The Global Epidemic of Noncommunicable Disease: The Role of Early-Life Factors

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Abstract

The rapid increase in prevalence of noncommunicable diseases (NCDs) is probably the most important global health problem of the 21st century. Already in every region except Africa, NCDs account for greater mortality than communicable, maternal, perinatal and nutritional conditions combined. Although modifiable lifestyle behaviors in adult life are the main risk factors, substantial evidence now suggests that factors in early life also have a major role in the development of NCDs. For instance, breastfeeding and a slower pattern of infant weight gain have been shown to reduce the risk of obesity, cardiovascular disease and diabetes in both low-income and high-income countries. The mechanisms involved are poorly understood, but include epigenetic changes and resetting of endocrine systems that affect energy metabolism and appetite. These early life factors may interact with and exacerbate the detrimental effects of a sedentary lifestyle and energy-dense diets later in life. As a consequence, the impact of early-life factors on long-term health may be particularly important in low- and middle-income countries, which face the fastest increases in urbanization and greatest changes to lifestyle. Strategies to optimize infant nutrition could therefore make a major contribution to stemming the current global epidemic of NCD.

Introduction

Although meeting the Millennium Development Goals and the prevention of undernutrition remains a major problem in many populations, the rapid increase in noncommunicable disease (NCD) has now become the highest prior-
ity for global public health. According to the WHO, in 2008 approximately 63% of all deaths (36 out of 57 million per year) were due to NCDs, comprising of cardiovascular disease (CVD), diabetes, cancers and chronic respiratory disease [1]. Of these, nearly 80% (29 million) occurred in low- or middle-income countries, with CVD, including diabetes, being the most common. In fact, contrary to popular belief, most deaths from CVD (80%) occur in low- or middle-income countries rather than in richer populations [1].

Whilst modifiable behavioral factors such as tobacco use, insufficient physical activity, the harmful use of alcohol, and unhealthy diets are the major risk factors, research over the last 10 years has highlighted the key role of early life factors in the development of NCD [1, 2]. Factors in utero, early postnatal life and throughout childhood have been shown to affect CVD by influencing the propensity to risk factors such as obesity, diabetes, hypertension and dyslipidemia: the so-called developmental origins of adult disease hypothesis. Many of these factors, such as infant and childhood nutrition, are modifiable, raising the possibility that interventions in early life could help stem the current global epidemic of NCD. The present review considers the role of these early life factors in the development of NCDs, focusing on the impact of infant nutrition on CVD in low- and middle-income countries. The review aims to highlight the experimental evidence where available, briefly summarize the mechanisms involved, and consider the implications for public health.

The Developmental Origins of Noncommunicable Disease

Historically, the concept that factors in early life such as nutrition can affect, or program, the development of NCDs emerged from animal work in the 1930s. McCay [3] 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. Subsequently, in the 1980s 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 [4]. These observations have been replicated many times including several studies from Sub-Saharan Africa linking lower birthweight with higher blood pressure in childhood [as reviewed in 2]. Of particular interest has been the association of birthweight with long-term body composition [5, 6]. In general, in both high- and low-income countries, body size in early life (birthweight and faster infant weight gain) is more strongly associated with greater fat-free mass than fat mass in adults, while there are some data linking low birthweight with greater visceral or central fat [6].
These epidemiological data, along with studies linking prenatal nutrition (e.g., famine during pregnancy, antenatal protein and energy intake, and maternal micronutrient supplementation) with later risk of obesity and CVD, suggest that nutrition during pregnancy is a modifiable risk factor for NCDs [5, 6]. However, there is little experimental evidence to support a causal link between prenatal nutrition and long-term CVD [7]. In one such study, supplementation of Nepalese mothers with fifteen micronutrients (compared to controls given only iron and folic acid) lowered systolic blood pressure in the offspring at 2–3 years of age [8]. However, this finding has yet to be replicated and, interestingly, there was no effect on diastolic blood pressure. The lack of randomized controlled trials (RCTs) is likely to be particularly important for associations between both birthweight and infant growth and later fat-free mass. Indeed, it is not surprising that ‘larger’ individuals (in height, body frame and hence in fat-free mass) are both larger at birth and have faster rates of infant weight gain, since both exposure and outcome will be strongly influenced by the same genetic factors. Therefore, although there is substantial ongoing research in this this area, currently there is little experimental evidence to suggest that modifying prenatal factors such as nutrition can help prevent later NCD.

Early Postnatal Factors and the Prevention of Noncommunicable Disease

Evidence that early postnatal factors program later health was first obtained in 1970 when faster weight gain in the first 6 months after birth was found to be associated with obesity at age 6–8 years [as reviewed in 9]. More recently, follow-up of adolescents born prematurely and randomly assigned to formula or human milk provided the first experimental evidence to show that breast milk feeding had long-term benefits for CVD risk factors such as obesity, dyslipidemia, raised blood pressure, and insulin resistance [10, 11]. Subsequently, five meta-analyses have confirmed that breastfeeding is associated with approximately 20% lower risk of obesity [summarized in 12–15], an effect size which is comparable to interventions for obesity later in life [13] and which is likely to be important for populations rather than for individual health. Compared to those formula fed, breastfed infants had lower fat mass rather than fat-free mass, a difference evident from as early as the first year of life [14].

Data to support benefits of breastfeeding for CVD risk factors other than obesity are more limited. All four systematic reviews and meta-analyses on the long-term effects of breastfeeding published since 2005 (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 summarized in 13] support a protective effect of breastfeeding against the risk of obesity but only the latter three suggested that breastfeeding reduced later blood pressure and risk of type 2 diabetes. However, all reviews highlighted the possibility of residual confounding in the studies included.

The issue of confounding has been considered in research from Brazil, where, unlike developed countries, breastfeeding is not associated with socioeconomic status [16]. Here, breastfeeding was associated with later IQ but not with blood pressure or BMI [16]. One explanation is that breastfeeding is only protective against obesity in the highest part of the BMI distribution [12], and such high levels of obesity are likely to be more common in the ‘obesogenic’ environment found in richer countries. Therefore, early-life factors may have a priming effect (for example by affecting appetite regulation – see below) but depend on an interaction with subsequent environment (e.g. an energy-dense diet) to produce effects on health. This potential interaction of early-life factors with later environment is supported by animal models which showed that adverse effects of maternal protein restriction and faster postnatal growth on obesity and lifespan were most marked in mice fed a high calorie, ‘cafeteria’ diet, after weaning rather than normal chow [17].

The issue of residual confounding in studies of breastfeeding was also addressed in a large-scale cluster-randomized trial in Belarus (the PROBIT study) [18]. This trial compared an intervention which promoted breastfeeding with a control group that received normal health care and found a lower risk of gastrointestinal infection and eczema in the intervention arm. At 6.5 years of age, IQ was higher in the intervention group, but there were no differences between randomized groups in blood pressure or fat mass [18]. However, it is important to note that because the intervention was designed to increase the degree and duration of exclusive breastfeeding and not its initiation, the study may be underpowered to detect differences in outcomes between breastfed and formula-fed infants [18]. Overall therefore, other than in infants born preterm, the evidence that breastfeeding has long-term benefits for CVD risk is almost entirely observational, a situation which, given the impossibility of RCTs directly comparing breastfeeding with formula feeding, is unlikely to change in the future.

The Role of Infant Growth in Programming Cardiovascular Disease

Various mechanisms have been proposed for the programming effects of breastfeeding including confounding by health behaviors that affect CVD risk, effects on appetite regulation, and the possibility of biologically active factors in human milk which could affect energy intake and metabolism [19]. However, perhaps
the most extensively studied hypothesis is that the long-term cardiovascular benefits of breastfeeding are a consequence of slower growth and relative undernutrition in breastfed compared to formula-fed infants – the growth acceleration hypothesis [11].

Over the last decade, substantial evidence has accumulated from both animal and human studies to support the growth acceleration concept [9, 11]. These data include several studies from low- and middle-income countries such as the Seychelles, Brazil and South Africa [as reviewed in 20]. In India, for example, men and women living in New Delhi who had features of the metabolic syndrome (increased waist circumference, higher blood pressure, insulin resistance and dyslipidemia) had more rapid weight gain in infancy than controls [21]. However, the size of these programming effects in cohorts from low- and middle-income countries appears to be small with, for example, a 1-SD change in early growth predicting less than a 1% change in adult body fat [6]. In contrast, 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 [as reviewed in 9]. Nonetheless, given the potential interaction of programming effects with later environment, and global changes in habitual diet and lifestyle, the contribution of infant growth to long-term health is likely to become increasingly important even in low-income countries.

Unlike potential programming effects of antenatal nutrition or breastfeeding, the hypothesis that *infant growth* affects long-term health is strongly supported by evidence from randomized, double-blind, clinical trials that can establish a causal link between exposure and outcome. For instance, adolescents born preterm and randomly assigned to a nutrient-enriched (preterm) formula that promoted infant growth had greater blood pressure and insulin and cholesterol concentrations than those assigned to less nutrient-dense diets (term formula or breast milk) [10, 11]. Similarly, compared to controls, infants born at term, but small for gestation, who were randomly assigned to nutrient-enriched formula for 6–8 months had higher blood pressure in childhood [22], and in two trials, greater body fat up to 8 years later [23]. Programming effects of infant growth are also seen in experimental studies in term infants with normal birthweight. In the European Childhood Obesity Study, a large, multicenter RCT, infants randomized to formulas with a higher protein concentration for the first year (which promoted faster weight and length gain) had greater BMI at 2 years of age than controls. Based on existing data from observational studies, the authors predicted that this would lead to a 13% increase in later risk of obesity [24]. Finally, in a trial from Chile, healthy full-term infants of mothers who had a BMI of >25, randomly assigned to a lower-protein formula from 3 to 12 months (1.65 g/100 kcal, 628 kcal/l) had lower BMI at age 2 years than those given a control
formula (2.63 g/100 kcal, 656 kcal/l) [Inostroza et al., unpubl.]. The latter study clearly illustrates that infant growth/nutrition has programming effects on the risk of obesity in middle-income countries.

Complementary Feeding

Whether the timing and quality of complementary feeding has an impact on long-term health is more controversial than effects of infant growth. A recent systematic review suggested that earlier introduction of solids, and especially before 4 months, was associated with a greater risk of obesity especially in infants fed formula [15]. This observation is consistent with the hypothesis that breast-feeding has a priming effect, possibly by favorably affecting appetite regulation. Infants given formula in the first few months after birth would be more susceptible to overfeeding if given solids earlier, which in itself could lead to faster infant weight gain and hence greater susceptibility to long-term obesity. Alternatively, since these studies are all observational, there is a high possibility of confounding. For example, fussy eaters or infants genetically susceptible to have a higher appetite are both more likely to be given solids earlier and are at greater risk of later obesity. The lack of experimental data therefore considerably limits our understanding of the impact of complementary feeding on long-term health.

Growth in Childhood and Programming of Cardiovascular Disease

A similar lack of RCTs limits interpretation of evidence linking faster weight gain in childhood with later CVD. This finding has been seen in both high-income and low-income countries. For instance, faster weight gain in children older than 2 years was associated with increased risk of death from CVD in a cohort from Helsinki [as reviewed in 9], while follow-up of children in Delhi found that glucose intolerance and type 2 diabetes were more common in children who had the greatest increase in BMI throughout childhood [25]. Faster growth in children is also associated with fat mass in adults in five cohorts from low- and middle-income countries [6]. Given the increasing evidence that childhood obesity is an independent risk factor for CVD, these observations have major implications for the prevention of CVD. However, although the above data strongly support the growth acceleration concept, it remains possible that both rapid growth in childhood and long-term risk of obesity and CVD are a consequence of the same underlying genetic tendency. For example, common genetic variants for adult obesity have been associated with faster weight and length gain in both infancy and childhood [26].
Mechanisms

Despite growing evidence for the developmental origins of adult disease, the underlying mechanisms remain poorly defined. Evidence from animal models and experimental studies in infancy suggest that confounding by environmental and genetic factors is unlikely to explain the impact of early growth/nutrition on later health [9]. However, the exact nature of the exposure in early life, its timing, and the 'coupling mechanisms' that link early nutrition with later health are all poorly understood.

In terms of exposure, it is difficult to separate the programming effects of growth in infancy from those of nutritional factors, such as protein intake, that influence growth. However, the relative importance of growth is supported by evidence from animal models [3, 9] and observations that faster growth is associated with later risk factors for CVD even in infants breastfed [22, 23]. The critical window for the effects of growth/nutrition may extend throughout childhood [25], but includes at least a window in the first year of life, a hypothesis supported by several RCTs [10, 22–24]. In fact, the most sensitive window for programming by infant growth may even be as early as the first few weeks after birth [9].

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 [as reviewed in 9]. The first, the role of epigenetic changes that persist throughout life, is supported by recent evidence in animal models. Plagemann et al. [27] showed that neonatal overfeeding in rats (which leads to development of the metabolic syndrome later in life) was associated with increased methylation of CpG residues in the insulin receptor promoter gene. Although this epigenetic change did not affect insulin receptor gene expression in the short term, the authors speculated that increased methylation of this allele could predispose to insulin insensitivity under adverse environmental conditions later in life.

The second hypothesis suggests that early growth acceleration permanently affects hormonal axes that regulate bodyweight, food intake and metabolism, and hence fat deposition. Hormonal changes in infancy (possibly via changes to the hypothalamic circuitry regulating appetite) could influence the satiety response and increase food intake throughout life, thereby increasing the risk of obesity and CVD. In support of this, formula feeding and infant-initiated bottle emptying in the first half of infancy was associated with excess weight gain during late infancy [28], while bottle feeding (with either infant formula or human milk), and faster infant weight gain were associated with a lower satiety response later in life [29]. The endocrine changes that allow a resetting of appetite are un-
known, but evidence of programming effects of early growth in genetically leptin-deficient ob/ob mice suggests that these effects are independent of leptin [30]. The adverse effects of faster early growth on long-term health are seen in diverse animal species, and so may reflect more fundamental biological processes. As first suggested by McCay [3], early growth may program long-term aging and age-related processes possibly by mechanisms that affect the insulin/IGF-1 systems [9].

**Public Health Implications**

The idea that modifiable factors in early life can affect the main risk factors for atherosclerosis provides a major opportunity for the primary prevention of CVD. For example, four of the six most common risk factors for mortality in both richer and poorer countries (high blood pressure, obesity, and high blood glucose and cholesterol concentrations; WHO statistics) are influenced by infant nutrition/growth. Furthermore, since early-life factors affect obesity and endocrine changes such as higher IGF-1 concentration, both of which are key risk factors for the development of malignant disease, optimizing nutrition and growth in infancy may have broader benefits for health.

Prevention will be particularly critical for low- and middle-income countries which face the greatest increase in NCDs. Already in every region except Africa, NCDs account for greater mortality than communicable, maternal, perinatal and nutritional conditions combined [1]. This prevalence is projected to increase further by 15% globally between 2010 and 2020, with the greatest increases occurring in Africa, Southeast Asia and the Eastern Mediterranean [1]. Importantly, greater mortality from NCDs in younger individuals (<70 years) in low-income compared to high-income countries disproportionately affects bread winners, and so is predicted to reduce family income, drive up health care costs, and exacerbate poverty. As a consequence, the rapid rise in NCDs even threatens to impede progress on meeting the Millennium Development Goals [1].

However, despite substantial evidence for the impact of infant nutrition on NCDs, public health policy in low-income countries faces several major obstacles to change. Although it is now well accepted that undernutrition in the first 1,000 days after conception has major adverse implications for long-term health and human capital [31], the concept that overnutrition in this critical period may also have harmful long-term consequences remains underappreciated. Countries such as India have heterogeneous populations, with many millions at risk of both overnutrition and undernutrition – the so called ‘double burden’ of dis-
ease [32]. Therefore, public health strategies need to be carefully targeted as a ‘one size fits all’ nutrition policy is unlikely to achieve optimal benefits for health [32]. Furthermore, given rapid changes in lifestyle, by focusing almost exclusively on undernutrition, the nutritional community in many low- and middle-income countries is in danger of fighting ‘yesterday’s battles’.

**Conclusions**

The WHO has identified NCDs as the most important global health issue of the 21st century. Consequently, in November 2012, WHO members agreed a global monitoring framework to help prevent NCDs, along with a voluntary target of reducing premature mortality from NCD by 25% by 2025. There is now increasing evidence to suggest that optimizing growth and nutrition in infancy will help achieve these targets.

**Disclosure Statement**

The author declares that no financial or other conflict of interest exists in relation to the content of the chapter.

**References**