Public Health Nutrition: 9(3), 359–368 DOI: 10.1079/PHN2006853

Milk as a food for growth? The insulin-like growth factors link

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Submitted 21 December 2004: Accepted 18 July 2005

Abstract

Objective: The mechanisms underlying the association of insulin-like growth factor-I (IGF-I) and leg length (a marker of prepubertal growth) with cancer risk are uncertain. One hypothesis is that diet in early childhood might provide the link. The aim of the present study was to examine the association between early diet – in particular, the intakes of cows' milk and dairy products – and height, leg length and IGF-I levels at age 7–8 years.
Subjects: Children participating in the Avon Longitudinal Study of Parents and Children.
Design: Diet was assessed using a 3-day unweighed food record. Anthropometry, IGF-I and insulin-like growth factor-binding protein-3 (IGFBP-3) were measured by standard methods.
Results: Data on both diet and height were available for 744 children (404 boys) and on diet and IGF for 538 (295 boys). After adjusting for energy, both cows' milk and dairy product intakes were positively associated with IGF-I ($P = 0.040$ and 0.027, respectively) and IGFBP-3 levels ($P = 0.082$ and 0.067, respectively). These associations persisted on adjustment for potential confounders, but were abolished on controlling for protein intake. In energy-adjusted models there was only weak evidence of associations of milk and dairy product intakes with anthropometry. In boys only, dairy product intake was positively associated with leg length (equivalent to a 0.058 (0.002, 0.114) standard deviation score increase in leg length per 100 g increase in daily intake).
Conclusions: These data provide some evidence that variation in childhood milk and dairy product intakes underlies associations of leg length, IGF-I and cancer risk. The association appears to be due to the protein content of milk.

Keywords
Insulin-like growth factors
Milk
Dairy products
Protein
Children
Growth
Leg length

Greater adult stature is associated with cancer risk, in particular with prostate, breast and gastrointestinal cancers[1]. Some evidence suggests that leg length, a marker for growth before puberty[2], is the component of height most strongly associated with risk[1,3]. Growth in leg length is thought to be more sensitive to environmental insults than truncal growth, and adult leg length has been suggested to be a marker of prepubertal influences on growth such as childhood diet[4]. This suggests that the biological mechanisms linking height with cancer risk may originate in factors that influence long bone growth in childhood. It is possible that these associations between prepubertal growth and cancer risk operate via dietary effects on levels of insulin-like growth factors (IGFs), as IGFs are key hormonal regulators of growth[5,6].

The IGFs are powerful mitogenic agents which stimulate cell differentiation and inhibit apoptosis. Higher circulating levels of insulin-like growth factor-I (IGF-I) are associated with increased risk of a number of cancers, including prostate[7,8], breast[9] and colon cancer[10], the same cancers most consistently associated with height. Some studies have found inverse associations between concentrations of insulin-like growth factor-binding protein-3 (IGFBP-3) and cancer risk[11,12], but a recent meta-analysis has suggested a positive association[13]. The risk of these cancers has also been associated with dietary factors, including positive associations with intakes of energy, red meat, animal fat, calcium and dairy products[14–18], and negative associations with fruit and vegetables[18–22]. Several cross-sectional studies in adults have investigated the relationship between diet and IGF-I levels. The results are mixed, but one of the more consistent relationships is a positive association between cows' milk or dairy product intake and IGF-I[10,23–25], although this is not observed in all studies[26–28]. Milk supplementation has also been observed to raise IGF-I levels in three studies, one of

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https://doi.org/10.1079/PHN2006853 Published online by Cambridge University Press

middle-aged men and women[29], one of adolescent girls[30] and one in 8-year-old boys[31]. However, it remains unclear what constituent of cows' milk/dairy products is responsible for their positive effect on circulating IGF-I.

Evidence that childhood diet may affect adult cancer risk is provided by a long-term follow-up of the Boyd Orr cohort, which found that childhood energy intakes were positively associated with cancer mortality in adulthood[32]. The associations of dietary intakes in prepubertal children with IGF levels and growth have been less often studied but are of considerable interest. Such associations could confirm that leg length measures are a marker of childhood nutrition and that IGF-I is the biological mediator of the associations of diet and anthropometry with cancer risk in later life. The associations of cows' milk and dairy products with IGF-I are of particular interest in this context, as children are high consumers of these foods, often marketed as 'healthy' foods for this age group. However, we are aware of only one study that has investigated the associations of milk and dairy product intakes with both IGF-I and measures of linear growth in children[33].

The aim of the present study was to investigate associations of cows' milk and dairy product intakes with levels of IGF-I and IGFBP-3 in a group of 7- and 8-year-old children in the South West of England. In addition we examined the associations between these foods and height and leg length – possible biomarkers of IGF-I[4,6].

Methods

This study was based on the Avon Longitudinal Study of Parents and Children (ALSPAC), a geographically based cohort study investigating factors influencing the health, growth and development of children[34]. All pregnant women resident within a defined part of the former county of Avon in South West England with an expected date of delivery between April 1991 and December 1992 were eligible. Between 80% and 90% of these enrolled (14 541 pregnancies resulting in 14 062 live births)[35]. Ethical approval for the study was obtained from the relevant local ethics committees. Data in ALSPAC are collected by self-completion postal questionnaires, abstracted from medical records, and from examination of the children at research clinics.

The children forming the basis of the present analysis were part of a randomly selected 10% sub-cohort of ALSPAC called Children in Focus (CIF) ($n = 1432$)[35]. The children attended research clinics at 7–8 years of age where diet was assessed, growth measurements were made and a blood sample was taken.

Assessment of diet

Diet was assessed using a 3-day unweighed dietary record completed by the child's carer in advance of the clinic, and checked for completeness by a trained assistant during the clinic visits. These were coded using the coding package DIDO[36], and analysed using a database consisting of the 5th edition of *McCance & Widdowson's The Composition of Foods*[37] and its supplements[38–46]. Nutrient intakes from dietary supplements were not assessed; 9.3% of children were reported to take a vitamin or mineral supplement of some kind, and 0.7% of children took cod-liver oil.

Measurement of anthropometric variables

Height, leg length and sitting height were measured to the last completed millimetre using a Harpenden stadiometer, a sitting height table and an anthropometer as described by Cameron[47]. Weight was measured to the nearest 50 g using a Tanita weighing scale (Tanita UK Limited, Uxbridge). Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2.

Measurement of other variables

Information on maternal education, housing tenure, paternal social class and maternal smoking in pregnancy was obtained from a self-completion questionnaire sent to the mother at 32 weeks' gestation. Birth weight, sex of the child and gestation were obtained from hospital records. Gestational age was assessed on the basis of date of last menstrual period, ultrasound assessment and other clinical indicators.

Assessment of IGF levels

Serum levels of IGF-I were determined in venous blood by radioimmunoassay using a monoclonal antibody (Blood Products, Elstree, Hertfordshire, UK) and recombinant peptide (Pharmacia, Stockholm, Sweden) for standard and tracer, following iodination using the chloramine-T method. Samples were analysed following acid–acetone extraction to remove the IGFBPs with an excess of IGF-II added to the extract in order to saturate any residual binding proteins[48]. Serum levels of IGFBP-3 were determined by radioimmunoassay using an in-house polyclonal antibody raised against recombinant non-glycosylated IGFBP-3. The assay was calibrated against recombinant glycosylated IGFBP-3 (Dr C Maack, Celitrix, Santa Clara, CA, USA). The molar ratio of IGF-I/IGFBP-3 was calculated by multiplying the concentration ratio by 5.33 (based on the molecular weights of IGF-I (7500) and IGFBP-3 (40 000)). The average coefficients of variation for intra-assay variability for IGF-I and IGFBP-3 were 6.7% and 3.6%, and for inter-assay variation were 12% and 14%.

Statistical methods

All hormone levels and anthropometric variables were adjusted for age. IGF-I, IGFBP-3 and IGF-I/IGFBP-3 were transformed to the natural logarithm prior to age adjustment in order to reduce skewness. Age-adjusted anthropometric variables were converted to sex-specific Z-scores (Z-scores were produced with reference to the ALSPAC cohort).

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Intakes of cows' milk and dairy products were the main predictor variables of interest. Cows' milk was defined as the sum of whole, semi-skimmed and skimmed milk. Dairy products were defined as the sum of cows' milk, other milk (i.e. dried milk, evaporated milk and cream), cheese, yoghurt, milk-based sauces, ice cream and milk chocolate. Intakes of calcium, protein and animal protein were also considered as possible mediators of the effects of cows' milk and dairy products. Intakes of calcium, protein and animal protein were adjusted for energy using the residuals method[49].

The following confounding variables were considered: maternal education, housing tenure, birth weight and the child's BMI. Highest maternal educational level was grouped as CSE (Certificate of Secondary Education) or equivalent or no qualifications, vocational qualifications, O-level or equivalent, A-level or equivalent, or university degree (CSE and O-levels are respectively lower and higher levels of qualifications taken at around 16 years of age, A-levels are the standard qualifications taken at around 18 years of age). Housing tenure was grouped as council rented (i.e. government housing), other rented, and owned/mortgaged. Birth weight was adjusted for gestational age and converted to sex-specific *Z*-scores. Paternal social class and maternal smoking in pregnancy were also initially considered as potential confounders, but found to be minimally associated with IGF or growth once the other confounders had been considered.

Only white children not from multiple births were included in analyses, as preliminary analyses suggested that the growth and IGF levels of children from non-white ethnic groups differed from those of white children, and there were too few children from non-white ethnic groups to analyse separately. After excluding subjects who were non-white or from multiple births, there were 744 subjects with both diet and height measures (i.e. 59% of the white singleton children in the CIF sub-cohort) and 538 with both diet and IGF. Multivariate models are based on a smaller subset of subjects ($n = 521$ children, 287 boys) with complete information on all confounders.

Linear (least squares) regression models were used. Initial statistical analyses were performed firstly for both sexes together and then separately for boys and girls, as previous studies have shown that IGF-I and IGFBP-3 levels differ between boys and girls[6,50], and the relationship between IGF-I and IGFBP-3 and age is also different between boys and girls[50]. In the first instance the association between cows' milk and dairy products and the outcome variables was assessed controlling for energy only. Subsequent multivariable regression analyses included other confounders and were based on a subgroup of children where complete data were available; the confounding variables included in the statistical models were as follows: (1) energy intake (Model 1); (2) energy intake, housing tenure, maternal education, birth weight and BMI (Model 2); (3) factors included in Model 2 plus IGF-I for models looking at height, leg length and sitting height, or height in models looking at IGF-I, IGFBP-3 and IGF-I/IGFBP-3 (Model 3); (4) in Models 4–6 we examined the effect of adjusting additionally for those nutrient variables that we felt might mediate any associations with cows' milk and dairy products, i.e. calcium, protein and animal protein.

In order to assess the possible effects of underreporting of dietary intake, all analyses were repeated excluding those children reporting an energy intake of less than 1.39 × estimated basal metabolic rate (BMR) for boys or 1.30 × BMR for girls[51].

All analyses were performed using SPSS version 10 (SPSS Inc., Chicago, IL, USA).

Results

Response rate and representativeness of sample

Some characteristics of study members are displayed in Table 1. IGF-I and IGFBP-3 were higher in girls than boys, but IGF-I/IGFBP-3 was similar in the two sexes. The children were slightly taller and heavier than national growth standards[52].

Girls (but not boys) for whom data on IGF levels were available were significantly taller with longer legs than those for whom data on IGF levels were not available (mean height and leg length in those with and without IGF measures were 125.5 cm and 124.1 cm, $P = 0.019$ and 57.8 cm and 57.0 cm, $P = 0.031$ respectively). Children with data on IGF were less likely to live in council housing

Table 1 Mean (SD) IGF-I and IGFBP-3 levels, growth measures and dietary intakes in boys and girls

	Boys	Girls
	$n = 404$*	$n = 340$*
Mean age (years)	7.48 (0.12)	7.49 (0.11)
Height (cm)†	125.9 (5.0)	125.2 (5.4)
Weight (kg)‡	25.7 (4.4)	25.7 (4.8)
Sitting height (cm)	68.1 (2.7)	67.6 (2.7)
Leg length (cm)	57.8 (3.0)	57.6 (3.4)
BMI (kg m^{-2})	16.1 (1.9)	16.3 (2.3)
Cows' milk intake (g)	278 (195)	243 (187)
Dairy products intake (g)	348 (209)	313 (193)
Energy intake (kJ)	7295 (1339)	6858 (1211)
Calcium intake (mg)	810 (280)	757 (256)
Protein intake (g)	56.7 (12.8)	52.8 (11.5)
Animal protein intake (g)	33.8 (11.4)	31.4 (10.4)
	$n = 295$§	$n = 243$§
IGF-I (ng ml^{-1})	145 (55)	154 (52)
IGFBP-3 (ng ml^{-1})	4883 (1669)	5122 (1943)
IGF-I/IGFBP-3	0.167 (0.063)	0.172 (0.058)

SD – standard deviation; IGF-I – insulin-like growth factor-I; IGFBP-3 – insulin-like growth factor-binding protein-3; BMI – body mass index.
* The sample used is those boys and girls with both a diet and a height measure.
† Median height from UK reference data: 124.9 cm (boys)/124.3 cm (girls)[52].
‡ Median weight from UK reference data: 24.3 kg (boys)/24.4 kg (girls)[52].
§ The sample used is those boys and girls with both IGF and a diet measure.

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(8.4% vs. 14.3%, $P < 0.001$) and less likely to have a mother whose highest educational qualification was CSE or less (10.4% vs. 18.7%, $P < 0.001$).

Univariable analyses

Table 2 shows geometric mean levels of IGF-I, IGFBP-3 and IGF-I/IGFBP-3 by quartile of cows' milk and dairy products intakes. Among both sexes after adjusting for energy intake, cows' milk and dairy products were positively associated with IGF-I ($P = 0.040$ and 0.027, respectively) and weakly positively associated with IGFBP-3 ($P = 0.082$ and 0.067, respectively). Among boys, after adjustment for energy intake, cows' milk was weakly positively associated with IGF-I ($P = 0.084$) and significantly positively associated with IGFBP-3 ($P = 0.024$). Dairy products were also positively associated with IGF-I and IGFBP-3, with a difference in IGF-I concentrations of approximately 20 ng ml^{-1} between the lowest and highest quartiles of dairy products intake. Among girls, neither cows' milk nor dairy products intake was associated with either IGF-I or IGFBP-3. These gender-specific subgroup findings should be interpreted with caution, as there was little statistical evidence that effects of diet on IGF differed in boys and girls. The *P*-values for the interaction terms gender × cows' milk and gender × dairy products on IGF-I were 0.37 and 0.16, respectively, and for IGFBP-3 were 0.13 and 0.16, respectively. IGF-I/IGFBP-3 was not associated with cows' milk or dairy products in either the whole sample or boys and girls separately (data not shown).

Table 3 shows mean *Z*-scores for height, leg length and sitting height according to intakes of cows' milk and dairy products. On adjusting for energy intake there were no clear associations between intake of either food group and anthropometry, except for a weak positive association between dairy products and leg length in boys ($P = 0.069$). There was some evidence that diet–anthropometry associations differed in boys and girls. The *P*-values for the interaction terms cows' milk × gender and dairy products × gender with respect to height were 0.040 and 0.043, respectively, and for leg length were 0.013 and 0.015, respectively.

Multivariable analyses

Table 4 shows the associations of cows' milk and dairy products with IGF-I and IGFBP-3 in multivariable analyses in all children. The univariable positive associations between cows' milk and dairy products and IGF-I remained significant in the subset with complete data. Of the possible confounding/mediating factors investigated, only protein/

Table 2 Geometric mean (95% CI) IGF-I and IGFBP-3 levels according to quartile of cows' milk or dairy products intake (quartiles calculated separately in boys and girls)

	Quartile of intake					
	1 (low)	2	3	4 (high)	*P**	*P*†
Both sexes						
Cows' milk	($n = 143$)	($n = 135$)	($n = 136$)	($n = 124$)		
Median intake (g)	67	187	301	462		
IGF-I (ng ml^{-1})	133.6 (125.4, 142.4)	139.0 (130.5, 148.2)	141.0 (133.1, 149.3)	141.8 (134.1, 150.0)	0.017	0.040
IGFBP-3 (ng ml^{-1})	4467 (4262, 4681)	4661 (4434, 4899)	4709 (4477, 4953)	4749 (4503, 5009)	0.011	0.082
Dairy products	($n = 131$)	($n = 141$)	($n = 133$)	($n = 133$)		
Median intake (g)	113	257	401	631		
IGF-I (ng ml^{-1})	133.8 (125.3, 143.0)	138.8 (130.3, 147.9)	138.0 (130.3, 146.1)	144.3 (136.6, 152.4)	0.010	0.027
IGFBP-3 (ng ml^{-1})	4451 (4230, 4683)	4599 (4389, 4819)	4688 (4457, 4931)	4831 (4588, 5088)	0.005	0.067
Boys						
Cows' milk	($n = 76$)	($n = 72$)	($n = 75$)	($n = 72$)		
Median intake (g)	67	200	314	503		
IGF-I (ng ml^{-1})	123.7 (112.4, 136.1)	137.2 (126.5, 148.8)	136.8 (125.8, 148.7)	139.5 (128.8, 151.1)	0.023	0.084
IGFBP-3 (ng ml^{-1})	4359 (4080, 4656)	4474 (4216, 4748)	4635 (4322, 4970)	4809 (4486, 5155)	0.003	0.024
Dairy products	($n = 70$)	($n = 76$)	($n = 74$)	($n = 75$)		
Median intake (g)	123	260	397	588		
IGF-I (ng ml^{-1})	125.3 (113.7, 138.1)	132.5 (121.7, 144.3)	132.9 (122.6, 144.0)	145.5 (134.5, 157.5)	0.006	0.031
IGFBP-3 (ng ml^{-1})	4383 (4073, 4716)	4410 (4180, 4652)	4540 (4229, 4873)	4933 (4617, 5272)	0.002	0.022
Girls						
Cows' milk	($n = 67$)	($n = 63$)	($n = 61$)	($n = 52$)		
Median intake (g)	65	167	293	442		
IGF-I (ng ml^{-1})	145.9 (135.0, 157.8)	141.2 (127.4, 156.4)	146.3 (135.3, 158.2)	145.1 (134.1, 157.0)	0.34	0.29
IGFBP-3 (ng ml^{-1})	4592 (4293, 4911)	4883 (4496, 5304)	4801 (4456, 5174)	4668 (4288, 5081)	0.61	0.90
Dairy products	($n = 61$)	($n = 65$)	($n = 59$)	($n = 58$)		
Median intake (g)	109	228	358	499		
IGF-I (ng ml^{-1})	144.3 (132.3, 157.3)	146.6 (133.2, 161.4)	144.6 (133.4, 156.8)	142.7 (132.3, 154.0)	0.53	0.44
IGFBP-3 (ng ml^{-1})	4530 (4218, 4865)	4830 (4460, 5241)	4880 (4540, 5245)	4703 (4326, 5112)	0.49	0.84

CI–confidence interval; IGF-I – insulin-like growth factor-I; IGFBP-3 – insulin-like growth factor-binding protein-3.
* *P*-value for continuous variable.
† *P*-value for continuous variable adjusted for energy intake.

https://doi.org/10.1079/PHN2006853 Published online by Cambridge University Press

Table 3 Mean (95% CI) height, leg length and sitting height (*Z*-scores) according to quartile of cows' milk or dairy product intake (quartiles calculated separately in boys and girls)

	Quartile of intake					
	1 (low)	2	3	4 (high)	*P**	*P*†
Both sexes						
Cows' milk	($n = 196$)	($n = 184$)	($n = 185$)	($n = 179$)		
Height (SDS)	−0.043 (−0.182, 0.097)	0.030 (−0.113, 0.174)	0.124 (−0.017, 0.265)	0.063 (−0.069, 0.195)	0.16	0.77
Leg length (SDS)	−0.055 (−0.185, 0.075)	0.071 (−0.064, 0.207)	0.091 (−0.057, 0.239)	0.070 (−0.066, 0.205)	0.23	0.85
Sitting height (SDS)	−0.017 (−0.165, 0.131)	−0.027 (−0.177, 0.124)	0.133 (−0.007, 0.272)	0.040 (−0.090, 0.170)	0.19	0.73
Dairy products	($n = 189$)	($n = 189$)	($n = 184$)	($n = 182$)		
Height (SDS)	−0.082 (−0.223, 0.058)	−0.027 (−0.174, 0.119)	0.155 (0.020, 0.291)	0.129 (−0.002, 0.261)	0.022	0.80
Leg length (SDS)	−0.066 (−0.197, 0.064)	−0.004 (−0.143, 0.136)	0.116 (−0.026, 0.258)	0.129 (−0.006, 0.264)	0.042	0.71
Sitting height (SDS)	−0.082 (−0.233, 0.069)	−0.049 (−0.195, 0.097)	0.164 (0.025, 0.304)	0.099 (−0.032, 0.230)	0.040	0.95
Boys						
Cows' milk	($n = 103$)	($n = 103$)	($n = 99$)	($n = 99$)		
Height (SDS)	−0.263 (−0.450, −0.077)	−0.003 (−0.194, 0.187)	0.269 (0.090, 0.447)	0.065 (−0.104, 0.234)	0.013	0.43
Leg length (SDS)	−0.273 (−0.439, −0.108)	0.056 (−0.124, 0.235)	0.226 (0.044, 0.409)	0.108 (−0.059, 0.275)	0.007	0.17
Sitting height (SDS)	−0.188 (−0.398, 0.022)	−0.073 (−0.267, 0.121)	0.253 (0.073, 0.433)	−0.003 (−0.178, 0.173)	0.090	0.96
Dairy products	($n = 104$)	($n = 102$)	($n = 99$)	($n = 99$)		
Height (SDS)	−0.268 (−0.446, −0.090)	−0.032 (−0.230, 0.167)	0.247 (0.067, 0.426)	0.124 (−0.043, 0.291)	0.002	0.22
Leg length (SDS)	−0.245 (−0.404, −0.086)	−0.003 (−0.193, 0.188)	0.192 (0.011, 0.373)	0.177 (0.013, 0.341)	0.001	0.069
Sitting height (SDS)	−0.230 (−0.432, −0.029)	−0.059 (−0.257, 0.139)	0.251 (0.065, 0.438)	0.030 (−0.144, 0.204)	0.023	0.78
Girls						
Cows' milk	($n = 93$)	($n = 81$)	($n = 86$)	($n = 80$)		
Height (SDS)	0.202 (0.000, 0.404)	0.073 (−0.150, 0.295)	−0.043 (−0.264, 0.179)	0.061 (−0.152, 0.273)	0.55	0.20
Leg length (SDS)	0.187 (−0.009, 0.382)	0.092 (−0.118, 0.301)	−0.065 (−0.304, 0.175)	0.021 (−0.204, 0.247)	0.31	0.11
Sitting height (SDS)	0.172 (−0.034, 0.377)	0.032 (−0.208, 0.273)	−0.006 (−0.222, 0.211)	0.093 (−0.104, 0.291)	0.94	0.59
Dairy products	($n = 85$)	($n = 87$)	($n = 85$)	($n = 83$)		
Height (SDS)	0.144 (−0.075, 0.364)	−0.022 (−0.243, 0.199)	0.049 (−0.157, 0.256)	0.136 (−0.076, 0.348)	0.95	0.33
Leg length (SDS)	0.152 (−0.058, 0.362)	−0.004 (−0.215, 0.206)	0.028 (−0.198, 0.254)	0.072 (−0.154, 0.298)	0.60	0.19
Sitting height (SDS)	0.100 (−0.127, 0.326)	−0.037 (−0.258, 0.183)	0.063 (−0.149, 0.274)	0.181 (−0.019, 0.382)	0.61	0.76

CI−confidence interval; SDS − standard deviation score.
* *P*-value for continuous variable.
† *P*-value for continuous variable adjusted for energy intake.

https://doi.org/10.1079/PHN2006853 Published online by Cambridge University Press

Table 4 Percentage change in IGF-I and IGFBP-3 per 100 g increase in cows' milk or dairy products consumption among both sexes ($n = 521$)

	Cows' milk		Dairy products	
Outcome variable	*B* (95% CI)	*P*	*B* (95% CI)	*P*
IGF-I				
Model 1	2.12 (0.40, 3.87)	0.014	2.12 (0.50, 3.87)	0.011
Model 2	2.33 (0.60, 3.98)	0.007	2.12 (0.50, 3.77)	0.011
Model 3	2.33 (0.70, 3.98)	0.004	2.02 (0.50, 3.67)	0.009
Model 4	2.02 (−0.80, 4.92)	0.17	1.41 (−1.88, 4.71)	0.42
Model 5	0.90 (−0.80, 2.74)	0.29	0.60 (−1.09, 2.33)	0.47
Model 6	1.11 (−0.70, 2.94)	0.24	0.70 (−1.09, 2.53)	0.46
IGFBP-3				
Model 1	1.41 (0.00, 3.23)	0.046	1.41 (0.00, 2.74)	0.046
Model 2	1.51 (0.10, 2.94)	0.036	1.31 (−0.10, 2.63)	0.061
Model 3	1.51 (0.10, 2.94)	0.032	1.31 (−0.10, 2.63)	0.061
Model 4	2.63 (0.10, 5.13)	0.039	2.53 (−0.30, 5.55)	0.077
Model 5	1.41 (−0.09, 2.94)	0.074	1.11 (−0.40, 2.63)	0.14
Model 6	1.82 (0.20, 3.36)	0.029	1.51 (−0.10, 3.15)	0.058

CI – confidence interval; IGF-I – insulin-like growth factor-I; IGFBP-3 – insulin-like growth factor-binding protein-3.
Model 1 – adjusted for sex and energy intake; Model 2 – adjusted for sex, energy intake, housing tenure, maternal education, birth weight and body mass index (BMI); Model 3 – adjusted for sex, energy intake, housing tenure, maternal education, birth weight, BMI and height; Model 4 – adjusted for sex, energy intake, housing tenure, maternal education, birth weight, BMI, height and calcium intake; Model 5 – adjusted for sex, energy, housing tenure, maternal education, birth weight, BMI, height and protein intake; Model 6 – adjusted for sex, energy, housing tenure, maternal education, birth weight, BMI, height and animal protein intake.

animal protein intake strongly attenuated the association of IGF-I with cows' milk and dairy products. There was no strong evidence of confounding of the IGFBP-3 association with cows' milk and dairy products. Controlling for calcium increased the size of the regression coefficient of cows' milk/dairy products on IGFBP-3. No significant associations were observed between cows' milk or dairy products intake and IGF-I/IGFBP-3 (data not shown).

As mentioned above, the only confounding factor to markedly attenuate the association of cows' milk/dairy products with IGF-I was protein. Cows' milk and dairy products were a major source of protein, with dairy products accounting on average for 40% of the children's animal protein intake, in comparison with 17% and 14% from poultry and processed meat, the next two highest sources. The regression coefficients (β (standard error)) for the energy-adjusted associations of total, dairy and non-dairy protein with IGF-I were respectively 0.00747 (0.00171), $P < 0.001$; 0.00493 (0.00217), $P = 0.023$; and 0.00506 (0.00185), $P = 0.006$. The regression coefficients for dairy and non-dairy protein were very similar, implying that protein *per se* rather than

Table 5 Change in height and leg length *Z*-score for each 100 g increase in cows' milk/dairy product consumption among boys ($n = 287$)

	Cows' milk		Dairy products	
Outcome variable	*B* (95% CI)	*P*	*B* (95% CI)	*P*
Height				
Model 1	0.023 (−0.038, 0.084)	0.46	0.038 (−0.020, 0.096)	0.20
Model 2	0.029 (−0.024, 0.083)	0.28	0.035 (−0.016, 0.085)	0.18
Model 3	0.004 (−0.047, 0.055)	0.87	0.011 (−0.037, 0.059)	0.65
Model 4	−0.022 (−0.113, 0.070)	0.64	0.000 (−0.102, 0.103)	1.00
Model 5	0.015 (−0.042, 0.072)	0.60	0.023 (−0.031, 0.076)	0.41
Model 6	0.012 (−0.047, 0.071)	0.68	0.022 (−0.035, 0.078)	0.45
Leg length				
Model 1	0.047 (−0.012, 0.106)	0.12	0.058 (0.002, 0.114)	0.041
Model 2	0.050 (−0.004, 0.105)	0.069	0.054 (0.003, 0.105)	0.038
Model 3	0.027 (−0.025, 0.079)	0.31	0.032 (−0.017, 0.081)	0.20
Model 4	−0.022 (−0.116, 0.071)	0.64	−0.008 (−0.113, 0.096)	0.88
Model 5	0.043 (−0.015, 0.101)	0.15	0.048 (−0.006, 0.103)	0.083
Model 6	0.041 (−0.019, 0.101)	0.18	0.049 (−0.008, 0.106)	0.094

CI – confidence interval.
Model 1 – adjusted for energy intake; Model 2 – adjusted for energy intake, housing tenure, maternal education, birth weight and body mass index (BMI); Model 3 – adjusted for energy intake, housing tenure, maternal education, birth weight, BMI and insulin-like growth factor-I (IGF-I); Model 4 – adjusted for energy intake, housing tenure, maternal education, birth weight, BMI, IGF-I and calcium intake; Model 5 – adjusted for energy intake, housing tenure, maternal education, birth weight, BMI, IGF-I and protein intake; Model 6 – adjusted for energy intake, housing tenure, maternal education, birth weight, BMI, IGF-I and animal protein intake.

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dairy protein was the important factor. Thus these results are consistent with the cows' milk–IGF-I associations being mediated by protein.

Table 5 shows the multivariable associations of cows' milk and dairy products with anthropometry in boys. This analysis was restricted to boys as there was no evidence of any association of anthropometry with cows' milk/dairy products in females (see above). Leg length was the anthropometric variable with the strongest relationship with dairy products. Of the confounding factors investigated, only adjustment for IGF-I and calcium strongly attenuated the association between dairy products and leg length, indicating that these factors may mediate the association. A similar pattern was obtained in the models with height as the outcome, but the regression coefficients were smaller in each case. There was no evidence of a positive relationship between dairy products and sitting height (data not shown).

Effect of excluding underreporters

The analyses were repeated excluding possible underreporters (76 children excluded). The results were similar, but the associations between dairy products and IGFBP-3 and between dairy products and leg length in boys were slightly attenuated (data not shown).

Discussion

Among this group of 7- and 8-year-old children we found a number of associations between milk and dairy products consumption and IGF-I and its main binding protein IGFBP-3. Higher intakes of cows' milk and dairy products were significantly positively associated with concentrations of IGF-I and IGFBP-3 in all children and in boys, even after adjusting for a number of possible confounders. However, there were no associations between cows' milk or dairy products and the molar ratio IGF-I/IGFBP-3, a possible marker of IGF-I bioavailability. There were also no associations between IGF levels and cows' milk or dairy products in girls.

The associations between cows' milk/dairy products and IGF-I and IGFBP-3 were considerably more attenuated on adjustment for total or animal protein than for calcium. Furthermore, protein and animal protein from both all sources and non-dairy sources were positively associated with IGF-I in boys, and the strength of the associations with dairy and non-dairy protein were similar. This suggests that the apparent relationship between milk and IGF-I could reflect an underlying association with protein rather than with milk *per se*. In this group of children dairy products comprised the largest source of animal protein in their diet (see Appendix).

Dairy product intake was positively associated with leg length in boys. This association was considerably attenuated by adjustment for IGF-I, suggesting it may be one of the biological mediators of this association, although studies in adults on the association between IGF-I and height/leg length have had mixed results[53,54]. We speculated that the absence of associations between diet and anthropometry in girls might be related to the early onset of adrenarche or puberty in some of the older girls. Therefore the analysis was repeated in girls aged less than 8 years at the time of IGF measurement (approximately 40% of the original sample). In this subgroup we found, contrary to expectations, an inverse association between cows' milk and leg length (in Model 3, $\beta = -0.109$ (-0.196, -0.022) standard deviation score in leg length per 100 g increase in cows' milk intake). However, these were *post hoc* analyses and so should be interpreted with caution. In addition, there was no evidence of a statistical interaction between cows' milk/dairy products and age with respect to their effect on IGF-I (among girls the *P*-values for the interaction terms age × cows' milk and age × dairy products were 0.19 and 0.14, respectively).

Strengths and limitations of the current study

As far as we are aware, this is the first study to relate childhood diet to both leg length and IGF-I. Previous studies of diet–IGF associations have generally used food-frequency questionnaires. We assessed diet using a 3-day unweighed food record. Unweighed food records have been shown to compare well with the results of weighed intakes, generally considered the gold standard of dietary assessment[55]. One problem with food-frequency questionnaires is their limited ability to estimate energy intake, which has been shown to be positively associated with IGF-I levels[56]. As a result, despite attempts to control for energy intake, residual confounding by this factor may remain. The current study had good information on a range of sociodemographic confounders – most previous studies have made no attempt to control for any measure of social status. Controlling for these confounders had very little effect on the observed associations, suggesting it is unlikely that socially patterned confounding accounts for the relationships we have observed. However, a limitation of the analysis is its cross-sectional nature, which means it cannot determine the causality of any relationships between IGF-I levels and diet. In addition our sample was slightly biased in terms of socio-economic status, and in favour of taller girls, which may have removed some of the variation in diet and IGF levels and made it harder to detect significant relationships.

Findings of other studies

Most previous studies of the relationship between cows' milk and IGFs have been conducted in middle-aged and elderly men. Two large studies in the USA[10,23] and one in the UK[24] have found positive associations between milk/dairy intake and IGF-I levels that persisted on adjustment for potential confounders. Relationships with protein intakes in these studies were less consistent. Two small

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studies of elderly men in Greece ($n = 153$[27] and 112[28]) found no association between cows' milk/dairy products and IGF-I, but may have lacked the statistical power to detect associations of the size seen in the other studies. There have been two studies in women, one in the USA[25] and one in the UK[26]. Only the US study found a positive association with cows' milk/dairy products, but both studies found evidence of positive associations between protein intake and IGF-I.

We are aware of only one other study that has investigated the relationship between milk intake and IGF-I and linear growth in children. Among 90 Danish 2-year-olds, intakes of milk and animal protein were positively associated with serum IGF-I and height in an analysis adjusting for body size, while intakes of vegetable protein and meat were not[33].

Conclusions

We have found a positive association between cows' milk and dairy products and IGF levels in 7–8-year-old children that appears to be at least partly mediated by levels of protein intake. These results are in line with the majority of adult studies. Dairy product intake in boys was also positively associated with leg length, providing a possible mechanistic link with IGF-I mediating the effects of nutrition on long bone growth and the risk of cancer in adulthood. Conversely, cows' milk intake in the younger girls was inversely associated with leg length. It is unclear from these results how a recommendation to reduce intake of dairy products would affect IGF-I levels and prepubertal growth. Furthermore, there are a number of possible detrimental effects of reducing IGF-I levels. Lower IGF-I levels in adults have been linked to heart disease[57], diabetes[58] and unfavourable changes in body composition in later life. In addition, higher IGF-I levels are associated with increased bone mineral density. Milk supplementation studies have found favourable effects on bone remodelling in adults[29] and on bone mineral content in children[30], in addition to the effects on IGF-I. Any dietary recommendations should await a more complete understanding of the complex effects of IGF-I on long-term health and more conclusive evidence on the relationship between diet and IGF-I.

Acknowledgements

We are extremely grateful to the mothers who took part in this study and to the midwives for their co-operation and help in recruiting the mothers during pregnancy. We would like to acknowledge the dedicated work of the ALSPAC Study Team; this includes interviewers, computer technicians, clerical workers, research scientists, volunteers and managers. ALSPAC is part of the World Health Organization-initiated European Longitudinal Study of Pregnancy and Childhood. The ALSPAC study could not have taken place without the financial support of the University of Bristol, the Medical Research Council, the Wellcome Trust, the Department of the Environment, the Ministry of Agriculture, Fisheries and Food, various medical charities and commercial companies. This part of the study was funded by the World Cancer Research Fund.

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Appendix – Correlation matrices of hormonal, anthropometric and dietary variables

	Height	Leg length	Sitting height	Cows' milk	Dairy products	Calcium	Protein	Animal protein	Energy
Boys									
IGF-I	0.388***	0.358***	0.332***	0.144*	0.175**	0.141*	0.235***	0.191**	0.114*
IGFBP-3	0.268***	0.271***	0.201***	0.143*	0.166**	0.111	0.143*	0.087	0.153**
Molar ratio	0.186***	0.151**	0.184**	0.022	0.041	0.057	0.130*	0.129*	−0.004
Height		0.909***	0.872***	0.171**	0.200***	0.105*	0.096	0.064	0.253***
Leg length			0.589***	0.177***	0.205***	0.144**	0.082	0.065	0.205***
Sitting height				0.111*	0.134**	0.038	0.089	0.048	0.247***
Cows' milk					0.961***	0.771***	0.369***	0.410***	0.367***
Dairy products						0.799***	0.370***	0.435***	0.429***
Calcium							0.482***	0.483***	NA
Protein								0.875***	NA
Girls									
IGF-I	0.189**	0.112	0.231***	0.007	−0.020	0.055	0.115	0.090	−0.021
IGFBP-3	0.202***	0.154**	0.207***	0.048	0.056	−0.032	−0.029	−0.049	0.101
Molar ratio	0.014	−0.022	0.050	0.016	−0.021	0.085	0.142*	0.135*	−0.112
Height		0.912***	0.868***	−0.042	0.005	−0.020	−0.049	−0.085	0.159**
Leg length			0.588***	−0.069	−0.028	−0.045	−0.041	−0.077	0.135*
Sitting height				−0.009	0.036	0.000	−0.046	−0.073	0.147**
Cows' milk					0.945***	0.721***	0.412***	0.462***	0.170**
Dairy products						0.756***	0.415***	0.485***	0.250***
Calcium							0.491***	0.505***	NA
Protein								0.890***	NA

IGF-I – insulin-like growth factor-I; IGFBP-3 – insulin-like growth factor-binding protein-3; NA – not applicable.
*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

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