Introduction


Growth and Later Health: A General Perspective

Alan Lucas

The MRC Childhood Nutrition Research Centre, Institute of Child Health, London, UK

Abstract

Whilst growth and its derangement in disease have been a long-standing focus in pediatrics, increasing evidence points to a further, fundamental role of early growth in the programming of later health. In studies on animals and humans, rapid early growth is associated with higher risk of obesity and cardiovascular disease, and in animals, senescence and life span – a concept encapsulated in the postnatal growth acceleration hypothesis. This hypothesis explains the benefits of breastfeeding to infants for reduced cardiovascular disease risk in terms of their slower early growth and the fetal origins hypothesis in terms of the adverse postnatal catch-up growth in infants born small. Early growth, notably prior to full term, also influences brain development and cognition – and emerging evidence suggests diverse, broader effects, for instance cancer and the onset of puberty. Understanding the mechanisms, triggers and windows for such effects is important, given the major public health implications, including potential new opportunities for primary prevention of adult disease.

In humans, growth is a key feature that distinguishes the pediatric from adult population. Growth is the traditional measure of overall nutritional status. Much scientific attention has been paid to its measurement and derangement in a wide variety of diseases.

More recently, a new focus has been its association with long-term health outcomes, and in animal models, also senescence and lifespan [1, 2]. Emerging research on the importance of early growth is providing insights into developmental biology, the early influences on adult health, and potential strategies for primary prevention of disease.
Central to this field is programming [3] – the broader concept that a stimulus or insult at a critical period may have long-term or lifetime effects.

The first studies on critical periods related to imprinting in birds [4]. In the last 80 years, much work has shown programming effects of early nutrition or growth. The first experimental studies were in animals. McCay, in the 1930s [2], showed reduced energy intake in rats, resulting in growth stunting, increased lifespan and favorably affected several later health outcomes. Conversely McCance [5] showed faster early growth in the first 3 weeks in rats, achieved by reducing litter size, increased final size; using a similar model, Hahn [6] showed adverse long-term metabolic effects, notably cholesterol levels. Since then, manipulation of early nutrition and growth has been shown in numerous animal studies to influence long-term or lifetime blood pressure, lipid metabolism, body fatness, insulin resistance, atherosclerosis, bone health, learning and behavior [2, 6–9]. Such long-term effects have been found in humans in observational studies and, importantly, random intervention trials (RCTs) that can establish causation [3, 10–13].

Growth is fuelled by nutrition, making it difficult to extricate the influence of these two early factors on later health. Yet, a central programming influence of growth itself is suggested by the close association between growth and outcome across numerous species [14] including humans.

Programming of Obesity and Risk of Cardiovascular Disease

Animal studies provide extensive evidence on the programming of obesity and cardiovascular disease (CVD) risk factors, including atherosclerosis itself. Lewis [7] showed in infant baboons that an energy-enriched diet, which produced transient excessive weight gain during the intervention, programmed late emergence of obesity in adolescence and adult life. Ozanne and Hales showed in rats that postnatal catch-up growth after nutrient restriction in utero increased later fatness and reduced lifespan [1]. These examples illustrate potentially deleterious effects of rapid early growth now demonstrated across diverse species including invertebrates, fish, rodents and primates, reviewed by Metcalfe and Monaghan [14] who present the concept of ‘grow now, pay later’, referring to the long-term cost of any short-term advantage of rapid growth.

In 1982, Lucas [15] set up experimental studies (RCTs) in humans to test the programming concept, initially in preterm infants. Those assigned diets that promoted more rapid early growth had, 16 years later, higher blood pressure, cholesterol, insulin resistance, leptin resistance and greater endothelial dysfunction (as the earliest marker of the atherosclerotic process) [13, 16]. A subsequent RCT in healthy, full-term but small (SGA) infants showed
those fed an enriched formula that promoted catch-up growth in infancy had elevated blood pressure [11] and a 37% increase in fat mass 8 years later.

Based on the animal evidence and these trials, Singhal and Lucas [13] proposed the postnatal growth acceleration hypothesis – that rapid early growth (upward centile crossing) increases the risk of later CVD and obesity. Recently, this hypothesis has been supported by over thirty-five observational studies showing early growth – including in healthy full-term infants – is associated with later fatness or obesity, blood pressure cholesterol and insulin resistance – the key risk factors for CVD [10, 17–19].

This emerging evidence has major implications for practice and is increasingly underpinning current recommendations.

**Breastfeeding and CVD Risk**

Numerous observational studies show breastfeeding is linked to reduced obesity risk, blood pressure, cholesterol and insulin resistance in later life [13, 20]. Opportunities for experimental studies to confirm causation have been limited, but in preterm infants Singhal and Lucas [13] were able to examine cardiovascular risk factors in those infants randomized to banked donor breast milk or formula 16 years later. The breast milk-fed group had a >3 mm reduction in diastolic pressure and 10% reduction in cholesterol (both large effects in population terms), and a reduction in insulin and leptin resistance.

It is proposed that these apparently beneficial effects of breastfeeding on later obesity and CVD risk, in accord with the postnatal growth acceleration concept, relate to the slower growth of breastfed infants [13]. That this is a plausible interpretation is supported in several ways. Firstly, comparative studies of breast- and formula-fed infants, although complex in their findings, generally support slower growth in early infancy in the breastfed group. Secondly, Lucas et al. [21] showed neonatal insulin response to a breastfeed was substantially less than that to a formula feed, plausibly signifying lower nutrient intake in the breastfed group. Finally, extensive studies (Lucas et al.; 1970s–1980s), both using mechanical devices and stable isotope kinetics [22], showed that the energy content of breast milk was lower than expected. Thus, expressed breast milk which varies greatly in fat content and is used for breast milk analyses, contains a higher mean energy content than milk consumed by the infant (‘suckled breast milk’). Infant formulas have been traditionally based on the content of expressed milk and contain around 15% more energy than in suckled breast milk. Thus, even modern formulas may contain excessive nutrient content, plausibly causing faster growth. Further evidence that growth is a central factor for cardiovascular risk comes from our finding (unpublished data) that amongst exclusively breastfed term infants, those with the fastest growth had the worst cardiovascular risk profile.
Lucas

**Fetal Programming of CVD**

In the later 1980s–1990s, Barker [23] observed low birthweight was associated with increased risk of CVD. This was hypothesized to reflect adverse programming caused by reduced fetal growth. However, this construct, based on retrospective observations rather than experimental studies, has been re-examined. Thus, Lucas et al. [24] noted the association between low birthweight and later blood pressure was generally seen only after adjusting for current weight (when blood pressure was recorded). Yet, this effectively adjusted birthweight for current weight – a measure of postnatal growth acceleration. Hence, a reinterpretation of these studies is that low birthweight is a marker for future rapid growth rather than prior fetal programming. The postnatal growth acceleration hypothesis was proposed to unify the fetal and postnatal origins of adult disease, explaining the previous fetal origins concept in terms of the adverse effects of postnatal catch-up growth following reduced fetal growth. Indeed, in our own data sets, when birthweight and postnatal growth [13] are allowed to ‘compete’ for the impact on CVD risk, the birthweight effect is often small or absent.

**Overview**

Extensive evidence shows early growth is related to later obesity and CVD risk opening up major opportunities for early interventions to reduce later morbidity.

Finally, for early programming to influence outcome, subsequent environment is critical. For instance, Mott’s study in baboons [8] showing the adverse interaction between breastfeeding and subsequent Western style diet for later atherosclerosis risk is an instructive model.

Nevertheless, besides programming, clearly genetic and, of relevance here, other environmental factors, affect long-term obesity and CVD risk. In practical terms, a balance of risks is needed. Thus, much evidence supports the view that term infants born small, who are well and come from low risk environments should not be fed enriched diets to promote catch-up. However, early growth promotion should be given precedence over any long-term considerations in undernourished infants in poor health, and in particular, those in the developing world where poor early growth adversely affects morbidity and mortality risk.

**Early Growth and the Brain**

Malnutrition, which may cause stunting and reduced brain growth, has been much studied in relation to future cognitive ability.

Rodents are often used to test for effects of early nutritional deprivation on performance because their brain growth spurt occurs during the suckling period, when nutrition can readily be modified, e.g. by maternal nutritional
deprivation or manipulating litter size. However, behavioral disadvantages for underfed pups are open to alternative explanations [9]; for instance, nutritional interventions may affect the interaction between pup and mother, important for behavior.

Of relevance to humans (below), a review of studies comparing performance in previously well-nourished vs. undernourished rats showed a disadvantage for undernourished animals was more likely if the period of undernutrition included gestation; and performance was most often affected in males.

**Epidemiological Studies in Humans**

Numerous observational studies explore whether children with undernutrition or stunting underperform [25]. In many, though not all studies, poor nutritional status was associated with reduced cognition or attainment. However, these studies are generally highly confounded by poverty, morbidity and lack of stimulation found in malnourished populations.

Some studies have attempted control for this. For instance, a Guatemalan study was conducted in four villages, with similar populations and lifestyles. In two villages, a high-energy, high-protein drink was supplied, and in the others, a low-calorie drink – both available ad libitum to pregnant women and children up to age 7 years. Those fed the high-energy, high-protein drink had greater school achievement in adolescence. Sibling controlled studies have also been used; and in approximately half of these, undernourished children performed less well than control siblings.

**Randomized Trials in Full-Term Infants and Children**

In humans, the so-called critical brain growth spurt takes place between the last trimester of fetal life and 2 years after term, and has been considered a vulnerable period for undernutrition. Some RCTs of early nutrition have been conducted during this window, largely in undernourished or stunted infants from developing countries [25, 26].

In a Taiwanese study, high-risk mothers were randomized to a nutrient-supplemented or placebo drink during pregnancy and lactation. Infants of supplemented mothers had a small advantage in motor but not mental development at 8 months, which had disappeared by age 5 years.

In Bogota, Colombia, nutritionally at-risk pregnant women were randomly allocated to six groups; the women, their children, or both received supplementation during different periods of up to 3 years. At 7 years, nutrient-supplemented children performed better in reading readiness tests.

In Jamaica, Grantham-McGregor [25] studied stunted children aged 9–24 months randomly allocated to no intervention, nutrient supplementation, supplementation and stimulation, or stimulation alone. After a 2-year intervention, both supplemented and stimulated children had significantly higher Griffith's mental development scores than controls. But the effects largely dissipated with longer-term follow-up.
In West Java, day-care centers for 6- to 20-month-old infants were randomly designated nutrient supplement-providing centers or control centers. Nutritional intervention lasted 90 days, after which supplemented children had higher Bayley motor scale scores. Longer follow-up data are unavailable.

*Randomized Trial in Preterm Infants*

In 1982, Lucas and colleagues initiated RCTs of early diet in hospitalized preterm infants. In one illustrative trial, neonates randomized to a preterm vs. standard formula had faster weight, length and head growth. At 7.5- to 8-year follow-up, males fed the preterm formula had a 12-point advantage in verbal IQ (VIQ); and more infants fed the term formula had ‘low’ VIQ (<85): 31 vs. 14% for both sexes (p < 0.02). Unpublished data showed the VIQ effect has persisted into adolescence and hence was likely to be permanent.

These effects on cognition may be underpinned by structural effects on the brain. Using MRI studies in this same cohort, for instance, use of the preterm formula resulted 16 years later in a selective 10% increase in size of the caudate nucleus – a structure linked in previous studies to IQ.

That the predominance of the effects of early diet on both IQ and later brain structure is in *males* accords with animal data and other human studies and requires explanation.

*Intrauterine Undernutrition*

Several studies examine the effect of intrauterine growth on later development, but these studies lack experimental design and are confounded by the potential influence of parental or demographic factors and gestation. A study on monozygous twins [Edmonds et al., unpubl.] discordant for birthweight was conducted to investigate the impact of poorer intrauterine growth in the smaller twin. The study design ensured comparability within each twin pair for genes, parental IQ, gender and gestation. For each kg reduction in birthweight in the smaller twin, a large reduction in later VIQ was seen, comparable to the effect of preterm vs. term formula (above). This and the preterm study above suggest the period prior to full term is a critical one for nutrition/growth and brain development.

*Brain Growth and Later Cognition*

It is widely held that reduced brain growth relating to suboptimal nutrition adversely affects cognition. Whilst likely, this has been difficult to explore. In the preterm trial above, use of a standard vs. preterm formula resulted in reduced short-term head, and therefore brain growth and later impaired VIQ. However, in a parallel trial, comparing more extreme diets – unsupplemented donated breast milk vs. preterm formula and resulting in a major difference in early head growth – there was no difference in later cognition. Perhaps human milk provided factors that ameliorated its low nutrient content; but regardless of mechanism, head growth alone was not an explanation of the cognitive outcome.
Furthermore, studies relating head size to later cognitive performance cannot infer nutritional causation since head size is a key biological marker of cognitive performance regardless of any pre-existing malnutrition or illness [28]. The significance of head growth needs further exploration.

*Individual Nutrients and Cognition*

A number of individual nutrients that may influence growth process are believed to affect cognitive development – notably iron and zinc. Most studies on iron deficiency, however, are potentially confounded by adverse factors such as poor social circumstances accompanying iron deficiency.

Of current interest are bioactive factors present in breast milk and now incorporated into infant formulas, including nucleotides (possible conditionally essential nutrients in infancy) and long-chain polyunsaturated fatty acids (LCPUFA) both of which are believed to influence growth.

Nucleotides have been shown to promote head growth in SGA infants and in healthy infants (unpubl.). Cognitive outcome studies are pending. However, LCPUFA supplementation, despite extensive research, is proving less effective than hypothesized. Two reviews (one in preterm and another in healthy infants) including 29 RCTs have failed to show convincing effects on growth or neurodevelopment [29].

*Windows for Programming by Early Growth*

For programming of CVD risk, current evidence emphasizes the relative importance of the postnatal rather than prenatal period. The window is undefined, and whilst some studies suggests early infant growth (first weeks) is critical [13, 18, 30], other evidence suggests growth in the 2nd year is also influential for later obesity [17] – an important area for future study.

For the brain, the most sensitive period appears to be prior to full term (fetus or preterm neonate). In full-term infants, evidence for a cognitive impact of early growth and nutrition is more difficult to interpret. Trials of nutrient supplementation in malnourished populations yield relatively subtle effects of unknown longer term significance. Our RCT of nutrient supplementation in term SGA infants showed no cognitive benefits. The cognitive benefits of breastfeeding have been recently challenged. The effects of iron supplementation need more rigorous RCTs to remove potential confounding. LCPUFA supplementation has proved unconvincing. Nevertheless, further work is indicated.

Paradoxically, fast early growth has advantageous effects on the brain but adverse effects on later obesity and cardiovascular health. However, this conflict mostly applies to preterm infants in whom the brain is highly sensitive. On balance, rapid growth promotion in preterm infants appears the best compromise, to avoid major neurodeficits. Indeed, preterm infants
growing fast have no worse CVD risk than healthy infants; and whilst CVD risk may be reduced by undernutrition, this is unsafe in the preterm population.

**Mechanisms for Programming Effects**

A key question is how the ‘memory’ of an early event is ‘stored’ through many cell generations during growth and development to be expressed as an outcome effect later in life [13]. Such memories may be stored through epigenetic mechanisms. However, for CVD programming increasing evidence supports the early setting of influential endocrine axes, notably those involving insulin and leptin – which may influence subsequent satiety [30].

Of biological interest is the range of outcomes that may be influenced by early growth which include, in humans, not only CVD risk, obesity and brain development, but possibly lifetime infection and cancer risk. In animals, an even larger range of outcome effects has been uncovered, including lifespan [1, 2]. Thus, it is possible that the initial programming stages lead to a ‘cascade’ of multiple downstream effects. This programming cascade needs to be defined since, hypothetically, future potential pharmaceutical interventions could affect health outcomes by favorably manipulating the coupling mechanism during critical periods.

**Future Perspectives**

The new understanding of the impact of growth on health raises key research questions, notably what are the critical programming stimuli, windows and mechanisms? Current assessment of an individual’s growth itself, using reference charts, is conceptually flawed, since such charts do not identify ‘desirable’ growth in terms of health outcomes. Furthermore, we know little about what aspects of growth and related body composition best predict later health. These issues have major relevance to public health.

**References**

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Discussion

Dr. Haschke: A very challenging introductory lecture, food for thought and a lot of hypotheses which showed the work of your group during the last 20–30 years. One fundamental question is how is early nutrition of term infant later influencing growth?
You indicated that slower growth is better during the first months (the window of opportunity). We know that breastfed infants during that period grow faster, which is documented by all international growth charts. The Europe Growth charts indicated higher weight and length gain of exclusively breastfed infants than of formula fed infants during the first few months of life. How does this match your hypothesis?

Dr. Lucas: I think there are two separate questions there. One is whether breastfed infants grow more slowly, and that is a complex question because there are periods when breastfed infants grow faster and slower than formula-fed infants. I am suggesting that it’s at the critical periods that they are growing slower because they are consuming lower intake; later on, they may grow faster. In terms of the overall window, I am not suggesting that the window is purely in the first few weeks of life. In fact, there is evidence that rapid growth right away up to 2 years of age can adversely influence long-term outcome. It’s just that earlier in life where growth rate is intrinsically faster and where things are being set that you might actually expect a greater programming effect.

Dr. Mobarak: In your lecture you stated that the faster growth phenomenon of a preterm infant is important in terms of parents’ anxiety as they want their baby to grow fast. At the same time, neonatologists or pediatricians also want the preterm infant to grow faster for better handling of the baby. But you say that this fast growth phenomenon has two implications: one is negative and concerns cardiovascular disease, and the other is positive and concerns cognitive development or mental development. How were these randomized control trials conducted in terms of ethics, and to which diets should we assign newborns to balance the risk of cognitive and cardiovascular problems later in life?

Dr. Lucas: In terms of ethics, at the time when we did these studies in the early 1980s it was simply not known which diets were best and all we were doing was randomly assigning babies to diets that already existed, and in fact we introduced preterm formulas which weren’t being used in any of the units that we were doing research in in order to do the trials. So, in a sense, trials actually upgraded the nutrition in some respects. In terms of the balance of risk, there is no question that you do want premature babies to grow rapidly. You want them to grow rapidly because of the major importance of nutrition at that stage for brain growth. The reason why you don’t want them to grow slowly is because you would produce huge deficits, and we have shown major differences in mental and motor impairments in babies who are growing slowly. In terms of cardiovascular disease risk, what we found is that the fast-growing babies are no worse off than the healthy population. If you compare an infant born at term with a premature baby growing fast, you will not find a difference in the risk profile. The babies who do better from a cardiovascular disease risk point of view are those who are actually being undernourished in the preterm period, and we don’t believe that undernutrition is a safe thing to do in premature babies. So, everything in medicine is a balance of risk but on balance our view, and I think this is the view that is supported by current practice, is that you should promote rapid growth in premature babies on accounts of the brain, you should ignore the cardiovascular effects because you can only achieve them with what might be regarded as a rather dangerous intervention of deliberately underfeeding these babies with all the potential risks of that. So, in a sense, although there is potential conflict in the premature baby, in reality I think the decision is quite clear.

Dr. Moelgaard: How does body composition influence this outcome.

Dr. Lucas: At the moment, the vast majority of programming studies have looked at body mass that is weight, and actually in some of our studies we have also demonstrated that linear growth has a programming effect. However, you do raise an important question which I hint at in my paper that clearly we do need to understand
ultimately in more detail what aspect of growth it is that has greatest programming significance and that work really hasn’t been done. We are beginning to know more about what aspects of growth are programmed in terms of fat mass and so forth, but what we know much less about is what aspects of growth are most likely to trigger programming effects. At the present time, the whole of the world literature just about is based on body mass, there is very little more than that at the present time, I don’t know if you would agree with that Dr. Singhal?

Dr. Singhal: I think that’s my reading of the situation. However, growth has been shown to program fat mass rather than lean tissue.

Dr. Lucas: Sure, but that’s the outcome. This is the question of whether the composition of growth in the immediate postnatal period say is relevant to programming, in other words if you are more programmed by one quality of growth, and nobody has really looked at that in detail. I think that’s an important area for research.

Dr. Makrides: I have a conceptual question. You have made an excellent case for growth being a mediating factor for neurological development as well. Do you think there is room for nutrition or specific nutrients to influence neurological development independent of growth?

Dr. Lucas: Yes, absolutely, and when I produced the first slide with the construct I was saying that one of the prominent ways in which nutrition may operate is through the mediation of growth, implying that it may be that nutrition has a wide range of other effects. There are a number of essential nutrients like iodine, for instance, that have an effect on neurodevelopment and may not necessarily work through a growth process but might actually work by stimulating critical growth processes within the brain that then have subsequent effects. So we don’t know the answer to that, but I would suspect that nutrition can operate in other ways. The only reason I haven’t been talking about those is because this is a workshop on growth.

Dr. Daniel: With reference to prematurity, is there evidence to suggest that actual gestation makes a difference? Is the effect the same in the early gestation and the later gestation?

Dr. Lucas: It depends what you are talking about. If you are talking about brain programming, the more mature you are probably the less sensitive you are. If you are talking about cardiovascular programming, our data at least suggest it doesn’t matter when you are born, whether you are born at 26 weeks gestation or term, the postnatal period is an important one for cardiovascular programming. So it would appear as though brain development is on a chronological time clock if you like, whereas cardiovascular programming depends to an extent on birth whenever that occurs. That’s the best interpretation of current data; obviously, we have got several days ahead of us to argue about these important details.