Milk and Linear Growth: Programming of the IGF-I Axis and Implication for Health in Adulthood

Richard M. Martin\textsuperscript{a, b}, Jeff M.P. Holly\textsuperscript{c}, David Gunnell\textsuperscript{a}

\textsuperscript{a}Department of Social Medicine, \textsuperscript{b}MRC Centre for Causal Analysis in Translational Epidemiology, Department of Social Medicine, and \textsuperscript{c}Clinical Sciences North Bristol, University of Bristol, Bristol, UK

Abstract
There is increasing awareness that childhood circumstances influence disease risk in adulthood. As well as being strongly influenced by genes/genetic factors, stature acts as a marker for early-life exposures, such as diet, and is associated with risk of several chronic diseases in adulthood. Stature is also a marker for levels of insulin-like growth factor (IGF)-I in childhood. Levels of IGF-I are nutritionally regulated and are therefore modifiable. Milk intake in childhood and in adulthood is positively associated with higher levels of circulating IGF-I and, in children, higher circulating IGF-I promotes linear growth. Studies conducted by our team and others, however, indicate that the effect of milk is complicated because consumption in childhood appears to have long-term, programming effects which are opposite to the immediate effects of consuming milk. Specifically, studies suggest that the long-term effect of higher levels of milk intake in early childhood is opposite to the expected short-term effect, because milk intake in early-life is inversely associated with IGF-I levels throughout adult life. We hypothesize that this long-term programming effect is via a resetting of pituitary control in response to raised levels of IGF-I in childhood. Such a programming effect of milk intake in early life could potentially have implications for cancer and ischemic heart disease risk many years later.

Introduction
The opportunities to directly examine the relationship between early nutrition and diseases in adulthood are limited because few cohort studies have information from birth until old age. To date, therefore, most epidemiological
studies investigating early life origins of chronic diseases have used indirect markers of childhood nutritional exposures (for example, birthweight, height and leg length) and their relation with outcomes such as cancer, diabetes and ischemic heart disease [1]. Taller individuals generally have an increased risk of developing cancer [2] and a reduced risk of insulin resistance and ischemic heart disease [3]. There is some evidence that these associations may be specific to the leg length component of stature [2, 4]. Peak growth in leg length is prepubertal while peak growth in trunk is postpubertal [1]. This is demonstrated by changes in the trunk length:height ratio during growth. At birth, the ratio of trunk length to total height is approx 0.66, but by puberty it has declined to 0.52 [1]. From puberty, linear growth occurs equally in the trunk and legs. Stronger associations of adult chronic diseases with leg length have led to speculation that exposures which influence prepubertal long bone growth (e.g. early diet) may be more important in determining adult chronic disease risk [1, 5].

It has been hypothesized that influences of diet in childhood on the insulin-like growth factor (IGF) system may contribute to stature-chronic disease associations [6–9]. IGF-I in childhood is raised in response to some aspects of diet, particularly cow’s milk and dairy product intake [10], and raised childhood IGF-I in turn leads to greater subsequent growth in stature [11]. There is both experimental and observational evidence that raised IGF-I levels in early life subsequently program long-term modifications in the regulation of the IGF system. The most important evidence supporting the long-term programming of the IGF system comes from a randomized controlled trial of milk supplements provided to pregnant women and their offspring up to 5 years of age [9]. In a long-term follow-up of the offspring of the mothers originally recruited to the trial, circulating levels of IGF-I were measured at age 25 years. Those offspring who received milk supplements up to age 5 years had markedly lower serum IGF-I levels when measured 20 years later. The findings are opposite to the likely immediate responses to milk supplementation, which would have been to increase hepatic production of IGF-I [10]. We have hypothesized that a relatively high IGF-I level at the time of supplementation could cause a resetting of the pituitary due to greater feedback on the growth hormone (GH) axis from the prevailing circulating IGF-I during a sensitive period of life. This long-term resetting of the pituitary to raise the threshold for stimulating GH release would result in relatively lower hepatic IGF-I production and serum levels in later life. The reverse effect would occur in response to lower nutritional intake in early life (for example, in response to breastfeeding), which would be expected to lower IGF-I levels in early life but may program, via pituitary resetting, higher observed levels in later life [8].

In this chapter, we examine evidence supporting the hypothesis for nutritional programming of IGF-I levels in response to dietary exposures in childhood and the potential long-term implications of this. Our review draws on a number of studies that the authors have been appreciably involved in, includ-
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Regarding the Boyd Orr cohort [12], the Avon Longitudinal Study of Parents and Children (ALSPAC) [10], Barry-Caerphilly Growth Cohort study [9], Prostate testing for cancer and Treatment (ProtecT) study [13] and the Promotion of Breastfeeding Intervention trial (PROBIT) [14].

Childhood Stature and Health in Adulthood

Tall adults have an increased risk of cancer [2, 13] and a lower risk of cardiovascular disease [15, 16]. Stature in childhood and adulthood is dependent on genetic as well as environmental factors. However, childhood stature may better reflect prepubertal growth influencing exposures than adult height, which reflects a combination of childhood growth and also age and duration of pubertal maturation. Recent research is beginning to identify specific periods of early growth that are important to the risk of cancer [17, 18] and cardiovascular disease [4, 19]. For cancer, the most consistent associations with childhood growth have been found in relation to breast cancer. For example, faster pubertal growth (between 8–14 years) was positively associated with incident breast cancer risk independent of final height and explained the positive association of earlier age at menarche with breast cancer [17]. This finding has support from an ecological study in Japan where rapid increases in the heights of girls year on year between 1946–1966 were paralleled by large increases in breast cancer incidence among women after a 30 year time lag (i.e. 1976–1996) [20]. Growth-influencing exposures that changed rapidly after World War II include a 20-fold increase in milk and dairy product intake in Japan [21]. Associations with childhood stature have also been found for other cancer sites, in particular colorectal cancer, prostate cancer, endometrial cancer and hematopoietic cancers [22].

In those studies that investigated associations of the components of stature and cancer, leg length (a suggested marker of exposures influencing prepubertal growth, such as early socioeconomic circumstances, infection load and nutrition [1, 5]) was the component of height most often associated with increased adult chronic disease risk. For example, in the Boyd Orr cohort, a long-term follow-up of children surveyed between 1937 and 1939 and followed up in adulthood, we found that childhood stature was inversely associated with premature cardiovascular mortality (age <65 years) and self-reported ischemic heart disease, with leg length being the component with the strongest associations [4, 23]. Associations were explained by having been breastfed and childhood socioeconomic circumstances, confirming that leg length is a proxy for these prepubertal exposures.

A previous report from the Boyd Orr cohort (based on follow-up to 1995) showed a positive association between childhood leg length and mortality from cancers unrelated to smoking [24], most obvious for fatal sex hormone-dependent cancers (breast, uterus, ovary, prostate, other genital organs): the
risk of death increased by 126% for every unit increase in z score for leg length (approximately 3–4 mm). There was no evidence that trunk length was associated with cancer. A recent extended follow-up to 2004 suggested that associations were weaker than originally observed [18], although odds ratios (ORs) remained broadly consistent with a slight increase in risk with increasing childhood stature. Contrary to previously suggested stronger links with leg length [24], however, no single anthropometry measure was of particular importance in this longer-term follow-up, underlining the challenges of interpreting epidemiological data. The strongest associations were seen for breast cancer [OR per standard deviation increase in foot length: 1.16 (95% CI: 0.90–1.51); shoulder breadth: 1.16 (0.91–1.49); trunk: 1.26 (1.00–1.60)] and prostate cancer [OR for foot length: 1.22 (0.86–1.75)]. Foot length is one of the first components to reach peak growth, while shoulder breadth is one of the last [25].

**Breast Milk, Cows Milk and Stature**

Analysis of the Boyd Orr cohort has shown that stature was a generalized marker for many aspects of diet, housing and socioeconomic position in the children [5, 26]. The individual components of stature most strongly associated with childhood environment were leg and foot length. More specifically, leg length (but not trunk length) in both childhood and adulthood has been associated with breastfeeding in infancy in analyses of the Boyd Orr cohort [27] and in the 43-year follow-up of the 1946 UK national birth cohort [28]. The specific association between breastfeeding and leg length, which persists after controlling for socioeconomic circumstances [27, 28], suggests that breastfeeding may be a biologically relevant early-life exposure, rather than a marker for a broader social class effect, underlining the observed associations of leg length with adult diseases. Positive, albeit weaker, associations of breastfeeding with childhood and early adult stature have also been observed in the 1958 British birth cohort (n = 10,953) [29], Brazil (n = 2,250) [30] and in the 6.5-year follow-up of 13,889 children cluster-randomized to a breastfeeding promotion intervention (43% exclusively breastfed at 3 months) vs. usual breastfeeding practices (6% exclusively breastfed at 3 months; PROBIT) [31]. The evidence from the PROBIT trial is particularly noteworthy since it provides experimental evidence based on an intention to treat analysis and so is unlikely to be explained by confounding or selection bias. In the Boyd Orr cohort, a mother’s leg length but not trunk length as a child was associated with her offspring’s birthweight, suggesting the intriguing possibility that early nutrition and growth may have transgenerational effects on later health [32]; however, the finding could also reflect that genetic influences on leg length are the same as those that determine birthweight.

There is a large literature on the effect of cow’s milk on stature [33], with intervention studies going as far back as Boyd Orr’s trial of food supplements...
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**Table 1.** Association of family milk intake and height of children in the Boyd Orr cohort, 1937–1939 (mean age 7.5 years)

<table>
<thead>
<tr>
<th>Quartiles of milk intake</th>
<th>1 (low)</th>
<th>2</th>
<th>3</th>
<th>4 (high)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median milk intake, g/day</td>
<td>89</td>
<td>163</td>
<td>255</td>
<td>471</td>
</tr>
<tr>
<td>Unadjusted OR</td>
<td>2.9 (2.3–3.7)</td>
<td>2.8 (2.2–3.5)</td>
<td>2.6 (2.1–3.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adjusted¹ OR</td>
<td>2.1 (1.6–2.6)</td>
<td>2.1 (1.7–2.7)</td>
<td>2.1 (1.7–2.7)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ORs are for the risk of having a below-average height for age and sex.
¹ Adjusted for childhood socioeconomic position and food expenditure.

given to Scottish school children, published in 1928 [34] and 1929 [35]. We also observed a strong effect of family milk consumption on childhood stature in Boyd Orr’s later Carnegie Survey that was conducted in 16 survey centers across England and Scotland (1937–1939), and which formed the basis for the reconstruction of the Boyd Orr cohort (see table 1, with acknowledgements to Jolieke van der Pols). However, in a contemporary setting (Bristol, UK, children born between 1991–1992), we observed only a weak positive association of milk consumption in childhood with leg length amongst boys (not girls) at ages 7–8 years [10].

**Milk and Health in Adulthood**

Some dairy products such as whole milk, butter and cheese have a high content of saturated fatty acids and cholesterol, and consumption of these in adulthood has been thought to contribute to cardiovascular disease risk, though evidence for this is not consistent [36]. Intake of dairy products may affect a mixture of pathways associated with carcinogenesis (summarized by van der Pols [37], and including increased circulating IGF-I, modification of vitamin D status, increased intake of calcium, conjugated linoleic acid and exposure to contaminants such as polychlorinated biphenyls). Overviews of the evidence from observational studies, however, suggest a reduction in risk of ischemic heart disease, stroke, diabetes and colorectal cancer (but possibly an increased risk of prostate cancer) associated with relatively high consumption of milk [38, 39].

To date, most studies of the associations of dairy consumption with cancer and cardiovascular disease risk have been based on estimates of adult dairy intake. In children, the blood lipid profile at different stages of the life course is associated with the type of milk consumed. In comprehensive systematic reviews conducted by Owen et al. [40, 41], mean blood total cholesterol con-
centrations in breastfed infants, compared with those who were formula fed, were higher in infancy, similar in childhood and lower in adult life (the lower levels in adulthood being a possible example of nutritional programming). Children who consume low-fat milk have lower serum saturated fat fractions and higher polyunsaturated fat concentrations compared to those who drink whole milk [42]. Furthermore, there is evidence that high calcium intake, of which dairy products are an important dietary source, is associated with lower diastolic and systolic blood pressure in children [43].

However, there are few cohort studies investigating whether consumption of dairy products in childhood has long-lasting effects on cardiovascular disease or cancer risk in adulthood. Our 65-year follow-up studies based on the Boyd Orr cohort used per capita household intake estimates for dairy products and calcium as a proxy for individual intake [37, 44]. We found no convincing evidence of any increased risk of coronary heart disease or stroke in people who as children had the highest milk or dairy consumption [44]. While chance or residual confounding cannot be ruled out, childhood calcium intake was inversely associated with stroke mortality (multivariable adjusted hazard ratio (HR) for highest vs. lowest calcium group: 0.41; 95% CI 0.16–1.05; p for trend = 0.04), but not coronary heart disease mortality. All-cause mortality was lowest in those with the highest family dairy (HR = 0.77; 95% CI 0.61–0.98; p for trend = 0.04) and calcium intake (HR = 0.77, 95% CI 0.60–0.98; p for trend = 0.05). This latter finding could reflect socioeconomic confounding, and we concluded that: ‘replication in other study populations is needed to determine whether residual confounding explains part of these findings’ [44].

We also investigated associations of dairy product and calcium intake in childhood with cancer risk [37]. High childhood total dairy intake was associated with an almost tripling in the odds of colorectal cancer (multivariable OR: 2.90, 95% CI: 1.26–6.65) compared to low intake, independent of meat, fruit and vegetable intake and socioeconomic indicators. Milk intake showed a similar association with colorectal cancer risk. High milk intake was weakly inversely associated with prostate cancer risk (p for trend = 0.11). Childhood dairy intake was not associated with breast and stomach cancer risk, and a positive association with lung cancer risk was confounded by smoking behavior during adulthood. These findings appear to be in sharp contrast to the steadily increasing pool of evidence for a protective effect of dairy consumption on colorectal cancer risk in adult populations [39]. Our finding that high childhood intake of milk is associated with reduced prostate cancer risk is also contrary to findings in studies of adult intake [39], although the confidence intervals in our study indicate that this association was imprecisely estimated. We did not show any strong evidence of associations between childhood dairy consumption and breast cancer risk, although our point estimate (OR = 0.83, CI 0.41–1.69, in the highest vs. lowest quartile of childhood milk intake) is in line with the case-control findings by Michels et al. [45] (according to which milk intake in childhood was associated with reduced risk of breast cancer).
Insulin-Like Growth Factors, Nutrition and Adult Chronic Disease Risk

IGFs are multifunctional peptides that regulate cell proliferation, differentiation and apoptosis and play a fundamental role in somatic growth. Six circulating IGF-binding proteins (IGFBPs 1–6) modulate the availability of IGF-I to tissue. Over 90% of circulating IGF-I is bound to either a binary or ternary binding complex involving IGFBP-3. Circulating IGF-I is positively associated with growth in height in childhood [11, 46], suggesting that height may be acting as an anthropometric marker for levels of IGF-I [2]. Since childhood stature is a marker of the activity of IGF-I, modulation of the IGF system could provide a mechanism explaining associations of height with adult disease risk [2]. While adult height is not strongly associated with IGF-I in cross-sectional studies [47], stature may be a marker for this growth factor in childhood, and this may be the period during which it acts to increase disease risk in later life.

IGF-I is mainly secreted from the liver in response to GH and insulin, but dietary intake also influences IGF-I levels, with energy- and protein-deficient diets resulting in marked reductions in IGF [48]. An analysis based on the Boyd Orr cohort [49] found that a lower household calorie intake in childhood was associated with lower cancer risk in later life (relative hazard for all cancer mortality and cancers not related to smoking = 1.15 and 1.20 per MJ, respectively, in fully adjusted models; p = 0.001). In animals, calorie restriction reduces risk of cancer at least partly by reducing circulating concentrations of IGF-I [50]. It is therefore plausible that height-cancer associations may reflect an association between early diet and cancer risk that is mediated via the IGF system.

Studies have related specific aspects of diet to IGF-I levels in well-nourished humans [51–53]. For example, in cross-sectional analyses based on 1,037 healthy women in the Nurses Health Study, total energy and protein intake were positively associated with IGF-I levels when adjusted for covariates [51]. The association with protein intake was largely attributable to higher IGF-I levels among women who consumed higher amounts of milk. Of all the dietary determinants linked with circulating IGF-I in cross-sectional studies of adults and children, it is increasing milk intake that appears to be most consistently associated with higher levels [10, 33, 53]. In a cross-sectional analysis of dietary determinants of serum IGF-I in 7- to 8-year-old children (n = 538, diet assessed using a 3-day unweighed food record), cows milk and dairy intake were the components of diet most strongly and positively associated with IGF-I (in energy-adjusted models) [10]. Cow’s milk was a major source of the child’s protein (40% of total animal protein intake), and controlling for total protein or animal protein intake attenuated the association of IGF-I with cow’s milk and dairy intake. Controlling for calcium intake, however, had no impact on the observed association. Evidence from experi-
Mental studies, summarized by Hoppe et al. [33], suggests that the association of cow's milk with IGF-I levels is likely to be causal.

Breastfed infants may be at reduced risk of early overnutrition and accelerated growth [54] compared with those who are formula fed, since formula-fed infants consume greater volumes of milk than breastfed infants and appear to have higher protein and energy intakes in infancy [55–58]. The lower energy and protein intakes of breastfed infants compared with those who are formula fed, may lower hepatic IGF-I production at the time of breastfeeding, which would be compatible with the slower growth rate of breastfed compared with formula-fed infants [54]. In a study based on 33 preterm infants (gestational age: 28–37 weeks) who were appropriate size for their gestational age, levels of IGF-I and IGFBP-3 were measured at 1 and 3 weeks after birth [59]. There were strong positive correlations of neonatal protein (r = 0.40; p < 0.01) and energy intakes (r = 0.45; p < 0.001) with IGF-I, suggesting that very early nutritional intake influences levels of these growth factors.

In a study of 942 appropriate weight for gestational age and term infants, IGF-I levels measured at age 3 months were lower in breastfed than formula-fed infants, independent of weight at 3 months [60]. Increasing exclusivity of breastfeeding was associated with lower levels of IGF-I in a dose-response pattern. Likewise, others have found that formula-fed infants have higher insulin levels compared with breastfed infants [61]. Thus, both changes in IGF-I and insulin could in part explain the higher initial postnatal growth rate in formula-fed vs. breastfed infants.

The associations of both childhood stature and milk intake with adult chronic disease risk have led to the speculation that a possible mechanism for these patterns is via the IGF system. Raised circulating IGF-I is positively associated with the development of premenopausal breast cancer, prostate cancer (particularly advanced prostate cancer [62], although confounding by the presence of benign prostatic hyperplasia has not been ruled out [63]), and colorectal cancer, the same sites for which height-cancer associations have been most frequently shown [6, 64]. In line with the inverse childhood height-cardiovascular disease associations, there is some evidence that raised circulating IGF-I is inversely associated with cardiovascular disease risk, perhaps because IGF-I enhances plaque stability [65]. Recent unpublished observations by our group suggest that men who gained a large amount of weight between childhood and adulthood had markedly lower circulating levels of IGFBP-2 in adulthood (irrespective of final weight) [Rowlands et al., submitted]. Lower IGFBP-2 levels indicate higher degrees of insulin resistance [66], which is in turn positively linked with cancer [67–69] and cardiovascular disease risk. Hyperinsulinemia may also increase IGF-I bioavailability by suppressing the hepatic production of IGFBP-1. Thus, IGFBP-2 may be a component of the IGF system that contributes to associations of weight increases over the life course with increased risk of cancer and cardiovascular disease.
Nutritional Programming of IGF-I

This section reviews the evidence linking early nutritional status with IGF-I levels in later life. Evidence from five long-term cohort studies to date supports the idea that the acute effects of greater nutritional intake, such as higher cow's milk intake, which leads to higher levels of IGF-I in the short-term are opposite to the long-term effects of greater childhood nutrition, which seems to be associated with a lowering of IGF-I levels many years later. Similarly, the acute effects of lower nutritional intake (resulting in a lowering of circulating IGF-I) appear to be associated with higher IGF-I levels many years later. First, in an analysis of the ALSPAC cohort, we observed that having been breastfed in infancy was associated with increased IGF-I levels in children at age 7–8 years [8]. There was some evidence of a dose-response relationship: in age- and sex-adjusted analyses, for each increase in category of breastfeeding exclusivity (never, partial and exclusive), there was on average a 7.1 ng/ml increase in levels of IGF-I, attenuated to 3.6 ng/ml after controlling for socioeconomic and dietary variables. This positive association is in line with the positive association observed between breastfeeding and childhood stature seen in several settings [27–31], but contrasts with the data (reviewed above) indicating that circulating IGF-I levels are lower while babies are being breastfed [59, 60], possibly due to the lower protein and energy content of breast milk compared with formula milk.

Second, in the 65-year follow-up of the Boyd Orr cohort, higher milk intake in childhood (which will result in an acute increase IGF-I levels) was inversely associated with IGF-I levels in old age [7]. Third, data from 40 participants in the Copenhagen Cohort Study showed an inverse association between IGF-I levels at 9 months and IGF-I levels at 17 years of age (r = –0.39) [70]. A 1 ng/ml higher IGF-I concentration at 9 months was associated with a 0.95 ng/ml lower IGF-I concentration at 17 years. In line with this finding, infants who were fully breastfed (vs. those never breastfed) had lower levels of IGF-I in infancy (93 vs. 130 ng/ml, respectively) but higher levels in adolescence (328 vs. 292 ng/ml, respectively). These data are consistent with the above studies in suggesting that those with higher IGF in infancy will have lower IGF levels in adulthood (and vice versa).

Fourth, a natural experiment, based on 87 postmenopausal women living in Utrecht [71], provides evidence for an effect of early nutrition on long-term levels of IGF. In this study, the degree of childhood exposure to the 1944–1945 Dutch famine (when daily rations dropped from 1,500 kcal in September 1944 to below 700 kcal in January 1945 until liberation in May 1945) was associated in a dose-response manner with increased plasma levels of IGF-I and IGFBP3 at age 50–69. These data suggest that a relatively short period of caloric restriction was associated with increased long-term levels of IGF-I. No differences were found for c-peptide levels, a marker of insulin resistance.
The results are opposite to immediate responses seen under starvation, which would have caused a lowering of IGF-I.

Fifth, the Barry-Caerphilly trial, conducted in the 1970s, was a randomized controlled trial of milk supplements provided to pregnant women and their offspring up to 5 years of age [9]. The women in the supplemented group were provided with tokens that entitled them to free milk delivered by their milkman. In the long-term follow-up of the offspring of the mothers originally recruited to the trial (the Barry-Caerphilly Growth cohort), circulating levels of IGF-I and IGFBP-3 were measured in 663 subjects aged 25 years on average. Those individuals whose mothers were randomized during pregnancy to milk supplementation and who received milk supplements up to age 5 years had markedly lower serum IGF-I levels when measured 20 years later. The findings are opposite to the likely immediate responses to milk supplementation, which would have been to increase IGF-I [10]. These are important results because they provide experimental data, analyzed by intention to treat, on the role of early life programming of the IGF system, occurring either in the intrauterine or postnatal period. Such experimental data provide important evidence that long-term programming of IGF-I levels could be causally linked to nutritional intake earlier in life.

Altogether, these findings (summarized in table 2) from ALSPAC, Boyd Orr, Copenhagen, the Dutch famine and the Barry-Caerphilly Growth cohort, are compatible with increased nutritional intake in infancy or childhood, primarily protein intake, causing a direct increase in hepatic IGF-I production which then feeds back to suppress pituitary GH output with a long-term resetting of the pituitary resulting in lower IGF-I levels in the long-term [8].

**Implications**

Hepatic production of IGF-I is controlled not only by pituitary GH but also by insulin and by many nutrients. The data provided here suggest that there

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**Table 2.** Interrelationships between diet and IGF at various points in life course

<table>
<thead>
<tr>
<th>High milk/protein intake</th>
<th>IGF-I levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>infancy</td>
</tr>
<tr>
<td>In infancy (bottle feeding)</td>
<td>+</td>
</tr>
<tr>
<td>In childhood</td>
<td>–</td>
</tr>
<tr>
<td>In adulthood</td>
<td>–</td>
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\(+ = \) Positive association; \(– = \) inverse association.
may be critical or sensitive periods in childhood when nutritional exposures could result in long-term resetting of the pituitary, programming adult IGF-I levels.

There are several implications of these findings. A relatively low IGF-I level at the time of breastfeeding would be consistent with the slower infant growth rate at that time, and a consequent resetting of the pituitary, due to less feedback, could then result in a relatively high IGF-I level subsequently in later life. This would be compatible with our findings of greater height in later childhood and adulthood associated with breastfeeding [27]. Such ‘programming’ of the IGF-I system in later life provides a possible biological mechanism underlying the finding that exclusive breastfeeding was associated with greater childhood IQ in the experimental PROBIT trial [72], since IGF-I in childhood is positively associated with IQ [73].

The findings provide hints at possible sensitive periods in life when environmental exposures influence the future risk of various chronic diseases and suggest that the timing of these sensitive periods may differ for different outcomes. As discussed by van der Pols et al. [37], our observation that high intake of dairy foods in childhood is associated with an increased risk of colorectal cancer may indicate that it is the effect of childhood dairy intake on childhood (rather than adult) levels of IGF-I that is the important mediator of future risk, given the positive association between dairy intake and IGF-I concentrations in childhood [10] but inverse association between childhood dairy intake and adult IGF-I levels [7] and the positive link between adult IGF-I concentrations and colorectal cancer risk [64]. Our finding that a lower household calorie intake in childhood was associated with lower overall cancer risk in later life [49] could also reflect the importance of levels of IGF-I in childhood for carcinogenesis.

Our finding that childhood consumption of milk in the highest intake group is associated with reduced prostate cancer risk is contrary to findings in adult intake studies [74], but is in keeping with the possible long-term programming effect of childhood nutrition on adult IGF-I, and with the inverse association between childhood dairy intake and adult IGF-I levels observed in this study population [7]. This does assume, however, that for prostate cancer, it is levels of IGF-I in adulthood that are important.

These data fit in with the growth acceleration hypothesis proposed by Singhal and Lucas [75, 76]. In this case, dietary factors causing accelerated growth in infancy (such as nutrient-enriched formula milks) would be hypothesized to program lower levels of IGF-I in later life, a potential pathway linking rapid early growth with adult insulin resistance and cardiovascular disease.

Further studies, preferably experimental, should now be conducted to confirm or refute the hypothesis that variations in IGF-I explain associations of early-life environmental exposures with health in later life. Currently, robust data supporting the IGF-I programming hypothesis are provided by one randomized controlled trial (BCG cohort [9]) and one natural experiment.
The long-term follow-up of experiments (such as the PROBIT trial, in which infants were cluster randomized to a breastfeeding health promotion intervention vs. usual practice [14]) would provide further robust evidence on which to base inference about the causal nature of the observed long-term effects of early nutrition on the IGF system.

The complex interrelationships, which seem to vary depending on when exposure occurs during the life course, between dietary intake, IGF-I levels and adult disease risk indicate that there will need to be a careful appraisal of the overall health-balance sheet (benefits vs. adverse effects) of any potential preventative measures based on manipulating childhood dietary intakes that modify the IGF system in either or both the short and long-term.

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References

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Discussion

Dr. Gibson: You raised the issue of epidemiologists being skeptical; biochemists are even more skeptical especially about the work of epidemiologists, which raises the issue to me about causation vs. association. In the early days of the cholesterol theory or hypothesis, there was a great deal made by the fact that the associations between cholesterol levels and coronary heart disease were not necessarily causative but were associative, and we are still debating the causation of cholesterol to this day. Are you really inferring from your data that IGF is somehow causative of all of these events.
such as cancer and heart disease? How do we relate that to the fact that as nutritionists we are trying to improve growth all the time and then you are coming along and telling us that, I think if I understand it correctly, that increased growth is associated with IGF levels in some way and that's a cause of greater risk now.

Dr. Martin: You are absolutely right, most of what I have shown relates to associations. When we examine association data, we look for consistency and patterns in the results. We find consistent evidence from several studies [1–5] that circulating IGF-I levels are programmed from early life. We can't assume that the acute effects of milk intake in childhood on IGF are going to reflect the pattern of IGF levels later in life. This is shown by the Barry-Caerphilly randomized controlled trial, which does allow causal assessment when analyzed by intention to treat [5]. So there is randomized evidence suggesting that the regulation of the IGF system is more complex than would appear from cross-sectional studies. We therefore need more prospective studies with long-term follow-up, such as the Copenhagen Cohort Study [3]. The relationship of IGF-I with cancer risk is all observational, and caution is required in interpreting observed results. For example, the positive relationship of IGF-I with prostate cancer could be explained by detection bias. If IGF-I causes benign prostatic hyperplasia and its symptoms, prompting men to seek a PSA test and be diagnosed with prostate cancer, this generates an artifactual association of IGF-I with cancer. You are correct to be skeptical, and I think we should put more effort in obtaining experimental evidence looking at programming of the IGF system. For example, long-term follow-up of the randomized PROBIT trial, involving 17,000 children, is currently investigating, in an intention-to-treat analysis, associations of prolonged, exclusive breastfeeding with IGF-I at age 11.5 years [6]. This will provide unique experimental evidence on whether there is a real programming effect of early nutrition on later IGF-I levels.

Dr. Mølgaard: What about the relationship between one of the main killers, smoking, and the IGF-I levels? In your last paper, you said that you could not control for smoking, and smoking is related to lower milk intake as far as I remember.

Dr. Martin: In one paper, we investigated associations of dairy products and calcium intake in childhood with cancer risk [7]. We found that childhood dairy intake was positively associated with lung cancer risk, but felt this relationship was confounded by smoking behavior during adulthood.

Dr. Mølgaard: But smokers had lower IGF-I levels.

Dr. Martin: We don't find a very strong relationship of IGF with smoking [8], although the smoking variable was relatively crudely measured. The association of IGF-I with milk intake is the strongest [9].

Dr. Prentice: As a biochemist working in pregnancy, I often wondered about the use of a concentration value in the circulation as a marker of hormone output or indeed of impact. I am assuming that the children who had high IGF-I levels in childhood were bigger as adults? If so, I just wondered, although I am sure this is not an original thought, if one was able to correct for body volume or at least blood volume, rather than relying on concentration, whether that would provide a true measure of the production of IGF-I during the day, and whether that would explain the associations you see?

Dr. Martin: You mean were the children taller as adults?

Dr. Prentice: The children given milk in childhood grew bigger, and I am making the assumption that they are bigger individuals as adults, so could blood concentration be confounded by body size is the question, I think.

Dr. Martin: I guess that's possible. There is not a strong relationship of IGF-I with BMI and obesity, and controlling for that doesn't make much of a difference [8].

Dr. Prentice: BMI is not a measure of size; it is a measure of adiposity or shape [10].
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_Dr. Martin:_ It is the relationship of circulating levels with tissue levels that ultimately would determine any link of serum IGF-I with disease. Some of the changes in IGF-I associated with disease are actually quite small, although they increase over lifetime. Nevertheless, associations of circulating IGF-I with disease exist, so such levels are a proxy for something. Endocrinologists tell me that circulating levels are a reasonable proxy for what is going on at the tissue level. You need population-based studies to determine whether findings on tissues and in animal experiments actually translate into an impact at the population level.

_Dr. Melnik:_ I would like to thank you for this very impressive talk, and I think we should also mention two very important epidemiological studies which presented epidemiological evidence for the association between milk and dairy protein consumption and elevated serum IGF-I levels [11, 12]. Moreover, Jacqueline Major from the Department of Family and Preventive Medicine at the University of California San Diego recently reported that serum IGF-I levels show a correlation with the overall cancer mortality in elderly men [13]. IGF-I is the strongest mitogen we know. It promotes cell proliferation and inhibits apoptosis. IGF-I signaling plays a serious role in cancer promotion [14].

_Dr. Martin:_ I agree, the observational evidence is strong, providing similar data to the sort of data that we are providing, and the biochemistry makes perfect sense. As others point out, you do have to be skeptical. Ultimately, only randomized controlled trial evidence could robustly show if there is causation and a population health impact. Such trials may be difficult, but, for example, you could investigate men at high risk of prostate cancer progression and determine experimentally whether reducing milk intake in such men lowers IGF-I levels and ultimately leads to a reduction in risk of progression. I think we can do such trials, particularly in populations where the benefit to risk ratio allows equipoise.

_Dr. Clemens:_ I appreciate Dr. Melnik’s comment about the signaling pathways. As we look at the data from yesterday, the comment about the β-lactoglobulins and α-lactalbumins in breast milk and then we look at the casein-dominant components in cow’s milk and obviously in cheese, would you expect to see that any of the peptides derived from these particular proteins may be part of the signaling pathways that may trigger some of these outcomes?

_Dr. Martin:_ There was some evidence yesterday relating casein to raised IGF-I, but I don’t know the literature on those kind of peptides.

_Dr. Gibson:_ You said there was this association between tallness and IGF. Is it also extended to obesity, that is weight as well?

_Dr. Martin:_ The relationship between IGF-I and obesity is complex. We have shown in a very large study with 1,000 men an inverted U-shaped relationship, so that the highest levels of IGF-I are amongst those in the second and third quartiles of BMI [8]. There is a much stronger association of IGF-binding protein 2 (IGFBP-2) with obesity, such that obesity is associated with lower levels of IGFBP-2 [8], which at the cellular level may increase the bioavailability of IGF-I. So, IGFBP-2 is another component that might be involved in signaling mechanisms and progression of disease. The relationship of the IGF system with obesity has interested us as a possible mediator of reported associations of breastfeeding with obesity, although our systematic reviews [15, 16] and the PROBIT [17] did not find convincing evidence that there is a strong inverse association of breastfeeding with obesity.

_Dr. El Barbary:_ How do you explain the finding that at the age 3 months the infants who were never breastfed had a higher level of IGF-I in comparison to those who were exclusively breastfed, and at the age of 7 to 8 years this situation was reversed?

_Dr. Martin:_ Lower levels of IGF-I in those who were exclusively breastfed may be due to lower protein and energy intake at that time [18]. To explain the later switch
in the direction of associations at the age of 7 years, that is where we speculate that there may be a programming effect such that the lower IGF-I levels in infancy reset pituitary control, so that there are higher levels in later life [19].

Dr. Makrides: Apart from dietary factors, what other factors may program or influence IGF concentrations?

Dr. Martin: IGF-I is a nutritionally regulated peptide, so that is where we have concentrated most of our research efforts in programming. There are a myriad of exposures that could influence and regulate IGF-I, including mitogenic factors such as insulin, estrogen and antiproliferative agents such as vitamin D or retinoic acid. IGF-I is an important intermediate between upstream exposures and downstream signaling, integrating a whole host of exposures and signaling pathways.

References

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