

The Role of Infant Nutrition in the Global Epidemic of Non-Communicable Disease

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Abstract

Non-communicable diseases (NCDs), and atherosclerotic cardiovascular disease in particular, are the most important health problems of the 21st Century. Already in every world region except Africa, NCDs account for greater mortality than communicable, maternal, perinatal and nutritional conditions combined. Although modifiable lifestyle factors in adults are the main determinants, substantial evidence now suggests that factors in early life also have a major role in the development of NCDs; commonly referred to as The Developmental Origins of Health and Disease Hypothesis. Factors in utero, early post-natal life, and throughout childhood, have been shown to affect NCD's by influencing risk factors for cardiovascular disease such as obesity, diabetes, hypertension and dyslipidaemia. Infant nutrition (e.g. breast-feeding rather than bottle feeding) and a slower pattern of infant weight gain have been shown to be particularly protective against later risk of obesity and cardiovascular disease in both low-income and high-income countries. The mechanisms involved are poorly understood, but include epigenetic changes; effects on endocrine systems regulating body weight, food intake, and fat deposition; and changes in appetite regulation. As a consequence, strategies to optimize early life nutrition could make a major contribution to stemming the current global epidemic of NCD. This review will consider the role of early life factors in the development of NCDs, focusing on the impact of infant nutrition/growth on obesity and cardiovascular disease. The review will highlight the experimental (randomised) evidence where available, briefly summarize the underlying mechanisms involved, and consider the implications for public health.

Introduction and Historical Overview

Atherosclerotic CVD is the leading cause of death and disability, the major consumer of health care resources and the most important public health priority worldwide⁽¹⁾. Yet, despite great progress in medical care, its prevalence is increasing sharply. Thus primary prevention is a major priority for global health policy and research⁽¹⁾.

While the 'obesogenic' environment with abundant availability of energy dense foods and sedentary lifestyle is clearly the major contributor to risk of NCD's, strategies based on prevention of lifestyle risk factors in adults have met with limited success. However, recent evidence from animal models and epidemiological data from humans has led to the hypothesis that nutrition in *early life* (pre-pregnancy, pregnancy, and infancy) rather than in adults may also impact long-term risk of obesity, CVD and type 2 diabetes⁽¹⁻⁷⁾. Optimising nutrition during critical windows early in life could therefore provide a new opportunity for primary prevention and hence reduce lifetime risk of NCD's⁽¹⁻²²⁾.

The idea that nutrition during critical windows in early life may influence later health is part of a broader process, generally called ‘*programming*’, which reflects “the impact of a stimulus or insult during a critical or sensitive window, in producing long-term changes in the structure or function of the organism (as reviewed⁽³⁾). Whilst the concept of ‘critical periods’ was conceived in the 19th century, evidence that early nutrition had long-term biological effects first emerged in the 1930’s when McCay showed that calorie restriction in early life reduced chronic disease and increased lifespan⁽³⁾. Then McCance in the 1960’s showed in animals that early postnatal nutrition, during a brief critical window, had life-time effects⁽³⁾. Of relevance to CVD, in the 1970’s Hahn found rats overfed during suckling developed higher plasma insulin and cholesterol in adulthood; and later, Lewis found over-feeding in infant baboons programmed obesity, an effect that emerged only in adolescence, showing that programmed effects may be ‘remembered’ but not expressed as a phenotypic consequence until later⁽³⁾. Now, extensive evidence in animal models shows that nutrition in early postnatal life programmes the major risk factors for CVD (insulin resistance, obesity, dyslipidaemia and blood pressure⁽³⁻⁵⁾), atherosclerosis⁽⁶⁾, and even longevity⁽²³⁻²⁶⁾.

In humans, one of the first studies to show programming effects was by Eid (1970) who found that faster weight gain in the first 6 weeks of life increased the risk of obesity 6 to 8 years later⁽²⁷⁾. Subsequently, in the 1980’s and 90’s strong and consistent associations of low birth weight with CVD and type 2 diabetes in adulthood⁽²⁾, led to a change in focus from nutritional programming in infancy to the effects of nutrition in fetal life (commonly known as the Fetal Origins of Adult Disease or ‘Barker’ hypothesis⁽²⁾). However, the key limitation of such observational studies has been the lack of experimental evidence for a causal role of early nutrition in programming human health. Thus, early nutritional practices have not been backed by rigorous experimental evidence of efficacy and safety expected in other areas of public health; and have the potential to cause harm. For example, ‘intuitive’ attempts to promote growth in small, growth-retarded newborns could significantly increase later CVD and obesity^(3-5,8-14). This lack of a sound evidence-base has prevented changes to nutritional and public health practice in infancy in order to prevent later NCD’s.

More recent research has emphasised the importance of experimental (randomised) evidence in the field of nutritional programming. Follow-up of randomised trials in preterm infants initiated in the 1980’s provided the first experimental evidence that early nutrition had programming effects on major risk factors for CVD (as reviewed⁽³⁾). For instance, in randomised trials comparing breast milk feeding to formula feeding (possible in preterm infants), breast-milk was shown to have major beneficial effects on obesity, dyslipidaemia, high blood pressure, and insulin resistance and blood

pressure in adolescence⁽³⁾. These trials, together with extensive epidemiological studies and evidence of dose-response effects of breast feeding, supported a causal link between infant nutrition and later cardiovascular health, with important implications for inequalities in health and public health policy in nutrition. Effect sizes in these studies, although small for individuals, were substantial on a population basis. For example, breast-feeding and diets promoting slower infant weight gain reduced later diastolic blood pressure by around 3 mm Hg^(3,13), expected, on a population basis, to prevent over 100,000 cardiovascular events annually in the USA alone (as reviewed⁽³⁾). The 10% lowering of LDL cholesterol with breast-feeding⁽³⁾ is expected to reduce CVD incidence by 25% and mortality by 13-14%⁽³⁾. Nutritional interventions in early life therefore have the potential to have a major impact on disease prevalence, quality and quantity of life as well as health care costs.

Growth in the first few months: a critical window for programming of obesity and CVD

Plausible explanations for the effects of breast-feeding on later obesity and CVD risk have included residual confounding by socio-economic, demographic and behavioural differences between infants breast- or formula-fed. However, based on previous epidemiological evidence of an association between infant weight gain and later risk of obesity, randomised trials in infants born preterm⁽³⁾, and subsequently in infants born at term but small for gestational age^(13,14), we suggested that the benefits of breast-feeding for later risk factors for CVD may be due to slower growth and relative under-nutrition in breast-fed compared to formula-fed infants - the Growth Acceleration Hypothesis⁽³⁾. This hypothesis proposed that faster postnatal growth (upward centile crossing for weight or length) programmed the major components of the metabolic syndrome including higher blood pressure, obesity, and endothelial dysfunction. Furthermore, postnatal growth acceleration could also explain, in part, adverse programming effects seen in infants born small for gestation who show 'catch-up' growth immediately after birth⁽³⁾.

Since this early research, more than fifty studies now support the growth acceleration concept. For instance, faster weight gain in infancy (upward centile crossing for weight) is associated with a greater risk of later obesity in more than 30 studies (summarized in 5 systematic reviews⁽⁸⁻¹²⁾ including an individual-level meta-analysis in 47,661 participants from 10 cohorts⁽¹¹⁾). This association is seen for the main components of the metabolic syndrome, in breast-fed and formula-fed populations, in high-income and low-income countries representing many different ethnic groups⁽⁷⁻¹²⁾, and is consistent for cohorts during the last 80 years⁽⁸⁾. The association is biologically plausible and experimentally reproducible in several animal models⁽⁷⁾. For example, in mice faster growth during lactation, after growth restriction in the fetal period, alters the expression of several

genes encoding enzymes involved in lipid/carbohydrate metabolism⁽²⁸⁾. In fact, the idea that faster growth in early life adversely affects long-term survival (concept of 'grow now, pay later') appears to be a widespread, evolutionary conserved phenomenon seen across diverse animal species⁽²⁹⁾.

The association of faster early growth with adverse effects on long-term health is not confined to infants with low birth weight^(5,10), is evident in both infants born preterm and at term⁽³⁻⁵⁾, and can be detected even as early as the first few years of life^(20,30). For instance, faster weight gain in infancy was associated with abdominal adiposity at two years of age⁽²⁰⁾, and SGA infants who showed catch-up growth (weight gain >0.67 SDS) had higher fasting insulin concentration at 1 year of age than those without catch-up growth⁽³⁰⁾. The effect of faster infant growth appears to be greatest for central or visceral adiposity⁽²⁰⁻²²⁾, a key risk factor for CVD and type 2 diabetes, and, at least in data from observational studies, is seen in adults as well as children. Leunissen et al showed that faster weight gain in the first 3 months of life was associated with lower insulin sensitivity and HDL-cholesterol concentrations, and greater waist circumference, triglyceride concentrations, percentage body fat, and central adiposity at 18 to 24 years of age⁽¹⁶⁾. These studies suggest a large effect size. For example, over 20% of later obesity risk can be explained by the rate of infant weight gain (as reviewed⁽⁵⁾) and the relative risk of later obesity associated with more rapid weight gain in infancy ranges from 1.2 to as high as 5.7⁽⁸⁾.

However, despite extensive epidemiological data linking faster infant weight gain with later cardiovascular risk factors, data for an effect of growth patterns in infancy on long-term *clinical* outcomes are contradictory. In a cohort from New Delhi, rapid gain in BMI in the first year was associated with development of the metabolic syndrome in adulthood but (in contrast to this finding) low gain in BMI was associated with glucose intolerance⁽¹⁵⁾. In fact, previously, faster growth over the first 2 years has been suggested to offset the adverse programming effects of fetal growth restriction and low birth weight⁽³¹⁾. For example, in the Helsinki and New Delhi Birth Cohorts, individuals with LBW who had *lower weight gain in the first 2 years* and upward crossing of weight centiles in childhood were noted to be at highest risk of CVD and type 2 diabetes^(31,32). These data have supported the practice of actively promoting rapid weight gain in infancy to benefit long-term health especially in countries in transition such as India where under-nutrition in childhood is common and of more immediate concern.

The discrepancy in the effects of early weight gain for later obesity and CVD risk can be partly explained if different periods within the first year of life have different programming effects. Gillman noted that in the Helsinki cohort, the BMI of those who eventually developed CVD had

actually increased in the first 3 months before decreasing⁽³³⁾. Similarly, in the New Delhi cohort, gain in BMI in the first 6 months was associated with greater BMI in adulthood⁽³³⁾. Recent studies have confirmed the role of weight gain in the first 3 months on programming of obesity and CVD. Chomtho et al, in a study focused on the effect of weight gain in different periods in infancy on body composition in childhood (age: 11.4 +/- 3.8 y), showed that faster weight gain between 0 to 3 months and 3 to 6 months (but not between 6-12 months) was associated with greater total and truncal fat mass in childhood⁽¹⁷⁾. Faster weight gain during a critical window in the first few months of life may therefore have adverse consequences for the risk of later NCD's in diverse populations.

Experimental (Randomised) Evidence for Growth Acceleration

The concept that faster infant growth can causally impact on later risk factors for CVD is now strongly supported by randomised studies in infants born prematurely⁽³⁾, SGA at term^(13,14), and in healthy term infants^(18,19). For example, infants born preterm randomly assigned to a nutrient-enriched diet, that promoted faster weight gain in the first few weeks after birth, had higher fasting concentrations of insulin, cholesterol, and C-reactive protein, as well as leptin resistance in adolescence than controls⁽³⁾. Similarly, infants born SGA at term and randomly assigned to nutrient-enriched formula that increased weight gain had higher diastolic blood pressure at age 6–8 years⁽¹³⁾ and, in 2 trials, 18-38% greater fat mass at age 5-8 years than controls⁽¹⁴⁾. Notably, differences in fat mass or blood pressure in childhood were related to the rate of weight gain in infancy suggesting a 'dose-response' association between early growth and later CVD risk^(13,14). More recently, programming effects of infant nutrition/growth have been confirmed in experimental studies of term infants with appropriate birthweight for gestation. These effects have been seen in both high-income and low-income countries (e.g. Chile¹⁹), thereby supporting the concept that programming of CVD risk by faster early growth is a fundamental biological finding seen across populations^(18,19).

Central to the growth acceleration hypothesis is that fact that breast-fed infants grow more slowly than those fed formula, particularly in the first few weeks after birth and again between 3 and 12 months of age. This effect is probably because of the lower protein content of breast-milk (approximately 10 g/L compared to up 15g/L in some formulas), which means that formula-fed infants receive on average 0.5g/kg/d greater protein than breast-fed infants⁽³⁴⁾. These differences in rate of weight gain and protein intake between bottle- and breast-fed infants has provided an opportunity to investigate the growth acceleration concept using randomised trials in health term infants.

In the largest study, the European Childhood Obesity Trial, formula-fed babies were randomly assigned to formulas with different protein concentrations and followed to age 6 years⁽¹⁸⁾. The assigned diets were given as a standard infant formula (after the parents had decided to add formula) to age six months (1.25 g/100 ml in the lower protein formula versus 2.05 g/100ml in the higher protein formula) followed by a follow-on formula to age 12 months (1.6 g/100 ml in the lower protein formula versus 3.2 g/100 ml in the higher protein formula). Consistent with an effect of protein intake on infant growth and later risk of obesity, babies given the higher protein formula had a faster rate of weight gain in the first year, higher BMI at 2 years of age, and 2.4x greater risk of obesity at 6 years of age than those in the lower protein group⁽¹⁸⁾. However, although strongly supporting the growth acceleration concept, the protein content of formulas used in this trial was much higher than those commonly used today, thereby limiting the practical relevance of this study.

Nonetheless, the possibility that a lower protein intake in the first year can reduce the later risk of obesity is strongly supported by a randomised trial from Chile in which infants of mothers with a BMI >25 kg/m², were randomised to one of two infant formulas between 3 and 12 months of age. Infants were assigned either a standard-nutrient (protein: 1.77g/100 ml, energy: 65.6 kcal/100 ml), or a new low-nutrient formula with much lower protein concentration than conventional formula (protein: 1.04 g/100 ml, energy 62.8 kcal/100ml)⁽¹⁹⁾. Compared to controls, infants given the lower protein formula had 1.8 g/d slower weight gain between 3 and 6 months of age (primary outcome) and lower BMI at age 2 years⁽¹⁹⁾. However, whether these effects on adiposity persist into later life and are observed in infants whose mothers are not overweight are unknown and remain key research questions.

Overall, although five randomised studies now support a causal link between faster infant weight gain and later risk factors for CVD, several research questions remain. Four out of five previous studies are in children aged 2-8 years^(13,14,18,19), (the 5th study was in adolescents⁽³⁾) and therefore the impact of growth acceleration in infancy on *adult* CVD risk is unknown. Furthermore, these studies have not been able to demonstrate a causal link between early growth and later visceral adiposity, a suggested intermediate risk factor by which faster infant growth increases CVD risk⁽²⁰⁻²²⁾. Finally, it is unknown whether there is a particularly sensitive or critical window in infancy for these programming effects and whether programming effects of infant nutrition/growth persist into adult life and amplify with age (as in animal models), or are 'overwhelmed' by conventional CVD lifestyle risk factors in adulthood.

Mechanisms

A major limitation of the Development Origins of Health and Disease field is a relatively poor understanding of the underlying biological mechanisms involved. Nonetheless, there has been some progress in our knowledge of the ‘coupling mechanisms’ that link early nutrition/growth with later VD. These can be grouped into four main inter-related categories.

Endocrine Mechanisms

Nutritional programming has been suggested to permanently affect endocrine systems that regulate body weight, food intake and metabolism, and fat deposition in both humans and animal models⁽³⁵⁾. Studies in animals suggest that the set points or ranges for endocrine feedback mechanisms may be influenced by the concentrations of the hormones themselves early in life⁽³⁶⁾. Similar mechanisms may occur in humans. For instance, higher nutrition postnatally may programme high leptin, and particularly, high insulin concentrations, which by predisposing to higher concentrations later in life, increase the threshold to satiety signals and hence the propensity to obesity. Consistent with this, preterm infants randomised to a protein-enriched neonatal diet had hyperinsulinism and leptin resistance in adolescence⁽³⁾.

Similarly, hypercortisolism in infancy could predispose to hypercortisolism throughout life⁽³⁶⁾. There is evidence to suggest that higher Insulin like Growth Factor 1 (IGF-1) concentrations facilitate catch-up growth in SGA infants in early life, but this permanently increases the activity of the hypothalamic-pituitary-adrenal (HPA) axis so that infants born SGA have higher IGF-1 concentrations later in life⁽³⁷⁾. Infant nutrition may also programme the HPA axis. For example, IGF-1 concentrations are lower in breast-fed compared to formula-fed infants (who have more rapid weight gain) and, in a large RCT, lower in infants given a standard versus a high protein infant formula⁽³⁸⁾. However, whether these effects on IGF-1 persist into adult life, and their impact on development of appetite regulation, obesity (particularly visceral adiposity) and CVD are currently unknown.

Appetite regulation

Observational evidence suggests that early nutrition/ growth affects appetite regulation which could affect energy intake and metabolism⁽³⁹⁾. For example, formula rather than breast-feeding, rapid weight gain in infancy, and the technique of feeding (e.g. breast versus bottle feeding) are all associated with a higher set point for appetite and recognition of satiety in early childhood which, when exposed to a nutrient dense diet, is likely to predispose to obesity^(40, 41). However, the lack of experimental data means that a causal association between infant growth/nutrition and long-term

appetite regulation in humans has not been established and whether these programming effects persist longer-term, into adult life, where they may have a greater impact on the risk of CVD is unknown.

Epigenetic programming

One of the most researched mechanisms for nutritional programming has been into epigenetic regulation of gene expression, particularly in the role of programmed changes in DNA methylation. There is extensive evidence from animal models and emerging evidence from humans that changes in early nutrition and growth are associated with changes in DNA methylation in the offspring⁽⁴²⁾. Much less attention has been directed towards the role of post-transcriptional programming of gene expression although programmed changes in miRNA expression have been shown to substantially impact on adipocyte lipid storage capacity and therefore whole body insulin sensitivity⁽⁴³⁾.

Accelerated Biologic Ageing

Many of the conditions associated with faster infant growth, such as type 2 diabetes and CVD, are considered diseases of ageing, suggesting that nutritional programming may be mediated by effects on ageing processes. This hypothesis is strongly supported by data from animals models showing that faster growth in early life is associated with reduced life span⁽²³⁻²⁶⁾, shorter telomere length (a marker of cellular aging)^(23,44) and increased expression of mediators of cellular senescence such as p16 concentrations⁽⁴⁴⁾. However, whether rapid infant growth affects accelerated cellular ageing leading to increased whole body ageing in humans is unknown. This issue is of critical importance since effects of early life factors on biological ageing may be a common underlying pathway for the impact of infant growth/nutrition on diverse outcomes such as obesity, CVD, and diabetes and other NCD's, and could explain associations between shorter telomere length and ageing-related CVD in humans⁽⁴⁵⁾.

Nutrition programming and Low-income countries

Low-income countries face a massive increase in NCDs. For example, in India alone, by 2030 there will be an estimated 80 million people with type 2 diabetes and Asian Indians will account for approximately 40% of the global burden of CVD⁽⁴⁶⁾. There is therefore an urgent need for primary prevention programmes, but whether the growth acceleration concept is relevant to low-income countries is uncertain⁽⁴⁷⁾. This question is particularly relevant for countries such as India which have the highest global burden of term infants born small for gestation, who are at higher risk of CVD⁽²⁾, but in whom the optimal pattern of weight gain for long-term term health is not known⁽⁴⁷⁾.

Clearly, growth patterns in infancy are likely to have a different impact on health according to the environment in which the population lives. For instance, infants with slower weight gain may be at higher risk of infections and under-nutrition and hence the overall risk-benefit may favour faster infant growth in many populations from low-income countries. However, low-income countries have very heterogeneous populations with a growing middle class at risk of long-term obesity and CVD. As in the West, faster weight gain in infancy is associated with later risk of obesity in several middle and low-income countries such as the India, Seychelles, Brazil and South Africa⁽⁹⁾. In many of these countries promotion of rapid weight gain in infancy is normal cultural practice and, in order to achieve this, inappropriate addition of animal milks (including cow's milk, buffalo milk and donkey's milk) is common. Further research is therefore needed to define the risk-benefits of growth acceleration and guide infant nutrition policy in these countries⁽⁴⁷⁾.

Public Health Implications

The impact of infant nutrition/growth on future risk of NCD's has considerable implications for public health and nutrition practice. For instance, there is substantial agreement from systematic reviews and meta-analyses from scientific advisory authorities (Dutch State Institute for Nutrition and Health 2005; WHO 2007; US Agency for Healthcare Research and Quality 2007; and the UK Scientific Advisory Committee on Nutrition 2011) [as summarised⁽⁴⁸⁾] for a protective effect of breast-feeding against the risk of later obesity. Breast-feeding should therefore be promoted for its long-term as well as short-term health benefits. The strength of the evidence supporting the growth acceleration hypothesis has also led to changes in nutritional practice. Professional bodies such as the Institute of Medicine in the US, and the Royal College of Paediatrics and Child Health, and the Scientific Advisory Committee on Nutrition in the UK have recognized the role of faster infant weight gain in increasing the risk of long-term obesity. Consequently, health care professionals are advised to prevent inappropriate upward centile crossing as well as growth faltering in infancy. The new WHO growth charts based on the exclusively breast-fed infant are likely to help in the prevention of over-feeding in infancy. Furthermore, contrary to previous medical and public opinion, promoting catch-up growth by nutritional supplementation in healthy term infants born small for gestation may not be appropriate⁽⁴⁹⁾.

Finally, the benefits of a slower rate of infant weight gain as seen in breast-fed compared to formula fed infants has led to changes to infant formula to try to reduce the risk of over-feeding in formula-fed infants. These include reduction in the protein content of infant formulas and changes in recommendations for the composition of formula. For example, the European Food Safety Authority (EFSA) recently recommended a reduction in the maximum permitted protein content in

infant formula and suggested recently that ‘infant formula and infant follow-on formula should ensure that the growth and development of infants fed infant formula are similar to those of infants who are exclusively breast-fed during the first 6 months of life’⁽⁵⁰⁾.

Conclusions

In November 2012, the WHO identified NCDs as the most important global health issue of the 21st century and agreed a target of reducing premature mortality from NCD by 25% by 2025. Strong evidence now suggests that optimising growth and nutrition in infancy will help achieve these targets.

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