Does Early Growth Affect Long-Term Risk Factors for Cardiovascular Disease?

Atul Singhal

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

Abstract

The concept that early growth and nutrition have long-term biological effects is based on extensive studies in animals dating from the 1930s. More recently, compelling evidence for a long-term influence, or programming effect, of growth has also emerged in humans. Substantial evidence now supports the hypothesis that ‘accelerated’ or too fast infant growth increases the propensity to the major components of the metabolic syndrome (glucose intolerance, obesity, raised blood pressure and dyslipidemia), the clustering of risk factors which predispose to cardiovascular morbidity and mortality. The association between infant growth and these risk factors is strong, consistent, shows a dose-response effect, and is biologically plausible. Moreover, experimental data from prospective randomized controlled trials strongly support a causal link between infant growth and later cardiovascular risk factors. These observations suggest therefore that the primary prevention of cardiovascular disease could begin from as early as the first few months of life. The present review considers this evidence, the underlying mechanisms involved and its implications for public health.

Introduction

Monitoring growth, which at the simplest level is defined as the quantitative increase in mass or size, is an essential part of good pediatric care. The pattern of growth is not only a marker of the immediate physical and emotional well-being of the child but also has long-term implications for health. Previously, however, research and clinical practice in pediatrics have focused almost exclusively on achieving adequate growth and the prevention of growth faltering. More recently, compelling evidence has emerged for the adverse long-term consequences of ‘accelerated’ or too fast growth. The
present review considers this evidence, focusing on the role of accelerated infant growth in long-term risk factors for cardiovascular disease (CVD).

Evidence from Animal Models

The concept that early growth affects long-term biology was first proposed by McCay as far back as 1933 [1]. He showed that rats whose growth was stunted by restricting their food intake had a lower incidence of tumors, kidney disease, vascular calcification and chronic pneumonia and consequently a substantial 35% increase in lifespan. In fact, the effect of calorie restriction during phases of development on extending longevity has now been demonstrated in organisms as diverse as yeast and mice [2]. The mechanisms involve the glucose or insulin/IGF-1 pathways, which are partially conserved throughout these species, and which act by downregulation of antioxidant enzymes and heat shock proteins, or by reducing glycogen or fat accumulation.

In contrast to the benefits of calorie restriction, early overfeeding leading to rapid postnatal growth has been shown to have adverse effects on long-term health. McCance first demonstrated in the 1960s that overfeeding rats during a critical window in early postnatal life permanently increased later body size [as reviewed in 3]. Subsequently, Lewis found that infant baboons given a nutrient-enriched formula, which provided 33% more energy had greater mesenteric and omental fat depots, an effect that emerged only after adolescence [3]. More recently, Ozanne and Hales [4] showed that catch-up growth prior to weaning in mice (particularly in animals growth restricted in utero) increased later adiposity and reduced lifespan. Obesity was greatest in mice fed a highly palatable ‘cafeteria’ diet rather than normal chow after weaning, suggesting an interaction between early growth and the dietary environment later in life [4].

The long-term influence, or programming effect, of faster growth is not confined to obesity. Faster early growth in several animal models has been demonstrated to increase the risk of later dyslipidemia, insulin resistance, and the metabolic syndrome [5]. In fact, the trade-off between faster growth on one hand, and longevity and adverse biological effects on the other, is seen across animal species [6]. Whether such effects are evident in humans is uncertain, but is a critical question for public health policy and future nutrition research.

Evidence from Humans

The idea that early growth could affect long-term health in humans, as in animals, first emerged in the 1980s when observational studies suggested an association between suboptimal fetal growth (as measured by low
birthweight) and long-term risk of CVD – the ‘fetal origins’ of adult disease hypothesis [7]. Similar associations between low weight at 1 year of age and later CVD mortality suggested that promotion of infant growth could reduce CVD risk, although more recent data do not support such an intervention. In both high income and low income countries, faster weight gain in childhood (particularly in those born small) is associated with increased CVD mortality and incidence of type 2 diabetes [8, 9]. However, data for programming effects of faster growth in the 1st year, and particularly for the potential critical window in the first postnatal months, are less consistent [8].

Evidence that growth in infancy could affect later health was published in 2002. Faster weight gain in the first 4 months of life was independently associated with a greater risk of being overweight at 7 years of age [10]. Based on these observational data and long-term follow-up of our experimental intervention studies, we proposed that faster growth, particularly in infancy, increased the later risk of obesity and CVD [3]. We found that infants born preterm and randomly assigned to formula rather than human milk had greater propensity to obesity, dyslipidemia, raised blood pressure, and insulin resistance, while faster early growth programmed insulin resistance, markers of inflammation, higher blood pressure and endothelial dysfunction (an early stage in the atherosclerotic process) [3]. As a unifying hypothesis, we proposed that postnatal growth acceleration (upward centile crossing) could explain, in part, adverse programming effects in infants born small for gestation (who show ‘catch-up’ growth immediately after birth) and long-term cardiovascular benefits in babies breastfed (who are relatively undernourished and have slower growth compared to those given formula) [3]. Over the last 5 years, substantial evidence from observational studies and, importantly, from intervention studies that suggest a causal association, supports the growth acceleration hypothesis. Faster infant growth has been shown to increase the propensity to the major components of the metabolic syndrome, the clustering of risk factors (glucose intolerance, obesity, raised blood pressure and dyslipidemia) which predispose to cardiovascular morbidity and mortality. The current review considers this evidence and its implications for public health.

**Obesity**

Data from more than twenty-seven studies (much of it summarized in three systematic reviews) [11–13] support the hypothesis that faster weight gain in infancy increases the risk of long-term obesity. This association is consistent for cohorts over the last 80 years and has been seen for effects of both faster weight and length gain, for obesity in adults and children, in both low and high income countries, and in infants born preterm or at term. Infant growth appears to have a large effect on later obesity risk [11–13]. For instance, nearly 20% of the risk of being overweight in childhood can be attributed to weight gain in the highest quintile in infancy [10]. Furthermore,
programming effects of early growth are independent of potential confounding factors such as parental obesity and socioeconomic status, and appear to be stronger for body fat rather than bodyweight, BMI, or lean body mass [14, 15]. Importantly, no study has shown evidence of an interaction with birthweight, which suggests that adverse effects of early growth acceleration are similar in both normal and low birthweight infants [13].

The association between infant growth and later obesity is likely to be causal. The association is strong, consistent, and biologically plausible, shows a dose-response effect, and is experimentally reproducible in animal models [16]. Causality is supported by data from a prospective randomized controlled trial (RCT), which found that infants fed a nutrient-enriched infant diet (that contained 28% more protein and promoted faster weight gain) had 30% greater body fat (measured by bioelectric impedance analysis) up to 8 years later [Singhal et al., unpubl.]. Although further experimental data using more sophisticated measures of adiposity are required, these observations support the hypothesis that programming effects of infant weight gain may be independent of genetic factors such as those influencing appetite, which could affect both the risk of overfeeding in infancy (and hence the rate of growth) as well as the later risk of obesity.

Recent data from the European Childhood Obesity Study, a large multicenter RCT, strongly support a causal link between infant growth and later obesity. Compared to controls, infants randomized to formulas with a higher protein concentration for the 1st year (which promoted faster weight and length gain) had greater BMI at 2 years of age. Based on existing data from observational studies, the authors predicted that this would lead to a 13% increase in later risk of obesity [17]. Although further follow-up, beyond the period of nutritional intervention is required, this prospective RCT suggests a critical window for programming of obesity in the 1st year of life.

Nevertheless, several key questions remain unanswered. First, the most sensitive window for programming effects is uncertain. Faster weight gain from as early as the 1st postnatal week is associated with a 30% increase in risk of being overweight in adulthood [5]. However, the 2nd year may also be important and there is an estimated 60% increased risk of obesity if the duration of rapid weight gain is increased from 1 to 2 years after birth [13]. Second, the relative contribution of genetic, nutritional and other environmental factors to infant growth and its effects on later obesity are unknown. For instance, a higher nutrient intake leads to faster weight gain, but it is difficult to separate the contribution of nutrition from that of growth. Nonetheless, the primary programming role of infant growth rather than nutrition is supported by observations that faster weight gain is associated with greater adiposity even in those who were breastfed, and that programming effects of infant growth are independent of protein intake and method of infant feeding [11–13].

Third, the interaction of early growth with later environment requires clarification. There appears to be a smaller programming effect with obesity
assessed at later ages [13] possibly due to a greater contribution of other environmental determinants of obesity. Further evidence from longitudinal studies with serial measurement of body composition in children and adults is required to test this hypothesis. Programming effects are also more marked in ‘obesogenic’ environments, suggesting that there is an interaction between infant growth and later environment, analogous to data from mice [4]. Although the mechanisms for this are unknown, programming of appetite (e.g. a lower set point for satiety) would increase the tendency to obesity particularly in populations exposed to energy-dense diets.

Fourth, the role of recently highlighted gender differences in programming effects is uncertain. For instance, breastfeeding has been shown to be more protective against later obesity in boys than girls [18]. Similarly, in one of the largest studies to address this issue (n >6,000), faster weight gain in infancy was also associated with a stronger effect on obesity risk in boys than girls [19]. One potential explanation for these gender differences is that early growth acceleration amplifies the effects of sex steroids on the development of adipose tissue. Programming of higher androgen concentrations by infant growth, for instance, could increase central fat deposition in boys.

Finally, the effect of faster infant weight gain on different fat depots needs further investigation. For example, early growth acceleration is particularly associated with programming of visceral adiposity, a key risk factor for insulin resistance and the metabolic syndrome [20]. Compared to controls, visceral fat is increased in children born small for gestational age (SGA) who tend to show early postnatal catch-up growth. This effect is seen even in children who are not overweight and is related to the rate of postnatal weight gain [20], observations consistent with the hypothesis that faster early growth affects later CVD risk via programming of visceral adiposity. These effects are evident from very early in life. Visceral fat is remarkably preserved in growth-retarded newborns, while increases in adiposity in the first 6 weeks correlate with linear growth [21]. Serial measurement of body composition and visceral adiposity in infancy and childhood could therefore help define the role of these early changes in body composition for the development of later obesity and CVD.

Despite these unresolved questions, overall, the consistency and strength of the evidence (up to a 2- to 3-fold increase in obesity risk [13]) strongly support the impact of faster infant growth on later adiposity. As discussed below, these findings are leading to major changes in public health policy.

**Blood Pressure**

Whilst the evidence is strongest for obesity, faster infant growth also programs CVD risk factors such as raised blood pressure. This association is evident in several (>6) but not all studies [as reviewed in 22, 23] in both formula-fed and breastfed infants, for both diastolic and systolic blood pressure, and for blood pressure in children and adults [22–24]. Like the data for
obesity, this association is seen for both length gain and weight gain in infancy, is independent of potential confounding factors such as body fatness and gender, and shows no interaction with birthweight [22–24]. Again, the most sensitive window is not known, but in the Avon Longitudinal Study of Parents and Children, diastolic blood pressure was 2 mm Hg higher in 10-year-old children who were in the highest quartile for weight gain in just the first 2 months compared to those in the lowest quartile [24].

One experimental study supports a causal link between infant growth and later blood pressure. Infants born SGA and randomized to a higher protein diet that promoted growth had approximately 3 mm Hg greater diastolic blood pressure than controls [22]. The size of this effect was substantial and, on a population basis, would be expected to prevent over 100,000 myocardial and cerebrovascular events per year in the US alone [see 3]. The pattern of infant growth could therefore have a major impact on population health.

**Insulin Resistance**

Insulin resistance is fundamental to the metabolic syndrome originally described by Reaven in 1988 and is strongly associated with growth acceleration immediately after birth. In one study, adolescents born preterm and randomly assigned at birth to a nutrient-enriched formula that promoted faster weight gain had 20% greater 32–33 split proinsulin concentration (a marker of insulin resistance) than controls [3]. Interestingly, the sensitive window for this effect was as early as the first 2 weeks of life. Faster early growth is also associated with insulin resistance in term infants with both normal [25] and low birthweight [26]. In this latter study, faster infant weight gain was related to insulin sensitivity at 1 year of age, raising the possibility that insulin resistance could precede (and hence lie on the causal pathway) for programming of other CVD risk factors such as raised blood pressure.

While most research has focused on insulin resistance, there is relatively little evidence to support an effect of early growth on the development of type 2 diabetes itself. One potential explanation for this is that the risk of developing type 2 diabetes depends mainly on determinants of β-cell mass and hence the ability to maintain insulin secretion in the face of increasing insulin resistance [25].

**Dyslipidemia and Endothelial Function**

Evidence that growth acceleration affects the development of dyslipidemia is more limited than for other cardiovascular risk factors. In infants born preterm, both faster weight gain in the first 2 postnatal weeks, and random assignment to breast-milk rather than formula, were associated with 10% lower cholesterol concentration and 14% lower ratio of LDL to HDL up to 16 years later [3]. Such an effect size is important for public health and could lower CVD incidence by 25% and mortality by 13–14% [see 3]. Faster weight gain in the first 6 months was also independently associated with a clustered
metabolic risk score (comprising fasting triglyceride, high-density lipoprotein cholesterol, glucose and insulin concentrations, together with waist circumference and blood pressure). The effect on other CVD risk factors remained after removing the effect of adiposity, suggesting an independent influence of early growth on components of the metabolic syndrome [27].

The effect of early growth acceleration on cardiovascular risk factors would be expected to effect the development of atherosclerosis itself. Consistent with this, faster growth (both weight and length gain) in the first 2 postnatal weeks was associated with later endothelial dysfunction, an early stage in the atherosclerotic process. Like data for insulin resistance and dyslipidemia, the effect size was substantial and similar to the effect of smoking or insulin-dependent diabetes on endothelial function in adults [3]. Similarly, faster growth in the first 3 months has been recently associated with a worse cardiovascular and metabolic risk profile in adults, including increased carotid intima media thickness, a maker for generalized atherosclerosis which is predictive of cardiovascular events [28]. Overall, therefore, there is strong evidence to support programming of atherosclerotic CVD by infant growth. The key challenge is whether we can unravel the mechanisms involved to benefit human health?

**Mechanisms**

Probably the most intriguing aspect of the developmental origins of disease concept is the delay between exposure (in the first few months, or even weeks after birth) and outcome several decades later. Understanding how the memory of the exposure becomes ‘hard wired’ at the physiological, cellular or molecular level is therefore critical to understanding this concept. Two main generic hypotheses have been proposed to explain the ‘coupling mechanisms’ linking early exposures such as growth with later biological effects such as CVD risk. The first hypothesis, the role of epigenetic changes that persist throughout life, is supported by recent evidence in humans. Individuals who were exposed prenatally to famine during the Dutch Hunger Winter in 1944–45 had less DNA methylation of the imprinted IGF2 gene, 6 decades later, compared with their unexposed, same-sex siblings, observations consistent with the hypothesis that very early mammalian development is a crucial period for establishing and maintaining epigenetic marks [29].

The second hypothesis suggests that early growth acceleration permanently affects hormonal axes that regulate bodyweight, food intake and metabolism, and hence fat deposition [5]. Studies in animals indicate that set points or ranges for endocrine feedback mechanisms may be influenced by the concentrations of the hormones themselves early in life [5]. Similar mechanisms may occur in humans. For instance, a higher plane of nutrition in early postnatal life may increase leptin, and particularly insulin concentra-
tion, which programs higher concentrations of these hormones later in life. Hormonal changes in infancy (possibly via changes to the hypothalamic circuitry involving leptin pathways [5]) that reduce satiety and increase food intake will help drive early postnatal catch-up growth. Whilst beneficial in the short-term, this higher set point for satiety may predispose to later obesity. Finally, early growth and nutrition could affect endocrine systems that control developmental processes [2]. Consistent with this, faster weight gain in infancy has been linked with more rapid maturation and an earlier onset of puberty [30].

**Public Health Implications**

Despite our incomplete understanding of mechanism, the strength of the evidence supporting the growth acceleration hypothesis is challenging established public health practices. Professional bodies in the UK such as the Royal College of Paediatrics and Child Health, and the Scientific Advisory Committee on Nutrition have both recognized the role of faster infant weight gain in increasing the risk of long-term obesity [31]. Consequently, health care professionals are advised to prevent inappropriate upward centile crossing as well as growth faltering. The new WHO growth charts based on the exclusively breastfed infant are likely to help in the prevention of overfeeding in infancy [31]. Furthermore, contrary to previous medical and public opinion, promoting catch-up growth by nutritional supplementation in healthy term infants born SGA may not be appropriate [32]. Clearly, however, the risk-benefit of faster early growth depends on the population involved. For instance, faster weight gain may improve long-term cognitive function in infants born preterm and has short-term advantages for morbidity in infants with low birthweight from low income countries [see 3]. Even in low income countries, however, massive changes in diet and rise in urbanization means that large sections of society are at increased risk of obesity and CVD and so susceptible to programming effects of early growth [9].

**Conclusions**

A rapidly increasing prevalence makes CVD the most important health issue of the 21st century. The dramatic rise in obesity alone is expected to decrease life expectancy and threatens to reverse the reduction in cardiovascular mortality achieved in the past decades through control of hypertension, dyslipidemia and smoking. Evidence that patterns of early growth can influence its development, could provide therefore a unique opportunity for the primary prevention of CVD to begin from as early as the first few months of life.
References


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Discussion

Dr. Mendiola: What do you think is the ideal weight gain of a preterm infant given the trade offs that were mentioned by you and Dr. Lucas a while ago, and how do you define rapid weight gain.

Dr. Singhal: I would argue that appropriate weight gain for a preterm infant is along the centile the baby was born on. The problem is that they never stay on that centile. As you know, because it is hard to maintain an adequate nutritional intake, preterm infants nearly always have growth failure. Because they are often sick, and have high energy and protein energy requirements, infants born prematurely need a high nutrient intake just to maintain their growth centile. The second question is how do you define rapid weight gain? Well, the data linking growth acceleration with later outcomes are continuous and there isn’t a cutoff. People have arbitrarily defined catch-up growth as crossing 2 centile lines or 0.67 standard deviations, but the epidemiological data are continuous.

Dr. van Buuren: I have a question about the slide you showed of the Fall data which showed a gradual growth into obesity except for the very first part and the control.

Dr. Singhal: The data from the Delhi Birth Cohort?

Dr. van Buuren: The data about the critical windows. The trajectory starts below zero, do you have an explanation for that?

Dr. Singhal: There are two explanations. One is that growth trajectories are often compared to a different reference population (e.g. NCHS). Populations such as those from India have a birthweight and early growth below this reference population and hence below zero z scores. However, in the study from Fall, adults who developed the metabolic syndrome (index group) were compared with the rest of the cohort who did not (controls; hence both populations were from India). This showed that the index group tended to have a lower birthweight (approximately –0.1 z scores), which is consistent with the evidence that a low birthweight baby that shows faster postnatal growth has an increased risk of later cardiovascular disease. However, one thing that isn’t often recognized is that for postnatal growth acceleration there is a different order of magnitude of effect than for low birthweight. In the Fall study, and
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other similar data, birthweight z score is 0.1–0.2 lower in populations who develop the metabolic syndrome compared to controls. In contrast, for catch-up growth, infants often show >2 standard deviation increase in postnatal growth rate and a much larger effect on later cardiovascular outcomes.

Dr. Giovannini: How do we separate optimal growth from excessive growth, and what is the effect of hypothalamic programming? Is there any experimental evidence?

Dr. Singhal: No, I don’t think there is any experimental evidence for hypothalamic programming in humans similar to that in animal models. We have looked at the effects of early nutrition on leptin resistance, but only for outcomes later in life, and not in terms of its early hypothalamic effects. However, although we don’t have the sort of sophistication to look at leptin surges and so on, the work of Sebastian Bouret and others is exciting because phenotypic data on programming effects are similar in animals and humans, and so similar early hypothalamic mechanisms may apply in both. The first part of the question was what is the optimum rate of growth? I think we have to base this in terms of outcomes of growth. We should not be unnecessarily promoting faster growth. While an ill infant with a clinical problem is a different story, ideally healthy term infants born on the 10th centile should grow along the 10th centile. However, they won’t because they show catch-up growth anyway, a phenomenon that we can’t stop. However, we shouldn’t be adding fuel to the fire by giving them a high nutrient intake on top of their natural catch-up growth.

Dr. Cooke: The term ‘catch-up’ is confusing, both quantitatively, i.e. the rate of gain is defined differently by different investigators [1], and qualitatively, i.e. it generally refers to weight gain with little attention to the nature of the gain. While it is now generally regarded as undesirable, it is sometimes forgotten that it is a normal ‘recovery’ response that occurs after growth faltering [2]. The nature of the gain depends on the nature of the diet. A diet that is high in energy but low in protein will be associated with weight gain and fat accretion [3, 4]. A diet with a higher protein to energy content is associated with increased weight gain, linear growth and lean mass accretion [5]. Infants who are ‘recovering’ and hungry will eat whatever is fed, perhaps overcompensating when dietary protein intake is low [6].

Dr. Singhal: I completely agree, and that’s why I have always called it ‘growth acceleration’ rather than ‘catch-up’ growth because growth acceleration takes into account ‘catch-up’ growth (catch-up growth is one type of growth acceleration). Growth acceleration may be a different phenomenon. For instance, if you give a healthy (and appropriate for gestation) term infant a high protein intake, he/she will grow faster. That’s growth acceleration, but it’s not necessarily catch-up growth, because they may not be born small.

Dr. Cooke: It is important to think not only about rate but also composition of the weight gain.

Dr. Singhal: I agree. Ideally, we should be looking at the composition of growth and particularly how that affects long-term health. Ideally, the baby should grow along a centile, but this is extremely difficult to achieve for the reasons you say. Infants born small will cross centiles upwards, but all we can say in terms of intervention is that we don’t add extra protein and energy.

Dr. Cooke: Protein to energy content of the diet is, perhaps, a better way of thinking about nutritional rehabilitation in these infants.

Dr. Singhal: The data from the European Growth study [7] suggest that only protein is the critical nutrient. This study randomized infants to a diet with different protein content (but the same energy) and produced differences in growth at age 6 months, IGF-I concentrations, and in obesity risk at age 2 years. I think you are absolutely right, it can be energy but, as this study suggests, it can also be protein.
Dr. Klassen-Wigger: I have a question related to the impact of behavior versus genetic and epigenetic factors on food intake, particularly in formula-fed infants. A recent paper in Pediatrics has shown that if a baby finishes the bottle completely by its own will, as compared to the mother re-offering it, only the babies that finish the bottle on their own will show an increased risk of obesity later in life. My question is therefore: To what magnitude do you estimate the impact of feeding behavior of the mother, e.g. overfeeding, etc. as compared to the impact of genetic and epigenetic factors?

Dr. Singhal: I don't know the answer to that because I can't proportion the amounts of growth due to individual factors such as genes. In the ALSPAC study [8], one of the strongest predictors of catch-up growth was paternal height, and so, as you would expect, genetic factors are important. The Fels cohort [9] showed that genetic factors explained >50% of the variance in weight gain. Regarding volume of milk intake, I would argue that breastfed babies have a lower rate of weight gain over the 1st year than those fed formula for two reasons: (1) the protein content of formula is too high and (2) it is more difficult to regulate appetite in formula-fed infants. But I don't know of any data to show that manipulating volume of milk intake affects later outcomes. From the study you cite in Pediatrics, it appears that stopping mothers from giving their babies too much formula may be of benefit, but that has yet to be proven.

Dr. Klassen-Wigger: Actually not, I mean it was the opposite, it was just when the baby at once would just not even stop and just get the whole bottle emptied as compared to when mothers were offering this a second time, it means the behavior of the mother. So it was more the baby itself that was not supplementing itself by intake so that touches also the variability of food intake which can be enormous.

Dr. Singhal: I think Margaret Ounsted's work in the 1970s [10] showed that infants born small for gestational age had a greater appetite. This is not really surprising in order for them to show catch-up growth. However, which comes first? You have to have a bigger appetite to get the calories and protein for catch-up growth, but does faster growth as a result of excess nutrition drive a bigger appetite?

Dr. Elmouzan: I would like to ask you about breastfed babies whose weight continues to drop. For how long should we be confident and reassure the mother that this is a normal slow growing and how long should it take before they go back to a normal slow growth.

Dr. Singhal: I think it depends on the charts you use to show that the baby's weight is dropping. In the UK, we use charts based on formula-fed infants. So breastfed infants often show a falling off in centiles and so we use clinical acumen to make sure the baby is otherwise healthy. If the mother is successfully breastfeeding, then we would just monitor the baby. Therefore, I don't think there is a cutoff – it depends on the clinical situation. With the new WHO growth charts, I would hope that fewer breastfed babies are regarded as having poor growth, but we have to wait and see what happens.

Dr. Batubara: With the growth charts, we would like to see our children grow along the 50th percentile, for instance. You said that rapid catch-up growth is not good in later life. How long should a child grow along the centiles; shouldn't he/she increase one centile at a time to attain a normal growth rate?

Dr. Singhal: I think it's important to recognize that I presented epidemiological data, and for an individual it is difficult to use growth acceleration to predict outcome. So the message is different for the individual and for public health. I would argue that in public health terms we don't overfeed our babies. But for the individual, I don't think the evidence shows that a particular baby that shows growth acceleration is going to be obese later in life. So, in practice, we do not do anything about upward centile crossing in breastfed infants. However, we don't give healthy babies born small
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for gestation, a higher calorie intake or use nutrient-enriched formulas to actively promote faster growth.

**Dr. Batubara:** Do you see any differences in children crossing 2-centile lines or 3-centile lines?

**Dr. Singhal:** No, I don’t have any data to show how much upward centile crossing adversely affects later health. However, growth acceleration is a continuous variable. Infants with the most growth acceleration had the worse later outcomes in terms of population health, not necessarily in terms of the individual.

**Dr. Ke:** You made it very clear that the centile for a premature baby is the centile with which the baby was born, but what is the target centile for an SGA baby who is already less than the 3rd centile?

**Dr. Singhal:** I think it depends if there is a clinical reason for that baby to be below the 3rd centile. If the cause of being small at birth is idiopathic and the baby is otherwise healthy, I would make sure that the baby is breastfed because this might reduce the amount of postnatal growth acceleration. I would not give the baby a calorie-dense formula to try to make that baby catch up. That’s all you can reasonably do. There is no evidence that you can screen or you can predict outcome in that baby.

**Dr. Ke:** The hypoplastic babies may not catch up. What about the malnourished, asymmetric IUGR babies who we always expect or want to catch up?

**Dr. Singhal:** They will catch up if they are given adequate nutrition. You can’t stop catch-up in these babies, but you shouldn’t add nutrient-dense formulas to actively promote catch-up.

**Dr. Lucas:** Just one comment and then a question. As far as the first question is concerned, at what rate should a premature baby grow, just to throw in a figure there, in our preterm trials the best brain development was for babies growing at 18 g per kg per day which is more than the intrauterine rate as Dr. Singhal pointed out. Then you need to make these babies grow faster to catch them up, and that’s ignoring the cardiovascular issues which I think we should do for the reasons discussed this morning. The question I wanted to ask is to do with energy supplementation rather than energy plus protein or just protein. The early studies that were done by Thyman and Brooke and others suggest that if you wanted to achieve catch-up growth with energy, after a while the baby downregulated volume intake, whereas we have never demonstrated that babies downregulate on protein intake, so if you are actually trying to achieve catch-up growth would you not be giving a predominantly protein-enriched diet anyway?

**Dr. Singhal:** I agree. Three randomized trials have been conducted with high-protein versus lower protein formulas in term babies [11], in preterm infants [12] and in the European Obesity Study [7]; they have all shown that by giving a high-protein formula you increase the rate of early growth. I don't know of the studies for energy alone, apart from one by Fomon et al. [13] which showed that infants given energy-dense formulas downregulated intake.

**Dr. Cooke:** I was just going to comment. Term infants fed a term formula with a marginally low protein to energy content upregulate volume of intake to compensate. However, energy intake is also increased and paralleled by increased fat accretion [6]. This has important implications for preterm infants 'recovering' after 'growth faltering' who may be fed marginally low protein intakes before [14] and after hospital discharge [15]. It is important not only to measure weight and length but also consider body composition when considering what is desirable and what is not.

**Dr. Singhal:** I think that’s what we should try to do but, currently, is there a mechanism which allows us to do this?

**Dr. Lucas:** I mean would you not say that recovery was potentially deleterious, I mean you are implying that recovery is just something you’d naturally want to do to
get back to where you started, but the whole point about an SGA baby recovering to the 50th centile is that that might actually be deleterious, the long-term cardiovascular risk and obesity. Perhaps you would like to comment on that Atul.

**Dr. Singhal:** I don’t know the answer. I completely agree with Prof. Cooke that we should talk about weight gain and length gain but should we be defining whether they are putting on fat or lean tissue? That is the key question.

**Dr. Cooke:** Yes, and how this relates to your metabolic risk. Prof. Lucas made the point about recovery. To me, ‘desirable’ recovery is a rate of weight and length gain that takes the infant back to the birthweight percentile. If they overshoot it, in terms of weight, then perhaps one should consider measuring body composition.

**Dr. Singhal:** Certainly, I accept that. We tend to focus on weight, but all of the data we have looked at also apply to length. The three trials of formulas with different protein concentrations (see above) all produced faster length gain in infancy which adversely affected later outcomes. Ideally, we need to be more sophisticated, and work out whether differences in growth in fat or in lean tissue contribute to later outcome. I think this is the next stage.

**Dr. Lucas:** If you actually look at the epidemiological data it doesn’t factor out whether you got back to where you started, it simply talks about upward centile crossing in relation to later outcome. If you have an SGA baby, it’s a reasonable assumption that that baby might be intended to be on the 50th centile on average and it’s maybe on the 3rd centile, but actually getting back to the 50th centile rapidly after birth, which you might regard as recovery, is deleterious in the studies; we are looking at weight here and because that’s what most of the studies have been based on.

**Dr. Cooke:** I agree, but we are talking of weight and I think we have moved on from there and we really like to be thinking of things in metabolic mass and the extent to which an increased or altered metabolic mass is an indicator of concern for subsequent cardiovascular disease.

**Dr. Singhal:** There are studies which show that increase in length correlates with fat in the first 6 postnatal weeks [16].

**Dr. Cooke:** What her data show is that at hospital discharge kids are shorter, have a reduced total fat mass but an increased intra-abdominal fat.

**Dr. Singhal:** That’s what I mean, yes, intra-abdominal fat.

**Dr. Cooke:** Yes but these kids are shorter.

**Dr. Singhal:** No, I am talking about the correlation between length and intra-abdominal mass. That’s what I am saying, which is I think what we agreed on.

**Dr. Hussain:** I find this confusing. We have always said that catch-up is something we should promote in SGA babies, but today some people are telling me that catch-up is harmful. What is the recommended optimal growth pattern for an SGA baby?

**Dr. Singhal:** Let me tell you what the data show. If a baby is born small for gestational age, >80% of the catch-up will have occurred by 6–12 months of age [17], regardless of whether they are breastfed or formula fed. You cannot stop a baby from catching up and so you cannot intervene clinically. All you can do is not give the baby a higher nutritional intake to try and promote even faster catch-up because of the evidence suggesting that faster upward centile crossing is linked to adverse long term outcomes. The reason why it is confusing is that it would be nice to say that the baby’s growth should do X. However, we don’t have that much control over how these babies grow.

**Dr. Hussain:** What percentile should we be aiming at before we say it’s too much?

**Dr. Singhal:** I don’t think you will alter the pattern of growth and the baby will show upward centile crossing particularly in the first 2 months of life. Most babies born small have caught up by 1–2 years of age irrespective of what you do. So, I don’t think you should be trying to manipulate the growth of that baby. You can’t.
Dr. Gillman: As I was saying this morning, I think part of the confusion comes from the fact that we use the word growth and we use the word catch-up growth, and we fail as Prof. Cooke says to distinguish between length and either weight for length or even better measures of body composition physiology, and until we start sort of decomposing all of those things and looking at them separately I think we are still going to be confused. And after all, taller people, especially those with longer legs, have less cardiovascular disease, they also weight more because they are taller, so that’s why it gets confusing, and until we start separating these things out I think we are still going to be confused.

Dr. Singhal: I completely agree with that, but as a clinician all you have is weight and length. At the moment, clinicians do not have growth in fat or lean mass.

Dr. Gillman: And one more comment is it’s really hard to measure length. We have to do that accurately for research and for clinical care.

References

1 Ong KK: Catch-up growth in small for gestational age babies: good or bad? Curr Opin Endocrinol Diabetes Obes 2007;14:30–34.