Evidence on Interventions and Field Experiences

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Abstract
Maternal nutritional deficiencies and excesses during pregnancy, and faster infant weight gain in the first 2 years of life are associated with increased risk of noncommunicable diseases (NCDs) in adulthood. The first 1,000 days of life (from conception until the child reaches age 2 years) represent a vulnerable period for programming of NCD risk, and are an important target for prevention of adult disease. This paper takes a developmental perspective to identify periconception, pregnancy, and infancy nutritional stressors, and to discuss mechanisms through which they influence later disease risk with the goal of informing age-specific interventions. Low- and middle-income countries need to address the dual burden of under- and overnutrition by implementing interventions to promote growth and enhance survival and intellectual development without increasing chronic disease risk. In the absence of good evidence from long-term follow-up of early life interventions, current recommendations for early life prevention of adult disease presume that interventions designed to optimize pregnancy outcomes and promote healthy infant growth and development will also reduce chronic disease risk. These include an emphasis on optimizing maternal nutrition prior to pregnancy, micronutrient adequacy in the preconception period and during pregnancy, promotion of breastfeeding and high-quality complementary foods, and prevention of obesity in childhood and adolescence.

Introduction
Adult health, intellectual capacity, and well-being have developmental origins beginning in the preconception period. Poor prenatal growth and development manifested as low birthweight (LBW) and small size for gestational age (SGA)
at birth are strongly related to increased likelihood of adult short stature, reduced cognitive capacity, and lower educational attainment [1, 2]. A large body of animal and epidemiologic evidence also demonstrates that obesity and many adult noncommunicable diseases (NCDs) have origins as early as the periconception period. In particular, inadequate fetal nutrition, usually related to poor maternal nutritional status or impaired placental transport, is a key early life exposure that can elicit anatomical, hormonal, and physiological changes to enhance short-term survival but contribute to NCDs when nutritional resources are more plentiful later in life [2]. At the other end of the nutrition spectrum, maternal obesity, excess pregnancy weight gain and an oversupply of nutrients to the fetus relate to higher offspring birthweight, increased adiposity, and alterations in glucose metabolism in the offspring which in turn, increase risk of cardiometabolic disease risk later in life [3]. After birth, the trajectory of growth influences adult body size and composition, cognitive and brain function, and cardiometabolic and other NCD risk [2].

Given the importance of early development for adult health, it is vital to identify age-specific interventions that not only improve health but also optimize long-term health and human capital. Taking a life cycle perspective, the main goal of this chapter is to briefly synthesize information about major stressors, mechanisms through which they program disease risk, specific consequences, implications for intervention, and quality of the evidence base to support interventions, with a focus on the vulnerable periods that characterize the first 1,000 days of life. Owing to the extensive literature in these areas, recent reviews are cited to link readers to original sources. Optimizing early life nutrition is critical for attaining the Millennium Development Goals (MDGs), but it takes on an additional importance given the rapidity of economic development and the spread of obesity and NCDs worldwide.

**Periconception**

Maternal nutritional status at conception influences offspring health and development because the mother creates the earliest environmental exposures for the developing individual. Maternal short stature and low body mass index (BMI) are associated with increased risk of intrauterine growth restriction (IUGR) and LBW in the offspring [4]. Prepregnancy obesity is related to higher fetal growth rates, higher adiposity, and larger size for gestational age at birth [3]. Periconception maternal micronutrient status influences placental development, development of fetal tissue, and regulatory processes [5, 6]. Maternal weight status at conception can alter expression of genes implicated in the regulation of growth
(insulin-like growth factors), and circulating levels of micronutrients, especially methyl donors, may influence DNA methylation in the early embryo to set the course of fetal development [7].

Since maternal nutrition at conception is important, some prevention efforts must focus on optimizing prepregnancy maternal nutritional status. This requires an intergenerational focus as well as attention to current conditions, because maternal stature, body composition, and response to dietary intake are influenced by her own early development. Delaying first birth and lengthening pregnancy intervals may also improve nutritional status at conception and reduce risk of IUGR [8, 9]. Recent initiatives, including the Bill and Melinda Gates Foundation’s ‘Start with a Girl: A New Agenda for Global Health’ and the Center for Global Development’s ‘Girls Count: A Global Investment and Action Agenda’ have focused on young girls as an important target for improving long-term offspring health. This emphasis is also important in light of the sharp increases in obesity in postmenarcheal girls in several low- and middle-income countries, such as South Africa and Guatemala [10], putting young women at risk for pregnancies complicated by obesity as well as micronutrient deficiencies.

The focus on maternal micronutrient status can be more immediate. Since micronutrient status is largely influenced by current diet, adolescent girls and young women can be targeted for prepregnancy interventions that may include nutrition education, or food-based or micronutrient supplements. Given current understanding of mechanisms, multiple micronutrients are important for many health outcomes, but methyl donors are critical not only for their role in reducing neural tube defects, but also for their epigenetic effects [5].

The relationship of periconceptional nutrition (up to 12 weeks’ gestation) to birth outcomes and the effectiveness of short-term interventions targeted to that period were recently reviewed [6]. While the authors found evidence of significant associations of poor maternal nutrition status (low BMI, low iodine intake, iron deficiency anemia) with risk of IUGR or LBW, they also concluded that evidence supporting a link between maternal periconception interventions and infant birth outcomes was of low quality and inconsistent except for reduction of neural tube defects by folate.

**Pregnancy**

An extensive literature documents how maternal weight status, gestational weight gain, and micronutrient status relate to birth outcomes [5]. Fetal nutritional stressors include inadequate or excess energy and specific nutrients to supply building blocks for developing organs or regulate development and met-
abiotic processes. Nutrient supply reflects maternal stores, dietary intake and placental function. Maternal short stature, underweight and inadequate pregnancy weight gain are related to lower birthweight and smaller size for gestational age, while maternal overweight and obesity (independent of, and with gestational diabetes) are related to greater newborn adiposity and larger size for gestational age [3].

Limited or excess energy and nutrients can influence fetal growth and long-term health and susceptibility to disease through several pathways. Nutrient restriction may differentially limit organ and tissue growth. For example, protein restriction produces relatively larger deficits in skeletal muscle and kidneys than in heart or brain [2]. Such deficits have long-term consequences because they are difficult to reverse later in life, and smaller organs (e.g. kidneys with fewer nephrons or a pancreas with fewer β-cells) may have reduced functional capacity [11]. Yajnik et al. [12] have noted the phenomenon of the ‘thin-fat’ India baby who, following maternal undernutrition, is born with large deficits in skeletal muscle but not adiposity. These babies are at increased risk of later developing insulin resistance and diabetes, emphasizing the importance of fetal body composition [13].

An inadequate supply of nutrients may trigger a cascade of metabolic adaptations that enhance survival in the short run but increase risk of metabolic diseases when nutrients are no longer in short supply. According to the ‘thrifty phenotype hypothesis’ [14, 15], glucocorticoid exposure subsequent to maternal stress or poor nutritional status may program the insulin and hypothalamic-pituitary-adrenal (HPA) axes for high levels of metabolic efficiency [2], leading to impaired glucose metabolism and insulin resistance in the face of dietary excesses later in life. Gestational diabetes creates an intrauterine environment with high levels of glucose and insulin, resulting in fetal macrosomia and altered fetal and newborn glucose regulation. Growing evidence suggests that maternal obesity, even without gestational diabetes, is a risk factor for child obesity through a pathway related to fetal overnutrition [3].

Specific nutrients may alter gene expression in regulatory pathways related to the HPA axis, glucose metabolism, blood pressure and fetal growth, with important consequences for NCDs later in life. Experimental animal studies show specific effects of maternal intake of methyl donors with implications for the development of adiposity [7], but evidence from human studies is quite limited [16]. Dutch adults prenatally exposed to famine had altered patterns of DNA methylation [17], and increased IGF gene methylation was observed in blood from 17-month-old children whose mothers had taken periconception folic acid [18], but these studies are unable to isolate effects of prenatal exposures. Studies of newborns show inconsistent associations of maternal diet with methylation in cord blood: maternal folate intake was not related, but choline intake was re-
lated to cord blood methylation in a folate-replete population in the US [19]. A recent pilot study in the Gambia found that micronutrient supplementation reduced methylation levels at 2 imprinted growth-related loci [20], but evidence from other trials is lacking. A concern about folate supplementation was raised based on the Pune, India, study [21], where high maternal folate and low vitamin B_{12} during pregnancy were associated with increased adiposity and insulin resistance in the offspring, but a Nepal study found no effect of maternal folate or other micronutrient supplements on insulin resistance in school-aged offspring [22]. Another relevant consideration is that since epigenetic marks are preserved across generations, exposures in pregnant women may affect not only their sons and daughters but also their grandchildren [7].

A recent collection of systematic reviews and meta-analyses evaluated the effects of a wide range of maternal interventions on birth outcomes [23]. In most cases, the evidence base for effects was evaluated as weak and inconsistent, but numerous studies showed modest effects of maternal iron, calcium, vitamin D, vitamin B_{6}, n-3 long-chain polyunsaturated fatty acids, multiple micronutrient, and balanced protein-energy supplementation supplements on birthweight (50–100 g) and/or reduction of LBW (15–20%).

Based on strong evidence linking birthweight to adult size, body composition, and NCD risk, we would expect such improvements in birthweight to have important, but modest long-term benefits related to NCDs. For example, in a pooled analysis from 5 low- and middle-income countries, 1 kg higher birthweight was related (after adjustment for adult size) to 1.8 mm Hg lower systolic blood pressure and about 0.6 mmol/l lower blood glucose [24]. However, it is notable that each kg of birthweight related to 3.3 cm of adult height, 0.3 years of attained schooling and 208 g of birthweight in the next generation, stressing the importance of prenatal growth for these aspects of health and well-being.

The implications of interventions benefitting birthweight are also limited because birthweight fails to tell the full story of early life risk development. In addition to organ-specific deficits that may not be reflected in birthweight, alterations in metabolism and long-term disease risk occur in the absence of significant effects on birthweight [25]. Understanding the consequences of such alterations will require more nuanced assessments of infant nutritional status of birth, particularly since altered fetal metabolism may act through altered susceptibility to later environmental influences.

In sum, prevention prior to and during pregnancy needs to focus on maternal health, starting with the prior generation to promote good linear growth and optimal body composition, and then on ensuring adequate nutrient stores, adequate macro- and micronutrient intakes to meet maternal and fetal needs, adequate pregnancy weight gain, and freedom from stress and infections.
Infancy

The well-established associations of infant underweight and stunting with adult stature, school attainment and productivity [26] have provided a strong rationale for many interventions aimed at improving early child growth. A goal of many postnatal interventions is to enhance weight gain among children born SGA-age or to promote recovery from severe or moderate malnutrition because compensatory growth is associated with reduced morbidity and mortality, and improved cognitive development [27, 28]. However, ‘rapid growth’ during infancy is sometimes associated with increased risk of obesity, insulin resistance, and elevated blood pressure in childhood and adulthood [29]. A key concern is thus whether benefits of interventions which promote faster growth in low- and middle-income countries outweigh the possible long-term risks. Critical questions relate to age when rapid weight gain occurs and whether weight gain is accompanied by linear growth and accumulation of lean mass as well as fat tissue.

Studies of birth cohorts in five low- and-middle income countries (Brazil, Guatemala, India, The Philippines and South Africa) explored these questions in relation to adult stature, body composition, school attainment, blood pressure and plasma glucose. Initial findings were that higher weight-for-age z score at 2 years is related to taller adult stature, higher attained schooling, higher BMI, but lower blood pressure and blood glucose [30]. In subsequent work, the COHORTS team disentangled the consequences of faster linear growth versus relative weight gain at different ages [31]. Faster linear growth through early childhood was more strongly related to taller young adult stature and better attained schooling, but only weakly related to higher BP, and unrelated to fasting glucose. Faster relative weight gain was related to higher adult BMI, fat and fat-free mass, blood pressure and fasting glucose. The associations with adverse outcomes were weak in the first 2 years but strengthened with age: relative weight gain after mid-childhood was a much more important risk factor for later chronic disease risk than was relative weight gain in the first 2 years. Of particular note is the beneficial effect of early weight gain on the development of fat-free mass, emphasizing the importance of body composition rather than weight gain alone. The study also underscores the importance of early linear growth.

It is assumed that promoting healthy postnatal growth will also promote long-term health. Key factors are optimal diet, responsive care, and protection from infection [32]. For the young infant, this means breastfeeding according to well-established guidelines. An extensive literature documents the benefits of breastfeeding for promoting growth, and reducing morbidity and mortality. The long-term effects of breastfeeding are more controversial, and causal inferences are limited by lack of randomized controlled trials. Some studies relate breast-
feeding to lower risk of obesity and NCDs, while other studies show no effects [33], but no studies show any adverse effects.

Highly effective strategies to improve child growth have yet to be developed. Bhutta et al. [32] concluded that food supplements in food-insecure populations increase height-for-age z scores, but recent Cochrane reviews concluded that community-based supplementary feeding had only small or negligible effects on growth of children under 5 years of age [34], and home fortification of foods with micronutrient powders improved iron status but did not influence growth [35]. Zinc supplementation appears to be one of the more effective means to improve linear growth [36].

Composition and quality of the weaning diet may also be important. The WHO recently convened a panel to examine effects of complementary feeding on development of NCDs [37]. Reviews of specific aspects of diet with potential long-term health consequences suggest roles for excess protein intake in the development of obesity, excess sodium intake in the development of hypertension, and high intake or dietary imbalances of fat composition for atherogenic lipid profiles, but most studies cited a lack of clear evidence from follow-up of controlled trials.

Few studies have directly evaluated the effects of childhood nutrition interventions on later risk of NCDs [38]. In Guatemala, adults who were exposed to a protein and multiple micronutrient-fortified food supplement (atole) had lower fasting glucose and systolic blood pressure when exposed to atole from 24–60 months, higher HDL cholesterol and lower triglycerides when exposed during gestation and the first 3 years. Atole was unrelated to adult total or LDL cholesterol [39]. In the Gambia, follow-up of a protein-energy supplement trial in the second half of pregnancy at ages 11–17 years showed marginally lower fasting glucose but no differences in blood pressure, body composition or cholesterol levels in those exposed to supplements [40]. In a shorter-term follow-up of the Maternal and Infant Nutrition Interventions trial in Bangladesh, multiple micronutrient supplements provided to rural women during pregnancy did not affect offspring body composition at 54 months of age [41].

**Discussion and Conclusions**

MDG 1 focuses on the reduction of hunger, which remains unacceptably high in Sub-Saharan Africa and Southern Asia outside of India and is increasing in southern Africa. Large urban-rural and wealth-related disparities in underweight prevalence remain [42]. At the same time, rates of obesity and chronic disease are rising rapidly in low- and middle-income countries with the most dramatic increases among the poor [43]. Thus, while the primary focus for at-
taining MDGs needs to remain on reducing mortality and undernutrition, the MDG call for more emphasis on nutrition in the development agenda could also benefit from a stronger focus on linear growth and a forward look to the prevention of adult disease.

Prevention of IUGR and stunting may not be sufficient since long-term disease risk varies across the full spectrum of early life nutrition. Optimal diet composition for prevention of early obesity is also important, although the evidence base for this needs development as research is needed to define an optimal weaning and early child diet that promotes linear growth and lean body mass while minimizing excess adiposity.

By identifying vulnerable periods and tailoring prevention efforts to those vulnerabilities, we can try to capitalize on the same developmental plasticity that alters susceptibility to disease [44]. We know what the vulnerabilities are, and we know quite a bit about how they influence NCDs in the long run. Our knowledge gap reflects inadequate information on effective interventions. In the absence of a strong evidence base on how early life interventions relate to adult outcomes (particularly NCDs), at present we must presume that interventions aimed at improving maternal, fetal, and infant growth will also be effective for improving adult outcomes. The limitations in effective strategies for short-term maternal and child health are thus shared when considering long-term effects.

**Disclosure Statement**

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

**References**


23. Special Issue: Improving maternal, newborn, and child health outcomes through better designed policies and programs that enhance the nutrition of women. Paediatr Perinat Epidemiol 2012;26:1–325.


34 Sguassero Y, de Onis M, Bonotti AM, Carroli G: Community-based supplementary feeding for promoting the growth of children under five years of age in low and middle income countries. Cochrane Database Syst Rev 2012;CD005039.


41 Khan AI, Kabir I, Hawkesworth S, et al: Early invitation to food and/or multiple micronutrient supplementation in pregnancy does not affect body composition in offspring at 54 months: follow-up of the MINIMat randomised trial, Bangladesh. Matern Child Nutr, E-pub ahead of print.

