Fetal Growth Restriction and Preterm as Determinants of Child Growth in the First Two Years and Potential Interventions

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Abstract

In 2010, 171 million children under 5 years old were estimated to be stunted globally, with 98% being from low- and middle-income countries. Low birthweight including fetal growth restriction is also common in these regions and may contribute to childhood undernutrition. As part of the Child Health Reference Group (CHERG) and using 14 longitudinal birth cohorts and anthropometric measurements taken at 24 months of age, pooled odds ratios (ORs) were calculated to examine the relationship between small for gestational age (SGA) and preterm birth and subsequent stunting and wasting in children. Relative to term adequate size for gestational age (AGA), the OR (95% confidence interval) for stunting associated with AGA-preterm, SGA-term and SGA-preterm was 1.94 (1.59–2.36), 2.82 (2.40–3.32) and 4.98 (3.79–6.55), respectively. A similar magnitude of risk was also observed for wasting and underweight. This analysis indicates that childhood undernutrition may have its origins, in part, in the fetal period, suggesting a need to intervene during an earlier life stage during pregnancy and even preconceptionally, but also putting emphasis on maternal nutrition in general and adolescent nutrition. Interventions shown to impact fetal growth include antenatal supplementation with balanced calorie and protein, iron-folic acid, and multiple micronutrients. Nutrition-sensitive interventions such as delaying the first pregnancy, antimalarials and smoking cessation in some settings may be important.
Background: Fetal Growth Restriction and Childhood Undernutrition

Although much progress has been made in the last two decades, 171 million preschool children were estimated to be stunted globally in 2010, with 167.5 million from low- and middle-income countries (LMIC) [1]. This represents a prevalence of 26.7%, down from 39.7% in 1990. Secular trends in child stunting from 1990 to 2020 by region show significant progress in Asia, and continued improvements in Latin America but not in Africa, where a limited decline in stunting prevalence is recorded.

In LMIC, factors that influence linear growth in the first 2 years of life, the period during which growth faltering is found to be rapid, include: inappropriate breastfeeding and infant and young child feeding practices, i.e. inadequate frequency, quality and type of complementary foods; high incidence of infections including diarrheal morbidity [2]; a subclinical but ubiquitous condition in many settings such as environmental enteropathy [3], and mycotoxin exposures [4]. Postnatal interventions in the first 2 years of life that can have an impact include promotion of exclusive breastfeeding in the first 6 months of life and appropriate complementary feeding and other infant and young child feeding practices [5]. Integrated management of childhood illnesses may also impact stunting [6].

The recent focus on the first 1,000 days of life which includes the prenatal period draws attention to the need for intervening earlier in life, including during the critical period of fetal growth. Birthweight is a cumulative measure of intrauterine growth and gestational age. It is a commonly measured indicator of newborn health and is one of the leading factors influencing subsequent health and survival in many LMIC. Prevalence of low birthweight (LBW; <2,500 g) and its two contributory causes especially fetal growth restriction assessed using small for gestational age (SGA; defined as weight below the 10th percentile of a fetal growth reference for a given gestational age) continues to be high in LMIC [7]. The prevalence of LBW in 2010 is estimated to be 15%, whereas SGA is almost double of this at 27%, and may be as high as almost 45% in South Asia. The prevalence of preterm birth (gestational age <37 weeks) in LMIC is 11.4%. The three conditions may be discrete or have an overlap. In this example (fig. 1) [Christian et al., unpubl.] from rural Nepal, with prevalence of LBW, SGA, and preterm birth being 38.8, 55.4 and 21.2%, respectively, this overlap is seen, but there is still a considerable proportion of babies that are not LBW or preterm but are SGA. To note, the risk factors of SGA and preterm birth, and interventions to reduce these conditions are somewhat distinct. It is well recognized that SGA is a major cause of LBW in LMIC, unlike in high-income countries where preterm birth is more commonly an underlying biologic cause. High rates of LBW...
and childhood stunting coexist in many populations [8], indicating that small size at birth continues to track in the first 2 years of life. However, on average length-for-age z score of children at birth is closer to 0 to -0.5, which rapidly decreases to as low as -1.75 to -2.0 z score by 24 months of age, implicating postnatal rather than prenatal factors in causing this dramatic growth faltering. Still, studies linking birthweight and childhood undernutrition show a strong association [9], suggesting that growth in the first 1,000 days is better viewed as a continuum, but few analyses have examined systematically the contributions of fetal growth to childhood undernutrition.

**Association between SGA, Preterm Birth and Child Undernutrition**

As part of the Child Health Epidemiology Reference Group (www.cherg.org), we examined the contribution of fetal growth and preterm birth to childhood undernutrition in LMIC [10]. An extensive search of the existing literature was first undertaken to identify potential studies from LMIC that had collected prospective data on child (12–60 months of age) anthropometry in existing birth cohorts in which valid measurements of birthweight and gestational age were taken. In eligible cohorts, investigators were invited to provide data on birthweight, gestational age and child anthropometry. In a subgroup of these studies, child anthropometry was measured at 24 months of age. A total of 14 studies had

![Fig. 1. Scatter plot of birthweight, gestation age, and SGA in rural southern Nepal. Christian et al. (unpubl.).](image-url)
Table 1. Estimated risk for childhood undernutrition at 24 months of age by preterm birth, SGA and LBW categories in LMIC

<table>
<thead>
<tr>
<th></th>
<th>Preterm</th>
<th>SGA</th>
<th>LBW</th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>Stunting</td>
<td>1.65</td>
<td>1.42–1.91</td>
<td>2.68</td>
</tr>
<tr>
<td>Wasting</td>
<td>1.35</td>
<td>1.06–1.72</td>
<td>2.42</td>
</tr>
<tr>
<td>Underweight</td>
<td>1.61</td>
<td>1.27–2.05</td>
<td>3.06</td>
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Stunting defined as length-for-age <−2 z score. Wasting defined as weight-for-length <−2 z score. Underweight defined as weight-for-age <−2 z score.

taken measurements on children (n = 18,061) and were analyzed to examine outcomes of stunting (length-for-age <−2 z), wasting (weight-for-length <−2 z), and underweight (weight-for-age <−2 z) at 24 months of age (table 1). Thus, this analysis represents a subset of that undertaken for children between 12 and 60 months of age [10].

SGA was defined as less than the 10th percentile for gestational age using the US population-based standard for fetal growth by Alexander et al. [11]. Precalculated odds ratios (ORs) and standard errors/confidence intervals from each study were used to derive regional and global estimates using meta-analysis with random-effects models. Between-study heterogeneity was quantified using the I² statistic (expressed as %) and Cochrane’s Q (significance level <0.05). Forest plots were used to display pooled regional estimates. Analysis was done also by adjusting for child’s age, sex, multiple gestation, infection, intervention, and mother’s parity, socioeconomic status, education, infection and intervention, in data sets for which data were provided.

Figures 2 and 3 illustrate the ORs for stunting and wasting in children 24 months of age by categories of risk. Relative to adequate size for gestational age (AGA)-term birth, the ORs (95% CI) for stunting associated with AGA-preterm, SGA-term, and SGA-preterm were 1.94 (1.59, 2.36), 2.82 (2.40, 3.32) and 4.98 (3.79, 6.55), respectively, suggesting an additive risk in the presence of both conditions. A similar magnitude of risk was also observed for wasting and underweight (data not shown) among children. Preterm alone conferred a lower risk for stunting and the ORs were not statistically significant for wasting except in Latin America (fig. 3). Adjusted analyses showed limited attenuation of the ORs, indicating that confounding was unlikely to be a concern in this analysis. When the risk relationship was compared between those born SGA with normal birthweight and those who were born LBW and SGA, a dose-response relationship became evident; being born both LBW and SGA carried a higher risk.
This analysis reveals that childhood undernutrition, both stunting and wasting, may have its origins in the fetal period. Because fetal growth is strongly influenced by prepregnancy BMI and height, this analysis also shows that childhood undernutrition is related to maternal undernutrition prior to pregnancy. Despite the large variation in the prevalence of both SGA and preterm birth by region and country, the ORs of undernutrition associated with these exposures (OR: 3.07, 95% CI: 2.32–4.08) than being SGA alone (OR: 1.91, 95% CI: 1.60–2.28).

Fig. 2. Regional and overall ORs for childhood stunting at 24 months of age by size for gestational age and preterm and term birth combinations. Reference group is children born AGA and term.

Fig. 3. Regional and overall ORs for childhood wasting at 24 months of age by size for gestational age and preterm and term birth combinations. Reference group is children born AGA and term.
appeared to be quite comparable between regions, indicative of common underlying causes for fetal growth restriction and preterm birth. Latin America had the highest ORs, but the smaller sample sizes and lower prevalence of exposures in the studies from this region yielded more imprecise estimates of risk. As has been shown in other settings, the prevalence of SGA is higher than LBW. Strikingly, the coexistence of both preterm and SGA was remarkably low in many settings (1–2%). It has been shown that the etiologies of these conditions differ [12]. In addition, the lower prevalence of the two conditions combined was examined only in the surviving cohort of 24-month-olds, and the risk of mortality is shown to be highest in the group with both SGA and preterm [13]. Preterm-only babies have a lower probability of experiencing fetal growth restriction. One consideration is that the shorter time in utero, especially closer to term, may result in a lower risk of SGA among these babies.

Maternal Nutrition and Fetal Growth

Kramer [12] demonstrated over two decades ago that maternal nutritional factors account for more than 50% of the etiology of LBW in low-income countries. These factors included low prepregnancy weight, short stature, and low caloric intake during pregnancy or inadequate weight gain as well as maternal LBW itself, suggesting an intergenerational effect. Using data from a WHO collaborative study which included over 100,000 women, every 1 cm decrease in prepregnancy height or 1 unit decrease in prepregnancy BMI was associated with a 2-fold increased odds of intrauterine growth restriction [14]. Using cross-sectional data from 109 Demographic Health Surveys conducted between 1991 and 2008 in 54 developing countries and covering 2.6 million children aged 0–59 months, Özaltin et al. [15] showed that maternal height was inversely associated with risks of underweight, stunting, and wasting and child mortality. Compared with maternal height of >160 cm, those with height <145 cm had a 2-fold higher risk of their child being stunted. This is suggestive that the association of maternal stature with childhood nutritional status is mediated by the influence of maternal height on intrauterine growth [16]. While maternal height represents the culmination of environmental exposures from fetal to adulthood, including nutritional, infectious, lifestyle factors, and pregnancy in early adolescence, pre-pregnancy maternal BMI is more likely to capture aspects of short-term food availability, access to health care and other concurrent socioeconomic and cultural conditions at the onset of pregnancy.

Maternal short stature (<145 cm) continues to be high in many settings especially in South Asia [9]. Data from 54 demographic health studies that exam-
ined height among women 25–49 years of age from 1994 to 2008 revealed a wealth differential in the patterns of increase in mean height. In 35 of the countries, there was either a decline or stagnation in height among women, largely in the poorest wealth quintiles [17]. In many settings, early marriage leading to early pregnancies may impact adolescent nutritional status and growth. In a rural setting in northeastern Bangladesh, pregnancy in adolescence hampered linear and ponderal growth [18]. In this prospective cohort study, 162 adolescents in their first pregnancy were matched with 385 never-pregnant girls of the same achieved age and age since menarche. Annual growth in terms of height, weight, and mid-upper arm circumference, and percent body fat was significantly lower among pregnant girls compared to girls who did not become pregnant after adjusting for confounders. In fact, growth in height ceased in the pregnant girls, whereas the nonpregnant girls gained in height by 0.3 (SD = 0.8) cm over the course of the year-long follow-up. An estimated overall attained height loss ranging between 0.6 and 2.7 cm may have resulted from cessation of linear growth in adolescence due to an early pregnancy, which may be one contributory factor leading to adulthood stunting in women. Childbearing during the growth period from menarche through the teenage years is also associated with adverse birth outcomes such as premature birth and LBW. Potential strategies to prevent early pregnancy including incentives, legislation, availability of contraception, and registration of newly married may be important in many LMIC settings [19].

Potential Nutritional and Nonnutritional Interventions

Nutritional interventions during pregnancy have been shown to be beneficial for fetal growth as summarized by Ramakrishnan et al. [this vol., pp. 71–80]. Meta-analysis of trials of food (calorie and protein) supplementation during pregnancy has shown a reduction of 34% in the risk of SGA (RR: 0.68, 95% CI: 0.51–0.92) [20]. Daily iron folic acid and prenatal multiple micronutrient supplementation (without food) also shows a significant reduction in LBW with RR of 0.80 (95% CI: 0.71–0.90) [21], and in SGA with RR 0.83 (95% CI: 0.73–0.95), respectively [22]. Although routine iron-folic acid supplement use, despite widespread policy in many countries continues to be low [23], combining food and micronutrient intervention approaches in settings with maternal undernutrition and micronutrient deficiencies would help address the high burden of fetal growth restriction, and in addition yield better nutritional status in the offspring. Although evidence is limited [24], cash transfer or food vouchers for women during pregnancy in food-insecure settings may be beneficial and should be tested for their
impact on birthweight and fetal growth. Examples of food transfer systems are available from programs in India, Nigeria and Ethiopia [19]. Very few nutritional interventions have enhanced gestational length of a pregnancy or shown to reduce preterm birth, except perhaps for prenatal zinc [25] or calcium supplementation [26].

Although not nutritional, certain lifestyle interventions may be important for alleviating the burden of fetal growth restriction and preterm birth. For example, tobacco smoking is a well-known risk factor sharing a dose-response relationship with both the occurrence of LBW and preterm delivery. After adjusting for confounders, passive smoking is also known to elevate the risk of fetal growth restriction. Interventions targeted at smoking cessation can be effective in reducing adverse birth outcomes. A systematic Cochrane meta-analysis that included 72 trials, both individual and cluster-randomized, has shown reductions in smoking during pregnancy and in outcomes of LBW (RR: 0.83, 95% CI: 0.73–0.95) and preterm birth (RR: 0.86, 95% CI: 0.74–0.98) [27]. Globally, reproductive/urinary tract infections, HIV-1, and malaria may be the largest infectious causes of LBW and preterm. In malarious settings, the new WHO recommendation is to provide at least 3 doses of SP (sulfadoxine-pyrimethamine) during pregnancy. Seven trials comparing 3 or more versus 2 doses of SP did better in reducing placental malaria, and also in reducing mild to moderate anemia by 40% and LBW by 20% (RR: 0.80, 95% CI: 0.69–0.94) [28]. Bacterial vaginosis (BV) is also known to increase the risk of preterm birth. Asymptomatic BV is associated with a 2-fold increased risk of preterm birth, or nearly 3-fold when BV is detected prior to 16 weeks of gestation [29]. In a meta-analysis of 15 small trials, BV treatment during pregnancy resulted in no overall impact on risk of preterm birth, except among women treated before 20 weeks of gestation (OR: 0.63, 95% CI: 0.48–0.84) [30]. Interventions to reduce indoor air pollution seem promising. Exposure to pollution from solid fuel compared with cleaner fuels or stoves with chimneys has shown to significantly increase the risk of LBW and preterm birth by 38% (OR: 1.38, 95% CI: 1.25–1.52) [31]. In many LMIC, outdoor and vehicular air pollution especially in urban areas may be high and on the rise, and interventions for ameliorating their adverse effects need testing. Although deworming twice during pregnancy when provided as a service in a research setting was found to significantly reduce maternal anemia, severe anemia, LBW and infant mortality [32], the evidence from randomized controlled trials is lacking [33].

Beyond periconceptional folic acid use shown to reduce the risk of neural tube defects, there is limited evidence from rigorous randomized controlled trials to show the impact of pre- or periconceptional nutritional interventions on birth outcomes. Although numerous observational studies link maternal nutritional status, especially low prepregnancy maternal BMI and height, with out-
comes of fetal growth restriction, and to some extent with preterm birth, confounding may be a serious problem. There is a need to conduct large trials of preconception nutritional supplementation in settings with high rates of maternal undernutrition and fetal growth restriction [34].

Conclusion

The burden of child undernutrition continues to be high in many LMIC. The intergenerational cycle of growth failure exists in many of these settings, with coexisting high burdens of maternal undernutrition including short stature, fetal growth restriction, and childhood stunting. In industrialized settings and in wealthy households in LMIC, average maternal height has shown a systematic increase over time, in contrast to stagnating in underresourced, poorer households, suggesting that environmental influences could lead to improvements over time. The analysis linking SGA to risk of stunting and wasting in childhood provides further impetus for a life course approach for interventions as reflected in the emphasis on the first 1,000 days. Numerous prenatal interventions have shown to be effective in improving fetal growth and size at birth, including iron-folic acid that is policy in many areas of the world, as well as multiple micronutrient, and food/energy-protein supplementation in food-insecure conditions. In addition, the nutrition and health state of a woman when she conceives sets the stage for the well-being of the pregnancy and the trajectory of the growth and development of her fetus, suggesting that preconceptional and early-pregnancy interventions may be important, but data on impact are limited. There is an urgent need for future research to examine the additional benefit of pre- and periconceptional macro- and micronutrient interventions in enhancing birth outcomes, especially fetal growth and gestational duration. Focusing on an equally important life stage of adolescence may yield improvements in reproductive health outcomes, while at the same time enhancing the linear growth and nutritional status of girls. Delaying a first pregnancy could be a powerful intervention in this respect.

In conclusion, policy and programmatic focus on maternal nutrition and health are central for combating the large burden of fetal and childhood undernutrition as we evaluate progress towards the MDGs and develop future strategies.

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**Disclosure Statement**

The author has no conflicts of interest to declare.

**References**
