



Risk Factors and Adverse Perinatal Outcomes among Term and Preterm Infants Born Small-for-Gestational-Age: Secondary Analyses of the WHO Multi-Country Survey on Maternal and Newborn Health

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Abstract

Background: Small for gestational age (SGA) is not only a major indicator of perinatal mortality and morbidity, but also the morbidity risks in later in life. We aim to estimate the association between the birth of SGA infants and the risk factors and adverse perinatal outcomes among twenty-nine countries in Africa, Latin America, the Middle East and Asia in 359 health facilities in 2010–11.

Methods: We analysed facility-based, cross-sectional data from the WHO Multi-country Survey on Maternal and Newborn Health. We constructed multilevel logistic regression models with random effects for facilities and countries to estimate the risk factors for SGA infants using country-specific birthweight reference standards in preterm and term delivery, and SGA's association with adverse perinatal outcomes. We compared the risks and adverse perinatal outcomes with appropriate for gestational age (AGA) infants categorized by preterm and term delivery.

Results: A total of 295,829 singleton infants delivered were analysed. The overall prevalence of SGA was highest in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%), and Japan (16.0%), while the lowest was observed in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%). The risk of preterm SGA infants was significantly higher among nulliparous mothers and mothers with chronic hypertension and preeclampsia/eclampsia (aOR: 2.89; 95% CI: 2.55–3.28) compared with AGA infants. Higher risks of term SGA were observed among sociodemographic factors and women with preeclampsia/eclampsia, anaemia and other medical conditions. Multiparity (≥ 3) (AOR: 0.88; 95% CI: 0.83–0.92) was a protective factor for term SGA. The risk of perinatal mortality was significantly higher in preterm SGA deliveries in low to high HDI countries.

Conclusion: Preterm SGA is associated with medical conditions related to preeclampsia, but not with sociodemographic status. Term SGA is associated with sociodemographic status and various medical conditions.

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Introduction

Small for gestational age (SGA) refers to infants whose size and weight is less than the average range for infants of the same gestational age. GA is not only a major indicator of perinatal

mortality and morbidity [1,2], but also increases the risk of chronic diseases such as cardiovascular disease and diabetes or developmental outcomes later in life [3,4]. In a UK population-based cohort study from 1997 to 2003, 43% of stillbirths were related to SGA [5]. Among 135 million infants born in low- and middle-income

countries (LMICs) in 2010, it is estimated that 29.7 million (22%) were born term-SGA, 10.9 million (8.1%) were born preterm appropriate-for-gestational-age (AGA), and 2.8 million (2.1%) were born preterm-SGA [6]. However, it is a great challenge to define SGA in various ethnic groups in an international comparative study. Based on the secondary analysis using 20 cohort studies for national and regional estimates of SGA babies, 62% of SGA deliveries occurred in India, and 56% occurred in Nepal [7]. This overestimation arose due to the use of the Alexander reference in the analysis, which adapted very high-income country group (US) data from 1991 to low- and middle-income countries. The country-specific birth reference was required to avoid an under- or overestimate of SGA status, especially in low- and middle-income countries. Birthweight references based on neonatal birthweight at each gestational week have been used for nearly 50 years. This type of reference is not so effective under diagnosis in the early gestational weeks, especially for preterm SGA. Therefore, ultrasound-based estimated references of fetal weight are more suitable to overcome this problem. Mikolajczyk developed an ultrasound-based generic global reference to measure fetal weight and birthweight in low-, middle- and high-income settings [8]. Although this country-specific reference has already been used in a previous study to define macrosomia for international comparison [9], our study is the first to use this global reference to define SGA for international comparison.

The cause of SGA is multifactorial, and comprised of maternal, placental, fetal or environmental factors. Identified maternal factors of SGA include demographic variables and medical conditions, such as maternal age [10,11], nulliparity [11,12], cigarette smoking [12–15], short stature [12], caffeine intake [16], low or high maternal body mass index (BMI) [10], hypertension and preeclampsia [11,12,17], psychosocial stress [15], and socioeconomic status, including education [14,17–20]. Conflicting evidence exists for increased [21–23] or decreased [24,25], or unchanged [26,27] neonatal mortality and morbidity rates for preterm SGA compared with preterm AGA. Risk factors, interventions and sequelae for preterm SGA might differ from term SGA. Despite the high prevalence of SGA, only a limited number of studies exist due to a lack of gestational age data, especially in LMICs. Furthermore, few studies have considered risk factors for SGA in preterm and term deliveries compared with preterm AGA [10,23,28]. Therefore, we aimed to explore trends and risk factors associated with SGA and its mortality in preterm and term deliveries across multiple low- to very high- income countries by taking advantage of the WHO Multi-country Survey on Maternal and Newborn Health data, which covers 29 low- to very high-income countries globally.

Methods

This is a secondary data analysis of the WHO Multi-country Survey on Maternal and Newborn Health, which was conducted in 359 health facilities across 29 countries in Africa, Asia, Latin America and the Middle East. Methodological details of this survey have been published elsewhere [29,30]. In brief, a multistage cluster sampling method was used to obtain samples of health facilities in two provinces and each capital city of the 29 randomly selected countries. All women admitted for delivery plus all women with severe maternal outcomes regardless of gestational age were recruited in the study. Individual data on demographics and reproductive characteristics, medical conditions during pregnancy, birth outcomes, and complications were collected from the participants' medical records. Health facility capacity data were obtained, such as the capabilities of essential and

comprehensive obstetric and neonatal healthcare services, laboratory tests, and human resources and training. The study was implemented concurrently in 29 countries over two to four months from May 2010 to December 2012.

Study population and statistical analysis

The study population was restricted to pregnancies of at least 28 gestational weeks for comparability of viable gestational age between countries, and singleton births with no congenital malformation. We excluded deliveries with missing data on birthweight, gestational age, and infant gender, as well as pregnancies that lasted less than 22 weeks or more than 42 weeks with congenital malformation.

To overcome the existing deficiency in birthweight references in LMICs, and taking into account birthweight variations across countries, we adopted methodology to generate local (country-specific) fetal weight and birthweight references developed by Mikolajczyk et al. [8].

To generate a country weight-reference standard, first we used the mean birthweight for infants born to married mothers aged 20–34 years with schooling years ≥ 12 , who had no pregnancy complications, and who vaginally delivered singleton infants with no complications at 40 completed weeks of gestation (40 weeks+0 days to 40 weeks+6 days). Next, we based the birthweight (mean and SD) reference on a gestational age of 40 weeks, and we obtained the mean fetal-weight and percentiles across each gestational week for all countries participating in this study. We defined SGA as a birthweight below the 10th percentile, AGA as between the 10th and 90th percentiles and large-for-gestational age (LGA) as above the 90th percentile at the gestational ages of 28 to 41 weeks by infant gender. The study population was restricted to deliveries with a birthweight below the 90th percentile, excluding LGA due to the condition's high risk of adverse birth outcomes.

We considered the following variables as exposures at the individual level and further categorized them as shown in tables: maternal age defined as completed years at the time of delivery; marital status; years of education, parity; presence of chronic hypertension, preeclampsia or eclampsia, severe anaemia with haemoglobin < 7 mg/dl, malaria or dengue, HIV or AIDS and other conditions defined as the presence of disease or injury affecting the heart, lungs, liver and kidneys. Additionally, we adjusted our analysis for facility capacity and the human development index (HDI). Facility capacity was used in previous studies and is defined as the total score of essential and additional services provided by health facilities with further categorization into high, medium and low capacity [31]. The human development index (HDI) for each country was adopted from 2012 UN development program estimates [32].

Perinatal outcomes considered in the study were fresh stillbirths (excluding macerated stillbirths), early neonatal death, perinatal death (both fresh stillbirth and early neonatal death) and neonatal near miss [33]. Neonatal near miss is defined as a neonate who survived a life-threatening condition and presented with any of the following conditions: any intubation at birth or anytime within the first week of life, nasal continuous positive airway pressure, surfactant administration, cardiopulmonary resuscitation (cardiac massage), any surgery, or use of any vasoactive drug, anticonvulsants, phototherapy in the first 24 hours, steroids to treat refractory hypoglycaemia, or therapeutic intravenous antibiotics. Early neonatal deaths were defined as intra-hospital deaths that occurred on or before the seventh day after delivery.

Table 1. Birthweight and proportion of SGA by country.

HDI group	Country (by rank)	Total number of deliveries	Birthweight [mean (SD)]	Small for gestational age (SGA)			
				All [n (%)]	Gestational age (weeks) [n (%)]	37–41	
Very high	Japan	3,391	2975.3 (397.8)	543 (16.0)	2 (9.5)	27 (18.1)	514 (15.9)
	Qatar	3,744	3285.8 (477.2)	453 (12.1)	3 (42.8)	15 (10.5)	435 (12.1)
High	Argentina	9,416	3320.7 (516.7)	1,239 (13.2)	40 (50.6)	122 (25.4)	1,077 (12.5)
	Mexico	12,759	3054.3 (508.3)	1,669 (13.1)	69 (31.9)	234 (25.3)	1,366 (11.8)
	Lebanon	3,826	3175.5 (478.7)	384(10.0)	10 (23.8)	32 (14.3)	342 (9.6)
	Peru	14,450	3310.3 (521.8)	2,120 (14.7)	68 (40.9)	208 (31.2)	1,844 (13.5)
	Brazil	6,729	3161.0 (529.5)	964 (14.3)	39 (33.9)	116 (21.7)	809 (13.3)
	Ecuador	9,810	3070.1 (493.3)	1,335 (13.6)	45 (39.1)	121 (23.9)	1,169 (12.7)
	Sri Lanka	17,530	2925.5 (464.6)	2,249 (12.8)	37 (26.8)	194 (17.8)	2,018 (12.4)
	Jordan	1,066	3119.2 (542.6)	127 (11.9)	5 (27.7)	13 (15.3)	109 (11.3)
	China	12,780	3277.5 (468.4)	1,303 (10.2)	17 (17.5)	78 (12.8)	1,208 (10.0)
	Thailand	8,687	3062.1 (467.8)	841 (9.7)	19 (18.8)	68 (9.1)	754 (9.6)
Medium	Mongolia	7,095	3390.1 (502.0)	711 (10.0)	20 (25.6)	43 (16.9)	648 (9.6)
	OPT	884	3221.3 (502.6)	142 (16.1)	4 (44.4)	15 (27.3)	123 (15.0)
	Paraguay	3,492	3276.6 (535.2)	369 (10.6)	13 (36.1)	41 (18.5)	315 (9.7)
	Philippines	10,120	2923.9 (490.4)	1,520 (15.0)	40 (21.6)	139 (24.0)	1,341 (14.3)
	Vietnam	14,803	3185.3 (430.9)	2,141 (14.5)	15 (29.4)	91 (24.5)	2,035 (14.2)
	Nicaragua	6,231	3043.2 (496.3)	755 (12.1)	27 (26.0)	73 (18.2)	655 (11.4)
	India	30,034	2652.3 (494.3)	3,416 (11.4)	95 (11.6)	366 (14.8)	2,955 (11.1)
	Cambodia	4,525	3001.4 (481.2)	852 (18.8)	12 (11.7)	45 (31.0)	795 (18.6)
	Kenya	18,676	3067.3 (537.2)	2,637 (14.1)	99 (20.9)	251 (23.5)	2,287 (13.3)
	Pakistan	12,656	2945.5 (501.2)	1,316 (10.4)	54 (22.5)	173 (17.3)	1,089 (9.6)
Low	Angola	9,781	3140.8 (515.0)	1,083 (11.1)	19 (7.4)	24 (8.6)	1,050 (11.2)
	Nigeria	11,048	3126.7 (529.5)	1,247 (11.3)	60 (26.5)	110 (13.7)	1,077 (10.8)
	Nepal	10,474	2888.6 (493.7)	1,874 (17.9)	20 (14.0)	130 (27.5)	1,724 (17.5)
	Uganda	8,522	3227.8 (501.5)	566 (6.6)	23 (23.9)	59 (16.3)	484 (6.0)
	Afghanistan	24,932	3174.7 (455.8)	1,187 (4.8)	35 (14.4)	26 (9.8)	1,126 (4.6)
	DRC	7,631	3013.2 (514.1)	1,037 (13.6)	12 (8.4)	62 (8.9)	963 (14.2)
	Niger	10,737	3098.2 (496.2)	1,679 (15.6)	23 (43.4)	36 (38.7)	1,620 (15.3)
	All countries	295,829	3067.3 (527.5)	35,759 (12.1)	915 (21.8)	2,912 (18.6)	31,932 (11.6)

Numbers shown are for singleton births with gestational age 28 to 41 completed weeks.

OPT = Occupied Palestinian Territory; DRC = Democratic Republic of Congo.

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Statistical analysis

We divided our sample into two groups by gestational age: preterm (<37 weeks gestational age) and term (37–41 weeks gestational age) deliveries. The characteristics and outcomes of SGA compared to AGA infants in these groups were analysed separately. We compared preterm SGA vs preterm AGA, term SGA vs term AGA.

We performed the Chi-square test by taking into account the clustering and probability-sampling effects of the survey design. Also, after considering the study sampling design and clustering effects (health facility and country) on individual outcomes, we constructed multilevel logistic regression models with random effects for three levels: individual, facility and country. In our analyses of the association between SGA and fresh stillbirths and early neonatal death, we adjusted for maternal age, marital status, education, parity, medical conditions during pregnancy such as chronic hypertension, preeclampsia/eclampsia, severe anaemia, malaria/dengue and HIV/AIDS at the individual level, and capacity of health facilities at the facility level by four categorised HDI groups. The categories comprised as follows: very high HDI countries included Japan, Qatar and Argentina; high HDI countries included Mexico, Lebanon, Peru, Brazil, Ecuador and Sri Lanka; medium HDI countries included Jordan, China, Thailand, Mongolia, the Occupied Palestinian Territory, Paraguay, Philippines, Vietnam, Nicaragua, India and Cambodia, and low HDI countries included Kenya, Pakistan, Angola, Nigeria, Nepal, Uganda, Afghanistan, the Democratic Republic of Congo and Niger. In the ‘overall category’, we adjusted three-level structure random effects regression models to obtain odds ratios (ORs): individual (level 1), facility (level 2) and country (level 3).

Statistical analysis was conducted using Stata/MP version 12.0 (Stata Corp LP, College Station, Texas) and a *P*-value < 0.05 was considered statistically significant.

Ethics committee approval

The HRP Specialist Panel on Epidemiological Research reviewed and approved the study protocol for technical content. This study was approved by the WHO Ethical Review Committee and the relevant ethical clearance mechanisms in all countries. Written consent from individual participants was not required, although patient records was anonymized and de-identified prior to analysis.

Results

The WHO Multi-country Survey on Maternal and Newborn Health collected a total of 314,623 women’s data from 359 health facilities in 29 countries. Excluded from the analysis were deliveries with missing gestational age and birthweight (5,392), pregnancies that lasted less than 28 weeks or more than 42 weeks (6,191); multiple births (4,579), infants with congenital malformation (2,041) and missing infant gender (255). After the exclusions were made, a total of 295,829 deliveries were retained in the analysis. Table 1 presents the mean birthweight and the prevalence of SGA by each country. The overall prevalence of SGA was highest in Cambodia (18.8%), Nepal (17.9%), the Occupied Palestinian Territory (16.1%), and Japan (16.0%), while the lowest was observed in Afghanistan (4.8%), Uganda (6.6%) and Thailand (9.7%). With further exclusion of LGA infants, the sample size was reduced to 245,77, consisting of 210,047 (85.5%) AGA and 35,726 (14.5%) SGA infants, including 3,827 (26.6%) preterm SGA and 31,932 (13.8%) term SGA, respectively. Table 2 indicates rates of SGA by maternal and neonatal characteristics in preterm and

term deliveries. The rates of both preterm and term SGA deliveries were consistently high across HDI groups.

Table 3 shows risk factors for SGA in preterm and term deliveries. The risk factors of delivering preterm SGA infants were significantly higher compared to AGA risk factors among nulliparous women (adjusted odds ratio [AOR]: 1.17; 95% CI: 1.06–1.29), and women with chronic hypertension (AOR: 1.68; 95% CI: 1.22–2.30) and preeclampsia/eclampsia (AOR: 2.89; 95% CI: 2.55–3.28). Higher risks of term SGA compared with term AGA were observed among younger (AOR: 1.09; 95% CI: 1.04–1.14) and older women (AOR: 1.07; 95% CI: 1.02–1.13), single women (AOR: 1.11; 95% CI: 1.06–1.17), women with 1–6 years of education (AOR: 1.55; 95% CI: 1.46–1.65), nulliparous women (AOR: 1.45; 95% CI: 1.41–1.50), and women with preeclampsia/eclampsia (AOR: 2.05; 95% CI: 1.88–2.23), anaemia (HB < 7 mg/dl) (AOR: 1.30; 95% CI: 1.15–1.47), HIV/AIDS (AOR: 1.48; 95% CI: 1.22–1.80), and other medical conditions (AOR: 1.47; 95% CI: 1.24–1.74). Multiparity (> = 3) (AOR: 0.88; 95% CI: 0.83–0.92) was a protective factor for term SGA and, after adjusting for variables, country HDI had no significant association.

Prevalence of adverse perinatal outcomes for SGA by gestational weeks in each HDI country group is presented in Table 4. We observed a significant trend of higher mortality rates in SGA and all deliveries for lower HDI countries (*P* < 0.001).

The association between SGA deliveries and fresh stillbirths, neonatal near miss, early neonatal deaths, and perinatal deaths compared with AGA deliveries by HDI country group are presented in Table 5 and are stratified by preterm and term delivery. For preterm and term SGA, very high HDI countries had no significant increase in fresh stillbirth, early neonatal mortality and perinatal mortality, although low to high HDI countries had risks two to four times higher than preterm AGA. For neonatal near miss, both preterm and term SGA deliveries had 1.7 to 2.7 times significantly higher risk than AGA, although preterm SGA had a higher prevalence of near miss (50% to 80% among neonates of less than 32 weeks’ gestation) than term SGA, irrespective of HDI countries.

Discussion

Main findings

We determined the maternal risk factors and adverse perinatal outcomes in preterm- and term-SGA infants in 29 countries globally using a large multi-country dataset. After adjusting for country-, facility- and individual-level effects, we found no association between increased risks of preterm SGA and socio-demographic status, such as age or education, compared with preterm AGA; however, we did observe that nulliparity and medical conditions, such as chronic hypertension and preeclampsia/eclampsia, were significantly associated with increased risks of preterm SGA compared with preterm AGA.

Strengths and limitations

To the best of our knowledge, this is the most current and extensive multi-country study to compare and examine risk factors and their adverse outcomes in preterm SGA and term SGA deliveries compared with preterm and term AGA deliveries using country-specific generic references. We used SGA criteria that incorporates country-specific reference standards developed by Mikolajczyk et al. [8]. This generic, global reference for fetal-weight and birthweight percentiles is more effective in predicting adverse perinatal outcomes compared with non-customised fetal-weight references, and is easier to use than the customised fetal-

Table 2. Maternal and neonatal characteristics.

	Preterm delivery (≤ 36 weeks)		p value	Term delivery (≥ 37 weeks)		p value
	Total deliveries	SGA [n (%)]		Total deliveries	SGA [n (%)]	
All deliveries	14,360	3,827 (26.6)		231,413	31,899 (13.8)	
Age						
<20	1,840	530 (28.8)	p<0.05	25,283	4,508 (17.8)	p<0.001
20–34	10,608	2,753 (25.9)		179,550	24,132 (13.4)	
≥ 35 -	1,912	544 (28.4)		26,580	3,292 (12.3)	
Marital status						
Single	1,684	520 (30.8)	p<0.01	24,077	4,122 (17.1)	p<0.001
Married	12,570	3,277 (26.1)		205,625	27,585 (13.4)	
Education, years						
0	1,936	485 (25.0)	0.466	34,276	4,163 (12.1)	p<0.001
1–6	1,948	501 (25.7)		30,242	4,850 (16.0)	
7–9	2,988	776 (25.9)		44,161	6,386 (14.5)	
10–12	4,234	1,176 (27.8)		67,652	9,852 (14.6)	
>12	2,082	584 (28.1)		37,896	4,641 (12.2)	
Parity						
0	6,766	1,889 (27.9)	p<0.05	102,653	16,831 (16.4)	p<0.001
1–2	5,617	1,420 (25.3)		93,762	11,354 (12.1)	
≥ 3	1,958	511 (26.1)		34,696	3,681 (10.6)	
Mode of delivery						
Vaginal	8,801	2,109 (23.9)	p<0.001	169,114	23,157 (13.7)	0.298
Caesarean	5,538	1,708 (30.8)		62,022	8,709 (14.0)	
Medical conditions						
Chronic hypertension	228	96 (42.1)	p<0.001	703	134 (19.1)	p<0.001
Pre-/eclampsia	1,680	781 (46.5)	p<0.001	4,207	1,031 (24.5)	p<0.001
Anaemia (HB<7 mg/dl)	608	210 (34.5)	p<0.01	2,791	512 (18.3)	p<0.001
Malaria/dengue	55	17 (30.9)	0.540	193	46 (23.8)	p<0.001
HIV/AIDs	99	26 (26.3)	0.935	845	161 (19.1)	p<0.001
Others	318	115 (36.2)	p<0.01	1,221	218 (17.8)	p<0.001
Infant gender						
Male	7,605	1,994 (26.2)	0.248	118,483	15,856 (13.4)	p<0.001
Female	6,755	1,833 (27.1)		112,930	16,043 (14.2)	
Apgar score at 5 minutes <7	1,253	502 (40.1)	p<0.001	4,503	1051 (23.3)	p<0.001
Country HDI						
Very high	768	209 (27.2)	p<0.001	13,725	1,993 (14.5)	p<0.05
High	3,736	1,173 (31.4)		51,470	7,548 (14.7)	
Medium	5,443	1,239 (22.8)		76,203	10,938 (14.4)	
Low	4,13	1,206 (27.3)		90,015	11,420 (12.7)	
Facility capacity						
High	5,053	1,390 (27.5)	0.245	60,857	8,435 (13.8)	0.119
Medium	5,349	1,470 (27.5)		92,575	11,970 (12.9)	
Low	2,552	596 (23.4)		48,288	7,274 (15.1)	

Other medical conditions were included, such as chronic or acute injury or disorders affecting the heart, lungs, liver and kidneys (including pyelonephritis).
 Chi-square *p*-values adjusted for survey design.
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weight reference. A large sample size and the use of standardized questionnaires across countries allowed us to examine outcomes and stratify countries by five HDI groups.

Our study has several limitations. First, the quality of the data, especially birthweight and gestational age, is questionable in some countries. Errors might occur in dating the pregnancy, especially in countries where gestational age is based on the last menstrual

Table 3. Risk factors for SGA.

	Preterm delivery (≤ 36 weeks)			Term delivery (≥ 37 weeks)		
	OR	AOR	95% CI	OR	AOR	95% CI
Age						
<20	1.15*	1.04	(0.89–1.20)	1.39***	1.09	(1.04–1.14)***
20–34	reference					
≥ 35 -	1.13*	1.08	(0.94–1.24)	0.91**	1.07	(1.02–1.13)**
Marital status						
Single	1.27**	1.15	(0.98–1.34)	1.33***	1.11	(1.06–1.17)***
Married	reference					
Education, years						
0	0.85	1.07	(0.88–1.31)	0.99	1.50	(1.41–1.61)***
1–6	0.88	1.03	(0.86–1.23)	1.37***	1.55	(1.46–1.65)***
7–9	0.89	1.01	(0.86–1.19)	1.21***	1.34	(1.27–1.41)***
10–12	0.98	1.02	(0.89–1.18)	1.22***	1.22	(1.17–1.28)***
>12	reference					
Parity						
0	1.14**	1.17	(1.06–1.29)**	1.42***	1.45	(1.41–1.50)***
1–2	reference					
≥ 3	1.04	0.96	(0.83–1.12)	0.86***	0.88	(0.83–0.92)***
Medical conditions						
Chronic hypertension	2.02***	1.68	(1.22–2.30)**	1.47***	1.20	(0.96–1.49)
Preeclampsia/eclampsia	2.75***	2.89	(2.55–3.28)***	2.06***	2.05	(1.88–2.23)***
Anaemia (HB<7 mg/dl)	1.48***	1.24	(0.99–1.56)	1.41***	1.30	(1.15–1.47)***
Malaria/dengue	1.23	1.16	(0.58–2.32)	1.96***	1.26	(0.83–1.92)
HIV/AIDs	0.98	0.85	(0.50–1.44)	1.47***	1.48	(1.22–1.80)***
Others medical conditions	1.58**	1.24	(0.92–1.67)	1.36**	1.47	(1.24–1.74)***
Country HDI						
Very high	reference					
High	1.22	1.23	(0.64–2.34)	1.01	0.79	(0.39–1.59)
Medium	0.78*	0.88	(0.47–1.63)	0.98	0.85	(0.51–1.44)
Low	1.01	1.28	(0.68–2.42)	0.85*	0.61	(0.37–1.02)

Other medical conditions were included, such as chronic or acute injury or disorders affecting the heart, lungs, liver and kidneys (including pyelonephritis).

SGA = small-for-gestational age; HDI = Human Development Index; OR = odds ratio; AOR = adjusted odds ratio. Three-level structure random effects regression models were used to obtain ORs: individual (level 1), facility (level 2) and country (level 3).

*** $p < 0.001$ ** $p < 0.01$ * $p < 0.05$.

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period or where the birthweight is rounded up or down by a full 100 g. Due to this limitation, we focused on identifying the risk factors of SGA rather than focusing on SGA prevalence in each country.

Another limitation is a lack of data on maternal characteristics that have been noted in previous studies to be associated with the delivery of SGA infants, including smoking, alcohol and caffeine intake, maternal BMI, malnutrition, gestational weight gain, maternal stature, psychosocial stress, interpregnancy interval, and previous history of miscarriage [10–16]. Lack of adjustment for these variables may have led to an overestimation of the risk of SGA delivery, especially for women of a younger or older age, with less education or in low HDI-scoring countries.

Lastly, by using multilevel multiple regression analysis we were able to generalize our findings among facility-based settings; however, adverse perinatal outcomes and maternal medical conditions may have been overestimated because only the most

severe cases are presented in higher-level facilities. Furthermore, the risk of neonatal mortality and morbidity could be underestimated due to the 7-day period in this study for neonatal follow-up. It should be noted that mortality due to infections, necrotising enterocolitis and other complications may occur after this period. Thus, the outcomes and conditions cannot be considered representative of the general population.

Interpretation

Our results suggest that nulliparity, chronic hypertension and preeclampsia/eclampsia are associated with a higher risk of preterm SGA. This result is consistent with other studies [18,34]. In a national birth cohort study in Denmark, Catov et al. found that risk of preterm SGA increased 5.5 (95% confidence interval [CI] 3.2–9.4) times and term SGA increased 1.5 (95% CI 1.0–2.2) times among women with chronic hypertension [34]. The result is also consistent with the findings of Villar et al. who analysed data

Table 4. Prevalence of fresh stillbirths and early neonatal mortality by HDI country groups.

Outcome	SGA [n/N (%)]	HDI country group [n/N (%)]				p-value
		Very High	High	Medium	Low	
Fresh stillbirth						
All deliveries	2458/244382 (1.0)	31/14426 (0.2)	183/55096 (0.3)	578/81251 (0.7)	1666/93578 (1.8)	p<0.001
SGA deliveries						
≤32	144/797 (18.1)	3/44 (6.8)	20/248(8.1)	41/243 (16.9)	80/262 (30.5)	p<0.001
33–36	169/2748 (6.2)	3/160 (1.9)	27/890 (3.0)	55/920 (6.0)	84/778 (10.8)	p<0.001
≥37	520/31585 (1.7)	3/1987 (0.2)	31/7529 (0.4)	133/10837 (1.2)	353/11232 (3.1)	p<0.001
Neonatal near miss						
All live deliveries	11436/228831 (4.8)	454/14417 (3.2)	3210/54736 (5.9)	4550/80108 (5.7)	3222/91006 (3.5)	p<0.001
SGA deliveries						
≤32	355/484 (73.4)	32/40 (80.0)	160/201 (79.6)	115/145 (79.3)	48/98 (49.0)	p = 0.003
33–36	1011/2419 (41.8)	49/155 (31.6)	396/837 (47.3)	358/801 (44.7)	208/626 (33.2)	p = 0.019
≥37	1889/30785 (6.1)	58/1982 (2.9)	441/7480 (5.9)	826/10603 (7.8)	564/10720 (5.3)	p = 0.016
Early neonatal death						
All live deliveries	1534/241924 (0.6)	19/14426 (0.1)	160/54913 (0.3)	514/80673 (0.6)	841/91912 (0.9)	p<0.001
SGA deliveries						
≤32	162/653 (24.8)	1/41 (2.4)	23/228 (10.1)	56/202 (27.7)	82/182 (45.1)	p<0.001
33–36	152/2579 (5.9)	2/157(1.3)	23/863 (2.7)	61/865 (7.1)	66/694 (9.5)	p<0.001
≥37	267/31065 (0.9)	3/1984 (0.2)	15/7498 (0.2)	93/10704 (0.9)	156/10879 (1.4)	p<0.001
Perinatal death						
All deliveries	3992/244382 (1.6)	50/14457 (0.4)	343/55096 (0.6)	1092/81251 (1.3)	2507/93578 (2.7)	p<0.001
SGA deliveries						
≤32	306/797 (38.4)	4/44 (9.9)	43/248 (17.3)	97/243 (39.9)	162/262 (61.8)	p<0.001
33–36	321/2748 (11.7)	5/160 (3.1)	50/890 (5.6)	116/920 (12.6)	150/778 (19.3)	p<0.001
≥37	787/31585 (2.5)	6/1987 (0.3)	46/7529 (0.6)	226/10837 (2.1)	509/11232 (4.5)	p<0.001

SGA = small-for-gestational age; HDI = Human Development Index Chi-square p-values adjusted for survey design.
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from WHO antenatal care trials and observed that nulliparity, chronic hypertension and obesity are also risk factors for preeclampsia in developing countries, but not low socioeconomic status [18]. Preeclampsia may cause an inadequate vascular response to abnormal placentation in pregnancy and may represent a distinct pathogenesis, which might affect fetal growth [6,35]. Increased risk screening in antenatal care visits and referral to higher facilities for high-risk cases at an earlier stage in the pregnancy may help to reduce the incidence of severe preeclampsia or eclampsia.

We found that sociodemographic factors such as age, marital status and education were not significantly associated with the risk of preterm SGA, but sociodemographic status factors were related to term SGA. The results indicated that preterm SGA deliveries are more likely to be related to a maternal medical condition, especially preeclampsia, which tends to terminate the pregnancy earlier. On the other hand, term SGA may be more significantly relevant to lifestyle factors, such as sociodemographic status, malnutrition or other factors, and various medical conditions such as anaemia, HIV/AIDS and others. Our results are consistent with other studies that have observed a significant increased risk of term SGA associated with maternal age [10,11] and nulliparity [11,12]. Previous studies confirm that sociodemographic status is associated with a greater risk of SGA, although these studies did not divide SGA by preterm and term delivery [15,36]. Berg et al. conducted path analysis to examine the relationship between

maternal education and SGA using population-based cohort study data and showed that a significantly increased risk of SGA delivery among women with less education was related foremost to maternal smoking and, to some degree, to maternal height [15]. A population-based case-control study using Finnish birth register data also confirmed that between high and low socioeconomic status groups, 50% of the difference in risk of SGA was due to smoking [36].

Very high HDI countries showed no significant increase in the mortality risk for preterm and term SGA deliveries. This might be explained by the high quality of intrapartum care including access to care, human resources and drugs or medical equipment in very high HDI countries, which could reduce the mortality risk for preterm and term SGA deliveries. However, low to high HDI countries had risks two to four times higher compared to preterm AGA. These results are consistent with the population-based secondary analysis conducted in 20 cohorts in LMICs by the Child Health Epidemiology Reference Group (CHERG), which showed that the risk of early neonatal mortality increased about 16 times for preterm SGA delivery compared with preterm non-SGA delivery [37]. The reason for these different degrees of mortality risk might be due to the definition of SGA used by the authors, which they adapted from the US population birthweight reference standard and applied to LMICs. Another population-based cohort study in France showed that the risk of stillbirth was 2.6 times higher in preterm SGA deliveries, which is a similar result to our

Table 5. The association between SGA and perinatal outcomes compared with AGA by HDI country groups.

HDI group	Preterm delivery (≤ 36 weeks)		Term delivery (≥ 37 weeks)		All deliveries	
	AOR	95% CI	AOR	95% CI	AOR	95% CI
Fresh stillbirth						
Very high	0.31	(0.06–1.76)	1.79	(0.29–10.9)	1.46	(0.47–4.51)
High	2.31	(1.36–3.93)**	3.00	(1.75–5.12)***	3.70	(2.56–5.33)***
Medium	2.18	(1.62–2.96)***	3.08	(2.43–3.89)***	2.97	(2.47–3.56)***
Low	1.99	(1.54–2.57)***	2.89	(2.47–3.37)***	3.07	(2.69–3.51)***
Overall [§]	2.01	(1.66–2.42)***	2.95	(2.60–3.36)***	3.07	(2.77–3.41)***
Neonatal near miss						
Very high	2.34	(1.47–3.71)***	1.65	(1.13–2.42)**	2.61	(2.02–3.37)***
High	2.60	(2.17–3.11)***	1.69	(1.48–1.93)***	2.47	(2.24–2.71)***
Medium	2.32	(1.98–2.74)***	2.38	(2.17–2.61)***	2.43	(2.26–2.63)***
Low	2.43	(1.97–2.99)***	1.75	(1.57–1.95)***	2.03	(1.85–2.23)***
Overall [§]	2.65	(2.37–2.96)***	1.99	(1.87–2.12)**	2.39	(2.27–2.51)***
Early neonatal death						
Very high	1.19	(0.25–5.74)	1.39	(0.15–12.32)	2.14	(0.67–6.94)
High	3.77	(1.97–6.47)***	2.14	(1.09–4.20)*	3.92	(2.57–5.97)***
Medium	2.77	(2.08–3.68)***	3.44	(2.61–4.56)***	3.56	(2.93–4.32)***
Low	2.92	(2.21–3.83)***	2.94	(2.37–3.63)***	3.53	(3.00–4.16)***
Overall [§]	2.86	(2.36–3.46)***	3.01	(2.56–3.56)***	3.52	(3.12–3.96)***
Perinatal death						
Very high	0.69	(0.22–2.16)	1.78	(0.46–6.82)	1.76	(0.78–3.99)
High	2.89	(1.94–4.31)***	2.63	(1.73–3.99)***	3.80	(2.88–5.02)***
Medium	2.61	(2.10–3.25)***	3.27	(2.72–3.92)***	3.29	(2.88–7.77)***
Low	2.51	(2.06–3.06)***	2.92	(2.58–3.32)***	3.31	(2.98–3.67)***
Overall [§]	2.50	(2.17–2.87)***	3.00	(2.71–3.32)***	3.31	(3.06–3.59)***

The reference category is infants with a birthweight that is appropriate for gestational age in each subgroup analysis.

SGA = small-for-gestational age; AGA = appropriate-for-gestational age; HDI = Human Development Index, AOR = adjusted odds ratio.

Two-level structure random effects regression models were used to obtain ORs: individual (level 1) and facility (level 2). Adjusted for maternal age, marital status, education, parity, medical conditions during pregnancy such as chronic hypertension, preeclampsia/eclampsia, severe anaemia, malaria/dengue, HIV/AIDS at the individual level, and capacity of health facilities at the facility level.

[§]Three-level structure random effects regression models were used to obtain ORs: individual (level 1), facility (level 2) and country (level 3). Same adjustment at individual and facility level and additional adjustment for country HDI at the country level.

***p<0.001 **p<0.01 *p<0.05.

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overall mortality risks [38]. Simchen et al. found that singleton preterm SGA infants had a significantly higher mortality rate with more culture-proven sepsis episodes [23].

In our findings, the risk of mortality in both preterm and term SGA deliveries was higher compared to preterm and term AGA, respectively, in low to high HDI countries. However, very high HDI countries had no significant mortality difference between preterm SGA and AGA, but had higher risks of mortality for term SGA, especially in fresh stillbirths.

Our findings indicate that if LMICs give appropriate care comparable with very high HDI countries, such as including regular risk screening in antenatal care visits and providing adequate treatment and care to those who need treatment at an earlier stage, it might be possible to decrease perinatal mortality among preterm SGA infants. Term SGA infants were three to four times significantly more likely to experience perinatal mortality than term AGA infants, irrespective of HDI groups. This finding supports Lubchenco's report from 1976, which found that the risk of neonatal mortality was six times more likely in term SGA infants compared with term AGA infants [39]. Risk of perinatal mortality

is significantly higher among term SGA deliveries compared with preterm AGA deliveries, irrespective of quality of care.

Neonatal near miss is higher risk, irrespective of HDI, although it has a high prevalence in neonates born at less than 32 weeks' gestation. In very high HDI countries, 80% of neonates born at less than 32 gestational weeks experienced neonatal near miss, although perinatal mortality was around 11%. In low HDI countries, 49% of neonates born at less than 32 gestational weeks experienced neonatal near miss, and 70% of them died. The quality of neonatal intensive care is vital to prevent mortality.

Neonatal clinical management should be considered in the development of health policies for reducing neonatal mortality, such as screening high-risk neonates for early complications and the referral of pregnant women with hypertensive diseases for delivery in health facilities with special care units. Careful follow-up is necessary for SGA neonates who are at a higher risk of acquiring non-communicable diseases in the future.

Further research could define SGA using the customized rather than standard intrauterine growth curves, especially for countries that adopt curves based on populations from diverse ethnic

groups. Ideally the standard questionnaire should include variables such as weight gain during pregnancy and pre-pregnancy BMI.

Conclusion

Our results demonstrate that preterm SGA is associated with medical conditions related to chronic hypertension and preeclampsia/eclampsia, but is not associated with sociodemographic status. This result clearly identified that global prevention for preterm SGA should mainly focus on preeclampsia. Term SGA is associated with sociodemographic status and various medical conditions. Risk of fresh stillbirth and neonatal death was two to three times higher in preterm SGA in LMICs, except in the very high HDI group. Term SGA was significantly associated with perinatal deaths irrespective of HDI categories.

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Further information on the Multi-country Survey on Maternal and Newborn Health and derivatives can be found at: http://www.who.int/reproductivehealth/topics/maternal_perinatal/nearmiss

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Conceived and designed the experiments: EO TG. Performed the experiments: JPS RM. Analyzed the data: TG EO. Contributed reagents/materials/analysis tools: EO. Wrote the paper: EO. Contributed to the interpretation of the analysis and reviewed the manuscript: NM JPV CP EOP. Reviewed and approved final version of the manuscript: EO TG NM JPV CP EO JPS RM.

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