Early Growth and Later Atherosclerosis

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Abstract
The concept that early growth has long-term biological effects is based on extensive studies in animals dating from the 1930s. More recently, compelling evidence for a long-term influence of early growth on later health has also emerged in humans. Substantial data now support the hypothesis that ‘accelerated’, or too fast infant growth, increases the propensity to obesity, glucose intolerance, raised blood pressure, dyslipidaemia and endothelial dysfunction, the clustering of risk factors which predispose to the development of atherosclerotic cardiovascular disease (CVD). 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. These observations suggest, therefore, that the primary prevention of CVD should 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.

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

Historical Overview
The concept that factors in early life have long-term biological effects first emerged in the 1930s. McCay [1] showed that rats whose growth was stunted by restricting their food intake had a lower incidence of tumours, kidney disease, vascular calcification
and chronic pneumonia, and consequently a substantial 35% increase in lifespan. That manipulation of early growth could influence, or programme [2], later health was first demonstrated by McCance [3] in the 1960s. He found that overfeeding rats, during a critical window in early postnatal life, permanently increased later body size. Subsequently, Lewis et al. [4] showed that male infant baboons given a nutrient-enriched formula, which provided >30%, more energy, had greater mesenteric and omental fat depots, an effect that emerged only after adolescence.

Evidence that growth in infancy programmes the long-term risk of obesity in humans, as in animal models was first obtained in 1970 [5]. Eid [5] found that faster weight gain in the first 6 postnatal months was associated with obesity at age 6–8 years. Specifically, the prevalence of obesity (defined as >20% of expected weight for height and sex) was 7.4% in children with rapid weight gain (>90th centile) in the first 6 weeks compared to 1.9% in those with slower weight gain (<10th centile). Importantly, the main findings from this early research have been confirmed by subsequent studies. For instance, infants born low birth weight showed the most rapid infant weight gain; the critical window for the effects of faster weight gain was as early as the first 6 weeks of life; weight gain in infancy was a better guide to the risk of being overweight later in childhood than weight of the parents; and finally, the effects of infant growth were independent of whether infants were formula-fed or breastfed [5].

The work of Eid and potential programming effects of infant nutrition were largely overlooked in the 1980s when research focused mainly on the possible role of nutrition in fetal life. Observational studies in the late 1980s which linked low birth weight and weight at 1 year with adult CVD and its risk factors led to the ‘fetal origins of adult disease hypothesis’ [6]. This hypothesis suggested two strategies to prevent long-term CVD: firstly, nutritional interventions during pregnancy that increased birth weight could reduce the offspring’s later risk of metabolic disease [6] and, secondly, promotion of infant growth could help reduce the later CVD risk [as discussed in reference 7]. However, currently, there is little experimental evidence in humans to support either of these interventions. In one randomized trial, the offspring of mothers given a supplement of 15 vitamins and minerals over the second and third trimesters of pregnancy had 2.5 mm Hg (95% CI 0.5–4.6) lower systolic blood pressure at age 2.5 years [8]. However, other than this study, there are little experimental data from humans to support the idea that nutrition interventions in pregnancy can affect the offspring’s risk of CVD [9, 10]. Furthermore, there is now substantial evidence to suggest that active promotion of faster infant growth has adverse consequences for later risk of obesity and CVD [11].

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Evidence to replicate the work of Eid and support programming effects of postnatal growth was not obtained until 2002. Stettler et al. [12] showed in 19,397 children that each 100 g increase in weight per month over the first 4 postnatal months
increased the risk of overweight status at age 7 years by approximately 38% (95% CI 32–44%). Subsequently, in 2003, follow-up of randomized studies, initially in pre-term infants and then in infants born at term, suggested that faster infant growth not only influenced obesity, but programmed CVD risk [7, 13]. This ‘growth acceleration hypothesis’ proposed that rapid infant growth (as defined by upward centile crossing for weight or length) programmed the main components of the metabolic syndrome namely obesity, insulin resistance, higher blood pressure, and higher cholesterol concentration [7]. Furthermore, a slower rate of weight gain as a consequence of relative under-nutrition in breast-fed compared to formula-fed infants, particularly in the first few weeks of life, could explain the greater tendency to obesity and higher blood pressure in infants fed formula rather than breast-milk. Finally, because infants born small for gestational age tend to show catch-up growth immediately after birth, postnatal growth acceleration could explain, in part, adverse programming of effects of being born low birth weight for gestation [7].

Since this earlier work, more than 50 studies now support the growth acceleration hypothesis. For instance, faster weight gain (upward centile crossing for weight) in infancy is associated with a greater risk of long-term obesity in over 27 studies (as summarized in several systematic reviews) [14–16]. This association has been seen for obesity in adults and children, in breast-fed and formula-fed populations, for faster length gain as well as weight gain in infancy, in high income and low income countries, and is consistent for cohorts over the last 80 years [14–16]. The association is strong, shows a dose-response effect, is biologically plausible, and is experimentally reproducible in animal models [17]. The effect of infant growth is consistent (very few studies have not found a significant link between rapid infant growth and later obesity [16]), is independent of birth weight and is seen across the birth weight spectrum (i.e. is not confined to infants born low birth weight) [16]. Interestingly, the effects of faster weight gain during the first 3 months appear to be stronger for later fat mass than lean mass, assessed using the 4-component model [18]. Finally, rapid infant weight gain may have stronger programming effects on visceral or peritoneal fat (a major risk factor for CVD) compared to subcutaneous fat [19].

Importantly, the effect of faster growth in infancy in programming future health is not confined to later obesity [7, 20]. Early growth acceleration has been shown to programme greater insulin resistance, dyslipidaemia and raised blood pressure in both adolescents and adults [7, 20]. Interestingly, in a cohort of infants born small for gestational age, those who did not experience postnatal catch-up growth did not show adverse programming effects [20]. Moreover, faster neonatal length and weight gain explained the association between low birth weight for gestation and endothelial dysfunction (an early marker of early atherosclerosis) up to 16 years later [21]. These effects of faster infant growth on risk factors for CVD have been seen in most populations, including in infants born preterm [7, 22] and in cohorts from developing countries [23]. Finally, evidence from intervention studies in which infants born small for gestational age were randomly assigned to nutrient-enriched or standard (control)
infant formulas suggests that programming effects of early growth/nutrition are not confounded by factors such as appetite that could influence both postnatal weight gain and later adiposity [24, 25]. These studies, therefore, strongly support interventions aimed at modifying infant growth to prevent long-term obesity and CVD.

Despite the extensive evidence to support programming effects of infant growth, two key questions remain unanswered. First, the most sensitive window for the programming effects of postnatal weight gain is controversial. Previous data from a Finnish cohort showed that increasing body mass index from birth to age 2 years predicted a higher risk of clinical CVD in adults, but weight gain between birth and age 2 years had little effect [as reviewed, 26]. Similar observations were made for the risk of impaired glucose tolerance in a cohort from Delhi [as reviewed, 26]. However, re-examination of these studies suggests that even within these cohorts faster weight gain in the first 3–6 months had adverse programming effects on later CVD [26]. Nevertheless, the most sensitive window for effects of postnatal growth/weight gain is uncertain. For instance, although many studies suggest that faster weight gain throughout childhood is associated with risk factors for CVD such as blood pressure [27], the most sensitive window between birth and the end of childhood is unknown. Some data suggest that growth in the first year is particularly important and that, within the first year, longer exposure to rapid weight gain (e.g. 9 months compared to 6 months) may have stronger programming effects [16].

The most sensitive period for programming effects of infant growth may be as early as the first few weeks after birth. Faster weight gain in the first postnatal weeks was shown to programme later insulin resistance, inflammatory markers, cholesterol concentration, and endothelial function in both experimental and observational studies in adolescents born preterm [7]. This observation was confirmed by Stettler [17] in adults born at term; in an American cohort, greater weight gain in the first week was associated with overweight status up to 32 years later. These data are consistent with the hypothesis that relative undernutrition and slower growth associated with breast-feeding in the first postnatal week could explain the benefits of breast-fed compared to formula-fed infants for long-term risk of obesity and CVD [7, 13].

The second unanswered question is the mechanism linking infant weight gain with later CVD. Of particular interest are effects of infant growth and nutrition in programming of appetite and hormonal systems relevant to appetite and energy metabolism [7, 28]. Programming of higher concentrations of leptin, insulin and insulin-like growth factor-1 have all been suggested to influence a later risk of CVD. However, recent evidence of programming effects of infant growth gain in genetically leptin-deficient, ob/ob mice, suggests that these effects are independent of leptin [29]. In fact, the effects of growth on long-term health may reflect more fundamental biological processes. As first suggested by McCay [1], early growth may programme long-term aging and age-related processes. The effects of faster growth on increasing the tendency to obesity, diabetes and CVD may therefore represent the programming of
developmental processes and aging. The hypothesis that programming of CVD and aging are similar processes and have common underlying mechanisms in humans [7, 11], as in animals [30], is a key focus of current research.

The size of the effect of infant growth on later risk factors for CVD is substantial and implies important benefits for primary prevention. For instance, in a contemporary western environment, approximately 20% of the population risk of overweight in childhood can be attributed being in the highest quintile for weight gain in infancy [12, 17]. The magnitude of the effect on blood pressure is also important for public health. For example, the 3–4 mm Hg lowering of diastolic blood pressure associated with breast-feeding and slower growth in early life is greater than conventional public health interventions designed to reduce blood pressure and would be expected to reduce the number of cardiovascular events by 100,000 per year in the US alone [7].

Clearly, further experimental data are required to define the risks/benefits of promoting growth in infancy. This risk/benefit is likely to differ between populations. In nutritionally vulnerable infants, such as those born preterm or from low-income countries, faster weight gain may have benefits such improvements in cognitive function and lower morbidity respectively. However, active promotion of catch-up growth in healthy term infants from richer countries may not be desirable [as reviewed 11]. Nevertheless, in many populations, interventions aimed at achieving an optimal pattern of infant growth could play a key role in the primary prevention of long-term obesity and CVD.

References


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