Nutritional and Reproductive Risk Factors for Small for Gestational Age and Preterm Births

Naoko Kozuki\textsuperscript{a} · Anne C.C. Lee\textsuperscript{b} · Robert E. Black\textsuperscript{a} · Joanne Katz\textsuperscript{a}

\textsuperscript{a}Department of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, and \textsuperscript{b}Department of Newborn Medicine, Brigham and Women’s Hospital, Boston, MA, USA

Abstract

Approximately 32.4 million small for gestational age (SGA) babies and 13.7 million preterm babies are born annually in low- and middle-income countries (LMICs), of whom 2.8 million are both SGA and preterm. These newborns who are born too small and/or too soon not only experience heightened risk of neonatal and infant mortality, but also of long-term morbidities, like adulthood chronic disease. In order to reduce these burdens worldwide, it is critical to identify and understand the epidemiology of the risk factors that contribute to SGA and preterm births. As part of the Child Health Epidemiology Reference Group, we explored nutritional and reproductive health-related maternal risk factors associated with SGA and preterm outcomes in LMICs, including short maternal stature, young/advanced maternal age, low/high parity, and short birth interval. In this chapter, we highlight our findings and relevant existing literature, and also summarize literature on how low/high BMI and low weight gain during pregnancy, respectively, are associated with SGA and/or preterm outcomes.

Introduction

Low-birthweight (LBW) babies, or those born weighing less than 2,500 g, experience higher risk of neonatal and infant morbidity and mortality, as well as long-term impairments like physical and developmental delays \cite{1} and adulthood chronic disease \cite{2}. LBW babies comprise those who are low weight be-
cause they are born too soon (preterm) and/or because they are born too small (intrauterine growth restricted, IUGR). Small for gestational age (SGA), defined as being born below the 10th percentile of a sex-specific birthweight distribution at a specified gestational age, is often used as a proxy to identify IUGR neonates. Approximately 13.7 million preterm babies [3] and 32.4 million SGA babies [4] are born annually in low- and middle-income countries (LMICs), of whom 2.8 million are both preterm and SGA [4]. Those newborns born both preterm and SGA have the highest mortality risk, with a risk ratio (RR) of 16.20 (95% CI: 10.00–26.23) in the neonatal period and 9.59 (95% CI: 4.53–20.29) in the infant period, compared to those newborns who are born term and appropriate for gestational age (AGA; weighing over the 10th percentile of a sex-specific birthweight distribution at the specified gestational age) [5].

There is value in distinguishing LBW babies by whether they were born too soon and/or too small. While preterm and SGA births share some secondary and tertiary preventive interventions such as exclusive breastfeeding and thermal care, there is greater distinction in primary preventive interventions due to some exposures that are linked to preterm and SGA independently. Understanding the distinct epidemiology can help in designing efforts to prevent both. As part of the Child Health Epidemiology Reference Group (CHERG), we explored nutritional and reproductive health risk factors associated with SGA and preterm outcomes in LMICs, including short maternal stature, maternal age, parity, and short birth interval. In this chapter, we highlight our findings and relevant existing literature, and also summarize literature on how low BMI, high BMI, and low weight gain during pregnancy, respectively, are associated with SGA and/or preterm outcomes.

**Nutritional Risk Factors**

*Height*

Impaired linear growth is considered an indicator of chronic malnutrition in children and may result in low attained height in adolescence and adulthood. Low maternal height may in turn lead to, or be associated with, conditions resulting in poor birth outcomes. The existing literature has reported strong associations between maternal short stature and poor birth/neonatal outcomes. The WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes [6], an analysis including data from 25 studies from low-, middle-, and high-income countries, reported statistically significant associations of low...
maternal height with LBW [odds ratio (OR) 1.7, 95% CI: 1.6–1.8], SGA (OR 1.9, 95% CI: 1.8–2.0), and preterm birth (OR 1.2, 95% CI: 1.1–1.2), comparing the lowest quintile with the highest quintile of height for each dataset. The Knowledge Synthesis Group recently conducted a systematic review of the literature and showed very similar magnitudes of association for LBW (OR 1.81, 95% CI: 1.47–2.23) and preterm (OR 1.23, 95% CI: 1.11–1.37), using each study’s own definition of short stature. The analysis identified 2 studies reporting an IUGR outcome, for an adjusted OR of 1.39 (95% CI: 1.15–1.68) [7]. We, as members of the CHERG, are preparing to publish associations between maternal short stature and SGA/preterm birth, using data from 12 prospective cohort studies and 23 national surveys from the WHO Global Survey on Maternal and Perinatal Health conducted in LMICs. We analyzed each dataset using standard exposure and outcome variables, and estimated that women with a height <145 cm had adjusted RRs of 1.79 (95% CI: 1.63–1.97) for term-SGA, 1.52 (95% CI: 1.29–1.79) for preterm-AGA, and 2.00 (95% CI: 1.52–2.61) for preterm-SGA compared to the reference height group of ≥155 cm. The RRs followed a dose-response pattern, with the associations for each outcome becoming weaker as the height categories approached the reference group [Kozuki et al., under review]. See table 1a for a comparison of findings across existing meta-analyses.

Short maternal stature may be operating on SGA by limiting the uterine volume for fetal growth [8]. One study reported that girls born SGA have smaller uterine volume in adolescence [9], meaning there may be intergenerational effects of short maternal stature and subsequent SGA outcomes as well. Kramer et al. [8] reported an association between short stature and mild preterm, but not with moderate or severe preterm, hypothesizing that earlier filling of the pelvis may be linked to early labor. Existing literature has suggested that the main exposures that determine linear growth occur during the first 1,000 days, or the fetal period plus the first 2 years of life. Fetal growth restriction and stunting in early childhood have been linked as strong predictors for stunting later in life [10]. There has thus been emphasis on macro- and micronutrient supplementation and exclusive breastfeeding during this early period to target the reduction of eventual stunting. There is now increasing interest in exploring the potential for intervention in childhood or even in adolescence to promote catch-up growth [11].

It is also important to note that nonnutritional interventions may improve linear growth as well; a study from Bangladesh suggests that pregnancy slows or even completely halts a mother’s linear growth trajectory during and following the pregnancy, even if she had yet to attain her projected adult height [12]. Delaying pregnancy among adolescents may be invaluable in as-
**Table 1.** Comparisons of findings across existing meta-analyses

### a Summary of meta-analyses examining association between maternal short stature and SGA/preterm birth

<table>
<thead>
<tr>
<th>Publication</th>
<th>Exposure/reference</th>
<th>SGA</th>
<th>Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of height</td>
<td>crude OR 1.9 (1.8–2.0)</td>
<td>crude OR 1.2 (1.1–1.2)</td>
</tr>
<tr>
<td>Knowledge Synthesis Group [7]</td>
<td>varied by study</td>
<td>aOR 1.39 (1.15–1.68)</td>
<td>crude OR 1.23 (1.11–1.37)</td>
</tr>
<tr>
<td>CHERG (under review)</td>
<td>&lt;145 cm</td>
<td>aRR 1.77 (1.61–1.95)</td>
<td>aRR 1.44 (1.20–1.75)</td>
</tr>
<tr>
<td></td>
<td>145 to &lt;150 cm</td>
<td>aRR 1.50 (1.41–1.60)</td>
<td>aRR 1.13 (1.04–1.22)</td>
</tr>
<tr>
<td></td>
<td>150 to &lt;155 cm</td>
<td>aRR 1.31 (1.26–1.36)</td>
<td>aRR 1.10 (1.02–1.18)</td>
</tr>
<tr>
<td></td>
<td>≥155 cm (ref.)</td>
<td>ref.</td>
<td>ref.</td>
</tr>
</tbody>
</table>

### b Summary of meta-analyses examining association between acute nutrition indicators and SGA/birth

<table>
<thead>
<tr>
<th>Research group</th>
<th>Exposure/reference</th>
<th>SGA</th>
<th>Preterm birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low BMI WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of BMI</td>
<td>crude OR 1.8 (1.7–2.0)</td>
<td>crude OR 1.3 (1.1–1.4)</td>
</tr>
<tr>
<td>Knowledge Synthesis Group [14, 15]</td>
<td>varied by study</td>
<td>OR 1.81 (1.76–1.87)</td>
<td>aRR 1.29 (1.15–1.46)</td>
</tr>
<tr>
<td>High BMI Knowledge Synthesis Group [18]</td>
<td>varied by study</td>
<td>aRR 0.69 (0.63–0.76)</td>
<td>aRR 1.24 (1.13–1.37)</td>
</tr>
<tr>
<td>Low pregnancy weight gain WHO Collaborative Study [6]</td>
<td>lowest vs. highest quartile of weight gain, month 5–7</td>
<td>crude OR 2.7 (1.7–4.2)</td>
<td>crude OR 1.6 (1.0–2.6)</td>
</tr>
<tr>
<td>Knowledge Synthesis Group [19]</td>
<td>varied by study</td>
<td>N/A</td>
<td>RR 1.64, 95% CI: 1.62–1.54 (low total weight gain)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>RR 1.56, 95% CI: 1.26–1.94 (low weekly weight gain)</td>
</tr>
</tbody>
</table>

*a Measurement of weight gain by other gestational month cutoffs also available in original paper.
suring that women reach their full growth potential. Casanovas et al. [13] summarizes the need for multisectoral approaches to addressing stunting, as factors like maternal education, water, sanitation, and hygiene, and food security all influence stunting. For sustainable, population-level changes to occur, an appreciation for proximate and distal causes of stunting is necessary.

Body Mass Index

BMI \([\text{weight in kg/(height in meters)}^2]\) is an index of a weight-for-height ratio, and low BMI is considered a representation of acute malnutrition. The WHO uses the range 18.5–25 as normal weight, and categorizes women with BMI <18.5 as underweight. A systematic review examined the association between maternal underweight and preterm and LBW outcomes, respectively [14]. While the review found statistically significantly increased risk of preterm birth when pooling adjusted associations (RR 1.29, 95% CI: 1.15–1.46), a sensitivity analysis revealed no significant association among the 4 developing country studies contributing data (RR 0.99, 95% CI: 0.67–1.45). Underweight women had a statistically significant association with LBW birth, with a similar magnitude for developed and developing country settings (RR 1.52, 95% CI: 1.25–1.85 for developing countries). A more recently published systematic review examined the SGA outcome, and identified 10 studies reporting an association between underweight and SGA [15]. It reported a pooled OR of 1.81 (95% CI: 1.76–1.87). It should be noted that with both of the aforementioned systematic reviews, a variety of BMI cutoffs were accepted to define underweight, and the reference populations used to define SGA were not the same across studies. See Table 1b for comparisons across existing meta-analyses.

The associations between low BMI and poor neonatal outcomes can be a direct nutritional link; limited caloric intake may be restricting fetal growth. However, it can also be operating through other mechanisms like infections; malnutrition is a major cause of secondary immune deficiency [16] and could increase maternal susceptibility to pathogens/infections that may lead to preterm birth. Low BMI could also serve as a proxy for negative exposures like hard manual labor during pregnancy and smoking.

With the epidemiologic transition occurring in many LMICs, fetal and neonatal consequences of high maternal BMI will be of increasing interest. The prevalence of overweight and obesity is increasing worldwide, including LMICs, with rates in Africa reaching over 40% and in the Americas and the Caribbean over 70% [17]. A systematic review reported that overweight or obese women had similar or protective risk of LBW and SGA compared to their normal BMI.
counterparts. However, they experienced higher risk of other adverse neonatal outcomes, such as preterm (RR 1.24, 95% CI: 1.13–1.37) [18], large for gestational age (above the 90th percentile of birthweight for specified gestational age; RR 1.53, 95% CI: 1.44–1.63 for overweight mothers, RR 2.08, 95% CI: 1.95–2.23 for obese mothers), macrosomia (RR 1.67, 95% CI: 1.42–1.97), and offspring’s subsequent overweight/obesity (RR 1.95, 95% CI: 1.77–2.13, RR 3.23, 95% CI: 2.39–4.37, respectively) [15].

Weight Gain in Pregnancy

Low weight gain during pregnancy is another indicator of acute malnutrition. Han et al. [19] reported in a meta-analysis that both low total weight gain during pregnancy and low weekly weight gain are associated with increased risk of preterm birth (RR 1.64, 95% CI: 1.62–1.54, RR 1.56, 95% CI: 1.26–1.94, respectively). However, there is great heterogeneity in the literature as to how low weight gain is categorized and also whether each study took into consideration the mother’s pre-pregnancy BMI when determining appropriate weight gain in pregnancy. The meta-analysis used exposure cutoffs that were defined by the original studies, and therefore not standardized. Data from the WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes, which examined weight gain curves by birthweight and by clusters of countries contributing data, showed increased risk of LBW and IUGR, but found inconsistent associations with preterm, comparing women of the lowest to the highest weight gain quartile [6].

In addressing acute malnutrition during pregnancy, it is important to be cautious of the potential consequences of increasing fetal size through maternal protein-energy supplementation. In a study conducted in rural Nepal, Lee et al. [20] reported increased rates of birth asphyxia among newborns of women with height <145 cm (aRR 1.5, 95% CI: 1.1–2.0) and particularly high risk among infants weighing greater than 3,300 g, also born to women <145 cm (aRR 3.8, 95% CI: 2.2–6.5). These data underscore potential concerns in South Asia, a region with high maternal stunting rates. Larger fetal size there may potentially increase rates of cephalopelvic disproportion and obstructed labor. A recent systematic review reported statistically significant increases in birthweight and no increase in risk of neonatal mortality and stillbirths with maternal protein-energy supplementation, but the review only included one study from South Asia, where short stature would be of main concern [21].
Reproductive Risk Factors

Maternal Age and Parity

Our team published a meta-analysis of 14 studies from LMICs, examining the association of maternal age and parity with SGA/preterm outcomes [22]. We standardized the exposure definitions in each dataset before pooling by creating exposure categories that matched maternal age categories with parity categories. We created combinations of age <18, 18 to <35, or ≥35 with parity 0, 1–2, or ≥3, using those who were both age 18 to <35 and parity 1–2 as the reference group. This allowed us to better differentiate the impact of young/advanced age and nulliparity/high parity on neonatal outcomes, rather than solely depending on statistical control. We found that women who were both age <18 and nulliparous had the highest odds of SGA and preterm when compared to women in the reference category (age 18 to <35 and parity 1–2; table 2). Those who were nulliparous and age 18 to <35 had increased risk of SGA, but not of preterm, implying that young age is likely the driver for prematurity. Those who were parity ≥3 had heightened risk of preterm (in both age groups of 18 to <35 and ≥35), with the magnitude of the risk slightly higher in the higher age group. We saw no impact of advanced age or high parity on SGA. A systematic review examining parity similarly found increased risk of SGA and no increased risk of preterm among nulliparous women. However, in contrast to our findings, it found no increased risk of preterm associated with high parity [23]. Their RRs were not adjusted for age or other confounders.

The association between young age and adverse neonatal outcomes may have multiple biological mechanisms. The mother may have experienced incomplete physical growth prior to pregnancy, leading to lower stature and smaller pelvic dimensions, thus constraining fetal growth. The dual burden of growth (the

### Table 2. The associations between parity/age and SGA and preterm outcomes

<table>
<thead>
<tr>
<th>Age/parity category</th>
<th>SGA and preterm birth outcomes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>term-SGA</strong></td>
<td><strong>preterm-AGA</strong></td>
</tr>
<tr>
<td>Nulliparous, age &lt;18</td>
<td>2.02 (1.76–2.31)</td>
<td>1.92 (1.69–2.17)</td>
</tr>
<tr>
<td>Nulliparous, age 18 to &lt;35</td>
<td>1.46 (1.30–1.63)</td>
<td>ref.</td>
</tr>
<tr>
<td>Parity 1–2, age 18 to &lt;35</td>
<td>ref.</td>
<td>ref.</td>
</tr>
<tr>
<td>Parity ≥3, age 18 to &lt;35</td>
<td>1.19 (1.01–1.40)</td>
<td></td>
</tr>
<tr>
<td>Parity ≥3, age ≥35</td>
<td>1.37 (1.10–1.72)</td>
<td>1.62 (1.27–2.05)</td>
</tr>
</tbody>
</table>

Data from Kozuki et al. [22]. Figures indicate adjusted OR (ref.: term-AGA).
adolescent mother and the fetus) may be nutritionally taxing; in rural Nepal, a larger loss of mid-upper arm circumference in pregnancy was noted among adolescent mothers compared to their older counterparts [24]. Young age may also serve as a proxy for poor socioeconomic status and malnutrition; the literature suggests that controlling for socioeconomic status largely attenuates the associations between young maternal age and adverse outcomes [25]. Among mothers with advanced age, there is increased risk of congenital abnormalities and also of maternal morbidities, which may be linked to preterm birth (gestational diabetes, preeclampsia/eclampsia, etc.).

Any reported association between high parity and SGA or preterm may be partially, if not completely, driven by residual confounding. Characteristics correlated with high parity may not be sufficiently controlled by statistical adjustment in the existing literature, and thus, it may not be a biological mechanism driving this association. A study using data from Demographic and Health Surveys found that when examining child mortality rates across all births of mothers with the same completed fertility (the final number of children the mother had), there was no clear increase in the mortality rate with an increase in birth order [26]. Furthermore, for each birth order, children of mothers who had high completed fertility consistently had a higher mortality risk than children of mothers who had low completed fertility. As an example, figure 1a shows the crude under-5 mortality rates by a child’s birth order, stratified by the mother’s completed fertility, using data from the most recent Indian DHS. For each line (stratification by each unit of mothers’ completed fertility), there is no increase in the mortality rate as birth order increases. Figure 1b is a representation of the same data, but without the stratification by mother’s completed fertility. In this graph, we see the ‘parity effect.’ The study concludes that it only appears as if child mortality increases with parity because a larger proportion of children in higher birth orders are represented by mothers who have negative exposures correlated with high completed fertility. Hence, it may not be biological mechanisms but other confounding factors that are driving the association between parity and poor newborn/child outcomes.

**Birth Interval**

Several meta-analyses have reported an increased risk of SGA and preterm among those born after a short birth interval, although there is great variation in exposure definitions used across these analyses. Our meta-analysis, using five datasets from developing countries with standardized exposures and outcomes, estimated an adjusted OR 1.51 (95% CI: 1.31–1.75) for SGA and aOR 1.58 (95%
CI: 1.19–2.10) for preterm, comparing birth intervals (time between birth of previous child and the child of interest) of <18 months with a reference of 24 to <36 months [27]. Conde-Agudelo et al. [28] in their systematic review reported an aOR 1.26 (95% CI: 1.18–1.33) for SGA and 1.40 (95% CI: 1.24–1.58) for preterm, using the interpregnancy interval (IPI, time between birth of previous child and the child of interest) of <18 months with a reference of 24 to <36 months [27]. Conde-Agudelo et al. [28] in their systematic review reported an aOR 1.26 (95% CI: 1.18–1.33) for SGA and 1.40 (95% CI: 1.24–1.58) for preterm, using the interpregnancy interval (IPI, time between birth of previous

Fig. 1. a Crude under-5 mortality rates, stratified by mother’s completed fertility and birth order, India DHS (2005–2006). Figure reproduced from Kozuki et al. [26]. b Replication of a, not stratified by mother’s completed fertility and birth order, India DHS (2005–2006).
child and the conception of the child of interest) of <6 months, compared against a reference of 18 to <24 months. Long intervals had less consistent results; our meta-analysis found a weak but significant association between a birth interval ≥60 months and SGA but not preterm, while Conde-Agudelo et al. [28] reported stronger, significant associations for both SGA and preterm, using a cutoff of IPI ≥60 months. We report in a separate analysis that the effect of short birth intervals on adverse child outcomes may be modified by the frequency at which women experience these short intervals. We noted that while all short interval births had slightly increased risk of neonatal and infant mortality, short interval births that occurred in later birth orders experienced higher risk [29]. This could either be driven by an effect modification that occurs between short birth intervals and high parity (supporting the maternal depletion hypothesis), or it could be that women with characteristics associated with high fertility (e.g. poor socioeconomic status, malnutrition) may not be able to bear the nutritional and/or physiological burden of repeated short birth interval pregnancies.

Understanding birth interval as an exposure is difficult, particularly when using data from low-resource settings. IPI is the preferred measure of the exposure, compared to birth interval because the gestational length of the second pregnancy contributes to the interval in the latter. For instance, a preterm birth that occurs in the latter pregnancy of an interval may make the IPI look arbitrarily short. However, it is hard to have a proper measure of IPI without ultrasound dating to get an accurate reading of time of conception. It is also difficult to determine how best to account for spontaneous abortions and early stillbirths in these intervals, events that may not have as large a burden on the mother as a full pregnancy, but more than not having conceived at all. Long birth intervals may be a result of conscious family planning, or may instead be due to infertility or other poor health exposures. The failure to differentiate these mechanisms contributing to the length of a birth interval makes it difficult to arrive at conclusions pertaining to its impact on neonatal outcomes.

**Conclusion**

32.4 million SGA and 12.1 million preterm births occur in LMICs each year. These newborns experience increased risk of short- and long-term health consequences; for instance, newborns who are born both too small and too soon experience a 16-fold increased risk of neonatal mortality, compared to their term, appropriately sized counterparts [5]. Understanding causal mechanisms that lead to SGA and preterm birth is critical for reducing these adverse health outcomes. Existing literature highlights various nutritional and reproductive
health-related exposures associated with SGA and preterm birth. There are interventions that have demonstrated efficacy in reducing these outcomes, but there is generally less evidence of effectiveness. Chronic malnutrition may require intergenerational intervention, and potential consequences of increasing fetal size need to be taken into account when addressing acute malnutrition. While family planning can reduce the adverse effects of early pregnancy, increased access to contraceptives affects young age at first birth the least out of all reproductive health-related risk factors [30]. This suggests the need for more research on how to maximize the effectiveness of known, evidence-based interventions, but also for uncovering new, efficacious interventions, taking into account the independent and shared causal mechanisms operating on SGA and preterm outcomes.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the contents of the chapter.

References