult obesity with IGFs and IGFBPs have produced mixed results. Some large cohort studies have found a non-linear association of IGF-I, with the highest levels in the mid-range of BMI and decreased IGF-I in people with the lowest and highest BMIs [18, 29–33]. Low IGF-II has been linked to increased susceptibility to weight gain [34] and associations of adiposity with IGFBP-2 are consistently inverse [19, 25, 35].

Studies reporting the association of childhood BMI with adulthood IGFs have produced intriguing results. Childhood BMI has been inversely related to adulthood IGF-I and IGFBP-3, and weakly positively associated with IGFBP-2 [19–21]. Heavy adults who were thin as children had the lowest IGFBP-2 levels and heavy children who were thin as adults had the highest IGFBP-2 [19]. These associations raise the question of whether adiposity levels at different times during the life course have particular associations with IGF-related cancers, such as prostate cancer.

Our aim was to determine whether variations in circulating IGF and IGFBP levels in relation to measures of adiposity throughout the life course could underlie observed associations of obesity with prostate cancer. To investigate this, we studied associations of adulthood body mass index (BMI), waist circumference, and change in body shape between childhood and adulthood with levels of IGFs and IGFBPs in healthy middle-aged men. Specifically, we hypothesized that if BMI and waist circumference in adulthood are positively associated with prostate cancer risk via the IGF system [4, 36, 37], then we would expect these measures of adiposity to be positively associated with IGF-I, IGF-I/IGFBP-3 molar ratio and IGF-II (because they are positively associated with prostate cancer risk) and possibly inversely associated with IGFBP-2 (because IGFBP-2 is inversely associated with insulin resistance, and insulin resistance is positively associated with prostate cancer risk) [38]. Given previous reports on associations of adiposity in childhood or change in adiposity between childhood and adulthood in relation to the IGF system [19, 20, 39, 40], we investigated whether those who gained the most weight from childhood to adulthood had the lowest IGFBP-2 levels, and the highest levels of IGF-I and IGF-II.

Methods and study participants

Study population

The study participants were controls from a case–control study nested in a population-based investigation into the detection and management of prostate cancer: the Prostate Testing for Cancer and Treatment (ProtecT) study. All participants with no evidence of prostate cancer after PSA testing, digital rectal examination, and/or biopsy were eligible to be controls in nested case–control studies of the mechanisms of prostate cancer development and progression. The study received ethical approval from Trent Multicentre Research and Ethics Committee. Detailed descriptions of ProtecT and the protocol for nested case–control selection are published elsewhere [41].

Selected sample

This analysis is nested within the ProtecT PSA-tested cohort and includes a randomly selected sample of 1,106 men who had a PSA level <3.0 ng/ml or who had a PSA between 3 and 19.9 ng/ml and a negative prostate biopsy, and who provided, with informed consent, non-fasted blood samples at the initial appointment, for research purposes.

Measures of adiposity and co-variables

At the time of recruitment, usually before the result of the PSA test was known, participants completed a self-administered diet, health and lifestyle questionnaire. Included in the questionnaire were self-reported height, weight and waist measurements. The questions were "How tall are you (feet and inches)?" and "What is your weight in light clothing (stones and pounds)?." Participants were provided with a measuring tape to measure their waist in inches and returned both their reported measurement and the tape, on which was marked their reading, for confirmation. In addition, weight was measured by trained nurses in 93% of participants. We used weight measured to the nearest 0.1 kg (including self-reported weight in the 7% of men without a nurse-measure) and self-reported height, to compute body mass index (BMI, kg/m^2), which represents general adiposity. Waist circumference was used to represent central

adiposity. In a sensitivity analysis, we assessed whether associations of BMI with IGFs and IGFBPs were similar if the 7% of men with only self-reported weight were excluded.

Participants were also asked to select from nine pictograms those most closely representing their body shape at ages 10, 20, and 40 years and current age (50–69 years) (see "Appendix", developed by Stunkard [42]). The pictograms were grouped into three categories: lean body shape (pictures 1–3), normal body shape (pictures 4–5), and overweight/obese body shape (pictures 6–9). These categories have been shown to be valid classifications of obesity and thinness in adult men [43]. The questionnaire also collected data on smoking habits, alcohol consumption, family history of prostate cancer, exercise habits, and occupation. Less than 1% of the study population comprised non-white ethnic groups and therefore we could not investigate the effect of ethnicity on associations of IGF/IGFBP levels with adiposity.

Measurement of IGFs and IGFBPs

At the prostate check clinic appointment, non-fasted blood samples were collected for research purposes using the Vacutainer® system. Samples were kept at room temperature to allow clotting and then were centrifuged at 1,640 relative centrifugal force for 20 min within 2 h of collection. Samples were transferred in a cool bag to the laboratory for processing and storage at −80°C. More than 92% of samples underwent two freeze–thaw cycles before analysis, and the remainder went through three freeze thaw cycles.

Serum samples were assayed for total IGF-I, IGF-II, IGFBP-2, and IGFBP-3 at JH's laboratory in Bristol. Serum IGF-I, IGF-II, and IGFBP-3 were measured by in-house radioimmunoassay (RIA). Serum IGFBP-2 was measured using a one-step sandwich ELISA (Diagnostic Systems Laboratories, Webster). The molar ratio of IGF-I:IGFBP-3, which may reflect tissue bioavailability, was calculated as (0.13 × IGF-I concentration in ng/ml)/(0.025 × IGFBP-3 concentration in ng/ml). Results for all peptides were based on an average of two measures.

Statistical analysis

Pearson correlation coefficients were calculated between measures of adiposity and IGF and IGFBP levels. We used linear regression to calculate age-adjusted mean IGF and IGFBP levels by participant characteristics, and computed *p*-values for heterogeneity across categories using analysis of variance.

Linear regression was used to compute age-adjusted levels of IGFs and IGFBPs according to the distribution of each adiposity measure (quartiles, or categories). Linear regression models were developed to investigate the change in each growth factor level per standard deviation increase in adiposity measure. We also investigated whether there was evidence of any quadratic relationships by including BMI^2 in the model, in addition to the linear term. We categorized BMI into quartiles to ensure even numbers in each group. Categories were 17.7–24.5, 24.5–26.8, 26.8–29.2, and 29.2–45.9 kg/m^2. These approximate to the World Health Organization classification categories of underweight/normal, low overweight, high overweight, and obese [44].

We calculated change in body shape from childhood to adulthood by subtracting the childhood body shape (9 pictograms) from current (age 50–69) body shape (9 pictograms). We categorized the resulting difference in body shape between child- and adulthood into three groups of body shape change—lost weight or gained one pictogram (−4 to +1 pictograms change), gained a small amount of weight (+2 to +3 pictograms change), and gained a large amount of weight (+4 to +7 pictograms change). These categorizations were pragmatic and made to ensure a roughly even distribution of numbers of men in each category. We also modeled change in body shape as a continuous (ordinal) variable (from −4 to +7 category change in pictogram). We tested for interaction between current body size and change in body shape (both as categorical variables) on IGF/IGFBP levels, using likelihood ratio tests. Where there was evidence of interaction, we stratified associations by current BMI (above or below the median = 26.8 kg/m^2, to ensure equal distribution of numbers of men in each stratum).

A regression model controlling for age (5 groups) was compared with models controlling for age, centre (9 centers), smoking (three categories; current smokers, ex-smokers, and never smokers) social class (three categories; working, intermediate, and managerial/professional), exercise (three groups based on weighted levels of strenuous (exercise that makes the heart beat rapidly), moderate (exercise which isn't exhausting), and light activity (exercise which requires a minimum of effort)), current alcohol consumption (five categories; never, special occasions only, lowest, middle, and upper thirds of weekly units), duration of serum sample storage (continuous variable), and reagent assay/kit number used for the IGF/IGFBP assay. Our final fully adjusted model controlled for variables that appeared to confound at least one of the adiposity-IGF/IGFBP associations (by altering the regression coefficient by ≥10%). The lowest quartiles of adiposity measure were used as the reference category. We also fitted an additional model controlling for body shape at age 10 in addition to the fully adjusted model, to investigate whether associations of change in body shape with IGF/IGFBPs were independent of childhood weight.

The distribution of IGFBP-2 was positively skewed, and we therefore report geometric means for IGFBP-2 values across categories of adiposity, and the percent change in IGFBP-2 per standard deviation increase in adiposity measure. IGF-I, IGF-II, and IGFBP-3 were approximately normally distributed. All analyses were performed using Stata 11 (Stata Corp., College Station, TX).

Results

A maximum of 1,106 subjects were included in the study: slightly different numbers of subjects were included in each analysis, based on availability of IGF and covariate data (see Fig. 1). We found evidence that age-adjusted mean IGF-II, IGFBP-2, and IGFBP-3 levels among men who had an adiposity measurement and covariate data differed from those who did not have these data and who were therefore excluded from the analysis. Mean IGF-II was 884.1 ng/ml (95% CI 863.6–904.5 ng/ml) in included subjects and 819.6 ng/ml (95% CI 793.2–846.0 ng/ml) in excluded subjects. Mean IGFBP-2 was 640.2 ng/ml (95% CI 620.0–661.1 ng/ml) in included subjects and 585.5 ng/ml (95% CI 556.0–616.6 ng/ml) in excluded subjects. Mean IGFBP-3 was 4,618 ng/ml (95% CI 4,550–4,686 ng/ml) in included subjects and 4,407 ng/ml (95% CI 4,315–4,499 ng/ml) in excluded subjects. Baseline characteristics of participants are shown in Table 1. The mean age was 61.9 years at the time of blood sampling.

BMI and waist circumference were strongly positively correlated ($r = 0.79$, $p < 0.0001$). BMI and waist circumference were negatively correlated with ln IGFBP-2 ($r = -0.48, p < 0.0001$ and $r = -0.36, p < 0.0001$, respectively) but not correlated with IGF-I, IGF-II, or IGFBP-3 ($r \leq 0.08$). IGF-I was positively correlated with IGF-II ($r = 0.28$, $p < 0.0001$) and IGFBP-3 ($r = 0.48$, $p < 0.0001$), and negatively correlated with ln IGFBP-2 ($r = -0.21, p < 0.0001$). IGF-II was negatively correlated with ln IGFBP-2 ($r = -0.23$, $p < 0.0001$) and positively correlated with IGFBP-3 ($r = 0.56$, $p < 0.0001$). There was a weak negative correlation between IGF-II and IGF-I:IGFBP-3 M ratio ($r = -0.11$, $p = 0.001$). ln IGFBP-2 and IGFBP-3 were negatively correlated ($r = -0.27$, $p < 0.0001$).

Age-adjusted mean levels of IGFs and IGFBPs according to participant characteristics are shown in Table 2. IGF-I, IGF-II, IGFBP-2, and IGFBP-3 were all strongly related to age, with IGF-I, IGF-II, and IGFBP-3 decreasing with age, and IGFBP-2 increasing with age. Body shape was inversely related to IGFBP-2 at all ages, and inversely related to IGFBP-3 levels at age 20 and 40, but positively related to IGFBP-3 at current age.

Age- and fully adjusted means (IGF-I, IGF-II, and IGFBP-3) and geometric means (IGFBP-2) and the molar ratio of IGF-I/IGFBP-3 in relation to adulthood BMI are shown in Table 3. IGF-I and IGF-II showed non-linear associations with BMI (p for quadratic model = 0.04 and 0.06, respectively), being lowest at both low and high BMIs and higher for the mid-distribution of BMI. Adjustment for potential confounders did not materially alter the

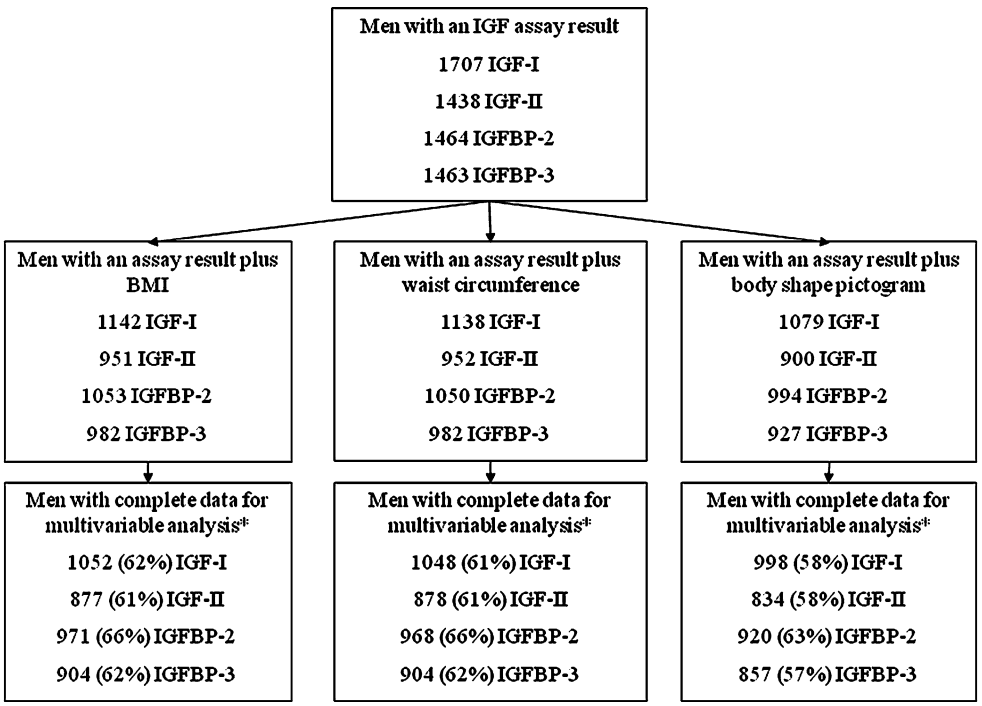

Fig. 1 Flow chart of subjects included in the analysis. Of those with an IGF assay result, fewer had had the measures of adiposity and complete covariate data. Percentages shown are the percentage of the total number of subjects with that particular IGF/IGFBP assay. *complete data for multivariable analysis includes measure of adiposity (BMI, waist circumference, or body shape change), age, centre, duration of sample storage, assay kit number, alcohol, smoking, and exercise

Table 1 Characteristics of study participants

Continuous variables	*N*	Mean	Median	SD	5th–95th percentiles
Age (years)	1,106	61.9	63.0	5.2	52–69
PSA (ng/ml)	1,106	1.5	1.1	1.7	0.3–3.9
IGF-I (ng/ml)	1,105	162.1	156.0	54.9	86–257
IGF-II (ng/ml)	926	884.1	845.5	317.1	430–1,530
IGFBP-2 (ng/ml)[a]	1,023	640.2	624.0	1.2	268–1,638
IGFBP-3 (ng/ml)	953	4,618	4,570	1,068	2,910–6,410
IGF-I/IGFBP-3 M ratio (%)	952	18.6	17.8	6.4	10.5–27.8
BMI (kg/m^2)	1,094	27.2	26.8	3.9	21.8–34.2
Waist circumference (cm)	1,091	96.1	94.3	9.9	81.3–114.3
Categorical variables	***N***	**%**			
Body shape at age 10[b]					
Lean	1,016	91.8			
Normal	46	4.2			
Overweight/obese	26	2.4			
Unknown	18	1.6			
Body shape at age 20[b]					
Lean	957	86.5			
Normal	120	10.8			
Overweight/obese	13	1.2			
Unknown	16	1.5			
Body shape at age 40[b]					
Lean	537	48.5			
Normal	504	45.6			
Overweight/obese	54	4.9			
Unknown	11	1.0			
Current body shape[b]					
Lean	276	24.9			
Normal	537	48.6			
Overweight/obese	232	21.0			
Unknown	61	5.5			
Smoking					
Current smoker	149	13.5			
Ex-smoker	580	52.5			
Never smoker	371	33.5			
Unknown	6	0.5			
Weekly exercise					
Low	184	16.6			
Moderate	291	26.3			
High	631	57.1			
Social class[c]					
Managerial/professional	524	47.4			
Intermediate	154	13.9			
Working	428	38.7			
Family history of prostate cancer (father/brother)					
Yes	55	5.0			
No	1,040	94.0			
Unknown	11	1.0			

Table 1 continued

Categorical variables	*N*	%
Current alcohol intake		
Never	51	4.6
On special occasions only	93	8.4
Lowest third (0.7–9.8 units/wk)	303	27.4
Middle third (9.9–19.6 units/wk)	323	29.2
Upper third (19.6–111.3 units/wk)	287	26.0
Unknown	49	4.4

Subjects in this table are those included in at least one analysis

[a] Geometric mean and logged SD

[b] Lean body shape <24.5 kg/m^2, normal body shape 24.5–26.8 kg/m^2, overweight/obese body shape >26.8 kg/m^2

[c] Three-class social class categorization from [65]

SD standard deviation

results. Adjusting for IGFBP-3 levels weakened the curved relationship, with the adjusted mean (95% CI) IGF-I in BMI quartiles 1–4 of 164.6 ng/ml (158.0, 171.2), 163.7 ng/ml (157.4, 170.1), 162.8 ng/ml (156.1, 169.5), and 158.7 ng/ml (152.1, 165.3), respectively (p for quadratic model = 0.47, p for linear trend = 0.21). IGFBP-2 was strongly inversely related to BMI (decrease of 22% in IGFBP-2 per standard deviation increase in BMI (95% CI: decrease of 19% to 24%), $p < 0.001$ for both linear and quadratic models). This corresponds to a 0.41 standard deviation decrease in ln IGFBP-2 for a standard deviation increase in BMI. IGFBP-3 was positively related to BMI ($p = 0.06$ for linear trend), with a 63.5 ng/ml (corresponding to a 0.06 standard deviation) increase in IGFBP-3 per standard deviation increase in BMI. The molar ratio of IGF-I/IGFBP-3 was not related to BMI. Adjustment for potential confounders attenuated the effect estimate for IGFBP-3 but the large positive association remained in the fully adjusted model.

Age- and fully adjusted means (IGF-I, IGF-II and IGFBP-3) and geometric means (IGFBP-2) and molar ratio of IGF-I/IGFBP-3 in relation to adulthood waist circumference are shown in Table 4. The associations were similar to those with BMI, but with smaller effects.

Table 5 shows the age- and fully adjusted means (IGF-I, IGF-II and IGFBP-3) and geometric means (IGFBP-2) and molar ratio of IGF-I/IGFBP-3 in relation to change in body shape between childhood and adulthood. IGF-I, IGF-II, and IGF-I/IGFBP-3 molar ratio were unrelated to body shape change ($p = 0.97$, 0.25, 0.15, respectively). IGFBP-2 was strongly inversely related to body shape change, so that men who gained the most weight had the lowest IGFBP-2, and men who lost weight or gained very little weight had the highest IGFBP-2. In a regression model, IGFBP-2 decreased by 9% per one pictogram increase in body shape from childhood to adulthood (95% CI: decrease of 7% to 11%), ($p < 0.001$). The association was stronger in a model controlling for body shape at age 10. The relationship also appeared to be independent of current body shape: controlling for current body shape; in line with this, men who were obese throughout life had mean IGFBP-2 levels of 526.1 ng/ml (95% CI: 390.6, 708.5), while men who were lean in childhood and obese as adults had the lowest mean IGFBP-2, at 468.0 ng/ml (95% CI: 439.0, 498.9), and men who had a normal body shape in childhood and were obese as adults had mean IGFBP-2 levels, at 515.1 ng/ml (95% CI:424.0, 625.7), that were intermediate between the two extreme body shape change categories.

IGFBP-3 was positively related to body shape change, with men gaining the most weight having the highest IGFBP-3, and men who lost weight or gained very little weight having the lowest IGFBP-3. IGFBP-3 increased 50.0 ng/ml per one pictogram increase in body shape ($p = 0.02$).

We found evidence of an interaction between current BMI and change in body shape for IGFBP-2 (p for interaction = 0.06) and IGFBP-3 (p for interaction = 0.05). We therefore stratified the fully adjusted analysis by current BMI, dichotomized into below or above median. For men with a current BMI below the median, IGFBP-2 decreased by 6.5% and IGFBP-3 increased by 76.8 ng/ml per one pictogram increase in body shape change. For men with a current BMI above median, IGFBP-2 decreased by 2.4% and IGFBP-3 decreased by 19.4 ng/ml per one pictogram increase in body shape. However, this result was not seen for IGFBP-2 when we stratified BMI using the World Health Organization cut-point of 25 kg/m^2 (IGFBP-2 p for interaction = 0.7) so this interaction may have arisen by chance. The sensitivity analyses excluding the

Table 2 Levels of IGFs/IGFBPs according to participant characteristics

Characteristic	Mean (SE) IGF/IGFBP (ng/ml)				
	IGF-I	IGF-II	IGFBP-2[a]	IGFBP-3	IGF-I/IGFBP-3 ratio[b]
Age group					
50–54	175.6 (5.5)	985.4 (35.9)	573.6 (0.05)	4,949 (121)	18.9 (0.7)
55–59	172.5 (3.8)	969.2 (23.9)	559.8 (0.04)	4,926 (78)	18.5 (0.5)
60–64	161.2 (3.1)	877.3 (19.5)	605.2 (0.03)	4,581 (64)	18.5 (0.4)
65–70	154.6 (2.7)	817.4 (17.4)	729.1 (0.03)	4,405 (56)	18.6 (0.3)
p heterogeneity	<0.001	<0.0001	<0.0001	<0.0001	0.97
	Age-adjusted mean (SE) IGF/IGFBP (ng/ml)				
Centre					
Sheffield	170.7 (4.4)	949.5 (26.3)	684.9 (0.04)	4,428 (88)	20.6 (0.5)
Newcastle	156.0 (4.4)	937.6 (26.8)	635.5 (0.04)	4,699 (90)	17.5 (0.5)
Bristol	151.1 (4.5)	904.8 (27.3)	626.8 (0.04)	4,758 (100)	16.9 (0.6)
Cardiff	153.5 (5.5)	915.5 (34.0)	640.6 (0.06)	4,927 (111)	16.2 (0.7)
Edinburgh	166.7 (6.7)	921.1 (44.7)	643.3 (0.07)	4,883 (150)	17.3 (0.9)
Birmingham	160.1 (10.9)	755.9 (66.7)	571.8 (0.11)	4,478 (219)	19.2 (1.3)
Leicester	166.1 (4.0)	765.1 (25.0)	645.0 (0.04)	4,562 (83)	19.3 (0.5)
Cambridge	167.3 (5.3)	834.6 (42.6)	613.5 (0.05)	4,226 (108)	20.6 (0.6)
Leeds	171.3 (5.2)	887.6 (31.3)	594.6 (0.05)	4,778 (105)	18.8 (0.6)
p heterogeneity	0.01	<0.0001	<0.0001	0.0001	<0.0001
Duration of sample storage					
<2 years	165.7 (9.9)	667.2 (184.1)	759.1 (0.30)	3,790 (615)	17.2 (3.7)
2–4 years	164.2 (2.0)	884.5 (12.7)	632.3 (0.02)	4,613 (41)	18.9 (0.2)
4+ years	157.9 (3.3)	885.7 (20.7)	642.5 (0.03)	4,674 (71)	17.9 (0.4)
p heterogeneity	0.16	0.43	0.75	0.27	0.10
Body shape at age 10[c]					
Lean	163.2 (1.8)	881.3 (11.1)	634.9 (0.02)	4,634 (37)	18.6 (0.2)
Normal	149.5 (8.5)	926.1 (54.9)	629.0 (0.08)	4,550 (175)	17.9 (1.1)
Overweight/obese	162.0 (11.3)	826.7 (75.2)	575.0 (0.10)	4,247 (247)	19.3 (1.5)
p heterogeneity	0.25	0.67	0.42	0.32	0.59
Body shape at age 20[c]					
Lean	163.0 (1.8)	887.7 (11.5)	640.7 (0.02)	4,659 (38)	18.5 (0.2)
Normal	158.5 (5.2)	847.7 (32.6)	584.2 (0.05)	4,364 (108)	19.5 (0.6)
Overweight/obese	153.2 (15.4)	735.1 (100.3)	503.9 (0.20)	4,309 (322)	18.8 (1.9)
p heterogeneity	0.65	0.15	0.05	0.02	0.25
Body shape at age 40[c]					
Lean	163.4 (2.4)	886.4 (12.3)	710.9 (0.02)	4,650 (50)	18.3 (0.3)
Normal	163.2 (2.5)	883.9 (15.9)	572.5 (0.02)	4,639 (52)	18.9 (0.3)
Overweight/obese	147.4 (8.2)	836.3 (53.3)	521.9 (0.08)	4,169 (173)	19.1 (1.0)
p heterogeneity	0.24	0.76	<0.0001	0.02	0.33
Current body shape[c]					
Lean	160.4 (3.4)	843.9 (21.7)	831.1 (0.03)	4,448 (70)	19.1 (0.4)
Normal	164.3 (2.4)	894.7 (15.3)	621.3 (0.02)	4,682 (50)	18.4 (0.3)
Overweight/obese	158.3 (3.7)	913.3 (23.9)	482.5 (0.03)	4,731 (77)	18.0 (0.4)
p heterogeneity	0.28	0.08	<0.0001	0.02	0.23
Smoking					
Current smoker	156.4 (4.6)	846.3 (28.8)	820.6 (0.04)	4,420 (95)	18.7 (0.6)
Ex-smoker	161.1 (2.4)	905.2 (15.0)	597.3 (0.02)	4,695 (50)	18.2 (0.3)

Table 2 continued

Characteristic	Mean (SE) IGF/IGFBP (ng/ml)				
	IGF-I	IGF-II	IGFBP-2[a]	IGFBP-3	IGF-I/IGFBP-3 ratio[b]
Never smoker	166.8 (2.9)	861.1 (18.4)	633.5 (0.03)	4,599 (61)	19.2 (0.3)
Unknown	188.8 (22.5)	1202.5 (129.5)	450.7 (0.20)	5,009 (475)	21.7 (2.8)
p heterogeneity	0.14	0.01	<0.0001	0.11	0.11
Weekly exercise					
Low	161.0 (4.2)	863.6 (26.1)	649.3 (0.04)	4,487 (86)	18.9 (0.5)
Moderate	162.9 (3.3)	860.1 (21.3)	602.5 (0.0)	4,597 (71)	18.7 (0.4)
High	162.9 (2.3)	900.9 (14.2)	647.0 (0.02)	4,679 (47)	18.5 (0.2)
p heterogeneity	0.92	0.17	0.26	0.11	0.84
Social class[d]					
Managerial/professional	162.3 (2.4)	871.4 (15.6)	626.8 (0.02)	4,649 (51)	18.4 (0.3)
Intermediate	169.3 (4.5)	894.0 (28.7)	603.3 (0.05)	4,606 (95)	19.5 (0.6)
Working	160.4 (2.8)	896.3 (17.5)	659.5 (0.03)	4,603 (58)	18.6 (0.3)
p heterogeneity	0.20	0.53	0.10	0.92	0.25
Family history of prostate cancer (father/brother)					
Yes	158.6 (7.5)	853.3 (45.1)	626.7 (0.07)	4,536 (149)	18.9 (0.9)
No	162.8 (1.7)	885.9 (11.1)	636.1 (0.02)	4,631 (37)	18.6 (0.2)
p heterogeneity	0.37	0.61	0.79	0.30	0.72
Current alcohol intake					
Never	161.6 (7.8)	735.3 (48.5)	656.9 (0.08)	4,348 (160)	19.6 (1.0)
On special occasions only	164.2 (5.8)	830.5 (36.2)	665.5 (0.06)	4,521 (121)	19.2 (0.7)
Lowest third (0.7–9.8 units/wk)	166.8 (3.2)	887.3 (20.2)	799.7 (0.03)	4,634 (67)	19.2 (0.4)
Middle third (9.9–19.6 units/wk)	165.1 (3.1)	887.7 (19.9)	622.8 (0.03)	4,624 (65)	19.1 (0.4)
Upper third (19.6–111.3 units/wk)	154.9 (3.3)	917.0 (19.8)	628.4 (0.03)	4,696 (66)	17.2 (0.4)
p heterogeneity	0.10	0.009	0.86	0.17	0.003

[a] Geometric mean and logged SE

[b] IGF-I/IGFBP-3 ratio expressed as %

[c] Lean body shape < 24.5 kg/m^2, normal body shape 24.5–26.8 kg/m^2, overweight/obese body shape > 26.8 kg/m^2

[d] Three-class social class categorization from [65]

SE standard error

7% of men with only self-reported weight produced no difference in the results.

Discussion

This study confirms an inverted U-shaped association of IGF-I and IGF-II with adulthood BMI. The highest levels of IGF-I and IGF-II were in the mid-range of the BMI distribution, and there were lower levels in the lowest and highest BMI categories. The relationship of IGFBP-2 (a potential marker of insulin sensitivity) with adulthood BMI and waist circumference was strongly inverse. Men who gained a large amount of weight between childhood and adulthood (i.e., an increase of +4 to +7 body shape pictograms) had the lowest circulating levels of IGFBP-2 and the highest levels of IGFBP-3. The relationship between body shape and IGFBP-3 was inverse in early-mid adulthood and then became positive in later adulthood.

The non-linear association of IGF-I with BMI has been shown in six other large cohort studies, including samples with men and women [18, 29–33]. The inverse relationship between IGFBP-2 and adiposity is in line with previous results [19, 25, 35]. The associations of IGFBP-2 and IGFBP-3 with weight gain are new findings. Previous studies into the relationship of adult obesity with IGFs and IGFBPs have produced mixed results. There are reports of inverse [22, 23, 40, 45–47], positive [48] and null [19, 21, 24, 25, 35, 49–53] associations for IGF-I; inverse [23], positive [19], and null [24, 25, 46] associations for IGF-II; and inverse [48] positive [19, 53], and null [22–25, 35, 49, 54] associations for IGFBP-3.

Table 3 Levels of adulthood IGFs/IGFBPs in relation to adulthood BMI

	n	Mean IGF/IGFBP levels (95% CI) (ng/ml) by quartile of BMI (kg/m^2)[a]				Change in IGF/IGFBP (95% CI) (ng/ml) per SD increase in BMI (*z* score)		*p* linear trend[b]	*p* quadratic model[b]
		1 (17.7–24.5 kg/m^2)	2 (24.5–26.8 kg/m^2)	3 (26.8–29.2 kg/m^2)	4 (29.2–45.9 kg/m^2)	Age-adjusted[a]	Fully adjusted[b]		
IGF-I	1,052	160.1(153.4, 166.7)	165.2 (158.6, 171.9)	165.2 (158.5, 171.9)	159.7 (153.0, 166.3)	−0.6 (−3.9, 2.8)	−0.6 (−3.9, 2.8)	0.73	0.04
IGF-II	877	844.4 (801.6, 887.3)	909.5 (868.1, 950.9)	903.5 (861.4, 945.6)	876.1 (9833.5, 918.7)	12.1 (−9.7, 34.0)	9.4 (−10.2, 29.0)	0.35	0.06
IGFBP-2[c]	971	940.8 (888.4, 996.1)	643.9 (626.6, 702.5)	561.4 (529.4, 595.4)	459.2 (433.4, 486.6)	−22% (−25%, −20%)	−22% (−24%, −19%)	<0.001	<0.001
IGFBP-3	904	4,405 (4,266, 4,544)	4,687 (4,552, 4,821)	4,704 (4,563, 4,846)	4,705 (4,566, 4,844)	82.8 (12.5, 153.1)	63.5 (−2.7, 129.8)	0.06	0.03
IGF-I/IGFBP-3 ratio[d]	903	18.8 (18.0, 19.7)	18.6 (17.8, 19.4)	18.8 (18.0, 19.7)	18.2 (17.4, 19.1)	−0.15 (−0.06, 0.03)	−0.03 (−0.4, 0.4)	0.89	0.25

Mean (SD) for BMI = 27.2 kg/m^2 (3.9 kg/m^2) $n = 1{,}052$

Quartiles of BMI based on the 1,052 subjects included in the IGF-I analysis

[a] Age-adjusted model

[b] Fully adjusted model (age, centre, duration of sample storage, assay kit number, alcohol, smoking, and exercise)

[c] Geometric mean and % for the change per SD increase in BMI

[d] IGF-I/IGFBP-3 ratio expressed as %

Strengths and limitations

This is the first study to investigate four measures of the IGF system (IGF-I, IGF-II, IGFBP-2, and IGFBP-3) in relation to adiposity in a large cohort of healthy middle-aged men, selected from the UK general population according to a standard recruitment protocol. Serum samples were assayed using validated robust in-house assays.

There are some limitations to the study. It was conducted in middle-aged men and, therefore, may not be generalized to younger men or to women. There were small numbers of men who reported being overweight or obese in childhood (measured by pictogram choice), and the body shape pictograms used have only been validated in adults over 18 years [43]. However, instead of using actual reported childhood body size in our analyses, we looked at how men perceived their change in body shape from childhood to adulthood. Change in body shape in individuals may be less prone to error compared with recalled actual body shape or other measures of adiposity. Although there was a small difference in IGF-II, IGFBP-2, and IGFBP-3 levels between subjects included and excluded from the analysis, we do not anticipate that this difference would likely affect our conclusions, because it is unlikely that associations of IGFs with adiposity would differ among those who were and were not in the analysis. We did not investigate prostate cancer as an outcome in this study and therefore can only speculate about the role of adiposity-related changes in IGFs and IGFBPs and cancer risk.

Biological roles of IGFs and IGFBPs in prostate cancer

The IGFBPs regulate transport of IGFs to cellular receptors and have been shown to have both inhibitory and stimulatory effects on cell proliferation and migration [55]. IGFBP-3 is the most abundant binding protein with IGF-dependent and IGF-independent inhibitory effects on cell growth. Our previous meta-analysis of published retrospective and prospective studies of IGFs/IGFBPs and prostate cancer found a positive association of IGF-I with prostate cancer, and a negative association of IGFBP-3 with prostate cancer [27]. For IGF-II, IGFBP-2, and IGF-I:IGFBP-3 M ratio, there were positive but weaker associations with prostate cancer risk [27]. A pooled analysis of twelve prospective studies investigating the association of IGFs and IGFBPs with subsequent prostate cancer risk found a similar relationship for IGF-I, but no association of IGF-II, IGFBP-2, or IGFBP-3 (after adjusting the IGFBP-3 model for IGF-I) with risk of prostate cancer [26]. The weak positive association of IGFBP-2 with prostate cancer is not consistent with IGFBP-2 being a marker of insulin sensitivity, which would be anticipated to be inversely associated with prostate cancer. It is important to note,

Table 4 Levels of adulthood IGFs/IGFBPs in relation to adulthood waist circumference

	n	Mean IGF/IGFBP levels (95% CI) (ng/ml) by quartile of waist circumference (cm)[a]				Change in IGF/IGFBP (95% CI) (ng/ml) per SD increase in waist (*z* score)		*p* linear trend[b]	*p* quadratic model[b]
		1 (66.7–88.9 cm)	2 (90.2–94.0 cm)	3 (94.2–101.6 cm)	4 (102.9–139.7 cm)	Age-adjusted[a]	Fully adjusted[b]		
IGF-I	1,048	160.7 (154.0, 167.3)	165.6 (158.8, 172.3)	164.9 (158.6, 171.1)	158.1 (150.8, 165.4)	−1.2 (−4.6, 2.1)	−1.2 (−4.6, 2.2)	0.48	0.24
IGF-II	878	875.8 (833.0, 918.5)	898.2 (855.6, 940.7)	892.7 (853.8, 931.6)	872.4 (826.6, 918.2)	0.17 (−21.4, 21.7)	−1.3 (−20.6, 17.9)	0.89	0.36
IGFBP-2[c]	968	852.4 (801.6, 906.3)	653.0 (613.4, 695.2)	594.4 (560.9, 630.0)	480.7 (449.6, 513.9)	−18% (−21%, −16%)	−18% (−20%, − 15%)	<0.001	0.001
IGFBP-3	904	4,510 (4,371, 4,649)	4,685 (4,545, 4,825)	4,680 (4,550, 4,811)	4,641 (4,491, 4,791)	37.0 (−32.8, 107.0)	37.3 (−28.8, 103.4)	0.27	0.12
IGF-I/IGFBP-3 ratio[d]	903	18.6 (17.8, 19.4)	18.8 (18.0, 19.6)	18.7 (17.9, 19.5)	18.3 (17.4, 19.2)	0.1 (−0.6, 0.3)	−0.1 (−0.5, 0.3)	0.54	0.65

Mean (SD) for waist circumference = 96.1 cm (9.9 cm) $n = 1{,}048$

Quartiles of BMI based on the 1,048 subjects included in the IGF-I analysis

[a] Age-adjusted model

[b] Fully adjusted model (age, centre, duration of sample storage, assay kit number, alcohol, smoking, exercise)

[c] Geometric mean and % for the change per SD increase in waist circumference

[d] IGF-I/IGFBP-3 ratio expressed as %

however, that the findings for IGFBP-2 were based on three case–control studies and two cohort studies and that interpretation of these case–control studies may be affected by reverse causality. IGFBP-2 levels have been shown to fall following surgical removal of the prostate [56], suggesting that IGFBP-2 in men with prostate cancer may be a tumor marker (i.e., raised levels may be a secondary tumor effect). Other effects of IGFBP-2 at the cellular level have been noted, for example regulation of the PTEN tumor suppressor gene [57].

IGF-I synthesis by the liver is primarily controlled by pituitary growth hormone (GH) and by nutritional stimuli [58]. The biological activities of the IGFs are modulated by IGFBPs which regulate transport of IGFs to cellular receptors, protect them from degradation, and regulate the interaction between IGFs and the IGF receptor [59]. IGFBPs also have direct effects on cell proliferation, survival, motility and adhesion, independent of their IGF-binding properties [55]. Chronic fasting results in low production of insulin, causing a reduction in hepatic GH receptor levels, resulting in GH resistance and reduced synthesis and blood levels of IGF-I [5]. Excess body weight can lead to prolonged hyperinsulinemia, which reduces the production of IGFBP-2, possibly resulting in increases in the level of bioavailable IGF-I. This may therefore be the mechanism by which adiposity could increase cancer risk, via the insulin-IGFBP-2 pathway. Alternatively, lower IGFBP-2 levels may be acting as a marker of increased insulin resistance. With increasing obesity, there is a fall in serum IGF-I levels, probably consequent to impaired hepatocyte function due to development of a fatty-liver and eventually non-alcoholic steatohepatitis (liver disease) [60]. However, the fall in absolute IGF-I levels is very small compared to the relatively large fall in IGFBP-2 levels: the fall in IGF-I, from BMI quartile 3 (which had the highest IGF-I) to BMI quartile 1, was only 5 ng/ml (approximately 10%), whereas IGFBP-2 decreased by 22% per SD increase in BMI. The observed positive associations of increased adiposity with prostate cancer progression and fatality could therefore result from increased tissue availability of IGF-I due to the relatively large decrease in IGFBP-2, despite the small decrease in absolute IGF-I level. However, given the limited evidence from few prospective studies investigating associations of IGFBP-2 with prostate cancer progression [26, 27], further research on the role of IGFBP-2 is required.

Conclusion

We provide evidence that adiposity and change in body shape from childhood to adulthood are related to the IGF system. Specifically, we have found evidence of non-linear associations of IGF-I and IGF-II with general adiposity

Table 5 Levels of adulthood IGFs/IGFBPs in relation to change in body shape between childhood and adulthood

	Mean IGF/IGFBP levels (ng/ml) by change in body shape from age 10 to adulthood							
	Three groups of body shape change[a]			Per one category body shape change (−4 to +7 categories)				
	Lost weight or gained 1 category (−4 to +1 categories)	Gained a small amount of weight (+2 to +3 categories)	Gained a large amount of weight (+4 to +7 categories)	Age-adjusted[a]	Fully adjusted[b]	Fully adjusted & body shape at age 10[c]	*p* linear trend[b]	*p* quadratic model[b]
n (for IGF-I only)	204	460	334					
IGF-I	158.3 (150.7, 165.8)	165.2 (160.2, 170.3)	161.6 (155.7, 167.5)	0.2 (−2.0, 2.3)	0.04 (−2.1, 2.2)	−0.8 (−3.3, 1.7)	0.97	0.67
IGF-II	863.1 (813.6, 912.6)	885.5 (853.9, 917.0)	911.6 (874.1, 949.2)	8.2 (−5.5, 21.8)	7.2 (−4.9, 19.3)	12.3 (−1.9, 26.5)	0.25	0.13
IGFBP-2[d]	793.9 (737.9, 854.1)	643.3 (613.1, 675.0)	535.3 (505.4, 567.0)	−9% (−11%, −7%)	−9% (−11%, −7%)	−12% (−14%, −10%)	<0.001	0.06
IGFBP-3	4,518 (4,357, 4,680)	4,620 (4,517, 4,724)	4,761 (4,637, 4,885)	68.2 (23.8, 112.7)	50.0 (8.0, 92.0)	51.2 (1.9, 100.5)	0.02	0.92
IGF-I/IGFBP-3 ratio[e]	18.6 (17.6, 19.5)	18.8 (18.1, 19.4)	18.2 (17.4, 18.9)	−0.2 (−0.5, 0.06)	−0.2 (−0.4, 0.07)	−0.2 (−0.5, 0.07)	0.15	0.62

[a] Age-adjusted model

[b] Fully adjusted model (age, centre, duration of sample storage, assay kit number, alcohol, smoking, and exercise)

[c] Fully adjusted model plus body shape at age 10

[d] Geometric mean and % for the change per SD increase in BMI

[e] IGF-I/IGFBP-3 ratio expressed as %

(measured by BMI) in middle-aged men, with highest levels of these IGFs in the mid-range of adiposity. The change in IGF-I level between BMI quartile 1 and BMI quartile 3 (which had the highest IGF-I) was only 5 ng/ml. Our previously published meta-analysis [27] showed that there was a 21% increased risk of prostate cancer for a standard deviation increase in IGF-I (which in this group of subjects equals 54.9 ng/ml). Therefore, there is unlikely to be a meaningful change in risk of prostate cancer as a result of BMI-related changes in IGF-I. Serum IGFBP-2 was strongly inversely related to general (BMI) and central adiposity (waist circumference), decreasing by 22% per SD increase in BMI. Men who gained a large amount of weight between childhood and adulthood had the lowest IGFBP-2 and the highest IGFBP-3.

We hypothesize that low IGFBP-2 levels (likely resulting from hyperinsulinaemia in obese individuals) may be one mechanism leading to increased risk of prostate cancer progression in overweight or obese men, and in men who had lean or normal body shapes as children and became obese in adulthood. Although current evidence from only a few prospective studies does not support an association of IGFBP-2 with prostate cancer progression [26, 27], there is evidence from clinical studies of patients with prostate cancer indicating that IGFBP-2 is associated with patient survival [61] with loss of tumor expression of PTEN [62] and with failure of hormone therapy [63]. In addition, there is considerable experimental evidence linking IGFBP-2 with prostate cancer progression [64]. The results suggest that circulating IGF-I levels may not be an important mediator of the association of adiposity with aggressive prostate cancer.

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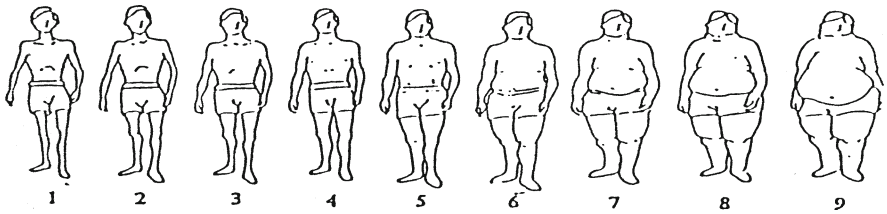
Appendix: Body shape pictograms and associated questions



Look at the pictures above and choose the figure that best matches the shape of your body at the age asked.

What is the number of the figure which looks most like you….

NOW	☐
when you were 10 years old	☐
when you were 20 years old	☐
when you were 40 years old	☐

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