

**Long-term Adverse Effects of Early Growth Acceleration
or Catch-up Growth**

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Abstract

Background: Whilst prevention of growth faltering has both short- and long-term health benefits, whether too fast, or accelerated infant growth adversely effects later health outcomes is controversial and a major focus of research.

Summary: Many observational studies suggest that rapid weight gain in infancy (upward centile crossing) increases the long-term risk of obesity and non-communicable disease. This association has been seen in infants from low-income and high-income countries, in infants born preterm or at term, and those born with normal or low birthweight for gestation. Experimental (randomised) studies in both breast-fed and formula-fed infants support a causal link between early growth acceleration and infant nutrition and later risk of obesity. These observations suggest that strategies to optimize the pattern of infant growth could make a major contribution to stemming the current global epidemic of non-communicable disease.

Key Messages: The optimal pattern of infant weight gain is likely to differ in different populations. The benefits of rapid infant weight gain for later neurodevelopment favours the promotion of rapid growth in infants born preterm. However, growth acceleration in healthy infants born at term (either normal or low birthweight for gestation) is likely to have adverse effects for long-term health.

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Introduction

Although growth can be defined most simply as the process of increasing in size, we know that growth is much more than a quantitative increase in body mass. Growth is complex interaction of closely regulated genetic, hormonal and environmental factors that prepares an organism for survival and reproduction. As a result, growth is an excellent index of a child's health, and monitoring growth is an essential part of paediatric care. However, growth is not only a marker of the immediate physical and emotional well-being of the child, but has long-term consequences for health [1]. Poor growth is associated with adverse health outcomes in adults [1] and hence prevention of growth faltering, and promotion of recovery from a period of poor growth has always been a high clinical priority.

More recently, however, there has been increasing interest in the long-term adverse effects of the recovery phase of growth, or 'catch-up growth'. There is now compelling evidence that 'accelerated' or too fast growth during critical or sensitive windows in early life has detrimental effects on long-term health, and particularly the risk of obesity and cardiovascular disease (CVD) [2]. The current review will consider this evidence and its implications for the health of infants born preterm or at term.

Catch-up Growth or Growth Acceleration?

'Catch-up' growth was first formally described in 1954 by Bauer who noted that children recovering from the nephrotic syndrome grew faster than the expected rate of growth (reviewed by Tanner [3]). A similar pattern of growth was observed in children recovering from several clinical conditions by Prader in 1963 and this pattern of growth, or 'catch-up growth', was defined as the acceleration in growth *in response to recovery from illness or starvation* [4]. This concept was extended to include children who were born small for

gestational age (SGA) and showed faster post-natal growth, a phenomenon assumed to be ‘catch-up’ growth as a result of recovery from under-nutrition in-utero [3].

However, early post-natal growth is strongly influenced by genetic factors and infants genetically predisposed to a large size, but born to small mothers, show fast post-natal growth (and vice-versa). This re-assortment of growth trajectories occurs soon after birth and had been described in earlier animal models. Walton and Hammond showed in 1938 that foals born to smaller Shetland horses crossed with larger Shire horses showed faster post-natal growth, but not vice versa (i.e. not if the female was the larger Shire horse) suggesting a strong genetic component to post-natal growth (as reviewed [3]). Similarly, in humans, twin studies suggest that both weight at age six months and the rate of weight gain in infancy are strongly influenced by genetic factors (heritability of 62% and 57% respectively) [5]. Therefore, faster growth after birth is strongly genetic and does not necessarily imply ‘catch-up’ growth defined as a faster growth rate following recovery from illness or starvation.

Catch-up growth in order to compensate for a period of growth faltering following adversity, occurs in species as diverse as mammals, birds, and fish, as well as in humans. This pattern of growth must therefore be an evolutionary conserved adaptive response [6, 7] whose benefits could include faster maturity (and hence greater reproductive success), and greater likelihood of survival as a result of a larger size in early life leading to protection from predators, infectious disease or starvation [6,7]. However, the observation that neither animals, nor humans, grow as fast as they are capable of (e.g. as seen with the high rates of growth during catch-up growth) suggests that fast growth must also have a biological cost. Therefore, there is likely to be a trade-off with short-term benefits of faster growth rates counter-balanced by adverse long-term costs, the concept of ‘grow now pay later’ [6].

Importantly, because the adverse effects of faster post-natal growth on obesity, non-communicable disease and risk of ageing are usually manifest in later life (i.e. after reproduction) [2], the costs of fast growth are likely to be under less selective pressure than the benefits.

In humans, other than genetic factors, nutrition is a major contributor to the rate of growth, particularly in early postnatal life, a critical period of development suggested to strongly influence long-term health. For instance, several studies have shown that formula-fed infants grow faster than those breast-fed and this pattern of growth is associated with an increased later risk of obesity and CVD [2]. These findings have been confirmed in experimental studies which found that infants born preterm (or SGA at term) and randomly assigned to formulas with high protein concentrations had increased risk factors for later CVD (adiposity, higher blood pressure, insulin resistance, dyslipidaemia and endothelial dysfunction [2]). Based on such findings, we proposed the post-natal ‘Growth Acceleration’ hypothesis [2], which suggests that upward centile crossing (for weight or length) could explain, in part, adverse long-term effects in infants born SGA (who show upward centile crossing immediately after birth) and long-term cardiovascular benefits in infants breast-fed (who are relatively undernourished and have slower growth compared to those given formula) [2]. Importantly, the term ‘Growth Acceleration’ makes no assumption about the causes of faster post-natal growth, whether this results from genetic factors, or as a result of recovery from illness, or starvation (i.e. ‘catch-up’ growth); or as a consequence of a higher plane of post-natal nutrition. Moreover, prevention of growth acceleration does not advocate not preventing growth faltering or stunting which are clearly harmful patterns of growth [1].

Postnatal Growth Acceleration and Long-term Health

Evidence that growth in early life can affect long-term health first emerged in the 1930's when McCay showed that rapid post-natal growth in rats increased the risk of chronic disease and reduced lifespan by up to 35% (reviewed in [2]). McCay argued that it is possible that rapid growth and longevity are incompatible.

In humans, one of the earliest studies to show adverse effects of growth acceleration found that faster weight gain in the first 6 weeks of life increased the risk of obesity 6-8 years later [8]. Since this early report, there has been a huge increase in evidence to support the growth acceleration concept. Faster infant growth (upward centile crossing for weight or length) has been associated with later obesity in 45/46 studies (summarized in 6 systematic reviews [9-11]) including an individual-level meta-analysis in 47,661 participants from 10 cohorts [11]. These associations are seen in both high-income and low-income countries, for both weight gain and linear growth, in infants born preterm or at term, in infants with normal or low birthweight for gestation, and in both breast-fed and formula-fed infants [9-11].

Importantly, there are now 5 randomised trials that support a causal link between slower infant growth and lower risk of later obesity [9]. These trials found that infants fed formulas with a higher protein content (and hence had faster weight gain) had a greater risk of later obesity than those given lower protein formulas [9, 12]. Similar benefits of slower infant weight gain are seen in breast-fed infants. A randomised trial of a responsive feeding intervention design to reduce over feeding in both breast-fed and formula fed infants showed that the intervention successfully reduced the rate of weight gain in the first 6 months but also reduced the risk of obesity at 1 year of age, six months after the intervention [13]. These

long-term effects of early growth have major implications for the nutritional management of infants globally as reviewed below.

Early Growth and the Preterm Infant

Evidence from experimental (randomised) studies showing that patterns of growth can influence long-term health was first obtained in infants born preterm in the 1980's. At the time, it was recognised that preterm infants required a high protein intake to achieve a post-natal growth rate closer to the intra-uterine rate of growth of a normal fetus of the same post-conception age, a goal regarded optimal for short- and long-term health. Subsequently, long-term follow-up of preterm infants randomised to a high protein formula (for an average of 4 weeks after birth) demonstrated beneficial effects on brain structure and function up to 16 years later (including 10% greater volume of the caudate nucleus and higher IQ [14]). Since this first large trial, numerous observational studies have demonstrated an association between poor growth in preterm infants and impaired long-term neuro-cognitive development; although more recent reviews suggest that this concept remains unproven [15].

In contrast to the benefits for neurodevelopment, longer-term follow-up the same preterm nutritional trials above suggested that faster post-natal weight gain increased later risk factors for CVD, a finding confirmed in numerous observational studies [15,16]. Given that adults born preterm are at greater risk of both impaired neurodevelopment and CVD, current nutrition policy for preterm infants is therefore based on a risk-benefit analysis. On balance, in view of the widely accepted consensus that supporting optimal neurodevelopment is the highest priority, current nutrition policy in preterm infants favours a higher protein intake and faster growth in order to improve later cognitive function, irrespective of any increase in CVD risk. However, this consensus is largely based on research focused on infants <31

weeks gestation and it is uncertain whether the risk-benefit analysis differs for larger, more mature, healthy preterm infants. Furthermore, the most sensitive window for these effects of early nutrition/ growth is unknown and so whether the same nutritional policy should apply after discharge remains controversial.

Early Growth and the Term SGA Infant

In contrast to the consensus for nutritional management of preterm infants, the optimal growth/nutritional strategy for term SGA is currently unclear and is likely to differ in different populations. In high income countries, faster post-natal growth in SGA infants appears to increase the later risk of obesity and CVD [16]. For instance, term SGA infants randomly assigned to nutrient-enriched formula that increased weight gain had higher diastolic BP at age 6–8 years and, in 2 trials, 18-38% greater fat mass at age 5-8 years than controls (as reviewed [9]). Interestingly, differences in childhood fat mass or blood pressure between randomised groups were related to the rate of weight gain in the first 6 months suggesting a ‘dose-response’ association between early growth and later CVD risk [9]. These effects seem to persist into later life. For example, SGA infants with faster weight gain in the first 3 months of life had lower insulin sensitivity and HDL-cholesterol concentrations, and higher triglyceride concentrations, obesity and makers of atherosclerosis at age 18-24 years [18]. In contrast, SGA infants who showed no catch-up growth had no adverse programming effects, findings similar to data from animal models [19]. Therefore, contrary to previous medical and public opinion, promoting catch-up growth by nutritional supplementation in SGA infants from high-income countries is unlikely to have any advantages for long-term health [20].

In contrast to data from richer countries, promotion of faster post-natal growth has been shown to reduce morbidity in low birthweight infants from low-income countries [21]. However, while prevention of stunting and promotion of linear growth clearly has long-term benefits for human capital [1], faster weight gain in infancy is also associated with a greater risk of obesity and non-communicable diseases in low-income countries [22]. As a result of changes in diet and rise in urbanization, large sections of society in low-income countries are at increased risk of obesity and CVD, and so susceptible to programming effects of early growth [21]. Therefore, whether post-natal upward centile crossing should be promoted in developing countries (as is common in many cultures by using bovine milks or early introduction of solid foods) is unknown, but is unlikely to be advantageous in view of the well-established benefits of exclusively breast-feeding for 6 months. Consequently, the optimal pattern of infant weight gain, and its implications for health throughout life, is dependent on different risk-balance considerations in various populations and one size may not fit all [21]. Clearly, further research is required in low- and middle-income countries to define healthy nutritional practices and patterns of growth, particularly using studies with an experimental design to establish causal links between early nutrition and long-term health.

(word count 1996)

Conflicts of Interest

None

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