Prenatal Origins of Undernutrition

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Abstract

Undernutrition continues to be high in many regions of the developing world. Birthweight, a common proxy measure of intrauterine growth, is influenced by nutritional, environmental and lifestyle factors during pregnancy and, in turn, affects immediate survival and function, and is a determinant of later life risk of chronic diseases. Maternal pre-pregnancy weight and height are independently associated with birthweight and also modify the effects of pregnancy weight gain and interventions during pregnancy on birthweight and perinatal mortality. Other prenatal factors commonly known to impact birthweight include maternal age, parity, sex, and birth interval, whereas lifestyle factors such as physical activity and maternal stress, as well as environmental toxicants have variable influences. Tobacco and other substance use and infections, specifically ascending reproductive tract infections, malaria, and HIV, can cause intrauterine growth restriction (IUGR). Few studies have examined the contribution of prenatal factors including low birthweight to childhood wasting and stunting. Studies that have examined this, with adequate adjustment for confounders, have generally found odds ratios associated with low birthweight ranging between 2 and 5. Even fewer studies have examined birth length or maternal nutritional status as risk factors. More research is needed to determine the proportion of childhood undernutrition attributable to IUGR so that interventions can be targeted to the appropriate life stages.

Introduction

Childhood undernutrition and its health consequences continue to contribute to the global burden of morbidity and mortality in many regions of the world even as rates of overweight and obesity are on the rise in these same regions. The recent series in the *Lancet* on maternal and child undernutrition estimates that stunting (height for age z score < –2 SD) and severe wasting
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(weight for age z score < –3 SD) using the World Health Organization (WHO) growth standards and intrauterine growth restriction (IUGR; term low birthweight) are together responsible for 2.2 million deaths and 21% of disability-adjusted life years for children younger than 5 years [1]. More than a decade ago, the synergy between infectious diseases and mild-to-moderate undernutrition in causing childhood deaths was brought to the forefront with an estimate that about half of all deaths in young children (<72 months) could be attributable to undernutrition [2]. The cause-specific population-attributable fractions were 45% for measles, 57% for malaria, 52% for pneumonia, and 61% for diarrhea [3]. Beyond immediate death and disease, childhood undernutrition has also been linked to shorter height and increased blood pressure in adulthood, less schooling, and lower productivity that translates into reduced adult health and human capital in many regions of the world [4]. The link to lower productivity may result from both the effects of undernutrition on physical work capacity and cognitive function. In women, short stature can lead to an increased risk of poor reproductive health, especially increasing the risk of cephalo-pelvic disproportion, and cesarean section [5].

Despite the high levels of undernutrition that continue to exist in the developing world, the burden of chronic diseases is also estimated to be the highest and on the rise in the developing world [6]. The ‘developmental origins of health and disease’ extends the consequence of fetal growth restriction and suboptimal postnatal growth to well beyond the childhood period to risk of chronic diseases in adulthood and old age. Countries undergoing the nutrition transition with high levels of low birthweight are likely to be faced with the dual burden of under- and overnutrition with each contributing to significant health consequences. This paper reviews the environmental, nutritional, lifestyle and other risk factors of fetal growth restriction and low birthweight. It will also examine the contribution of prenatal nutrition to childhood undernutrition, thereby drawing attention to a perhaps neglected relationship in an attempt to emphasize the need for prevention strategies to begin earlier than in the preschool years of life.

**Extent and Magnitude of Child and Maternal Undernutrition and Low Birthweight**

Rates of childhood undernutrition continue to be high in many regions of the world, based on analyses recently reported in the *Lancet* nutrition series [1] (fig. 1). Overall, 32% or 178 million children under 5 years of age throughout the developing world are estimated to be stunted and 3.5% or 19 million are severely wasted. Low birthweight (<2.5 kg) is estimated at 16% in developing countries, with rates higher in Asia than in Africa. About 10.8% are estimated to be term low birthweight or IUGR. It is not surprising that maternal undernutrition, which contributes to IUGR in developing
countries, is also common and high in both South Asia and sub-Saharan Africa [1] (fig. 2). Unlike in South and parts of Southeast Asia, maternal stunting in Africa ranges between 1 and 2%, except in Madagascar and Mozambique where it is higher at 5%. In Latin America on the other hand, wasting is less common, although stunting continues to affect a higher proportion of women of reproductive age, especially in countries such as Guatemala, Peru, and Bolivia. South Asia harbors the highest rates of maternal wasting and stunting in the world.

**Causes and Risk Factors of Fetal Growth Restriction**

Birthweight is a common, relatively easy measure of fetal growth taken at the time of birth or soon after. Birthweight is influenced by two biologic processes – growth in utero and the length of gestation. It is common knowledge that low birthweight is predominantly due to fetal growth failure in developing settings whereas preterm (gestational age at birth <37 weeks) contributes to low birthweight in many developed countries [7, 8]. Small for gestational age (SGA), defined as birthweight below the 10th percentile of a reference
population, is used to classify IUGR, although customized growth curves and birthweight percentiles (www.gestation.net) to define ‘customized SGA’ have been validated in some settings and are associated with increased risk of morbidity and perinatal and neonatal mortality [9]. This adjustment allows a better estimate of growth restriction vis-à-vis the true growth potential for a fetus taking into consideration factors such as maternal size, ethnicity, parity and fetal sex. The ponderal index (weight/length^3), reflecting fetal wasting, is also used to distinguish between symmetric versus asymmetric growth restriction. Causes of fetal growth restriction (or IUGR) are generally nutritional in origin, whereas environmental and lifestyle factors and infections are more likely to result in preterm birth. It is poor fetal growth due to preterm that is more strongly associated with neonatal and infant mortality whereas term low birthweight carries a lower risk [10]. Numerous reviews, summarized below, have examined the determinants of low birthweight.

Fig. 2. Prevalence rates of low BMI (<18.5) and low height (<145 cm) among women 15–49 years of age using the most recent national surveys (DHS or WHO) by region [1].
**Biological Factors**

**Maternal Age and Parity**

The optimal age at first birth is a tradeoff between the availability of time for growth during puberty vs. achieving reproductive success as reflected by increased newborn survival. Teen pregnancy is known to increase the risk of low birthweight due to the competing needs for growth of the mother and the fetus, with the youngest adolescent being at the highest risk. Literature to date has not been consistent in describing the risk of adverse birth outcomes related to young age, but this may be due to the diversity of settings and risk factors (behavioral and socioeconomic) under which adolescent pregnancy outcomes have been examined. Confounding due to these factors may attenuate or exaggerate the differences in birth outcomes between adolescent and adult women. In many developing countries, pregnancy in adolescence is a norm resulting from early age at marriage and low contraception prevalence to delay the first pregnancy. Recently it has been demonstrated that adolescents who ‘grow’ (assessed using knee height changes) and accumulate fat stores during pregnancy are likely to have smaller babies compared to those who cease growth [11], suggesting competition in the partitioning of nutrients between the maternal and fetal compartments. Second, primiparous adolescent girls (<19 years) may have an increased risk of preterm but not SGA compared with primiparous adult women in some settings, a difference that was not apparent between adolescent and adult women for parity 2 or more [12]. Primiparity is a well-known risk factor for low birthweight due to IUGR.

**Ethnicity**

Ethnicity/race is an interesting risk factor of low birthweight in some settings. In the US, African-American infants are born preterm and weigh on average 200–300 g less at birth than Caucasian babies resulting in an about 2-fold higher rate of low birthweight in this ethnic group. While sociobehavioral factors may underlie this racial/ethnic difference, a genetic component cannot be ruled out. South Asian women living in Europe or the USA are typically known to be at risk of low birthweight, although the low birthweight among them is more likely due to IUGR than preterm birth [13]. Given the intergenerational nature of the consequences of IUGR, only time will tell if low birthweight rates will decline among these ethnic groups over generations.

**Other**

Sex of the newborn (being female), multiple births, and a short inter-pregnancy interval are other biologic factors known to reduce birthweight, both due to the shorter duration of gestation and IUGR. A meta-analysis revealed that compared with 18–23 months, less than 18 and longer than 59 months are significantly associated with low birthweight, preterm birth and SGA adjusted for maternal age and socioeconomic status [14]. Maternal nutritional
depletion due to repeated pregnancies, especially of shorter birth intervals, does not allow catch-up in nutritional status from the high nutrient burden of pregnancy and lactation with the result that women are physiologically and nutritionally ill-prepared for the next pregnancy. It has been shown that women who are severely malnourished tend to gain more weight during a reproductive cycle at the same time as showing lower birthweight for the second compared to the first birth relative to marginally malnourished or well-nourished women who have lower weight gain but higher birthweight for the second offspring [15]. Few intervention strategies exist, especially in developing countries, to target women between pregnancies, especially those that are closely spaced. The increased risk of a long birth interval (>59 months) is hypothesized to be related to a gradual decline in reproductive capacity, resulting in the women becoming similar to primigravidae or perhaps due to confounding by factors related to low fertility such as reproductive tract infections which can also result in adverse birth outcomes [15].

**Lifestyle Factors**

Smoking is a well-known risk factor sharing a dose-response relationship with both the risk of low birthweight and preterm delivery [16]. Adjusted for confounders, even passive smoking is known to elevate the risk of IUGR [17]. The risk of fetal alcohol syndrome including IUGR are well known, whereas drug consumption including cocaine results in an increased risk of both preterm and IUGR, as well as other complications such as congenital malformations. Smoking, caffeine, alcohol and drug consumption behaviors tend to cluster and may have additive if not synergistic effects on adverse pregnancy outcomes.

Various elements of physical activity during pregnancy have been examined for their association with low birthweight and preterm delivery, although confounding is commonly not well considered. In a systematic review of studies from developed countries no more than a moderate effect size (relative risk ≤1.4) was found for the risk of low birthweight and preterm related to prolonged work hours, shift work, lifting, standing, and heavy physical workload [18]. Generally, moderate levels of work/exercise may be beneficial during pregnancy, but higher intensity of work may be harmful [17]. In settings where malnutrition, poverty, and morbidity are high, the relationship between physical work and birth outcomes tend to suffer from reverse causation; healthier women with better pregnancy outcomes may in fact report performing higher levels of physical activity compared to those who were ill and experienced adverse outcomes [19] resulting in what has been termed as the ‘healthy pregnancy/worker’ phenomenon.

Maternal psychosocial stress during pregnancy caused by a myriad of factors may result in poor birth outcomes and obstetric complications. Elevated
levels of anxiety and depression may be associated with increased odds of low birthweight, preterm and SGA, although inadequate control for confounders, and low precision and inaccuracy in assessments of anxiety and depressive moods, including assessment of their levels rather than a diagnosis of disorders of mood/anxiety are of concern [20]. The most likely biologic pathway underpinning this relationship is an altered hypothalamic-pituitary axis in pregnancy. Research is needed to elucidate the exact mechanism by which maternal stress (psychosocial or other) leads to poor pregnancy outcome. Indeed, nutritional deprivation, hunger, micronutrient deficiencies as well as inflammatory conditions can be viewed as ‘stressors’ and can lead to altered maternal-placental-fetal pathways that cause adverse outcomes. However, psychosocial support interventions in the past have failed to show significant reductions in birthweight, perhaps because many of the trials reviewed had methodology issues [21]. There is weak evidence for prenatal care and its various current components, even in the context of developed countries, to either adequately identify pregnancies at risk of preterm delivery or IUGR or to prevent these birth outcomes [22]. Few developing countries have adequate antenatal care delivery in place as reflected by low coverage for antenatal iron-folate supplementation and screening for malaria during pregnancy.

Infection

Globally sexually transmitted infections, HIV-1, and malaria may be the largest infectious causes of low birthweight and preterm [17, 23]. These infections also tend to coexist exacerbating pregnancy-related outcomes. Reproductive tract infections, especially ascending infections leading to endometritis can result in preterm and low birthweight. Untreated sexually transmitted infections such as gonorrhea, chlamydia and syphilis as well as bacterial vaginosis are well linked to an increased incidence of preterm and low birthweight. Malaria in pregnancy due to altered immunity to the infection results in severe anemia, placental parasitemia, and low birthweight, especially in primigravidae [1]. The risk of IUGR is higher if infection occurs towards the end of pregnancy [1].

Subclinical infection may also be associated with preterm birth [24]. Labor initiation normally involves inflammatory cascades, thus, determining if labor is induced by intrauterine infection would be difficult. Furthermore, pregnancy itself is considered an inflammatory state, and it is known that C-reactive protein normally increases throughout normal pregnancy. Yet, a recent study in Nepalese women reported finding that higher \(\alpha_1\)-acid glycoprotein in the third trimester was associated with lower birthweight [25].

Maternal HIV-1 infection needs special mention in the context of sub-Saharan Africa and increasingly in some parts of Asia. Infants of infected mothers have an increased risk of low birthweight, prematurity, and perinatal
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and neonatal mortality [26] but treatment with zidovudine is efficacious in reducing the risk of low birthweight as indicated by results from five placebo-controlled trials (pooled RR 0.75, 95% CI 0.57–0.99) [27].

Finally, in settings where geohelminths, especially hookworm, and low birthweight are common, deworming is associated with reductions in the incidence of low birthweight [28].

Environment

Epidemiologic evidence is convincing that maternal exposure to airborne particulate matter is associated with adverse outcomes including preterm and IUGR. Although the risk may be small and varies widely [29], some of the suggested biologic pathways include oxidative stress, inflammation, endothelial function and hemodynamic mechanisms that could potentially be modified by nutrition including intakes of vitamin- and mineral-rich foods [30]. Few studies have examined the risk in the context of the developing world, especially measuring different types of pollutants (CO, NO2, SO2, particulate matter, O3, etc.) and their levels in the ambient air. Among other environmental pollutants, arsenic in drinking water needs further investigation in countries such as Bangladesh, whereas lead exposure either directly or through mobilization of that accumulated in the bones during pregnancy can cross over to the placenta leading to IUGR and preterm.

Maternal Nutrition and Diet

Kramer [7] showed more than two decades ago that maternal nutritional factors may account for more than 50% of the etiology of low birthweight in developing countries. These factors included low pre-pregnancy weight, short stature, and low caloric intake during pregnancy (or weight gain) as well as maternal low birthweight. It is not a coincidence that rates of low birthweight are high in settings where maternal malnutrition is common. The intergenerational cycle of growth failure has long been used as a framework for considering the appropriate life stages for intervening. The following concepts and knowledge have emerged from years of research in this area: (a) food supplementation trials during pregnancy, targeting a narrow window in life, have shown limited efficacy and modest increments in birth weight; (b) nutrition interventions that begin earlier in pregnancy are likely to have stronger effects; (c) maternal short stature, which is strongly correlated with uterine volume, is independently associated with IUGR; (d) maternal stunting is also a risk factor for cesarean section deliveries and cephalo-pelvic disproportion; a meta-analysis found a 60% (95% CI 50–70%) increase in delivery assistance in the lowest quantile of maternal height compared
with the highest quantile [5], an association that is likely to be modified by newborn size, and (e) finally, pre-periconceptional nutrition may be a strong determinant of the fetal growth trajectory, the cues for which may be derived early on through processes involving placentation, placental vascularization and genetic imprinting. And yet, few studies examine interventions targeted during this period of the life.

Adequate caloric intake and weight gain are critical during pregnancy. Balanced energy protein supplementation in pregnancy based on randomized controlled trials has been shown to reduce IUGR by 32% (26–44%) [31]. Chronic micronutrient deficiencies, specifically those of iron, calcium, magnesium and other micronutrients, may contribute to IUGR [32]. The efficacy of multiple micronutrient interventions for a range of outcomes is reviewed elsewhere in this book.

Fruit and vegetable intake during pregnancy has been associated with improved birthweight in both developed [33] and developing countries [34] as has consumption of dairy (Chile, Denmark), perhaps due to increased micronutrient intake, although in the case of milk, IGF-1 concentrations in the blood of children were found to be higher [35]. Findings from these observational studies do not prove causality despite adjustment for confounders. Food-based micronutrient intervention trials during pregnancy are currently ongoing in India and are likely to shed light on their benefits for developing dietary guidelines, policy and programs for interventions beyond calories and proteins during pregnancy.

Maternal nutritional status, both pre-pregnancy and during pregnancy may also modify the effect of other risk factors and stressors associated with pre-term and low birthweight. For example, there is evidence that high maternal BMI or vitamin and mineral intakes may ameliorate the risk of adverse outcomes due to psychosocial stress, smoking, and environmental pollutants, underscoring the importance of maternal nutrition in reproductive function.

**Childhood Undernutrition: Contribution of IUGR**

Factors contributing to growth faltering and undernutrition are diverse and complex and include factors such as inadequate exclusive breastfeeding, frequency, energy density and micronutrient levels of complementary foods, diarrheal and acute lower respiratory infections, malaria, and increasingly, HIV in the context of Africa [1] where rates of stunting for the first time have superseded those in South Asia. Other factors that may contribute to undernutrition include parity, birth interval, maternal work and maternal education. The latter may take away from child care or bring in earned income that is spent on child nutrition and health. Improving linear growth in infancy and childhood is possible but food/nutritional interventions seem to be efficacious only before 2 or perhaps 3 years of age but not beyond. Growth during
adolescence in developing countries may be prolonged by up to 3 years with the onset of puberty often delayed. This results in some (but not all) catch-up for the early growth deficit in height [36].

Although it is well known that high rates of low birthweight and childhood stunting tend to coexist (fig. 3), few analyses have carefully examined the role of prenatal factors in influencing later life nutritional status. The contribution of fetal growth restriction among various other factors influencing childhood undernutrition is not well defined. While growth generally tends to track, ‘decanalization’ or ‘centile crossing’ or ‘catch-up’ will commonly occur among almost half of infants during infancy and early childhood which is considered a normal pattern of growth to meet one’s genetic potential following gestation [37] when fetal growth is more constrained. Mechanisms signaling catch-up or catch-down growth are not well understood but may involve programming of appetite [38]. The period of catch-up growth is also the time when growth is most responsive to food interventions [36].

Observational studies that examine birthweight as a risk factor for childhood nutritional status require a longitudinal design. Adjustment for confounding is critical as there are many factors that can predict low birthweight
and are also associated with childhood undernutrition including maternal age, parity, birth interval, socioeconomic status, and literacy among others. Table 1 describes such studies presenting adjusted odds ratios linking low birthweight to stunting, and in some cases, wasting and underweight among under 5-year-olds. Adjustment was done for anywhere up to 22 variables or in some studies for statistically significant confounders. Adjusted odds ratios ranged from 2 to 5 for stunting. The positive correlation between the rates of low birthweight and stunting observed in some settings such as Asia and Africa was not observed in Brazil where catch-up growth appeared to be higher. Studies also found this association to exist beyond preschool age. One study (not shown) showed a significant positive association between weight taken at birth and height and weight for age z scores at a later age of 5–12 years [47]. In the Philippines low birthweight was associated with more severe stunting in the first 2 years of life, and it also significantly reduced the likelihood of ‘recovery’ from stunting up to 12 years of age [48]. Among a cohort of children born very preterm (<32 weeks gestation) and very low birthweight (<1,500 g) followed at 10 years, SGA children (especially those very preterm) continued to experience stunting compared to adequate for gestational age children who experienced catch-up growth [49]. The cause and type of fetal growth restriction will determine catch-up in childhood as demonstrated in a study where symmetrically smaller infants at birth among smoking mothers showed complete catch-up growth in infancy as did infants of primiparous pregnancies who were thin at birth but became heavier and taller than infants of multiparous women [38].

Few studies have examined the prevalence of stunting at birth and whether it predicts stunting in childhood or later, although shortness at birth may be a strong predictor and even better than low birthweight or IUGR [36]. In a study among West Javanese infants, neonatal weight and length in multivariable analyses were the strongest positive predictors of nutritional status of infants and the strongest negative predictors of increases in weight and length during infancy [50].

In a follow-up study of rural Nepali children (n ~1,000) whose anthropometry was assessed at a mean age of 12 days (SD 8.6), stunting, wasting, and underweight were prevalent at 63, 53, and 13%, respectively, at 30–59 months of age. Both neonatal and maternal factors in this study were associated with the risk of undernutrition (table 2). The adjusted odds ratios ranged from 2 to 3 for low neonatal weight and height, both of which were independently associated with the risk of stunting and wasting. Neonatal weight was a stronger predictor of wasting relative to neonatal length which was more strongly associated with childhood stunting. Maternal nutritional status variables were tested in a separate model. While maternal BMI was associated with stunting and wasting in children, maternal height was only predictive for stunting. These data are unique in that they simultaneously examined neonatal and maternal factors both of which are reflective of the prenatal environment.
Table 1. Adjusted odds ratios for childhood stunting, wasting and underweight related to low birthweight

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>LBW %</th>
<th>Age</th>
<th>Stunting</th>
<th>%</th>
<th>AOR (95% CI)</th>
<th>Wasting</th>
<th>%</th>
<th>AOR (95% CI)</th>
<th>Underweight</th>
<th>%</th>
<th>AOR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Ricci and Becker [39]</td>
<td>Philippines, 2,885</td>
<td>15.0</td>
<td>12–29 months</td>
<td>34.1 (U)</td>
<td></td>
<td>1.7 (U)</td>
<td>11.8 (U)</td>
<td></td>
<td>1.5 (U)</td>
<td></td>
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<tr>
<td>Marins and Almeida [40]</td>
<td>Brazil, 2,194</td>
<td>9.0</td>
<td>14–59 months</td>
<td>5.1–8.1</td>
<td></td>
<td>2.9 (1.9–4.3)</td>
<td>3.5–7.0</td>
<td></td>
<td>2.6 (1.6–4.1)</td>
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<tr>
<td>Aerts et al. [41]</td>
<td>Brazil, 3,389</td>
<td>18.8</td>
<td>&lt;5 years</td>
<td>6.8</td>
<td></td>
<td>3.8 (2.4–6.0)</td>
<td>12.0</td>
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<td>8.3 (4.4–15.8)</td>
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<tr>
<td>Chopra [42]</td>
<td>South Africa, 868</td>
<td>16.3</td>
<td>3–59 months</td>
<td>26.3</td>
<td></td>
<td>5.2 (3.1–8.9)</td>
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<tr>
<td>Ukwuani and Suchindran [43]</td>
<td>Nigeria, 5,331</td>
<td>15.4</td>
<td>&lt;5 years</td>
<td>42.6</td>
<td></td>
<td>1.3*</td>
<td>8.9</td>
<td></td>
<td>1.6*</td>
<td></td>
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<tr>
<td>Mamiro et al. [44]</td>
<td>Tanzania, 378</td>
<td>11.0</td>
<td>2–23 months</td>
<td>35.0</td>
<td></td>
<td>5.1 (2.3–11.2)</td>
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<tr>
<td>Hong [45]</td>
<td>Ghana, 3,077</td>
<td>15.8</td>
<td>&lt;5 years</td>
<td>29.6</td>
<td></td>
<td>1.7 (1.4–2.5)</td>
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<tr>
<td>Ergin et al. [46]</td>
<td>Turkey, 1,400</td>
<td>4.4</td>
<td>&lt;5 years</td>
<td>10.9</td>
<td></td>
<td>2.5 (1.2–5.3)</td>
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U = Urban; R = rural; AOR = adjusted odds ratio; CI = confidence interval.

* p < 0.05.

1 Collected during the Demographic Health Surveys by asking mothers whether their baby was small, large or very large.
Maternal weight and to some extent height were also related with undernutrition in Indonesia [50] and the Philippines [51]. These prenatal predictors of childhood undernutrition are considered ‘constitutional’ to separate them from time-dependent and more proximate factors such as infection and feeding practices among others [51]. In Nepal we adjusted for socioeconomic variables in the model, some of which remained significant such as maternal literacy, housing material, and asset ownership. Previous work has suggested that socioeconomic determinants of undernutrition in children may operate in two ways: economic status or maternal schooling may work through prenatal factors whereas dwelling factors are likely to influence children’s nutritional status more directly [52]. More work is needed to better understand the contribution of prenatal factors to childhood undernutrition in different environments.

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Discussion

Dr. Agarwal: I am now talking about an Indian Council of Medical Research study which I conducted for over 7 years. This was for the Integrated Child Development Services (ICDS) and we observed data on over 6,000 deliveries in rural areas. One thing was very interesting and is associated with your Nepal study on preterm births: those undernourished anemic rural women had more preterm births than those who were undernourished but had less or no anemia. The brain development and growth of these babies was followed up to 18 years of age. So the stunting you have shown is continuous up to pre-adolescence, but when adolescence starts the undernourished as well as the well-nourished control children gain the same height during the adolescent period that normally one should gain. Although the nutrition supplementation by the ICDS was poor, it was still effective, effective in the length gained as well as the weight gained. The iron and folate distributed by the Ministry of Health were good enough to gain the weight reduced by low birthweight. Your studies support that anemia is more related to preterm and undernutrition, and more related to low birthweight babies.

Dr. Genuino: In your talk you mentioned that a child who is born small will stay small and I am particularly interested in whether you have come across any data showing an association between the final adult height of these children who are born small and adult chronic diseases?

Dr. Christian: Because I was focusing on childhood undernutrition I did not actually show the data that link birth size with adulthood height and stunting. In fact the data are there, and there is a linkage across life in terms of tracking. Regarding your second question on adult disease, somebody else will be talking about this and I specifically limited my discussion to undernutrition. Other speakers are going to talk about low birthweight and chronic diseases.

Dr. Chittal: The female fetus will have IUGR. Is IUGR intrauterine growth retardation or low birthweight?

Dr. Christian: Females are born with low birthweight but they also have IUGR more often.

Dr. Chittal: Would interventions help a female fetus?

Dr. Christian: From what I have seen interventions tend to help female fetuses more, but the effects are variable. So not all interventions have a better impact on females.

Dr. Chittal: Why were cheese and ice cream excluded from dietary supplementation as milk products?

Dr. Christian: I don’t know. Perhaps they are just considered not good sources.

Dr. Chittal: What dairy products were utilized? Milk alone or milk and yoghurt?

Dr. Christian: Milk and perhaps yoghurt.

Dr. Prentice: I would like to carry on from that previous question. This issue of whether we have more IUGR babies that are girls, is rather a matter of semantics. Girls are smaller, so if we present the data according to a growth chart for girl babies then we would not expect to see more IUGR. We do see more girl babies below 2.5 kg because that is a single cutoff that is used for both sexes. One of the important things we need to understand is the concept of an ‘appropriateness’, a ‘harmony’ of growth between the mother and the baby. When we say that shorter, smaller mothers have more IUGR, thank goodness they do, because, as you demonstrated, the difficulties in terms of obstetric outcome occur when you get a mismatch between a small mother and a big baby. This is one of the issues that in particular Dr. Yajnik is trying to get around. How do we break this cycle, how do we move to a bigger baby without breaking that inherent biological harmony between the size of the baby and the size of the mother.
Dr. Christian: With the customized percentile [1], the adjusted references, I think that is part of trying to characterize fetal growth a little better and perhaps we should do that more. Of course the factors that they take into account are maternal size as well as BMI and the sex of the fetus. Perhaps I am not a hundred percent sure but, apart from female babies being low birthweight, they are also more likely to be IUGR, but you can challenge me on that.

Dr. Yajnik: Can I make a comment? I was approached by someone in Fiji because they got very excited that all the IUGR babies in Fiji were Indian and all the LGA babies were Pacific Islander babies. They thought it was an ethnic difference. I suggested correction for maternal size and this explained a large part of the difference. So I think maternal size is not being considered in the definition of appropriateness of birthweight, which is a major problem. The second issue is that we are concentrating only on birthweight and sometimes on length. But we are not talking about body composition. For example a female child is more adipose than a male child, and has a different cord blood hormonal profile [2]. Hattersley and Tooke [3] recently published on this, and there is a gender insulin hypothesis. The complexities increase as we go from weight to BMI to body composition and physiology.

Dr. Christian: I wish we had better ways to assess fetal development because MRIs are very hard to do in communities, so how do we measure body composition? Measuring length is one step ahead and we have a long way to go.

Dr. Yajnik: Recently we showed in the Pune Maternal Nutrition Study that smaller leg length seems to predict a metabolic problem [4]. This was demonstrated by Leitch [5] about 5 years ago when she related short legs to cardiovascular risk. Thus there is complexity within length also and implications for the windows of opportunity.

Dr. Shahkhalili: I would like to make a comment. Fetal undernutrition is a consequence of placental insufficiency and not maternal nutritional status. A condition that is common in developed countries and also needs to be addressed.

Dr. Whitelaw: As a geneticist I am just interested that you don’t raise the issue of genetics as being involved in any of these studies. For example, when you correlate maternal BMI or size with fetal or newborn size, surely genetics is likely to play a contributing role. I realize it must be quite complicated to put that into the equation, but it seems likely.

Dr. Christian: In the nutritional community, at least in the context of developing countries, our understanding is that most of the stunting in adults has nutritional origins. If you take the example of a malnourished child being adopted into a well-nourished setting, then he/she experiences some catch-up growth, and when you talk about migrations of people from a developing country to a better setting, over generations an increase in height is actually seen. I think that the genetic component to explain stunting in a developing country is very low because when certain ethnic groups have lived for a substantially long period of time in a well-nourished setting, they tend to gain height.

Dr. Pandit: Nature always tries to correct itself in adverse situations by creating something favorable. For example the studies by Dr. Yajnik in Pune have demonstrated that gestational diabetes has now become a necessary evil for increasing birthweight. In your study did you see this effort of nature to have more gestational diabetes in all these IUGR?

Dr. Christian: In the two places in which I have worked, Nepal and Bangladesh, we find very little evidence of gestational diabetes. We did some standard measures of proteinuria and hypertension and did not find any evidence.

Dr. Kayal: Is there a laboratory model of specific micronutrient deficiency with low birthweight in animals?
Dr. Christian: Folate and B₁₂ deficiency has been looked at in sheep. I am not quite sure if I understand your question, but there are lots of studies in humans which have looked at specific micronutrient deficiencies.

Dr. Kayal: The results of human studies have been inconclusive. Are there any animal studies linking specific micronutrient deficiencies to low birthweight in the offspring, because we will be able to control those things?

Dr. Christian: The studies that I am aware of are human studies.

Dr. Yajnik: Over the last 5 years there have been a number of models. There are models for magnesium and calcium deficiency and also for protein deficiency. Recently a B₁₂ and folate model has been developed. Dr. Christian referred to the recently published sheep model for periconceptional B₁₂ and folate deficiency which actually replicated what we have shown in humans, that there is a growth restriction followed by higher adiposity and insulin resistance in the offspring. There are a number of models.

Dr. Matthai: You said that there is an association between low birthweight and subsequent smallness in adulthood. How much of this is environmental and how much of it is because the person started with a low birthweight?

Dr. Christian: To the extent that the environment influences low birthweight; I think it is environmental. What I was trying to show is that there is a certain fraction of variation in stunting or wasting in children that is explained by being born with a low birthweight which we cannot do anything about once the child is 2–5 years of age. That was the purpose of examining that association. I showed all the environmental factors that actually contribute to low birthweight and those would still be there as risk factors.

Dr. Matthai: Do you think that this person's growth potential would be similar to someone with normal birthweight?

Dr. Christian: Yes, but they have to be corrected before childhood; prenatally or even when the mother is growing as a child or in adolescence. So you are talking about a reproductive life stage approach for interventions but the data that I presented do not tell you the attributable fraction, which is what I said at the end; we should try to figure out what the fraction of risk is that is attributable to the prenatal factors.

Dr. Bhattacharya: Have you come across any syndromes, such as Down's syndrome or others, that can be linked to nutrition?

Dr. Christian: In our studies we have mostly assessed gross congenital malformations and defects. We have only been able to pick these up because these are community-base studies. Births are happening in the women's homes and getting to them on time is always a challenge. In a lot of instances when a congenital malformation is severe the baby dies. So if we reach and find them on time, they have to be surviving babies. This is of concern because we are only capturing survivors. But the congenitally malformed babies tend also to have lower birthweight.

Dr. De Curtis: In the last few years the rate of prematurity has increased in many developed countries. In the USA it has reached about 12–13% and in Italy it is about 7–8%. Is there a similar increase in developing countries? Have developing countries adopted local neonatal reference growth charts or are they using charts from developed countries? It is important to use local neonatal charts to rule out the possibility that many infants are considered SGA when they are actually normal for that region.

Dr. Christian: From what I understand the increasing trend in the US with regard to preterms is mostly associated with the indicated cesarean section preterm rate. It is not the spontaneous preterm rates that have gone up. There is a recent paper by Goldenberg and Culhane [6] showing the different kinds of preterms, and the increase is mostly indicated preterm cesarean sections which are considered for adverse pregnancies. Your second question regarding growth charts is actually a very controversial topic. If you take fetal growth references or standards and if you use Caucasian
or European standards for fetuses in developing countries, then you are comparing apples and oranges. No, I don’t think that we have adequate references and that is why adjustment for various factors is something that is recommended.

References
