OBSTETRICS

Small for gestational age subgroups have differential morbidity, growth, and neurodevelopment at age 2: the INTERBIO-21st Newborn Study

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BACKGROUND: Small for gestational age is a complex perinatal syndrome associated with increased neonatal morbidity, mortality, and impaired childhood growth and neurodevelopment. Current classifications rely primarily on birthweight, which does not capture the heterogeneity of the condition nor predict long-term health outcomes. Here we aim to identify and characterize distinct small for gestational age subgroups and assess their neonatal and early childhood health trajectories.

OBJECTIVE: To refine the classification of small for gestational age by identifying subgroups based on maternal, fetal, and environmental factors and evaluating their associations with neonatal morbidity, growth, and neurodevelopment at age 2.

STUDY DESIGN: Prospective cohort study. In six countries worldwide, between 2012 and 2018, the INTERBIO-21st Study enrolled small for gestational age and non-small for gestational age newborns defined by the <10th centile of international standards with moderate (≥third—<10th centile) and severe (<third centile) small for gestational age subgroups; we assessed their growth, health, nutrition, motor development, and neurodevelopment up to age 2. We used 2-step cluster analysis to identify small for gestational age subgroups, and a probabilistic approach to choose the optimal subgroup model based on a statistical measure of fit. We performed logistic regression analysis (odds ratio; 95% confidence interval) to assess health and development outcomes among subgroups using the non-small for gestational age as reference group, adjusting for key confounders.

RESULTS: We enrolled 5153 non-small for gestational age and 1549 small for gestational age newborns: moderate (≥third—<10th centile) small for gestational age=947 and severe (<third centile) small for gestational age=602. We identified 9 small for gestational age subgroups: "no main condition detected" (29.0%); "previous low birthweight or preterm birth" (14.6%); "severe maternal disease" (12.0%); "maternal short stature" (11.6%); "hypertensive disorders" (9.6%); "extrauterine infection" (6.8%); "previous miscarriage(s)" (6.5%); "smoking" (5.2%); and "maternal undernutrition" (4.7%). Severe small for gestational age newborns in the "severe maternal disease" (odds ratio, 3.2; 95% confidence interval, 1.8—6.0), "previous low birthweight or preterm birth" (odds ratio, 2.8; 95% confidence interval, 1.6—4.8), and "smoking" (odds ratio, 5.4; 95% confidence interval, 1.3—21.8) subgroups had increased risk of neonatal and long-term morbidity and low anthropometric measures at age 2 as compared to the non-small for gestational age group. Moderate small for gestational age newborns in the "hypertensive disorders" subgroup had increased risk of neonatal morbidity (odds ratio, 2.6; 95% confidence interval, 1.5—4.6) and higher odds of scoring <10th centile of normative values in language (odds ratio, 3.5; 95% confidence interval, 1.0—12.0) and positive behavior (odds ratio, 2.2; 95% confidence interval, 1.1—4.5). The "severe maternal disease" subgroup had also higher risk of deficit (<10th centile of normative values) in language (odds ratio, 5.7; 95% confidence interval, 1.3—24.8) and positive behavior (odds ratio, 3.4; 95% confidence interval, 1.5—7.6).

CONCLUSION: Small for gestational age comprises heterogeneous subgroups with distinct patterns of neonatal morbidity, postnatal growth, and neurodevelopmental outcomes up to age 2.

Key words: development, fetal growth restriction, morbidity, mortality, neurodevelopment, nutrition, syndrome

Introduction

Small for gestational age (SGA), defined as birthweight <10th centile for gestational age or sex, is a complex perinatal syndrome,[1] like stillbirth and preterm birth (PTB), that has several environmental risk and causal factors including malnutrition, infections, pollution, and smoking.

The syndrome is associated with increased neonatal morbidity and mortality and impaired childhood growth and neurodevelopment.[2] The gestational age at birth clearly influences an SGA infant's postnatal course; however, we hypothesize that etiological factors associated with SGA also have a profound effect on early childhood health, growth, and neurodevelopment.

SGA is a limited proxy for fetal growth restriction (FGR), often misclassifying small but healthy newborns. However, it remains a widely used measure of birthweight for gestational age. In this study, we use SGA as a practical anthropometric indicator at birth to explore the diversity of etiological subgroups and early outcomes. Therefore, to avoid relying solely on size and gestational age at birth as predictors of likely short- and long-term health outcomes, we propose subgrouping the syndrome based on previously identified characteristics, including etiological factors,

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AJOG at a Glance

Why was this study conducted?

Small for gestational age (SGA) is a complex perinatal syndrome with heterogeneous causes and outcomes.
Current classification relies solely on birthweight, neither capturing underlying etiology nor predicting childhood outcomes.
This study aimed to identify SGA subgroups using clinical and environmental factors and assess their neonatal and early childhood outcomes.

Key findings

Nine distinct subgroups were identified. Severe SGA newborns classified under "severe maternal disease," "previous low birthweight or preterm birth," and "smoking" had the highest neonatal morbidity and poorest growth or neurodevelopment at age 2.
The "hypertensive disorders" subgroup had increased risk of neonatal morbidity, language, and behavioral delays.
Subgroups exhibited differential umbilical artery Doppler flow patterns, suggesting distinct pathophysiological mechanisms.

What does this add to what is known?

This classification refines the definition of SGA, highlighting distinct subcategories with varying health trajectories.
Recognizing SGA subgroups at birth may enable targeted interventions and improved neonatal and early childhood care.

environmental exposures, and intrauterine measures of FGR.[1]

Methods

This study is part of the large prospective cohort INTERBIO-21st Newborn Study of pregnancies for the identification of the subgroups of SGA. Once these sub groups were identified, a prospective follow-up study design was used to evaluate outcomes during early childhood. SGA and non-SGA newborns were prospectively enrolled from 2012 to 2018 and followed from birth to age 2 in: Pelotas, Brazil; Nairobi, Kenya; Kilifi, Kenya; Karachi, Pakistan; Soweto, South Africa; Mae Sot, Thailand; and Oxford, UK. Detailed information about the sites and study populations has been provided elsewhere.[3] Fetal and newborn anthropometric classifications were based on the International Fetal and Newborn Growth Consortium (INTERGROWTH)-21st standards throughout the study, including SGA definition and postnatal growth comparisons. INTERBIO-21st was approved by the Oxfordshire Research Ethics Committee, institutional research ethics committees and corresponding regional authorities. All mothers provided written informed consent. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Eligible newborns were liveborn, naturally conceived singletons, born to mothers aged ≥18, residing in the catchment area. Birthweight centiles for gestational age or sex were assigned using INTERGROWTH-21st standards[4] and very preterm reference charts.[5] Severe SGA was defined as birthweight for gestational age and sex <third centile, moderate SGA as ≥third to <10th centile, and non-SGA as ≥10th centile.

Trained and quality-controlled ultrasonographers assigned gestational age by measuring crown-rump length $<14^{+0}$ weeks (75%) or head circumference$<24^{+0}$ weeks of gestation (25%) using INTERGROWTH-21st standards.[6,7] We also undertook fetal anthropometric and umbilical artery Doppler measurements in a subset of women who coparticipated in the INTERBIO-21st Fetal Study.[3] The detailed methodology and standardization and quality control processes have been previously described.[8]

At enrollment, we oversampled at lower gestational ages to obtain more severe SGA newborns to increase statistical power. To correct for oversampling in the present analysis, we generated a reference group, consisting of all non-SGA newborns with 10% randomly selected preterm cases, reflecting their actual prevalence in the population.

Outcomes

Neonatal and child morbidity

An unweighted composite neonatal outcome was used (Severe Neonatal Morbidity and Mortality Index) consisting of: a) severe morbidity (bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, anemia requiring transfusion, periventricular hemorrhage or leukomalacia, retinopathy, necrotizing enterocolitis [Bell stage ≥2], patent ductus arteriosus requiring intervention); b) neonatal intensive care unit (NICU) admission for ≥7 days, or c) neonatal death before hospital discharge. Hospital admission was evaluated at least once during follow-up.

Newborn and child anthropometry

The INTERGROWTH-21st anthropometric measurement protocols, training materials and quality control procedures have previously been described.[9] Dedicated anthropometrists obtained measures within 12 hours of birth (no later than 24 hours) using identical equipment. At ages 1 and 2, weight, length, and head circumference were measured using World Health Organization (WHO) protocols and compared to the WHO Child Growth Standards.[10]

Child motor and neurodevelopment outcomes

We assessed motor development from parental information against 4 WHO milestones,[11] and neurodevelopment at age 2 using the INTERGROWTH-21st Neurodevelopment Assessment (INTER-NDA) package,[12] constructed according to WHO's prescriptive guidelines. It includes culture-specific items measuring cognition, expressive and receptive language, motor skills (fine and gross), positive and negative behavior, and has been validated against

the Bayley Scales of Infant Development III edition.[13,14] Vision was assessed using the Cardiff Visual Acuity and Contrast Sensitivity tests for binocular vision.[15] Motor milestone ages and INTER-NDA scores are age-standardized or expressed as continuous age-related variables, accounting for the time dependency of early childhood development.

Data management and statistical analysis

All data were entered locally into the INTERGROWTH-21st online data management system (MedSciNet) and INTER-NDA tablet-based tool. Stata 15 software was used for all analyses (StataCorp. Release 15 College Station, TX).

Small for gestational age classification

We conducted a scoping review using a snowballing approach to identify, and then collect data on, conditions known to be etiologically associated with SGA (Supplemental Table 1). These fell into the following categories: 1) maternal undernutrition (hemoglobin level <third centile of international centiles,[16] or first trimester body mass index [BMI]<20 kg/m^2); 2) short stature (maternal height≤150 cm); 3) maternal extrauterine infection (eg, malaria, pyelonephritis, sexually transmitted diseases) or clinical chorioamnionitis treated with antibiotics; 4) pregnancy-related hypertensive disorders; 5) other severe medical conditions (eg, cardiac disease, chronic respiratory disease [including asthma], renal disease, cancer, systemic lupus erythematosus); 6) risk of adverse perinatal outcome after previous miscarriage(s), low birthweight (LBW) or PTB; 7) severe fetal anomaly diagnosed on ultrasound or at birth, and 8) early or mid or late pregnancy bleeding without preeclampsia. Full definitions for each category are decribed in Supplemental Table 1. Medication use during pregnancy (eg, antihypertensives, corticosteroids) was not adjusted for in the analysis as such treatments are closely linked to the underlying maternal conditions used to define SGA subgroups, and we aimed to avoid overadjustment.

Missing maternal hemoglobin values were imputed using univariate multiple imputation with chained equations via the uvis command in Stata 15. Separate imputation models were created for each trimester using relevant clinical thresholds, and included covariates (maternal age, height, first trimester BMI), SGA status, and study site. This approach allowed us to account for missingness while preserving key associations relevant to classification.

Cluster analysis

We performed 2-step cluster analysis to identify SGA subgroups using the SPSS (v.19) TwoStep cluster algorithm (IBM, Armonk, NY), which defines clusters using a model-based distance measure, derived from previous approaches.[17–19] This strategy first utilizes a distance measure to separate groups (preclustering) based on defining dense regions in the analyzed attribute space, and then a probabilistic approach to choose the optimal subgroup model based on a statistical measure of fit (Bayesian Information Criterion).[20,21] Between-group linkage was used as the cluster method, with log-likelihood as distance measure. We examined a range of cluster number options and concluded that a 9-cluster model provided a satisfactory clustering quality based on silhouette measures of cohesion and separation. The value of the silhouette statistic over all data of a cluster reflects how tightly grouped are the observations in that cluster. Clustering was considered satisfactory if the silhouette statistic was ≥0.6 on a −1.0 to +1.0 range.[22] Table 1 shows the cluster distribution according to conditions, showing that newborns allocated in a cluster share 1 dominant condition but could still comprise more than 1 factor. To explore the robustness of our cluster analysis, we conducted 10 random sample selection procedures, producing subsamples containing approximately half of the SGA newborns, and performed separate cluster analyses in each—a method widely used to identify groups in a given set of health-related data, which produces results consistent with other methods.[20,23–25] This algorithm handles large datasets efficiently, can be applied to continuous and categorical variables, and has features to help determine the optimal cluster number. The approach also identifies which combinations are important from all possibilities in the data and identifies the types empirically rather than imposing them from an a priori scheme.

Small for gestational age subgroups and umbilical artery Doppler

We prospectively analyzed uteroplacental perfusion patterns in a subset of the study population (SGA=397, non-SGA=2492) with ≥2 (mean=2.7) measures of umbilical artery Doppler pulsatility index (PI) values, obtained between 24^{+0} and $<38^{+0}$ weeks of gestation during coparticipation in the INTERBIO-21st Fetal Study.[3] z scores were estimated using gestational age-specific normative centiles[26]; 28 PI measures with z-scores >5 or <−5 were excluded.

To determine longitudinal PI trajectories for both groups, we constructed models for repeated measures of PI z-scores using linear models. Group mean growth patterns were modeled using Gaussian distributions by applying quadratic B-spline with 1 internal knot placed at the median. We used the *lm* function of the R package to fit the models.

Small for gestational age subgroups and postnatal outcomes

We performed logistic regression analysis to assess associations between SGA subgroups and neonatal and child morbidity indices, as well as neurodevelopment assessments. We present odds ratios (ORs) with 95% confidence intervals (95% CI) adjusted for study site, maternal age, and maternal education, using the non-SGA newborns as the reference group.

Due to the sampling strategy in the INTERBIO-21st Newborn Study, we opted to report ORs rather than relative

TABLE 1
Distribution of 9 subgroups of small-for-gestational-age newborns in the INTERBIO-21st Newborn Study

	Cluster name	N	%	Fetal anomaly	Bleeding without preeclampsia	Clinical chorioamnionitis	Extrauterine infection	Maternal nutrition	Hypertensive disorders (HD)	Previous LBW newborn(s)	Previous miscarriage(s)	Previous preterm newborn(s)	Severe maternal disease	Short stature	Smoked during pregnancy
				%	%	%	%	%	%	%	%	%	%	%	%
1	No main condition detected	449	29.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	Smoking in pregnancy	80	5.2	0.0	3.8	1.3	0.0	5.0	0.0	3.8	35.0	0.0	1.3	20.0	**100.0**
3	Maternal undernutrition	73	4.7	0.0	0.0	1.4	15.1	**100.0**	11.0	12.3	23.3	1.4	2.7	31.5	2.7
4	Short stature	179	11.6	0.0	0.0	0.0	0.0	0.0	0.0	17.3	20.1	10.6	0.0	**100.0**	0.0
5	Extrauterine infection	106	6.8	0.0	0.0	0.0	**100.0**	0.0	13.2	0.9	20.8	0.0	0.0	12.3	7.5
6	Hypertensive disorders (HD)	149	9.6	2.7	4.0	1.3	1.3	0.0	**100.0**	0.0	16.8	0.0	0.0	16.1	15.4
7	Severe maternal disease	186	12.0	19.9	22.6	14.0	15.1	1.1	5.9	1.1	29.6	0.5	**67.7**	8.1	10.8
8	Previous miscarriage(s)	101	6.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	**100.0**	0.0	0.0	0.0	0.0
9	Previous LBW or preterm newborn(s)	226	14.6	3.1	2.7	2.7	21.7	3.1	21.2	**83.2**	28.3	62.4	11.1	5.3	22.1
	Total	1549	100.0												

LBW, low birthweight.

Birthweight for gestational age or sex <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Bold indicates the phenotype that was assigned even though they could have other conditions.

risks. This is because the study was designed to oversample non-SGA newborns<38^{+0} weeks and SGA newborns across gestational age strata to ensure sufficient power, resulting in intentional overrepresentation of PTBs among non-SGA infants—a group at higher risk of adverse outcomes. To address this, we constructed a reference group including all non-SGA newborns and a 10% random sample of preterm cases. In this context, ORs offer a more conservative estimate, reducing bias from sampling imbalance. We used linear regression analysis to assess associations between SGA subgroups and neonatal and infant weight, length, head circumference, weight-for-length z-scores, and with age at achievement of the WHO gross motor development milestones. Using the non-SGA newborn population as the reference group, we present β coefficients (95% CIs) adjusted for study site, maternal age, maternal education, and gestational age at birth. The child's age when assessed was included in the models of neurodevelopment assessment, as well as age at achievement of the WHO gross motor development milestones. Robust standard errors were estimated in all association models. In sensitivity analyses, we ran all models excluding non-SGA newborns whose birthweight was >90th centile.

Results

We prospectively enrolled 7540 newborns, of whom 202 (2.68%) were lost to follow-up or their mothers withdrew consent; of the remaining 7338, 27 with missing birthweight were excluded, leaving 1549 SGA and 5762 non-SGA newborns. We then randomly excluded 609 preterm newborns to correct their oversampling in the original study design, leaving 6702 (3341 girls [49.8%]) for analysis. Of these, 947 were moderate SGA (mean standard deviation [SD] birthweight=2.5 [0.3] kg; mean [SD] gestational age at birth=38.6 [1.9] weeks); 602 were severe SGA (2.2 [0.4] kg; 38.4 [2.3] weeks of gestation), and 5153 were non-SGA (3.2 [0.5] kg; 38.8 [2.0] weeks of gestation, Supplemental Table 2).

Site contributions to the total study population ranged from 7.6% (Karachi) to 24.5% (Oxford). For the moderate and severe SGA groups, the ranges were 5.1% and 2.3% (Karachi) to 26.1% and 29.2% (Mae Sot), respectively.

Cluster analysis identified 9 maternally related SGA subgroups (Table 1, Supplemental Figure 1): "no Main (maternal, fetal or placental) condition detected" as an etiological factor (no main condition detected [NMCD], n=449, 29.0%); "previous LBW/PTB" (n=226, 14.6%); "severe maternal disease" (n=186, 12.0%); "short stature" (n=179, 11.6%); "hypertensive disorders" (n=149, 9.6%); "extrauterine infection" (n=106, 6.8%); "previous miscarriage(s)" (n=101, 6.5%); "smoking" (n=80, 5.2%); and "maternal undernutrition" (n=73, 4.7%).

At 1 year, 79% of SGA and 83% of non-SGA newborns were assessed; 2-year rates were 63% and 70%, respectively. The total sample that contributed to constructing the SGA subgroups (n=1549) and the 2-year sample (n=811) had similar baseline patterns (Supplemental Tables 1 and 4). Infants lost to follow-up were similar at birth to those completing the 2-year follow-up, except they were slightly more likely to be very preterm (<34 weeks of gestation) and been admitted to NICU.

Umbilical artery Doppler flow

Among the non-SGA newborns, umbilical artery PI, prospectively evaluated during pregnancy, decreased with advancing gestational age, as expected close to the 50th centile of the normative values. Overall, the PI was elevated from around 30 weeks of gestation in the severe SGA group; a later and less marked elevation was seen in the moderate SGA group (Figure 1, A). However, differential Doppler PI patterns were observed according to the subgroup of SGA: there is an increased PI after 32 weeks of gestation in the "NMCD," "short stature," and "previous LBW/PTB" subgroups (Figure 1, B, left); conversely, values in the subgroups "extrauterine infection," "previous miscarriage(s)," and "severe maternal disease" were close to the non-SGA newborns or did not increase late in pregnancy (Figure 1, B, right). Although, these findings should be interpreted cautiously due to the small sample sizes, it is of interest that different SGA sub groups are associated with differential blood flow parameters.

Neonatal and child morbidity

The composite outcome of Severe Neonatal Morbidity and Mortality Index occurred in 7.7% of non-SGA, 9.5% of moderate SGA, and 17.8% of severe SGA. Other markers of morbidity, anthropometric, neurodevelopmental, vision and motor outcomes according to SGA subgroup are presented in Supplemental Table 5. Figure 2 (Supplemental Table 6) presents ORs for the total SGA, SGA subgroup and non-SGA populations.

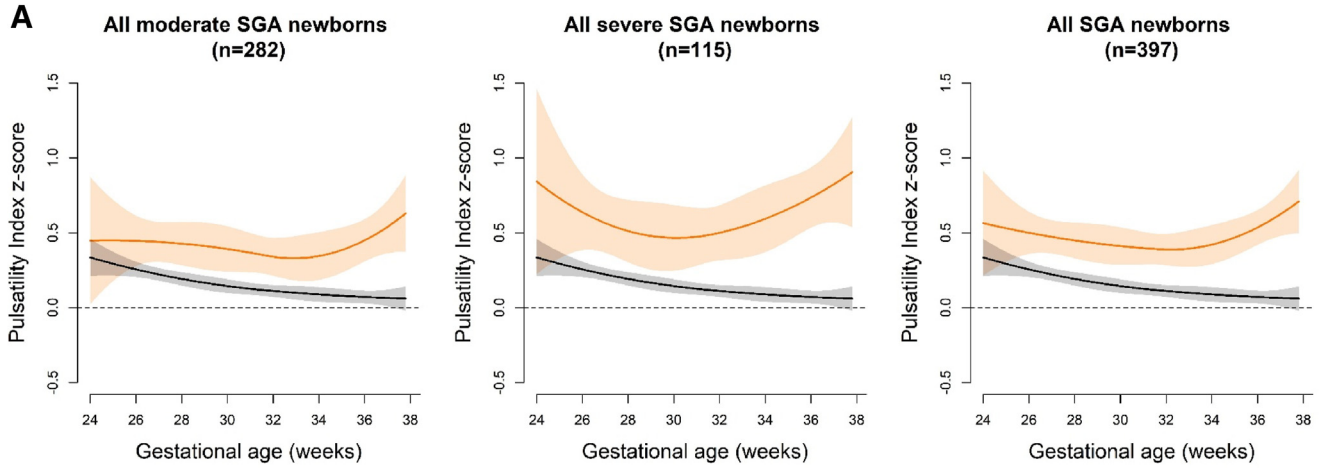
After adjusting for study site, maternal age and maternal education among moderate SGA, the "hypertensive disorders" (OR, 2.6; 95% CI, 1.5−4.6), "severe maternal disease" (OR, 2.6; 95% CI, 1.6−4.3), and "previous LBW/PTB" (OR, 1.9; 95% CI, 1.1−3.3) subgroups had increased ORs. The values in severe SGA were: "short stature" (OR, 1.9; 95% CI, 1.0−3.4); "hypertensive disorders" (OR, 8.8; 95% CI, 5.3−14.6); "severe maternal disease" (OR, 3.2; 95% CI, 1.8−6.0) and "previous LBW/PTB" (OR, 2.8; 95% CI, 1.6−4.8).

Figure 3 (Supplemental Table 6) shows the ORs for at least 1 hospitalization up to age 2 among the total SGA, SGA subgroup and non-SGA populations. The "smoking" subgroup among severe SGA had a higher OR of hospitalization than the non-SGA, after adjusting for study site, maternal age, and maternal education (OR, 5.4; 95% CI, 1.3−21.8). The "severe maternal disease" subgroup among severe SGA had double the OR (OR, 2.5; 95% CI, 1.1−5.3).

Newborn size and postnatal growth

Figure 4 (Supplemental Table 7) presents adjusted β coefficients for anthropometric z-scores from birth to age 2 according to SGA subgroup and SGA severity compared to the non-SGA population. These values, adjusted for study site, maternal age, and maternal

FIGURE 1
Trajectories of umbilical artery pulsatility index (PI) z-scores



A, Trajectories of umbilical artery PI z-score according to SGA severity. *Orange line* represents PI z-score trajectory for SGA newborns within each group. *Black line* illustrates the PI z-score trajectory for non-SGA newborns (n=2492). *Shaded bands* represent 95% confidence intervals for splines used to summarize group trajectories. Gestational age–specific z-scores were estimated for PI using the international gestational age-specific references for umbilical artery Doppler indices.[26] SGA: birthweight for gestational age or sex <third centile (all severe SGA newborns), >third to <10th centile (all moderate SGA newborns) and <10th centile (all SGA newborns) of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] **B**, Trajectories of umbilical artery PI z-score according to SGA subgroups*. Group membership determined by analysis of SGA subgroups. *Orange line* represents PI z-score trajectory for SGA newborns within each group. *Black line* illustrates the PI z-score trajectory for non-SGA newborns (n=2492). *Shaded bands* represent 95% confidence intervals for splines used to summarize group trajectories. Gestational age–specific z-scores were estimated for PI using the international gestational age-specific references for umbilical artery Doppler indices.[26] SGA, small for gestational age: Birthweight for gestational age or sex <third centile (all severe SGA newborns), >third to <10th centile (all moderate SGA newborns) and <10th centile (all SGA newborns) of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5]

LBW, low birthweight; PI, pulsatility index; *SGA*, small for gestational age. *Plots are shown for 6 of the 9 subgroups. The three remaining subgroups were excluded from the figure due to small sample sizes (<30 cases each).

education, should be interpreted as the difference in z-scores between each of the SGA subgroups and the non-SGA population, that is, a z-score of zero (white horizontal line in the figures).

Compared to the non-SGA newborns, the "severe maternal disease" subgroup had the highest mean difference in birthweight z-scores in moderate (β, −1.7; 95% CI, −1.9 to −1.6) and severe SGA (β, −2.5; 95% CI, −2.7 to −2.3) (Figure 4, A and B). At age 1, the differences in weight z-scores between SGA and non-SGA newborns were less in moderate SGA, although still 0.5 to 1.0 SD below the non-SGA population z-score, with the exception of the "extra-uterine infection" subgroup (β, −0.3; 95% CI, −0.7−0.0).

In severe SGA, all subgroups showed considerable catch-up growth, but the differences in the postnatal weight z-scores still ranged from −0.6 SD in the "previous miscarriage(s)" subgroup to −1.3 SD in the "hypertensive disorders" and "previous LBW/PTB" subgroups. By age 2, catch-up growth had mostly ended in moderate and severe SGA; the differences in weight z-scores persisted among the SGA subgroups but were particularly marked in severe SGA.

Figure 4, A and B show how the z-score trajectories for length at ages 1 and 2 tracked among the subgroups with moderate and severe SGA, and catch-up growth virtually ceased after the 1-year visit. As with weight, differences in length z-scores across SGA subgroups were more marked in severe SGA. Head circumference trajectories were similar to the patterns observed for length but with less pronounced differences across SGA subgroups in moderate SGA.

Most anthropometric measures by age 2 were consistently worse in the "severe maternal disease," "previous LBW/PTB," and "smoking" subgroups compared to the non-SGA population. Actual z-scores values are presented in Supplemental Table 7.

Neurodevelopmental outcomes

Table 2 shows the adjusted ORs for the INTER-NDA domains[12] for any neurodevelopmental delay, that is, scores <10th centile of the INTER-NDA standards for all domains except negative behavior (where the threshold for normality is ≥90th centile) according to SGA subgroup compared to the non-SGA population. Categories of low visual acuity (Logarithm of the Minimum Angle of Resolution>0.4) and high contrast sensitivity (>3%) were based on the Cardiff norms for age 2 to 3 (Supplemental Table 8). We adjusted for study site, maternal age and maternal education, and age of assessment.

The results show heterogeneity across SGA subgroups: children born with

FIGURE 1
Continued

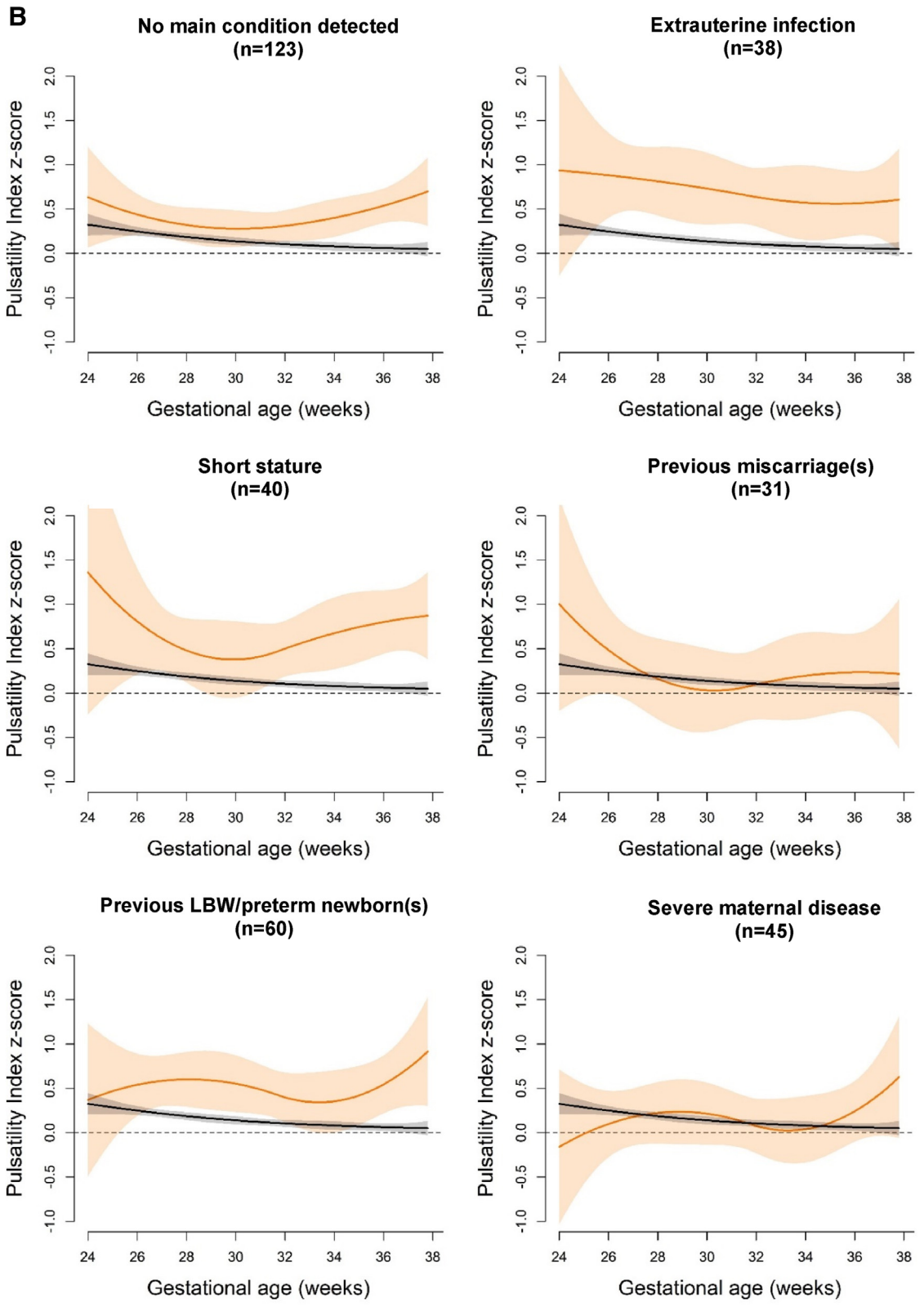
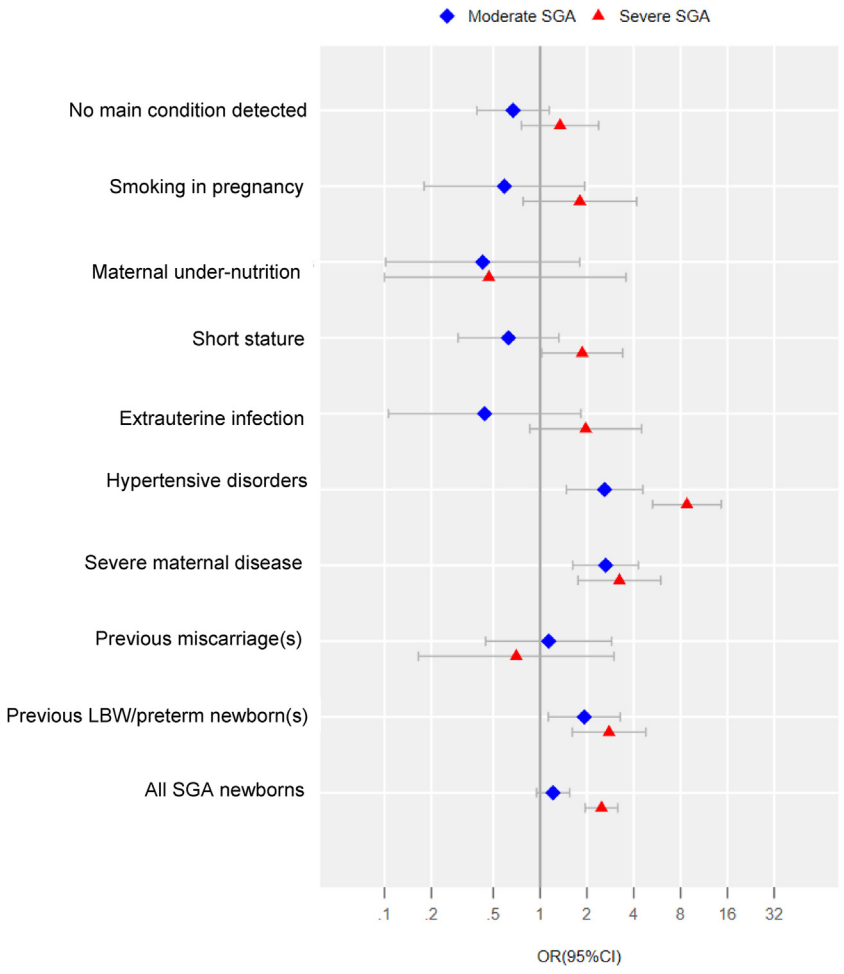


FIGURE 2
Adjusted* ORs (and 95% CIs) for severe neonatal morbidity and mortality index by SGA subgroup compared with non-SGA newborns



*Adjusted for study site, maternal age, and maternal education. X-axis is on log scale. Values for odds ratio are not log transformed. Moderate SGA, small for gestational age (n=947): birthweight for gestational age or sex ≥third to <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Severe SGA, small for gestational age (n=602): birthweight for gestational age or sex <third centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Severe neonatal morbidity and mortality index which includes: **A**) severe morbidity (any of the following conditions: bronchopulmonary dysplasia, hypoxic-ischemic encephalopathy, sepsis, neonatal anemia [requiring transfusion], periventricular hemorrhage or leukomalacia, retinopathy of prematurity, necrotizing enterocolitis [Bell stage 2 or greater], patent ductus arteriosus [requiring pharmacological treatment or surgery]); **B**) admissions to neonatal intensive care unit ≥7 days; or **C**) neonatal death before hospital discharge.

CI, confidence interval; *LBW*: low birthweight; *OR*, odds ratio; *SGA*, small for gestational age.

moderate SGA in the "maternal nutrition" SGA subgroup had the highest odds of cognitive delay (OR, 4.6; 95% CI, 1.6−14.7); those in the "hypertensive disorders" subgroup had the highest odds of scoring <10th centile in positive behavior (OR, 2.2; 95% CI, 1.1−4.5), and those in the "smoking" subgroup had the highest odds of scoring >90th centile for negative behavior (OR, 2.8; 95% CI, 1.1−7.1).

Children born with severe SGA in the "extrauterine infection" (OR, 4.5; 95% CI, 1.0−20.5) and "severe maternal disease" (OR, 5.7; 95% CI, 1.3−24.8) subgroups had the highest odds of language delay; "severe maternal disease" (OR, 3.4; 95% CI, 1.5−7.6) and "previous LBW/PTB" (OR, 2.0; 95% CI, 1.1−3.7) children had the highest odds of scoring <10th centile in positive behavior.

Figure 5 (Supplemental Table 9) shows adjusted β coefficients for age of achievement for the "age at walking alone" milestone according to SGA subgroup compared to the non-SGA population, adjusting for study site, maternal age, maternal education, and age of assessment. In severe SGA, the "severe maternal disease" subgroup was considerably slower in reaching the "walking alone" milestone, with a mean delay of 1.6 months (95% CI, 0.4−2.7). In addition, infants in the "NMCD" (β, 0.3; 95% CI, 0.1−0.6), "maternal nutrition" (β, 0.5; 95% CI, 0.0−0.9), "hypertensive disorders" (β, 0.6; 95% CI, 0.0−1.2), and "previous LBW/PTB" (β, 0.4; 95% CI, 0.0−0.9) subgroups reached the "sitting without help" milestone more slowly than non-SGA infants. "NMCD" (β, 0.6; 95% CI, 0.0−1.1) and "severe maternal disease" (β, 1.3; 95% CI, 0.4−2.2) infants were slower reaching the "crawling" milestone (Supplemental Table 9).

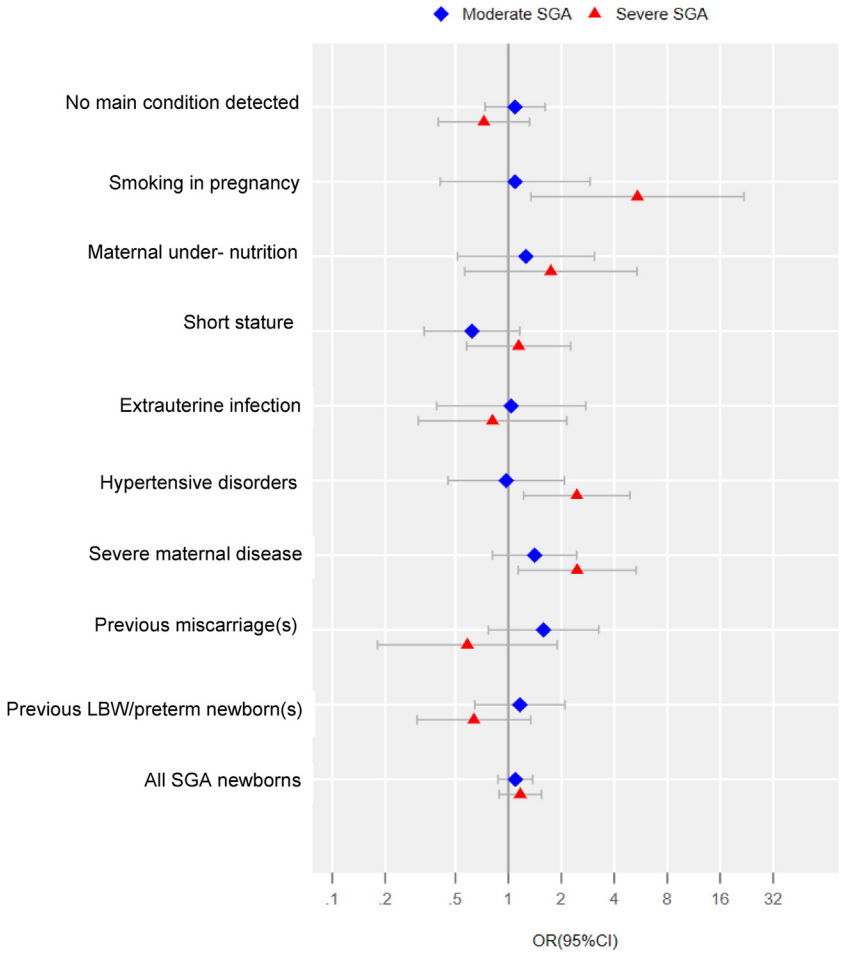
In sensitivity analyses excluding newborns with birthweight >90th centile, results were similar for all outcomes, as were those comparing actual and imputed maternal hemoglobin levels suggesting that findings were unlikely affected by selection bias (data not shown).

Comment

Principal findings

When a baby is born SGA, healthcare professionals and, above all, parents need as accurate an indication as possible of short- and long-term health outcomes. Reliance on clinical information currently collected at and after the birth (ie, birthweight for gestational age) is clearly important but provides an incomplete prognostic assessment and fails to take account of the wealth of valuable data collected during the pregnancy. That information, including the

FIGURE 3
Adjusted* odds ratios (and 95% confidence intervals) for hospitalization (at least once) over the first 2 years of life by SGA subgroup compared with non-SGA newborns in the INTERBIO-21st Newborn Study



*Adjusted for study site, maternal age and maternal education. X-axis is on log scale. Values for odds ratio are not log transformed. Moderate SGA, small for gestational age: birthweight for gestational age or sex ≥third to <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Severe SGA, small for gestational age: birthweight for gestational age or sex <third centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5]

CI, confidence interval; *LBW*: low birthweight; *OR*, odds ratio; *SGA*, small for gestational age.

mother's nutritional status, comorbidities (ie, infections), past obstetric history, and pregnancy-related conditions (ie, preeclampsia), has been used here to construct SGA subgroups, independent of known confounding variables, that have different patterns of neonatal and childhood health outcomes, as well as growth and neurodevelopment, with long-term implications. The predominant approach to SGA labels small babies as at risk only if they have abnormal Dopplers, and considers the remainder to be "healthy small." The classification system we describe here, which builds on similar work for the PTB syndrome,[27] takes into account more granular pre- and postnatal information, links to outcomes at 2 years of age, and should, therefore, provide a more nuanced approach to clinical care.

Research implications

Three subgroups were consistently associated with the worst outcomes: "previous LBW/PTB," "severe maternal disease," and "smoking" information that should heighten clinical vigilance in the prenatal period. The first was associated with higher umbilical artery Doppler PI, neonatal and child morbidity, postnatal growth restriction, and items indicative of early gross motor delay and positive behavior at age 2. The findings were similar for "severe maternal disease," which strongly suggests that the recurrence of such conditions in successive pregnancies is related to the sustained presence of putative causes. In the case of the "severe maternal disease" subgroup, which includes multiple medical conditions, further research should undoubtedly focus on the specific effect of each of these conditions in a sufficiently large sample.

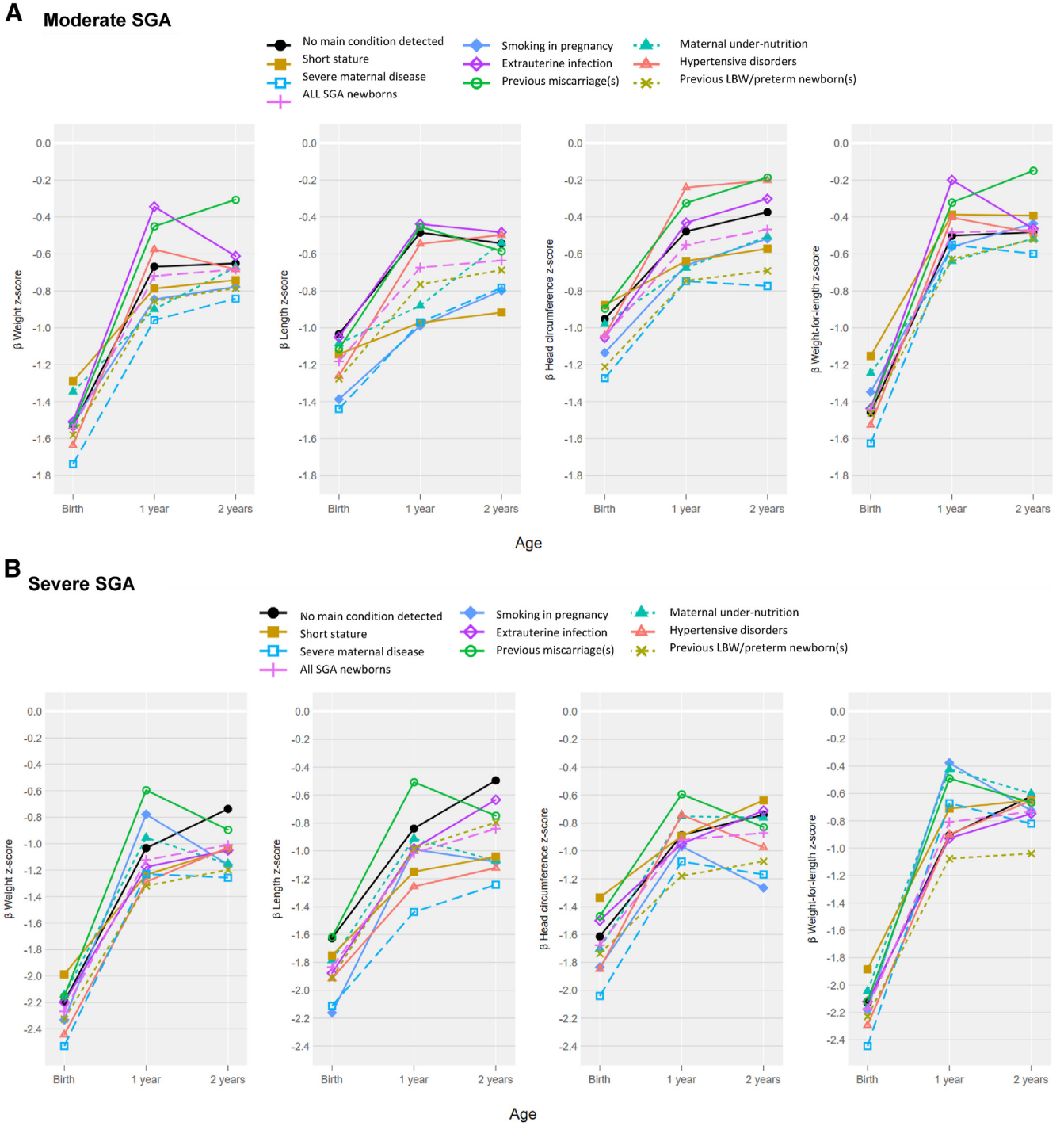
Other subgroups had negative effects on specific domains, for example, "smoking" on severe conditions during childhood requiring hospital admission; "maternal nutrition" on cognition and early gross motor development; and "hypertensive disorders" on language delay (Supplemental Table 10). Whether or not the observed domain-specific effect of selected SGA subgroups is related to their timing and duration remains to be understood.

Clinical implications

Importantly, from a clinical perspective, infants of short stature mothers had increased risk of neonatal morbidity and the poorest anthropometric measures by age 2. Thus, the practice of "adjusting" fetal size and growth measures based on maternal height—a marker of intergenerational malnutrition—is questionable. The "severe maternal disease" subgroup also had greater neonatal morbidity, higher risk of neurodevelopmental delay and lower anthropometric z-scores by age 2.

As previously reported,[28] FGR fetuses with abnormal Dopplers had poorer perinatal outcomes than SGA fetuses with normal Dopplers. This explains why SGA newborns without Doppler abnormalities are typically categorized as "constitutionally small," which applied to the 31% with moderate SGA that clustered in the "NMCD" subgroup.

FIGURE 4
Adjusted* β coefficients of anthropometric measures at birth, age 1, and age 2 by SGA subgroup compared with non-SGA newborns in the INTERBIO-21st Newborn Study



A, Moderate SGA. **B**, Severe SGA *Adjusted for study site, maternal age, and maternal education. Moderate SGA, small for gestational age: birthweight for gestational age or sex ≥third to <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Severe SGA, small for gestational age: birthweight for gestational age or sex <third centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth.[4,5] Age- and sex-specific centiles at 1 and 2 years of age compared with the international WHO child growth standards.

LBW: low birthweight; *SGA*, small for gestational age; *WHO*, World Health Organization.

TABLE 2
Adjusted[a] odds ratios of INTER-NDA domains ≤10th centile of the INTERGROWTH-21st neurodevelopment standards at 2 years of age according to SGA subgroup compared with non-SGA newborns in the INTERBIO-21st Newborn Study

		Moderate SGA				Severe SGA			
NDA domain	SGA subgroup	Infants, number	OR	95% CI	*P* value	Infants, number	OR	95% CI	*P* value
Cognition	No main condition detected	138	1.3	(0.6–2.7)	.557	73	0.7	(0.2–2.7)	.565
	Smoking in pregnancy	25	2.5	(0.6–10.3)	.208	16	3.1	(0.4–26.5)	.310
	Maternal undernutrition	24	4.9	(1.6–14.7)	.005	17	–	–	–
	Short stature	32	–	–	–	27	–	–	–
	Extrauterine infection	21	2.6	(0.8–8.7)	.116	28	–	–	–
	Hypertensive disorders	35	2.1	(0.7–6.5)	.188	39	0.7	(0.1–5.5)	.722
	Severe maternal disease	52	0.4	(0.0–2.9)	.346	23	1.2	(0.1–9.5)	.873
	Previous miscarriage(s)	40	0.6	(0.1–4.9)	.673	29	–	–	–
	Previous LBW or preterm newborn(s)	74	2.7	(1.2–6.2)	.017	38	1.8	(0.6–5.3)	.279
	All SGA newborns	441	1.5	(1.0–2.3)	.058	290	0.7	(0.4–1.5)	.391
	Non-SGA newborns	2980	1.0	[Reference]		2980	1.0	[Reference]	
Language	No main condition detected	138	1.1	(0.3–3.6)	.889	73	1.5	(0.4–6.1)	.595
	Smoking in pregnancy	25	–	–	–	16	6.1	(0.7–55.6)	.111
	Maternal undernutrition	24	2.7	(0.4–20.9)	.330	17	4.0	(0.5–33.6)	.200
	Short stature	32	2.5	(0.5–12.1)	.250	27	1.4	(0.2–10.9)	.741
	Extrauterine infection	21	2.0	(0.3–15.0)	.503	28	4.3	(1.0–18.8)	.054
	Hypertensive disorders	35	3.5	(1.0–12.0)	.051	39	1.5	(0.2–12.2)	.723
	Severe maternal disease	52	0.9	(0.1–6.8)	.953	23	5.7	(1.3–24.8)	.021
	Previous miscarriage(s)	40	–	–	–	29	–	–	–
	Previous LBW or preterm newborn(s)	74	2.1	(0.5–9.1)	.326	38	1.8	(0.4–8.2)	.465
	All SGA newborns	441	1.5	(0.8–2.7)	.197	290	2.2	(1.2–4.3)	.016
	Non-SGA newborns	2980	1.0	[Reference]		2980	1.0	[Reference]	
Gross motor	No main condition detected	138	0.6	(0.2–1.8)	.335	73	0.7	(0.2–2.9)	.616
	Smoking in pregnancy	25	1.5	(0.3–6.9)	.581	16	–	–	–
	Maternal undernutrition	24	2.4	(0.7–8.6)	.166	17	1.4	(0.2–12.8)	.747
	Short stature	32	0.8	(0.2–2.8)	.752	27	0.7	(0.2–2.9)	.607
	Extrauterine infection	21	3.6	(0.7–17.6)	.116	28	1.9	(0.4–9.8)	.453
	Hypertensive disorders	35	1.8	(0.6–5.9)	.324	39	2.3	(0.7–7.6)	.173
	Severe maternal disease	52	1.3	(0.4–3.6)	.648	23	–	–	–
	Previous miscarriage(s)	40	1.6	(0.3–7.1)	.557	29	2.5	(0.6–10.8)	.222
	Previous LBW or preterm newborn(s)	74	0.4	(0.1–2.7)	.330	38	1.0	(0.2–4.5)	.973
	All SGA newborns	441	1.1	(0.7–1.7)	.695	290	1.0	(0.5–1.7)	.889
	Non-SGA newborns	2980	1.0	[Reference]		2980	1.0	[Reference]	

(continued)

TABLE 2
Adjusted[a] odds ratios of INTER-NDA domains ≤10th centile of the INTERGROWTH-21st neurodevelopment standards at 2 years of age according to SGA subgroup compared with non-SGA newborns in the INTERBIO-21st Newborn Study
(continued)

		Moderate SGA				Severe SGA			
NDA domain	SGA subgroup	Infants, number	OR	95% CI	*P* value	Infants, number	OR	95% CI	*P* value
Positive behavior	No main condition detected	138	0.7	(0.4–1.1)	.091	73	1.2	(0.7–2.1)	.504
	Smoking in pregnancy	25	1.8	(0.7–4.8)	.250	16	1.6	(0.4–6.1)	.489
	Maternal undernutrition	24	1.1	(0.4–2.7)	.919	17	1.0	(0.3–2.9)	.939
	Short stature	32	0.9	(0.5–1.9)	.879	27	1.0	(0.5–2.1)	.991
	Extrauterine infection	21	1.2	(0.4–3.1)	.744	28	1.1	(0.4–2.9)	.786
	Hypertensive disorders	35	2.2	(1.1–4.5)	.029	39	0.9	(0.3–2.2)	.751
	Severe maternal disease	52	1.2	(0.6–2.3)	.638	23	3.4	(1.5–7.6)	.003
	Previous miscarriage(s)	40	0.3	(0.1–1.0)	.058	29	0.5	(0.2–1.9)	.341
	Previous LBW or preterm newborn(s)	74	1.1	(0.6–2.0)	.745	38	2.0	(1.1–3.7)	.032
	All SGA newborns	441	1.0	(0.7–1.2)	.759	290	1.3	(1.0–1.7)	.067
	Non-SGA newborns	2980	1.0	[Reference]		2980	1.0	[Reference]	
Negative behavior[b]	No main condition detected	138	0.9	(0.6–1.3)	.525	73	1.1	(0.7–1.9)	.634
	Smoking in pregnancy	25	2.8	(1.1–7.1)	.027	16	0.7	(0.2–3.2)	.657
	Maternal undernutrition	24	1.5	(0.6–3.4)	.393	17	1.1	(0.3–3.9)	.879
	Short stature	32	1.4	(0.8–2.6)	.278	27	1.2	(0.6–2.4)	.534
	Extrauterine infection	21	1.2	(0.4–3.1)	.737	28	2.2	(0.9–4.9)	.068
	Hypertensive disorders	35	1.3	(0.6–2.7)	.467	39	2.3	(1.0–5.3)	.045
	Severe maternal disease	52	1.3	(0.7–2.4)	.358	23	1.3	(0.5–3.3)	.550
	Previous miscarriage(s)	40	0.4	(0.1–1.0)	.059	29	0.2	(0.0–1.4)	.106
	Previous LBW or preterm newborn(s)	74	1.5	(0.8–2.6)	.192	38	1.0	(0.5–2.1)	.946
	All SGA newborns	441	1.1	(0.9–1.4)	.282	290	1.2	(0.9–1.6)	.182
	Non-SGA newborns	2980	1.0	[Reference]		2980	1.0	[Reference]	

CI, confidence interval; *INTER-NDA*, INTERGROWTH-21st Neurodevelopment Assessment; *LBW*, low birthweight; *OR*, odds ratio; *SGA*, small for gestational age.

INTER-NDA: The INTERGROWTH-21st Neurodevelopment Assessment. Results for fine motor development are not presented because there were no cases in most of the SGA phenotypes.

(–) indicated that there were no cases of outcome for that specific subgroup.

Moderate SGA, SGA: birthweight for gestational age or sex ≥third to <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5]

Severe SGA, small for gestational age: birthweight for gestational age or sex <third centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5]

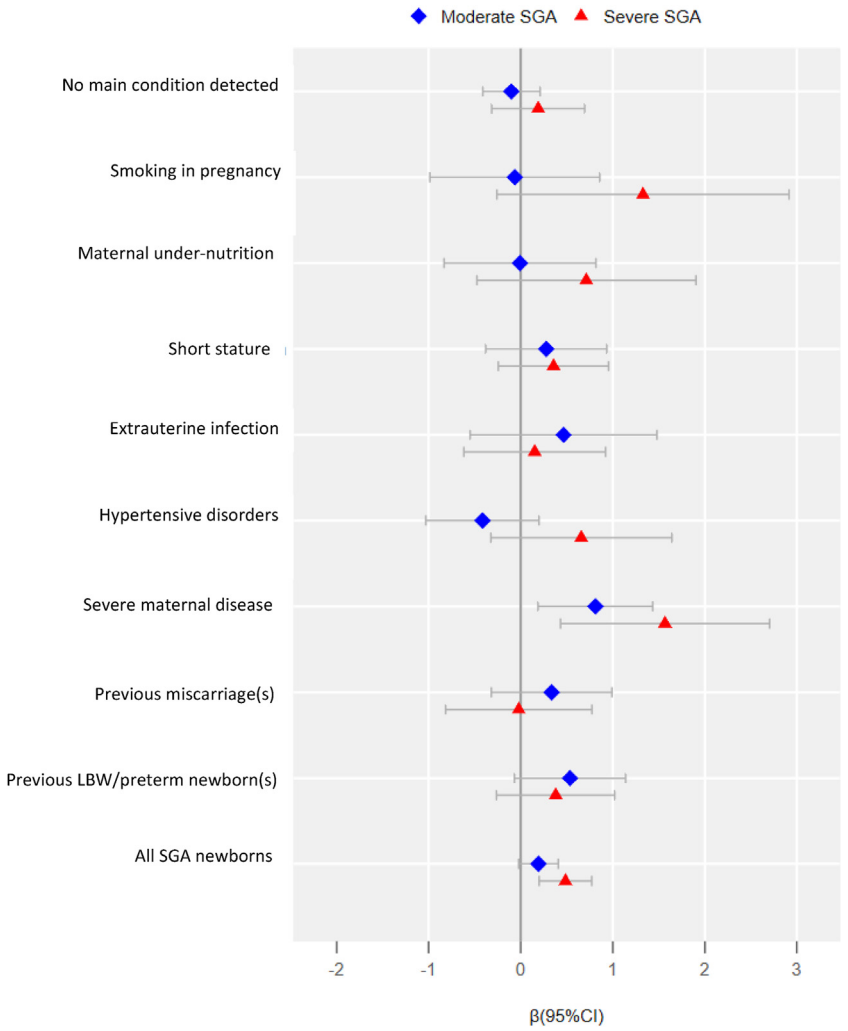
[a] Adjusted for study site, maternal age, maternal education, and age of assessment; [b] Negative behavior is defined as a risk of negative behavior that scored >90th centile on the INTERGROWTH-21st Neurodevelopment Assessment.

However, caution should be exercised in assuming "normality" because the "NMCD" subgroup had increased umbilical PI values after 32 weeks of gestation and slower neurological maturation, as measured by age at "crawling" and "sitting without help."

Results in the context of what is known

At present, the reliance on Dopplers to distinguish pathological FGR from constitutional SGA is understandable because of the relatively low occurrence of nutritional deficiency, maternal infections, smoking, and environmental exposures that contribute to SGA in high-income settings, where most Doppler studies have been performed. In our study, conducted in low-, middle-, and high-income countries, although PI was increased overall throughout

FIGURE 5
Adjusted* β coefficient of age (in months) of attaining the World Health Organization motor milestone "walking alone" according to SGA subgroup compared with non-SGA newborns in the INTERBIO-21st Newborn Study



*Adjusted for study site, maternal age, maternal education, and age of assessment. Moderate SGA, small for gestational age: birthweight for gestational age or sex ≥third to <10th centile of the INTERGROWTH-21st newborn size standards and very preterm size at birth reference charts.[4,5] Severe SGA, small for gestational age: birthweight for gestational age or sex <third centile of the INTERGROWTH-21st Newborn Size Standards and Very Preterm Size at Birth Reference Charts.[4,5]

CI, confidence interval; *LBW*: low birthweight; *SGA*, small for gestational age.

pregnancy in the SGA subsample, we found that uteroplacental blood flow restriction was associated selectively with certain etiological factors of SGA. This suggests that current distinction between pathological FGR and constitutional SGA based on Doppler findings alone may be too simplistic, as similar signs of prenatal cardiac dysfunction have been reported in late-onset small fetuses with both normal and abnormal Dopplers.[29] Hence, a more personalized strategy may be to use fetal echocardiography[30] or centralization of fetal blood flow[31] to identify small babies that are more likely to undergo cardiovascular remodeling in childhood.

Strength and limitations

Our study has several strengths. It was designed to explore a priori hypotheses associated with the heterogeneity of the SGA syndrome using an international, prospective, multicenter approach. We clustered 1 or more maternal, fetal, or placental conditions associated with SGA and FGR to allocate subgroup membership. Reassuringly, each subgroup's dominant pathological characteristics were associated with known complications and comorbidities, showing the strength of the clustering process and validating the selection clinically. Gestational age at birth was determined by ultrasound. The study's longitudinal nature allowed growth, morbidity, and neurodevelopment to be monitored from birth to age 2 using standardized data collection systems. Hence, we were able to assess growth trajectories over time accurately, which is not possible with cross-sectional data. We

defined suboptimal growth and delays in neurodevelopment against international standards, all based on the same normative population followed from early pregnancy to age 2, allowing—for the first time—standardized z-scores to be estimated across this period. Finally, the recruitment strategy of oversampling preterm newborns and those with a birthweight <third centile allowed us to maximize the number of high-risk subgroups.

Our study also has some limitations. As anticipated, by including rural and semiurban areas, the loss to follow-up at age 2 was higher than in our previous urban studies.[32] However, this was mitigated by the greater number of more severe exposures prevalent in such settings (eg, infection and malnutrition), and the follow-up rates are consistent with other similar prospective birth cohorts and multicountry studies.[33,34] In addition, this is unlikely to be a strong source of bias as rates across subgroups, with the exception of "smoking," were similar. While we recognize that the SGA, PTB, and stillbirth syndromes share some risks,[2] childhood follow-up was a fundamental element of the study, which precluded including pregnancies that resulted in miscarriage, termination or stillbirth. Live birth bias is unlikely to have materially affected our findings given the very small number of terminations (n=2) and fetal deaths (n=2) in the study population. Non-SGA infants were slightly more likely at age 2 to have had mothers who smoked, and been very preterm and had NICU admission; therefore, we cannot entirely rule out the possibility of selection bias. We acknowledge the definition of abnormal Doppler PI varies considerably,[35] which adds uncertainty to the diagnosis of "constitutionally small" newborns; we acknowledge that middle cerebral artery Doppler indices were not available, limiting evaluation of fetal blood flow redistribution. Placental histology was not available for this analysis, but some SGA infants may have had abnormal placental pathology. Similarly, other risks could not be assessed, such as maternal periodontal disease[36] and genetic polymorphisms[37] and paternal factors.[38] We recognize the limitations of historical obstetric information in this cohort that did not allow us to reliably distinguish a past history of SGA vs preterm, leading us to use the LBW category; this pragmatic option is commonplace in particular in low and middle income country settings. Maternal smoking and recreational drug use were assessed using validated antenatal questionnaires. While self-report may underestimate true exposure due to social desirability bias, this was the only feasible method at scale and likely results in conservative effect estimates. Given the low prevalence and potential for differential misclassification, the recreational drug use variable was not included in the models. Finally, we recognize that multiple tests have been carried out, which might have increased the risk of type 1 error; however, we did not use *P* value thresholds to guide our conclusions. We have interpreted our results with caution, based on patterns of results, the magnitude of estimates, and their CIs, rather than statistical significance.

Conclusions

Our findings reinforce concerns about the limitations of SGA as a proxy for FGR, and support the need for more refined, etiologically informed classifications of small newborns. We have shown that SGA is a complex perinatal syndrome composed of subgroups associated with differential, umbilical artery Doppler PI flow, neonatal morbidity, growth, and neurodevelopment at 1 and 2 years of age. This phenotypic classification, in particular among severe SGA newborns, provides a better understanding of the etiological factors and mechanisms associated with neonatal vulnerability and early childhood sequelae. Approximately one-third of SGA newborns were not associated with distinct clinical conditions detected in routine clinical practice; hence, more detailed biological understanding is required to disentangle the etiological factors associated with this subpopulation, as well as identifying those SGA that are "healthy small." From a clinical perspective, our findings could contribute to the kind of personalized stratification of pregnancy care for SGA proposed by others from mid-gestation biomarkers.[39]

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Data availability

Anonymized data will be made available upon reasonable request for academic use and within the limitations of the informed consent. Requests must be made to the corresponding author. Every request will be reviewed by the INTERBIO-21st Consortium Executive Committee. After approval, the researcher will need to sign a data access agreement with the INTERBIO-21st Consortium. ■

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