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ORIGINAL ARTICLE

# Risk factors and neonatal/infant mortality risk of small-for-gestational-age and preterm birth in rural Nepal

Naoko Kozuki[1], Joanne Katz[1,2], Steven C. LeClerq[1,2,3], Subarna K. Khatry[3], Keith P. West Jr[1,2], and Parul Christian[1,2]

[1]Department of International Health and [2]Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, and [3]Nepal Nutrition Intervention Project – Sarlahi, Kathmandu, Nepal

**Abstract**

*Objective*: Our study seeks to elucidate risk factors for and mortality consequences of small-for-gestational-age (SGA) and preterm birth in rural Nepal. In contrast with previous literature, we distinguish the epidemiology of SGA and preterm birth from each other.

*Methods*: We analyzed data from a maternal micronutrient supplementation trial in rural Nepal ($n = 4130$). We estimated adjusted risk ratios (aRR) for risk factors of SGA and preterm birth, and aRRs for the associations between SGA/preterm birth and neonatal/infant mortality. We used mutually exclusive categories of term-appropriate-for-gestational-age (AGA), term-SGA, preterm-AGA, and preterm-SGA (with term-AGA as reference) in our analyses.

*Results*: Stunted (<145 cm) and wasted (<18.5 kg/m$^2$) women both had increased risk of having term-SGA (aRR 1.36, 95% CI: 1.14-1.61, aRR 1.22, 95% CI: 1.09–1.36 respectively) and preterm-SGA (aRR 2.48, 95% CI: 1.29–4.74, aRR 1.99, 95% CI: 1.33–2.97 respectively), but not preterm-AGA births. Similar results were found for low maternal weight gain per gestational week. Those born preterm-SGA generally experienced the highest neonatal and infant mortality risk, although term-SGA and preterm-AGA newborns also had statistically significantly high mortality risks compared to term-AGA babies.

*Conclusions*: SGA and preterm birth have distinct risk factors and mortality patterns. Maternal chronic and acute malnutrition appear to be associated with SGA outcomes. Because of high SGA prevalence in South Asia and the increased neonatal and infant mortality risk associated with SGA, there is an urgent need to intervene with effective interventions.

**Keywords**

Maternal, neonatal mortality, preterm, SGA

**History**

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## Introduction

Approximately 20 million newborns have low birthweight (<2500 g, LBW) worldwide, 96% of whom are born in low- and middle-income countries (LMIC) [1]. LBW babies have higher risk of mortality and morbidity in early childhood and of long-term health consequences, such as neurodevelopmental impairment and adult chronic disease [2,3]. LBW can result from intrauterine growth restriction (IUGR), preterm birth, or a combination of both. Small-for-gestational-age (SGA), or weighing below the 10th percentile of a sex- and gestational-age-specific reference birthweight distribution, is often used as a proxy for IUGR. It was estimated that 32.4 million neonates are born SGA each year in LMICs, with national prevalence of SGA reaching as high as 60% in parts of South Asia [4]. In addition, 13.7 million neonates are also estimated to be preterm (gestational age <37 weeks) in LMICs each year [5]. Approximately 2.8 million of those infants are born with both conditions [4], a group that experiences the highest neonatal mortality risk [6].

Numerous factors contribute to the high burden of SGA and preterm birth, with less understood about preterm etiology. Undernutrition prior to and during pregnancy are associated with the large burden of SGA in many LMICs [7,8], while existing studies have reported weaker, but statistically significant, associations with preterm birth [9–12]. Other previously reported risk factors include nulliparity [13] and maternal HIV infection[14] for SGA, and young and advanced age [13] and urinary and reproductive tract infections [5] for preterm birth. The two conditions may share some risk factors, such as being born after a short birth interval [15]. Understanding the epidemiologic differences in their causes and consequences may help highlight ways to best prevent and triage these newborns born too small and/or too soon. Furthermore, it may be additionally instructive to comprehend how absolute birthweight influences the health outcomes of SGA or preterm babies.

Our study seeks to elucidate maternal risk factors and mortality consequences associated with SGA and preterm birth, using data from a community-based,

Address for correspondence: Parul Christian, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St. E2541, Baltimore, MD 21205, USA. Tel: (410) 955-1188. E-mail: pchrist1@jhu.edu

cluster-randomized controlled trial of maternal antenatal supplementation conducted in rural Nepal [16].

## Methods

Four-thousand nine-hundred twenty-six pregnant women were enrolled from December 1998 to April 2001 in a double-blind cluster-randomized community trial in rural Sarlahi District, Nepal to determine the effects of maternal micronutrient supplementation on birthweight. Details are available in another publication [16]. There were five micronutrient supplementation arms: folic acid (400 μg); folic acid and iron (60 mg); folic acid, iron and zinc (30 mg); multiple micronutrients (folic acid, iron, zinc, vitamin D 10 μg, vitamin E 10 mg, thiamine 1.6 mg, riboflavin 1.8 mg, vitamin B-6 2.2 mg, vitamin B-12 2.6 μg, vitamin C 100 mg, vitamin K 64 μg, niacin 20 mg, Cu 2 mg, Mg 100 mg); and a control group, with all five groups receiving vitamin A (1000 μg retinol equivalents). The study area consisted of 30 village development committees (VDC) (~200 000 individuals), and the VDCs were then divided into 426 sectors, each containing about 75–150 households. Sectors were randomized to a micronutrient allocation in blocks of five to assure equal distribution of each allocation per geographic area.

Female field workers conducted active pregnancy surveillance every five weeks by making home visits to married women of reproductive age (15–45 years old). Women who reported not having menstruated since the last home visit were given a pregnancy test (Clue, Orchid Biomedical Systems, Bambolim, India), and if pregnant, the women were consented and enrolled in the trial. Enrolled women were tracked until the end of pregnancy for birth outcomes. At enrollment, baseline information on maternal morbidity, food intake, alcohol and tobacco use over the previous week, anthropometry (weight, height, mid-upper arm circumference), and socioeconomic characteristics was recorded. Data on the same variables, except for height and socioeconomic status, were collected at a follow-up visit in the third trimester. The medians and inter-quartile ranges (IQR) of gestational age at enrollment and at the third trimester visit were 10 (8–13) and 34 (32–37) completed weeks, respectively. Newborns were visited and weighed immediately after the female workers were notified of the delivery, and followed through the first year of life [17].

### Risk factor analysis

We explored nutritional, socioeconomic, reproductive, and other risk factors of SGA alone, preterm birth alone, and both SGA and preterm birth. For nutrition, we included early-pregnancy maternal height (<145 cm, 145 to <150 cm, 150 to <155 cm, ≥155 cm as reference), body mass index (BMI, <18.5, 18.5 to <25 as reference, ≥25 kg/m$^2$), and mean maternal weight gain per week. BMI was calculated only for women who had a weight taken before 20 weeks gestation; among those women, the median and IQR of gestational age at which weight was taken were 10 (8–12) weeks. Both measures were used as proxies for maternal pre-pregnancy nutritional status, as weight gain is minor in early pregnancy. Mean maternal weight gain per gestational week was estimated by subtracting the maternal weight taken at enrollment from that taken in the third trimester and dividing by the number of weeks elapsed between the two measurements.

Socioeconomic variables included maternal education (no education, 1–9 years, ≥10 years), housing structure (mainly made of thatch, grass, and/or branches versus mainly made of wood, cement, and/or brick), land ownership (no land versus any land), and ethnicity. The study area, located in the lower plains of Nepal, has inhabitants largely from two ethnic groups: the Madheshis, who are of north Indian origin, and the Pahadis, who are of the hill regions of Nepal.

Reproductive variables included were maternal age at pregnancy enrolment (<18, 18 to <35, ≥35 years) and parity (0, 1–2, or ≥3 live births previous to index pregnancy). Sex of the child, maternal smoking at any point in pregnancy, and micronutrient supplement allocation were included in the analysis. The five micronutrient allocation groups were re-categorized into a binary variable by whether the allocation included iron-folate.

SGA was used as a proxy measure for IUGR. SGA is defined as birthweight below the 10th percentile of a sex- and gestational-age-specific, US-based birthweight reference distribution (Alexander reference) [18]. Only weights taken within 72 hours of birth were included to minimize bias associated with late weighing of babies; 87.8% of babies had weights taken within 72 hours. Preterm birth was defined as below 37 completed weeks of gestation. Gestational age was calculated using maternal recall of last menstrual period (LMP) at the time of enrollment in early pregnancy, recall aided by the dates of the pregnancy surveillance visits. Combined categories of preterm birth and SGA were used as outcomes, as follows: term-SGA, preterm-AGA, and preterm-SGA, with term-AGA as the reference category for each outcome. We also estimated associations for SGA and SGA by severity, creating categories of SGA <3% and SGA 3-<10%, with a reference category of SGA ≥10%. As the Alexander reference only provides the 10% cut-off, we used a U.S. reference population from 1999 to 2000 [19] that allowed for the calculation of the <3% cut-off. We also estimated associations for preterm birth and early/moderate/late preterm birth, creating categories of <32 weeks, 32 to <34 weeks, and 34 to <37 weeks gestation, with a reference category of ≥37 weeks gestation. We did not create combination categories with these severity categories due to the small sample size in each group.

We used a modified Poisson regression with robust error variance to calculate unadjusted and adjusted risk ratios (RR) for the outcomes [20]. Risk factors with statistical significance at $p < 0.10$ in the bivariate analyses with either SGA or preterm outcomes were included in the final multivariate models. Maternal age (which had a significance level of $p > 0.10$) was also included in the model along with parity to distinguish their associations. Interactions between the maternal anthropometric indicators with smoking and the micronutrient intervention allocations were tested respectively.

### Mortality analysis

We used the combination categories of SGA and preterm birth as the exposure variable of interest (term-SGA, preterm-AGA, preterm-SGA, and term-AGA as reference). We also

examined SGA and SGA by severity, as well as preterm birth and early/moderate/late preterm birth, as exposures. We did not create SGA and preterm combination categories stratified by severity due to the small sample size in each group.

Missing birthweight was in part related to early newborn mortality, so by failing to include their birthweights there is potential underestimation of mortality risk. Over 90% of births occurred at home, and of the 173 neonatal deaths that occurred, 85 (49.1%) did not have weights taken because they died soon after delivery and prior to the arrival of our staff for weighing. Thus, for this analysis, we ran multiple imputations [21] for those who did not have any weight taken, using gestational age, sex, and mortality (vital status at day three and at one year) as predictors of birthweight. Furthermore, weights taken beyond 72 hours of life were modeled back to time of birth (see Text S1 for details).

Outcomes of interest were neonatal (death within the first 28 days of life) and infant mortality (within the first 365 days of life). Outcomes were also examined as early neonatal (within the first seven days of life), late neonatal (between seven and 28 days of life), and post-neonatal infant (between 29 and 365 days of life) mortality.

We calculated unadjusted and adjusted RR between SGA/preterm exposures and mortality, controlling for early pregnancy height, BMI (with weight taken before 20 weeks gestation), parity, maternal age, maternal education, ethnicity, and supplement allocation group. We also examined term-SGA and preterm-AGA respectively stratified by LBW status. We used modified Poisson regression with robust error variance to calculate RR [20].

We used Stata version 12.0 (Stata Corp., College Station, TX, USA) for all analyses.

## Results

### Risk factor analysis

Four-thousand one-hundred thirty live births were recorded in the study. Characteristics of the mothers and newborns enrolled in the study can be found in Table 1. A large majority (81%) of women were enrolled in the first trimester (<14 weeks gestation). There were high prevalence of maternal stunting (height <145 cm, 16%) and wasting (BMI <18.5 kg/m$^2$, 37%). We report below the results for the SGA/preterm combination outcomes. The results for SGA (unstratified and stratified by severity) and preterm birth (unstratified and stratified by early/moderate/late preterm) can be found in Tables S2a and S2b.

Stunted (<145 cm) and wasted (<18.5 kg/m$^2$) women both had statistically significant increased risk of term-SGA and preterm-SGA, but not preterm-AGA births (reference: Term-AGA) (Table 2). Similarly, larger weight gain per gestational week decreased the risk of term-SGA and preterm-SGA, but not preterm-AGA.

Nulliparous births had an increased risk of all three outcomes, with the highest RR being for preterm-SGA. Female infants had a roughly 20% lower risk of being born preterm-AGA. Madheshi ethnicity compared to Pahadi ethnicity was associated with increased risk for all outcomes. Smoking at any time during pregnancy increased the risk of preterm-AGA and preterm-SGA, but not term-SGA.

Table 1. Background characteristics of participating households ($N = 4130$).

| Characteristics | *N* | Mean (SD) |
|---|---|---|
| Gestational age at enrollment (wk) | 4116 | 11.5 (5.3) |
| Height (cm) | 3883 | 150.2 (5.5) |
| Early BMI (<20 wk gestation) (kg/m$^2$) | 3020 | 19.1 (2.0) |
| Weight gain during pregnancy(kg/wk) | 2410 | 0.23 (0.13) |
| Maternal Characteristics | *N* | % |
| Height | | |
| <145 cm | 615 | 15.8 |
| 145 to <150 cm | 1225 | 31.6 |
| 150 to <155 cm | 1271 | 32.7 |
| ≥155cm | 772 | 19.9 |
| Early BMI (<20 wks gestation) | | |
| <18.5 kg/m$^2$ | 1228 | 36.6 |
| 18.5 to <25 kg/m$^2$ | 1773 | 58.7 |
| ≥25 kg/m$^2$ | 19 | 0.6 |
| Maternal age | | |
| <18 | 642 | 15.6 |
| 18–35 | 3268 | 79.4 |
| ≥35 | 204 | 5.0 |
| Parity | | |
| 0 | 1101 | 26.9 |
| 1 or 2 | 1590 | 38.8 |
| ≥3 | 1404 | 34.3 |
| Education | | |
| no education | 3318 | 81.1 |
| 1–9 y | 542 | 13.3 |
| ≥10 y | 230 | 5.6 |
| Ethnicity | | |
| Pahadi | 1209 | 29.6 |
| Madheshi | 2878 | 70.4 |
| Treatment group | | |
| Folate | 773 | 18.7 |
| Iron-folate | 872 | 21.1 |
| Iron-folate-zinc | 827 | 20.0 |
| Multiple micronutrient | 879 | 21.3 |
| Control | 779 | 18.9 |
| Ever smoked during pregnancy | | |
| Yes | 687 | 21.9 |
| No | 2448 | 78.1 |
| Newborn characteristics* | | |
| Low birthweight | 3325 | 38.8 |
| Small-for-gestational-age | 3325 | 55.7 |
| Preterm | 3325 | 21.2 |

*The Ns represent the total number of newborns who had weights taken within 72 hours of birth and had gestational age information, thus included in our analysis.

Interactions between maternal nutritional indicators and smoking or micronutrient intervention allocations were not statistically significant (data not presented).

### Mortality analysis

We used imputed weights for the mortality analysis. Table S1 summarizes how weight imputation altered the data included in the analysis. After imputation, all 4130 newborns enrolled in the study were included in the analysis, except for 14 without gestational age data. The prevalences of LBW, SGA, and preterm did not change much, but the 87 neonatal deaths and 112 infant deaths added back into the analysis changed the neonatal mortality rate from 26 to 42 per 1000 live births and infant mortality rate from 47 to 65 per 1000 live births. We report below the results for the SGA/preterm combination categories. The results for SGA (unstratified and stratified by severity) and preterm birth (unstratified and stratified by early/moderate/late preterm) can be found in Table S3.

Table 2. Multivariate associations between maternal characteristics and term-SGA, preterm-AGA, and preterm-SGA (reference: term-AGA).

| | Term-AGA ($N=931$) | Term-SGA ($N=1684$) | | Preterm-AGA ($N=521$) | | Preterm-SGA ($N=164$) | |
|---|---|---|---|---|---|---|---|
| Exposure | % | % | aRR (95% CI) | % | aRR (95% CI) | % | aRR (95% CI) |
| Maternal height | | | | | | | |
| <145 cm | 8.0 | 19.3 | 1.36 (1.14, 1.61) | 14.6 | 1.40 (0.95, 2.07) | 25.4 | 2.48 (1.29, 4.74) |
| 145 to <150 cm | 29.1 | 31.7 | 1.13 (0.97, 1.32) | 34.2 | 1.22 (0.90, 1.66) | 33.9 | 1.68 (0.94, 2.98) |
| 150 to <155 cm | 36.5 | 31.7 | 1.07 (0.91, 1.25) | 32.7 | 1.01 (0.74, 1.38) | 28.6 | 0.96 (0.51, 1.78) |
| ≥155 cm | 26.3 | 17.4 | Ref | 18.6 | Ref | 12.2 | Ref |
| Maternal early pregnancy BMI | | | | | | | |
| <18.5 kg/m$^2$ | 32.9 | 42.4 | 1.22 (1.09, 1.36) | 36.9 | 1.10 (0.87, 1.39) | 50.6 | 1.99 (1.33, 2.97) |
| 18.5 to <25 kg/m$^2$ | 66.3 | 57.1 | Ref | 62.4 | Ref | 48.8 | Ref |
| ≥25 kg/m$^2$ | 0.8 | 0.6 | 0.95 (0.49, 1.84) | 0.7 | 1.03 (0.25, 4.22) | 0.6 | – |
| Average weight gain per gestational week (in 100 g units) | Mean 264 g (SD: 139 g) | Mean 216 g (SD: 121 g) | 0.89 (0.85, 0.93) | Mean 252 g (SD: 163 g) | 0.93 (0.84, 1.03) | Mean 254 g (SD: 323 g) | 0.72 (0.60, 0.87) |
| Parity | | | | | | | |
| 0 | 17.0 | 31.1 | 1.28 (1.11, 1.49) | 24.4 | 1.46 (1.00, 2.12) | 33.4 | 1.86 (0.97, 3.55) |
| 1–2 | 42.1 | 38.9 | Ref | 34.1 | Ref | 30.1 | Ref |
| ≥3 | 40.8 | 30.1 | 0.87 (0.76, 0.99) | 41.5 | 1.08 (0.84, 1.41) | 36.0 | 0.99 (0.62, 1.60) |
| Age | | | | | | | |
| <18 | 8.3 | 15.8 | 1.03 (0.86, 1.22) | 14.2 | 1.28 (0.85, 1.93) | 16.0 | 1.35 (0.68, 2.69) |
| 18 to <35 | 87.2 | 79.0 | Ref | 79.6 | Ref | 76.0 | Ref |
| ≥35 | 4.5 | 5.2 | 1.10 (0.85, 1.42) | 6.2 | 1.17 (0.72, 1.89) | 8.0 | 1.84 (0.91, 3.73) |
| Ethnicity | | | | | | | |
| Pahadi | 40.3 | 28.3 | Ref | 18.3 | Ref | 17.7 | Ref |
| Madheshi | 59.7 | 71.7 | 1.21 (1.07, 1.36) | 81.7 | 2.49 (1.85, 3.36) | 82.3 | 2.61 (1.57, 4.35) |
| Sex | | | | | | | |
| Male | 50.0 | 48.6 | Ref | 54.1 | Ref | 54.9 | Ref |
| Female | 50.0 | 51.4 | 1.01 (0.91, 1.12) | 45.9 | 0.78 (0.62, 0.97) | 45.1 | 0.82 (0.56, 1.21) |
| Maternal smoking | | | | | | | |
| At anytime in pregnancy | 85.7 | 83.6 | 1.14 (0.98, 1.32) | 82.0 | 1.40 (1.03, 1.89) | 78.1 | 1.78 (1.09, 2.90) |
| Never | 14.3 | 16.4 | Ref | 18.0 | Ref | 21.9 | Ref |

SGA: small-for-gestational-age, AGA: appropriate-for-gestational-age.



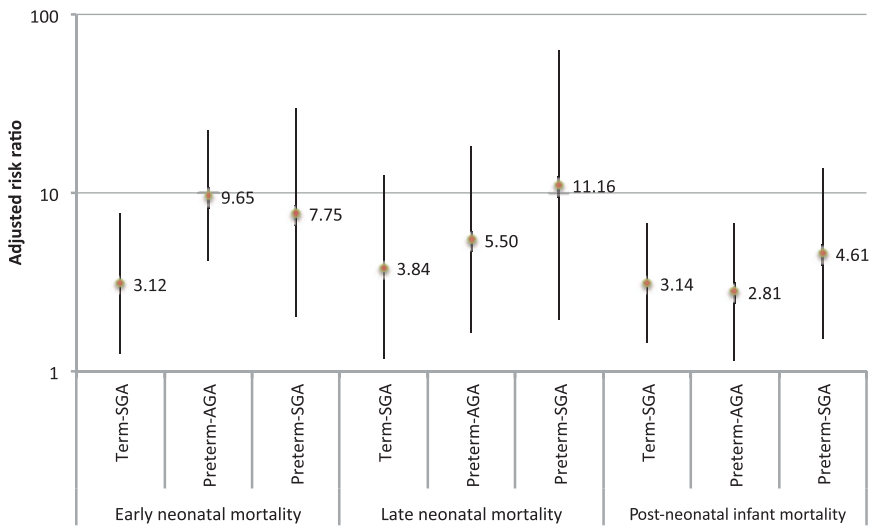


Figure 1. Associations between SGA/preterm birth and early, late, and post-neonatal infant mortality (Reference: Term-AGA).

We found increased risk in neonatal and infant mortality for SGA and/or preterm births (Figure 1). Term-SGA newborns had statistically significantly increased mortality risk through infancy, compared to term-AGA newborns (Table 3). Preterm-AGA babies had significantly heightened risk of mortality earlier in life, and that risk tapered through infancy while remaining statistically significant. Preterm-SGA babies experienced a higher mortality risk in the early neonatal period, but even higher risk in the late neonatal period.

When stratifying term-SGA babies by LBW status, those who were not LBW did not have statistically significantly increased mortality risk compared with term-AGA infants, although the magnitude of the RR was close to two through the neonatal and infant periods (Table 3). Term-SGA babies who were LBW had more than two-fold higher risk of their non-LBW counterparts across the early neonatal, late neonatal, and post-neonatal infant periods respectively, although the confidence intervals of the effect sizes overlapped. Similarly, preterm-AGA infants who were not LBW did not have statistically significant mortality risk compared to term-AGA babies, but the RRs had wide confidence intervals. Preterm-AGA-LBW newborns had increased risk across all mortality periods. The magnitude of associations was much

Table 3. Multivariate associations between SGA/preterm birth and neonatal/infant mortality.

| | Neonatal mortality | | Infant mortality | | Early neonatal mortality | | Late neonatal mortality | | Post-neonatal infant mortality | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total deaths = 171, Total $N = 4110$ | | Total deaths = 263, Total $N = 2917$ | | Total deaths = 121, Total $N = 4111$ | | Total deaths = 50, Total $N = 3989$ | | Total deaths = 92, Total $N = 2747$ | |
| | %* | aRR (95% CI) | % | aRR (95% CI) | % | aRR (95% CI) | % | aRR (95% CI) | % | aRR (95% CI) |
| Term-AGA | 29.3 | Ref | 28.1 | Ref | 29.3 | Ref | 30.0 | Ref | 29.3 | Ref |
| Term-SGA | 48.3 | 3.56 (1.64, 6.87) | 46.3 | 3.31 (1.90, 5.76) | 28.3 | 3.12 (1.26, 7.72) | 48.6 | 3.84 (1.17, 12.57) | 46.6 | 3.14 (1.45, 6.84) |
| Preterm-AGA | 18.7 | 8.42 (4.19, 16.93) | 21.4 | 5.34 (3.15, 9.05) | 18.7 | 9.65 (4.15, 22.41) | 17.9 | 5.50 (1.65, 18.26) | 20.1 | 2.81 (1.15, 6.85) |
| Preterm-SGA | 3.7 | 9.07 (2.95, 27.91) | 4.0 | 6.67 (2.96, 15.03) | 3.7 | 7.75 (2.01, 29.92) | 3.5 | 11.16 (1.95, 63.95) | 4.0 | 4.61 (1.54, 13.82) |
| Term-AGA (All not-LBW) | 6.0 | Ref | 8.2 | Ref | 3.3 | Ref | 12.3 | Ref | 29.2 | Ref |
| Term-SGA-LBW | 34.8 | 4.73 (2.17, 10.34) | 35.4 | 4.60 (2.51, 8.44) | 34.0 | 4.24 (1.63, 11.01) | 36.5 | 5.68 (1.61, 20.02) | 22.6 | 4.28 (1.88, 9.77) |
| Term-SGA-Not LBW | 7.7 | 1.89 (0.74, 4.87) | 10.9 | 1.95 (0.89, 4.29) | 7.3 | 1.88 (0.55, 6.40) | 8.8 | 1.88 (0.46, 7.74) | 23.8 | 1.97 (0.76, 5.12) |
| Term-AGA (All not-LBW) | 6.0 | Ref | 8.2 | Ref | 3.3 | Ref | 12.3 | Ref | 12.3 | Ref |
| Preterm-AGA-LBW | 34.6 | 19.10 (6.69, 54.52) | 25.9 | 10.61 (5.45, 20.64) | 39.3 | 41.46 (7.62, 225.50) | 23.5 | 7.84 (2.27, 27.10) | 9.9 | 3.48 (1.33, 9.10) |
| Preterm-AGA-Not LBW | 5.9 | 2.46 (0.36, 16.93) | 6.5 | 2.03 (0.59, 6.96) | 6.0 | 4.84 (0.50, 46.61) | 5.8 | 0.98 (0.05, 18.66) | 7.5 | 1.56 (0.25, 9.78) |

LBW: low birthweight, SGA: small-for-gestational-age, AGA: appropriate-for-gestational-age.
*Percent of deaths that belongs to the respective exposure categories.

greater than their non-LBW counterparts, although overlapping in confidence intervals. A similar stratified analysis was not conducted for preterm-SGA, as they were all LBW. All term-AGA babies were not LBW.

## Discussion

An estimated 32.4 million SGA and 13.7 million preterm infants are born in LMICs each year, and are likely to experience major short- and long-term health consequences. Our analysis revealed different maternal and sociodemographic risk factors for SGA and preterm birth independently and combined. Being born SGA or preterm alone increased the risk of neonatal and infant mortality, a risk that was additive when both conditions co-existed.

Early pregnancy height and BMI, as well as weight gain during pregnancy, were all strongly associated with term-SGA and preterm-SGA, but not with preterm-AGA. These findings are not directly comparable to much of the existing literature, as many have not differentiated SGA from preterm birth and/or have categorized the exposures differently. However, the statistically significant associations we report between maternal nutritional indicators and SGA (Table S2a) are similar in magnitude to those reported in meta-analyses by the WHO Collaborative Study of Maternal Anthropometry and Pregnancy Outcomes and by the Knowledge Synthesis Group [9–11]. However, we found no significant associations with preterm-AGA, which differs from the previously reported associations between maternal nutritional indicators and preterm birth [9–12]. This may be because SGA newborns who are also preterm were driving the association in the prior literature. By removing the SGA babies from the preterm births, our analysis suggests that maternal malnutrition may not be independently associated with preterm birth.

Chronic malnutrition (as reflected by short stature) and continued dietary inadequacy (as reflected by low BMI and by inadequate weight gain in pregnancy) were independently associated with SGA. This highlights both the potential for and the limitations of nutritional interventions during pregnancy. A systematic review reported a 34% reduced odds of SGA through balanced protein energy supplementation during pregnancy, with the effect being larger among undernourished mothers [22]. A separate systematic review reported a 13% reduction through daily multiple micronutrient supplementation [23]. While such supplementation promotes fetal growth to a degree, it is unclear how much it mitigates the impact of chronic undernutrition in these settings. Also, the existing literature has largely focused on the first 1000 days as the critical period of growth and for intervention [24], but there is increasing interest in exploring the impact of preconceptional interventions to reduce adverse birth outcomes. In addition, it may be possible to accelerate linear growth and reverse stunting with interventions later in childhood, or as late as adolescence [25].

First live birth was a risk factor for both SGA and preterm birth. This matches findings from a meta-analysis examining parity and maternal age as risk factors for SGA and preterm birth, however the meta-analysis suggested that young maternal age and/or its interaction with nulliparity largely drove the association with preterm birth [13]. We found no

association between parity ≥3 and adverse outcomes, which differs from the aforementioned meta-analysis. Madheshi ethnic origin was also a risk factor for both preterm birth and SGA, although it had a much stronger association with preterm birth. The Madheshi ethnic group generally belongs to a lower socioeconomic stratum [26], suggesting that the association may be largely driven by underlying socio-economic inequities. Male sex and smoking tobacco during pregnancy were associated with preterm birth, but not with SGA. A combination of maternal nutritional, reproductive, and lifestyle factors was associated with preterm-SGA.

It is well recognized that preterm newborns have increased mortality risk; prematurity as a direct cause contributes to almost a third of all neonatal deaths [27]. However, we found that SGA also had a consistently increased mortality risk through the neonatal and postneonatal periods, albeit generally with a lower magnitude than for preterm births. Preterm birth had a particularly heightened risk in the early neonatal period, but the risk tapered in the post-neonatal period. Those who were born both preterm and SGA generally had the highest mortality risk. Despite the higher mortality risk among preterm babies during the neonatal period compared to SGA babies, the absolute number of SGA births far exceeds preterm births, particularly in South Asia [4]. In our study, roughly 20% were preterm and 55% were SGA. Hence, there is a large absolute burden of infant death associated with SGA and a need to bring attention to these babies.

Among term-SGA and preterm-AGA babies respectively newborns who were LBW had higher risk compared to their non-LBW counterparts. However, babies who were not LBW also experienced about a two-fold increased risk compared with term-AGA infants who are all non-LBW, although the association was not statistically significant. The lack of statistical significance may be largely driven by sample size. These non-LBW SGA or preterm babies may represent a vulnerable population neglected by the commonly used LBW indicator.

While there are distinctions in primary prevention methods for SGA and preterm birth, shared interventions are available for secondary prevention of mortality and morbidity prevention of mortality becuase these two exposures are common. For example, exclusive breastfeeding [5], thermal regulation [28], and infection prevention, diagnosis, and treatment [29] are cross-cutting interventions that could protect SGA and/or from mortality or morbidity. Additionally, a number of interventions have been shown to be efficacious in reducing SGA and LBW. These include balanced energy and protein [22], iron-folic acid [30], and multiple micronutrient supplementation [8] in pregnancy. Although antenatal iron-folic acid use is already an international recommendation in settings with high prevalence of maternal anemia, food and multiple micronutrient supplementation programs are needed to reduce fetal growth restriction in low-income settings where maternal undernutrition is high.

The study conducted active monthly pregnancy surveillance to determine the most accurate gestational age possible based on LMP; however, we expect some misclassification. Also, we had missing weights due to early newborn death or weights deemed unusable because of the time elapsed between birth and weighing. We imputed the weights for the mortality analysis, which reduced bias of those estimates, but increased the uncertainty. We also did not have data on other previously reported risk factors, such as maternal infections [31], birth interval [15], and anemia [32], and limited data on maternal weight in the third trimester, potentially biasing our findings regarding pregnancy weight gain. Finally, the lack of statistical significance in some of the associations reported here may be driven by small sample size.

## Conclusion

Being born preterm has long been associated with high neonatal and infant mortality, but SGA also increases risk consistently throughout infancy. As the burden of SGA is high, especially in South Asia, there is a need to intervene with effective interventions during pregnancy. In designing interventions, it is important to know the incidence of SGA and preterm births and the prevalence of risk factors in specific contexts, and accordingly allocate resources to minimize associated mortality and morbidity burdens.

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## Declaration of interest

The authors report no declarations of interest.

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**Supplementary material avaiable online**

Supplementary Tables S1, S2a and S2b, S3