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Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries

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Background Low- and middle-income countries continue to experience a large burden of stunting; 148 million children were estimated to be stunted, around 30–40% of all children in 2011. In many of these countries, foetal growth restriction (FGR) is common, as is subsequent growth faltering in the first 2 years. Although there is agreement that stunting involves both prenatal and postnatal growth failure, the extent to which FGR contributes to stunting and other indicators of nutritional status is uncertain.

Methods Using extant longitudinal birth cohorts ($n = 19$) with data on birthweight, gestational age and child anthropometry (12–60 months), we estimated study-specific and pooled risk estimates of stunting, wasting and underweight by small-for-gestational age (SGA) and preterm birth.

Results We grouped children according to four combinations of SGA and gestational age: adequate size-for-gestational age (AGA) and preterm; SGA and term; SGA and preterm; and AGA and term (the

reference group). Relative to AGA and term, the OR (95% confidence interval) for stunting associated with AGA and preterm, SGA and term, and SGA and preterm was 1.93 (1.71, 2.18), 2.43 (2.22, 2.66) and 4.51 (3.42, 5.93), respectively. A similar magnitude of risk was also observed for wasting and underweight. Low birthweight was associated with 2.5–3.5-fold higher odds of wasting, stunting and underweight. The population attributable risk for overall SGA for outcomes of childhood stunting and wasting was 20% and 30%, respectively.

Conclusions This analysis estimates that childhood undernutrition may have its origins in the foetal period, suggesting a need to intervene early, ideally during pregnancy, with interventions known to reduce FGR and preterm birth.

Keywords Foetal growth restriction, preterm birth, stunting, wasting, childhood

Introduction

Childhood undernutrition marked by stunting (height for age <-2 *z*-scores) is very common, affecting 164.8 million (22.7%) children globally, 148 million of whom live in low- and middle-income countries (LMIC).[1] Additionally, 8% or 52 million children are severely wasted.[1] Childhood undernutrition is well known to increase the risk of short-term mortality.[2,3] In addition, height at 24 months of age is predictive of adult height, and childhood stunting is linked with cognitive deficits, less schooling and potential for income generation and employment, all of which contribute to reduced human capital in developing countries.[4]

The timing and pattern of growth faltering in the first 2 years of life is well established, with height for age *z*-scores in LMIC declining soon after birth to a nadir of -1.75 to <-2 *z*-scores by 24 months of age, and little if any subsequent catch-up growth being evident up to 5 years of age.[5] Numerous factors, including inappropriate breastfeeding and infant and young child feeding practices, lack of adequate quality and amount of complementary foods, infection and other environmental exposures are known to contribute to this pattern of growth faltering in under-resourced settings. The first 1000 days of life (conception through 24 months of age; www.thousanddays.org), during which critical human growth and development occur, is well recognized as a life-stage continuum between the foetal period and infancy and early childhood. Thus, foetal growth and birthweight as its culmination, are likely to influence childhood growth, and stunting in children may have prenatal origins.[6] For example, high rates of low birthweight (LBW, birthweight <2.5 kg) and childhood stunting tend to co-exist in many settings. LBW is estimated at 16% in developing countries, with rates higher in Asia than in Africa.[2] Underlying biological contributors to LBW include preterm birth (gestational age <37 weeks) and foetal growth restriction (FGR), which is usually described as small-for-gestational age (SGA), defined as a sex-specific birthweight below the 10th percentile for gestational age of a reference standard. In 2010, the Child Health Epidemiology Reference Group (CHERG) estimated 11.1% of all live births, or 14.9 million, to be preterm, worldwide.[7] The 2010 estimate of prevalence of SGA at full term ($\geqslant 37$ weeks) ranges from 5.5% of live births in Eastern Asia to 40.3% in Southern Asia.[8]

LBW and stunting are positively correlated in ecological country-level analyses[9] but few birth cohort studies have examined the associations between foetal growth and childhood nutritional status. Specifically, the effects of stunting and wasting related to SGA and preterm have not been previously estimated. SGA and preterm are important to examine separately as their aetiologies are known to differ, as may their relative contribution to childhood undernutrition.

The primary aim of this analysis was to estimate the risk of stunting, wasting and underweight in children 12–60 months of age, and when available at exactly 24 months of age, related to combinations of preterm and SGA categories and LBW, using data from birth cohorts and longitudinal studies.

Methods

Identification of birth cohorts

We conducted a detailed search for extant datasets from birth cohorts with anthropometric data in early childhood in LMIC. Studies were identified through Medline search and other known sources including: (i) the concurrent CHERG (www.cherg.org) working group, (ii) a meta-analysis of multiple micronutrient supplementation trials on birth outcomes,[10] (iii) the Consortium of Health Oriented Research in Transitioning Societies (COHORTS) profile[11] and

(iv) the principal investigator (Parul Christian) of the CHERG Prenatal origins working group.

Literature review (data inputs)

We developed five categories of Mesh and title/abstract (tiab) terms to identify studies with both birth and childhood (12–60 months of age) anthropometric data in LMIC: exposure, outcome, age group at follow up, study type and countries. Within each category, all search terms were combined with 'OR'. All categories were combined as follows: [Exposure] AND [Outcome] AND [Age group at follow up] AND [Study type] AND [LMIC]. The exposure category consisted of Mesh terms: 'birthweight', 'infant, low birthweight', 'gestational age', 'f(o)etal growth retardation', 'Infant', 'premature', 'premature birth', 'obstetric labor, premature', 'Infant, small for gestational age', 'pregnancy', 'pregnancy complications' and similar tiab terms including 'appropriate for gestational age' and 'small for gestational age'. The outcome category consisted of Mesh terms: 'growth', 'growth and development', 'child development', 'body weight', 'body size', 'body mass index', 'body height', 'body composition', 'anthropometry' and related tiab terms such as 'stunting'. The age at follow up category included 'infant', 'child' and 'child, preschool' Mesh and tiab terms. The study type category included Mesh terms: 'retrospective studies', 'prospective studies', 'longitudinal studies', 'epidemiological studies', 'case-control studies', and 'follow up studies'. LMIC were included according to the country classification by UN Millennium Development Goal (MDG) regional groupings. We limited the search to human studies published between 1 January 1990 and 8 June 2011. Language was not restricted if the abstract was available in English.

Titles of articles identified through Medline search were retrieved and evenly divided into three groups in order of publication date. Three PhD students at the Johns Hopkins Bloomberg School of Public Health each screened ~700 titles and abstracts for eligibility and coded them as potentially relevant or irrelevant. Irrelevant studies were filtered out, and full texts of potentially relevant articles were reviewed for eligibility. Unique cohorts were identified and further investigated for eligibility through confirmation of several publications. Studies with questionable eligibility were evaluated by the PI of the CHERG working group (P.C.). Inclusion criteria were: birth cohorts or studies with birth data with valid birthweights and gestational age measurements (last menstrual period, ultrasound, Ballard, Capurro, or Dubowitz methods); and anthropometric measures of children with a follow up of at least 12 months or at least one measurement between 12 and 60 months of age. We chose to include a minimum follow up of 12 months because linear growth faltering is rapid through the 1st year of life. Because growth faltering continues even through 24 months of age and stabilizes somewhat after this, we also examined the risk of stunting and wasting in a smaller group of studies in which measurement of anthropometry was done at exactly 24 months of age. Exclusion criteria were HIV infection in either mothers or babies, genetic disorders in children and small sample size ($n < 200$) of the original study. PIs of all eligible cohorts were contacted and invited to collaborate. PIs who agreed to participate were given the option of conducting a standard set of analyses independently and sending the results to the CHERG working group or to grant permission to use their dataset to conduct the analysis.

Data analysis

Data analysis was conducted for each cohort and estimates were used for meta-analysis.

We used SGA, preterm (<37 weeks of gestation) and LBW (<2.5 kg) for prenatal exposures. SGA was defined as less than the 10th percentile for gestational age using the US population-based standard of Alexander *et al.*[12] Children whose birthweights were measured more than 72 h after birth and those whose gestational ages at delivery were equal to or more than 44 weeks were excluded. We also excluded implausible combinations of gestational age and birthweights based on the method reported by Alexander *et al.*[12]

Outcomes included length/height for age standard deviation score (HAZ), weight for length/height (WHZ) and weight for age (WAZ), calculated according to the 2006 WHO child growth standards.[13] Stunting, wasting and underweight were defined as HAZ, WHZ and WAZ less than −2 *z*-scores. Child age was defined as the number of months from date of birth to date of anthropometric measurement. For children with longitudinal anthropometric measurements between 12 and 60 months of age, the last visit with complete anthropometry was used.

We estimated odds ratios (OR) and 95% confidence intervals (CI) for stunting, wasting and underweight associated with LBW, SGA and preterm. ORs were estimated instead of relative risks because incident stunting or wasting was not known in many studies, only a single measurement of anthropometry was available in some studies and, in those which had multiple measurements, we used only the last available measurement. We then evaluated the independent contributions of AGA and preterm, SGA and term, and SGA and preterm—compared with AGA and term as the reference category—to childhood undernutrition. Interaction between preterm and SGA was tested in the datasets provided to the CHERG working group. To examine a dose-response relationship, we performed an additional analysis estimating ORs of stunting associated with birthweight categories (≥2.5 kg and <2.5 kg) in infants born SGA and term, compared with infants born AGA and term. We also examined ORs for stunting associated with

sub-categories of gestational age (34 to 37 weeks, 32 to 34 weeks and <32 weeks) compared with the reference group, AGA and term infants. All analyses were conducted for children 12 to 60 months of age and a subset of children at 24 months of age. Child age was adjusted for in all analyses except for the analysis with children followed up at exactly 24 months.

Meta-analysis for overall (LMIC) and regional estimation

We used ORs and standard errors/CIs from each study to make regional and overall estimates using meta-analysis with random-effects models. The DerSimonian and Laird random effects method was used to incorporate an estimate of between-study variation (heterogeneity) in the weighting.[14] Between-study heterogeneity was quantified using the I^2 statistic (expressed as %) and Cochrane's Q (significance level <0.05). Forest plots were used to display individual and pooled estimates. Sensitivity analysis was done by running models adjusted for child's age and sex, twins, infection, child and maternal interventions, parity, socioeconomic status, maternal education and maternal infection, using the 10 datasets provided to the CHERG working group to examine whether confounding was a concern. Stratified analyses by maternal age (<20 years, 20–29 years and ⩾30 years), parity (0, 1–3 and ⩾4), child sex (male/female), cohort years (1970–80s, 1990s and 2000s) (data not shown) and preterm categories (<32 weeks, 32–34 weeks and 34–37 weeks) were performed to examine heterogeneity by subgroups. Funnel plots (not shown) were examined to assess publication bias that may affect pooled estimates. A forest plot using a random-effects model was used to present estimates of ORs for childhood stunting at 12 to 60 months by birthweight categories in children born SGA and term, with a reference group of children born AGA and term. All statistical analyses were performed with Stata software, version 12 (Stata Corp, College Station, TX).

Population attributable risk

In order to estimate population attributable risk (PAR) which would be over-estimated using OR and high prevalence rates of exposures, we derived relative risks (RRs) and 95% CIs from adjusted ORs and their 95% CIs by employing the method proposed by Zhang and Yu.[15] This approximation is applied when the prevalence of a condition in the study population is high. The validity of this method was examined by comparing with RRs estimated by Poisson regression among 10 available studies. For stunting, the approximated mean RR for SGA and term was almost identical (RR = 1.53) in the 10 studies when compared with that derived using the regression analysis (RR = 1.54). We calculated regional and LMIC PAR using Levin's formula:[16] $p(RR-1)/(1+p(RR-1))$ and 95% CIs of PAR were estimated using the delta method.[17] Population attributable burden was calculated by multiplying the PAR by the estimated number of children stunted or wasted. Regional and LMIC prevalence of size for gestational age and term combinations were based on the year 2010 extracted from the concurrent CHERG working group.[8] Estimated regional and LMIC prevalence and number of stunted and wasted children were based on the year 2011.[1] We derived pooled RRs from the two China studies and applied them to Eastern Asia with the following caveats: only one study had an estimate for stunting and wasting associated with AGA and preterm and was considered as representative; and neither study had estimates for wasting associated with SGA and preterm, because no children were wasted in this category, thus null associations were used. We calculated pooled RRs from the remaining Asian cohort studies and applied them to Southern, Southeastern and Western Asia. RRs for Sub-Saharan Africa and Latin America were applied to all African regions and Latin America and Caribbean, respectively. Overall (LMIC) RRs were applied to Oceania and Caucasus and Central Asia regions.

Results

Our search yielded over 2000 articles that were reviewed by title and abstract, and 1880 were excluded according to general criteria such as study not from LMIC, in an HIV population or being a review paper (Figure 1). Of the remaining 230 articles, 179 were excluded because of missing exposure or outcome variables, and identification of redundant cohorts. After this exclusion we had 51 unique cohorts, which, with 8 others from identified known sources, gave us a pool of 59 cohorts which we assessed for their eligibility for inclusion in this analysis. A total of 33 cohorts were deemed eligible and 19 datasets were ultimately analysed. Fourteen studies were excluded because they were deemed ineligible upon further examination ($n = 4$), or because the PI did not respond ($n = 7$) or declined participation ($n = 3$). Studies included in the analysis were conducted between 1970 and 2007. Ten of the datasets were analysed by CHERG researchers, whereas nine investigators conducted their own analyses using the analytic protocol and programs provided to them.

Weight and gestational age at birth were available for 58 317 out of a total 66 074 live births. Of the children who were followed ($n = 54\,611$), anthropometry was available in 44 374 (81.2%) children who were included in the analysis (Supplementary Figure 1, available as Supplementary data at *IJE* online).

Birthweight and gestational age across the 19 studies are shown in Table 1. Mean birthweight ranged from 2.63 kg in India to 3.43 kg in China. Mean gestational age was less variable at ~39.0 weeks,

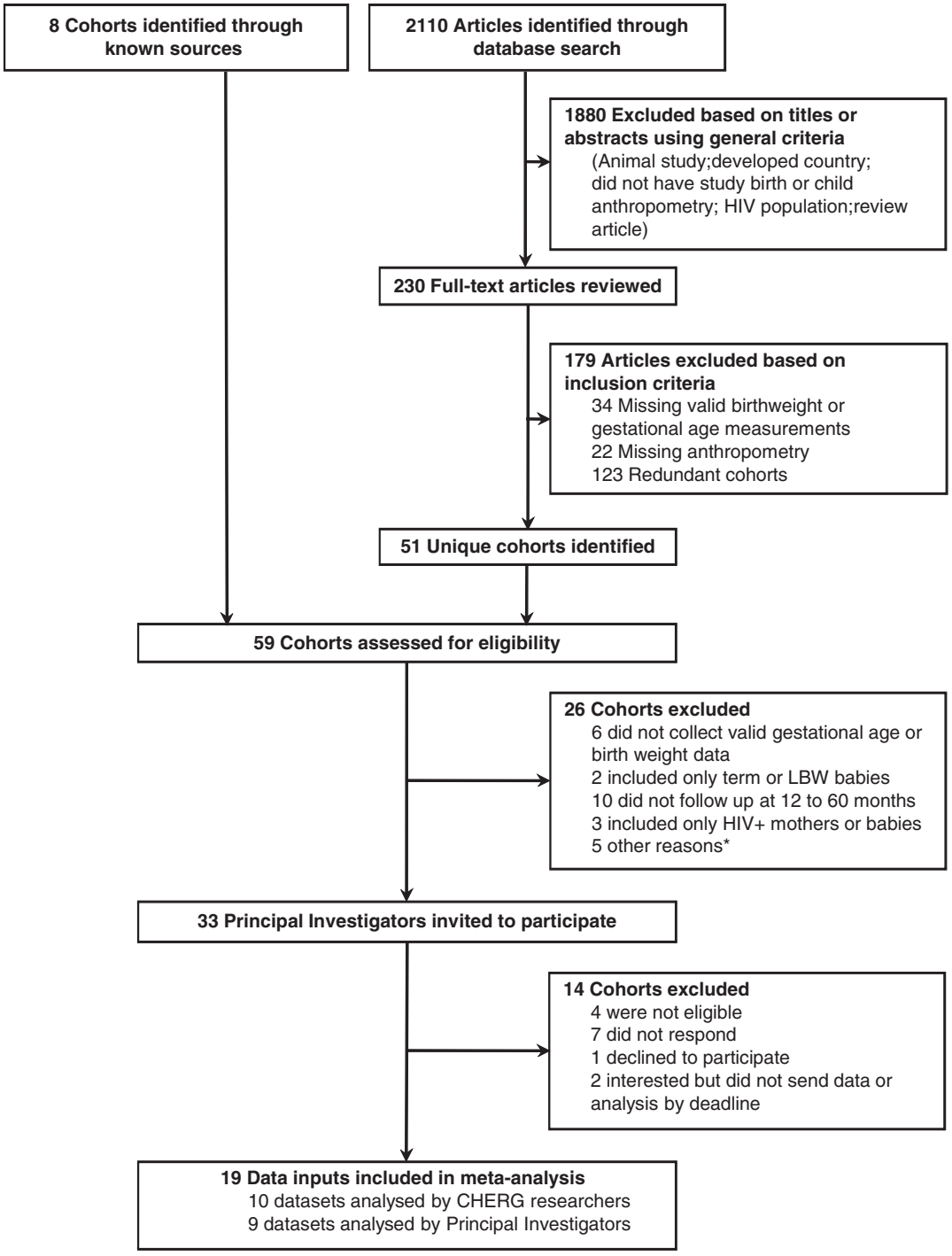

Figure 1 Flow diagram of literature search for cohorts

although two cohorts recorded a lower mean at 38.1 weeks. LBW prevalence was highly variable, ranging from 1.0% in Tianjin, China, to 31.0% in Nepal, with a similar variability in the prevalence of SGA ranging from 6.1% in China to 64.5% in India. Preterm birth ranged from 1.1% in China to 18.5% in Malawi. The prevalence of SGA and term was higher in South and Southeastern Asia than in East Asia, whereas SGA and preterm was not common across the cohorts, suggesting different underlying causes of preterm birth and foetal growth restriction. The burden of stunting was high in many cohorts, ranging between 50 and 70%, although older cohorts appeared to have a higher prevalence (Table 2). Wasting was less

Table 1 Birthweight and gestational age characteristics by study cohort

Study	*N*	Birthweight, kg mean (SD)	Gestational age, wks mean (SD)	LBW[a] (%)	SGA[b] (%)	Preterm[c] (%)	AGA Preterm (%)	SGA Term (%)	SGA Preterm (%)
Nepal (Janakpur Trial)[18]	909	2.79 (0.42)	38.9 (1.7)	21.1	50.5	6.7	4.2	48.0	2.5
Nepal (Newborn Washing Study, Sarlahi)[19]	1134	2.69 (0.45)	38.9 (2.3)	31.0	53.3	16.0	11.6	48.9	4.4
Bangladesh (MINIMat)[20]	2499	2.70 (0.40)[d]	38.8 (1.7)[d]	29.3	58.9	7.4	4.6	56.1	2.8
India (Pune Maternal Nutrition Study)[21]	674	2.63 (0.38)	39.0 (1.7)	31.6	64.5	9.5	5.9	61.0	3.6
India (Parthenon Study, Mysore)[22]	585	2.87 (0.44)	38.9 (1.6)	17.8	43.9	6.5	4.8	42.2	1.7
China (Shaanxi)[23]	1261	3.18 (0.41)	39.9 (1.5)	3.6	18.3	3.5	3.2	18.0	0.3
China (Tianjin)[24]	9289	3.43 (0.44)	39.3 (1.2)	1.0	6.1	1.1	0.9	6.0	0.2
Philippines (Cebu)[25]	2414	3.00 (0.42)	38.8 (2.1)	10.6	24.4	16.5	14.3	22.1	2.2
South Africa (BT20)[26]	1656	3.09 (0.51)	38.1 (1.9)	9.9	16.4	11.7	10.0	14.7	1.6
Burkina Faso (MISAME)[27–29]	1261	2.94 (0.42)	38.9 (2.1)	13.1	31.3	10.5	8.3	29.2	2.1
Zimbabwe (ZVITAMBO)[30]	5733	3.01 (0.44)	39.0 (1.4)	11.7	30.2	6.1	3.9	28.0	2.2
Malawi (LCSS)[31]	146	3.00 (0.51)	39.1 (3.1)	10.3	22.6	18.5	17.8	21.9	0.7
Tanzania (Dar es-Salam)[32]	6098	3.14 (0.50)	39.6 (2.8)	6.7	19.2	14.7	13.9	18.4	0.8
Kenya (ABCP)[33]	947	3.11 (0.43)	39.0 (1.1)	6.9	21.8	2.1	1.7	21.3	0.4
Brazil (Pelotas 1982)[34]	3571	3.25 (0.51)[e]	39.4 (1.8)[e]	5.9	16.5	5.4	4.4	15.6	0.9
Brazil (Pelotas 1993)[35]	1220	3.17 (0.53)	38.1 (1.6)	10.2	14.4	10.5	7.4	22.1	3.5
Brazil (Pelotas 2004)[36]	3600	3.17 (0.53)[f]	38.6 (2.3)[f]	9.1	14.6	13.9	11.8	12.6	2.0
Guatemala (INCAP)[37]	601	3.02 (0.47)	39.4 (2.4)	9.3	33.4	10.8	10.0	32.6	0.8
Mexico (Cuernavaca)[38]	776	3.23 (0.45)	38.7 (1.8)	4.8	9.2	9.0	8.9	9.0	0.1

LBW, low birthweight; SGA, small-for-gestational age.
[a]LBW defined as birthweight <2.5 kg.
[b]SGA defined as size <10th percentile for gestational age.
[c]Preterm defined as delivery at gestational age <37 weeks.
[d]Estimated using $n = 2735$.
[e]Estimated using $n = 3948$.
[f]Estimated using $n = 3830$.

Table 2 Child age and anthropometric measures by study cohort

Study	*N*	Age, mo. mean (SD)	HAZ mean (SD)	WHZ mean (SD)	WAZ mean (SD)	Stunting (%)	Wasting (%)	Underweight (%)
Nepal (Janakpur Trial)[18]	909	30.3 (4.2)	−2.23 (1.10)	−0.63 (1.04)	−1.68 (1.02)	58.0	7.6	37.2
Nepal (Newborn Washing Study, Sarlahi)[19]	1134	38.7 (11.1)	−2.50 (1.29)	−1.01 (1.00)	−2.14 (0.97)	62.5	11.8	57.3
Bangladesh (MINIMat)[20]	2499	54.6 (1.8)	−1.55 (0.92)	−1.31 (0.84)	−1.80 (0.87)	31.3	19.5	40.3
India (Pune Maternal Nutrition Study)[21]	674	59.2 (3.0)	−1.61 (0.87)	−1.34 (0.81)	−1.84 (0.84)	32.3	21.8	42.0
India (Parthenon Study, Mysore)[22]	585	59.5 (0.7)	−0.90 (0.90)	−1.40 (0.90)	−1.40 (0.90)	9.9	25.0	26.2
China (Shaanxi)[23]	1261	29.6 (3.3)	−0.89 (1.00)	0.16 (0.89)	−0.35 (0.84)	12.2	1.1	2.5
China (Tianjin)[24]	9289	48.7 (7.0)	0.19 (0.96)	0.15 (0.97)	0.23 (0.95)	1.1	0.9	0.6
Philippines (Cebu)[25]	2414	23.5 (2.1)	−2.56 (1.18)	−0.50 (1.00)	−1.70 (1.07)	67.4	6.8	36.8
South Africa (BT20)[26]	1656	29.7 (16.7)	−1.04 (1.25)	0.30 (1.38)	−0.32 (1.20)	20.8	4.4	7.1
Burkina Faso (MISAME)[27–29]	1261	22.0 (9.9)	−1.75 (1.28)	−0.74 (1.17)	−1.46 (1.09)	41.6	12.5	28.6
Zimbabwe (ZVITAMBO)[30]	5733	16.0 (5.3)	−1.23 (1.19)	0.11 (1.15)	−0.52 (1.09)	23.8	3.3	8.2
Malawi (LCSS)[31]	146	56.7 (11.0)	−2.37 (1.12)	0.13 (1.12)	−1.36 (1.04)	58.2	3.4	21.9
Tanzania (Dar es-Salam)[32]	6098	13.7 (2.7)	−1.14 (1.20)	−0.23 (1.21)	−0.72 (1.18)	21.7	7.1	12.6
Kenya (ABCP)[33]	947	34.0 (14.8)	−2.27 (1.59)	−0.36 (1.50)	−1.00 (1.29)	56.1	6.4	18.8
Brazil (Pelotas 1982)[34]	3571	43.2 (3.7)	−0.59 (1.08)	0.57 (0.97)	0.04 (1.03)	9.5	0.3	2.0
Brazil (Pelotas 1993)[35]	1220	54.0 (3.6)	−0.20 (1.12)	0.54 (1.15)	0.25 (1.17)	5.2	0.4	2.3
Brazil (Pelotas 2004)[36]	3600	49.5 (1.7)	−0.16 (1.05)	0.70 (1.17)	0.37 (1.19)	3.6	0.6	1.6
Guatemala (INCAP)[37]	601	44.8 (13.8)	−2.62 (1.01)	0.16 (0.89)	−1.44 (0.88)	73.4	1.2	24.6
Mexico (Cuernavaca)[38]	776	48.7 (5.8)	−0.50 (0.90)	0.10 (1.00)	−0.20 (1.00)	5.0	0.8	2.1

HAZ, height-for-age *z*-score; WHZ, weight-for-height *z*-score; WAZ, weight-for-age *z*-score.

Table 3 Regional and overall odds ratios for childhood undernutrition at 12 to 60 months among babies born low birthweight, small-for-gestational age, and preterm

Regions [number of studies]	*N*[e]	LBW[a] OR[d] (95% CI)	SGA[b] OR[d] (95% CI)	Preterm[c] OR[d] (95% CI)
Stunting				
Southern/Eastern Asia [8]	18 765	2.64 (2.30, 3.02)	2.13 (1.85, 2.46)	1.34 (1.15, 1.55)
Sub-Saharan Africa [6]	15 841	2.77 (2.12, 3.62)	2.32 (2.10, 2.56)	1.98 (1.72, 2.27)
Latin America [5]	9768	3.67 (2.96, 4.56)	3.07 (2.58, 3.66)	1.79 (1.25, 2.55)
LMIC [19]	44 374	2.92 (2.56, 3.33)	2.32 (2.12, 2.54)	1.69 (1.48, 1.93)
Wasting				
Southern/Eastern Asia [8]	18 765	2.42 (2.03, 2.88)	2.46 (2.15, 2.81)	1.20 (0.85, 1.69)
Sub-Saharan Africa [6]	15 841	2.48 (1.89, 3.25)	2.18 (1.89, 2.52)	1.76 (1.46, 2.12)
Latin America [5]	9768	7.48 (3.79, 14.80)	3.78 (1.85, 7.75)	3.78 (1.93, 7.39)
LMIC [19]	44 374	2.68 (2.23, 3.21)	2.36 (2.14, 2.60)	1.55 (1.21, 1.97)
Underweight				
Southern/Eastern Asia [8]	18 765	3.28 (2.86, 3.77)	3.14 (2.55, 3.87)	1.27 (1.10, 1.46)
Sub-Saharan Africa [6]	15 841	3.48 (3.06, 3.97)	2.60 (2.26, 2.99)	2.05 (1.68, 2.51)
Latin America [5]	9768	4.56 (3.14, 6.64)	3.78 (2.46, 5.80)	2.14 (1.56, 2.93)
LMIC [19]	44 374	3.48 (3.14, 3.87)	2.96 (2.61, 3.36)	1.66 (1.42, 1.95)

SGA, small-for-gestational age; LBW, low birthweight; LMIC, low- and middle-income countries.
[a]LBW defined as <2.5 kg measured within 72 h of birth, compared with ⩾2.5 kg.
[b]SGA defined as size <10th percentile for gestational age, compared with ⩾10th percentile for gestational age.
[c]Preterm defined as delivery at gestational age <37 weeks, compared with gestational age ⩾37 weeks.
[d]Adjusted for child age.
[e]Maximum number.

common across regions, with the exception of South Asia.

ORs for conventional exposure categories including LBW, preterm and SGA (Table 3) showed that LBW was associated with an overall increased odds of 2.92 (95% CI: 2.56, 3.33) for stunting.

Regional and overall LMIC risk estimates for stunting, wasting and underweight at 12–60 months of age are presented by SGA and preterm categories (Table 4, Figure 2). Relative to AGA and term birth, the ORs (95% CI) for stunting associated with AGA and preterm, SGA and term and SGA and preterm were 1.93 (1.71, 2.18), 2.43 (2.22, 2.66) and 4.51 (3.42, 5.93), respectively (Table 4), suggesting an additive risk in the presence of both conditions. A similar magnitude of risk was also observed for wasting and underweight among children. None of the SGA and preterm interaction terms had *P*-value of <0.05 (data not shown). There was limited regional variation in these risk estimates, although there was a trend of preterm alone being associated with a somewhat lower risk of undernutrition in Southern/Eastern Asia than in Africa and Latin America. In Latin America the risk for wasting among SGA and preterm was high at 21.57 (8.18, 56.90) given a low prevalence of wasting (<0.5%) in the referent category.

SGA and term infants without LBW had lower odds of stunting (OR = 1.92, 95% CI: 1.75, 2.11) vs SGA or term accompanied by LBW (OR = 3.00, 95% CI: 2.36, 3.81) (Figure 3). AGA but extremely preterm (<32 weeks), very preterm (32–34 weeks) and moderate-to-late preterm (34–37 weeks) had ORs (95% CI) of 3.93 (2.79, 5.54), 2.78 (1.75, 4.40) and 1.81 (1.63, 2.02), respectively (Figure 4).

Adjustment for confounders beyond child age, including sex, parity, twinning, infection, interventions, socioeconomic status, maternal education, prenatal intervention and infection did not change the risk estimates (Supplementary Table S1, available as Supplementary data at *IJE* online). ORs for the combinations of size for gestational age and preterm birth, using anthropometry at exactly age 24 months as the outcome, were also estimated (Supplementary Table S2, available as Supplementary data at *IJE* online).

PAR was estimated for childhood stunting and wasting for each of the risk categories (Table 5). The PAR for SGA and term for stunting and wasting was 0.16 (0.12, 0.19) and 0.24 (0.21, 0.26), respectively. The prevalences of SGA and AGA preterm are small, largely because of the low prevalence of preterm ranging from 1 to 3%. The combined PAR related to overall SGA for stunting was 0.20, and that for wasting was 0.30. PAR for LBW was estimated at 0.12 (0.09, 0.16) for stunting and 0.18 (0.14, 0.23) for wasting (data not shown). The attributable burden related to overall SGA for stunting was

Table 4 Regional and overall odds ratios for childhood undernutrition at 12 to 60 months of age, by adequacy of size for gestational age and preterm birth using AGA and term as the reference category

Regions [number of studies]	N^{d}	AGA and preterm[a,b] OR (95% CI)[c]	SGA and term[a,b] OR (95% CI)[c]	SGA and preterm[a,b] OR (95% CI)[c]
Stunting				
Southern/Eastern Asia [8]	18 765	1.56 (1.31, 1.87)	2.25 (2.03, 2.50)	3.63 (2.50, 5.28)
Sub-Saharan Africa [6]	15 841	2.13 (1.87, 2.42)	2.36 (2.09, 2.67)	5.95 (3.84, 9.22)
Latin America [5]	9768	2.21 (1.59, 3.08)	3.34 (2.78, 4.02)	4.31 (2.22, 8.36)
LMIC [19]	44 374	1.93 (1.71, 2.18)	2.43 (2.22, 2.66)	4.51 (3.42, 5.93)
Wasting				
Southern/Eastern Asia [8]	18 765	1.65 (1.03, 2.64)	2.58 (2.22, 2.98)	3.50 (2.25, 5.42)
Sub-Saharan Africa [6]	15 841	2.20 (1.54, 3.13)	2.42 (2.07, 2.82)	3.44 (2.21, 5.34)
Latin America [5]	9768	3.28 (1.04, 10.29)	3.73 (1.92, 7.21)	21.57 (8.18, 56.90)
LMIC [19]	44 374	1.96 (1.46, 2.63)	2.52 (2.27, 2.80)	4.19 (2.90, 6.05)
Underweight				
Southern/Eastern Asia [8]	18 765	1.58 (1.33, 1.88)	3.27 (2.67, 4.00)	4.57 (3.43, 6.08)
Sub-Saharan Africa [6]	15 841	2.36 (2.01, 2.77)	2.77 (2.36, 3.24)	6.10 (4.48, 8.30)
Latin America [5]	9768	3.05 (2.06, 4.52)	4.46 (2.82, 7.06)	6.67 (3.56, 12.52)
LMIC [19]	44 374	2.07 (1.76, 2.44)	3.17 (2.78, 3.62)	5.35 (4.39, 6.53)

AGA, adequate-for-gestational age; SGA, small-for-gestational age; LMIC, low- and middle-income countries.
[a]AGA defined as size ⩾10th percentile for gestational age; SGA defined as size <10th percentile for gestational age.
[b]Term defined as delivery at gestational age ⩾37 weeks; preterm defined as delivery at gestational age <37 weeks.
[c]Adjusted for child age.
[d]Maximum number.

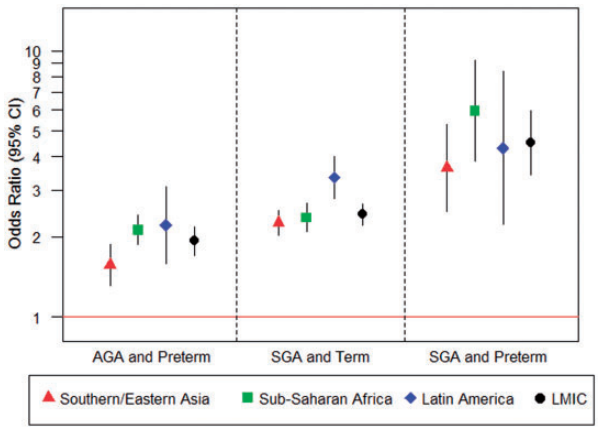

Figure 2 Regional and LMIC odds ratios for childhood stunting at 12 to 60 months of age by size for gestational age and preterm birth. Reference group is children born AGA and term; LMIC, low- and middle-income countries

about 32 million, whereas that for wasting was estimated at 15 million (Table 6).

Discussion

Our analysis estimated the odds ratios of childhood (12–60 months) stunting, wasting and underweight associated with SGA and preterm birth using data from 19 birth cohorts from LMICs. Relative to AGA and term, SGA and term birth was associated with a 2.4 and AGA and preterm birth with a 1.9 increased odds of stunting. The odds ratio was increased to 4.5 in births both SGA and preterm. Similar associations were observed for wasting and underweight. In LMIC, the attributable burden of stunting and wasting among children due to SGA was estimated at 32 and 15 million, respectively. The observational nature of these data does not permit causal inference, but is consistent with foetal origins of both childhood stunting and wasting.

We saw limited variation in the association between birth exposures and childhood undernutrition by region, which we consider to be biological. The risk of undernutrition associated with being born small or too soon was comparable across populations and regions, despite the large variation in the prevalence of both SGA and preterm birth, largely reflecting the common underlying causes in these settings of either foetal growth restriction or preterm birth. Latin America as a region had the lowest rates of both exposures, but the highest risk association, although the number of cohorts and sample sizes of the studies were small, yielding somewhat unstable estimates. Two studies contributed data from China,[23,24] which showed extremely low prevalence rates of both the exposure and the outcomes, with comparable or even lower rates of these seen in developed countries.

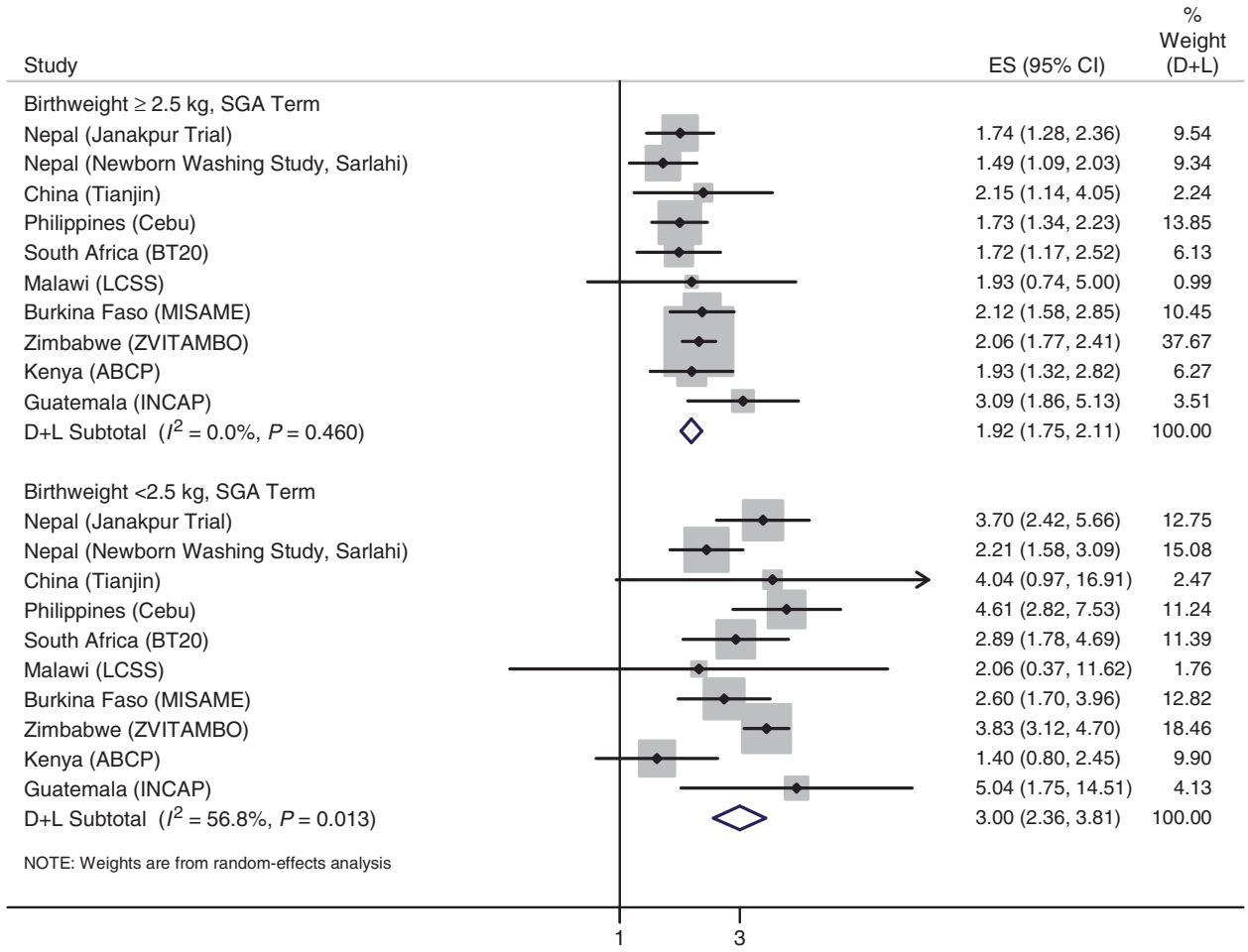

Figure 3 Random-effects model forest plot of odds ratios for childhood stunting at 12 to 60 months by birthweight categories in children born SGA and term. Reference group is children born AGA and term. Includes 10 cohorts, using data provided to CHERG working group

In general, the studies from Africa had younger ages at follow up, which may have attenuated the relationship.

Recently, preterm has been shown to be associated with a higher risk of neonatal mortality, with relative risks ranging from 6 to 9, vs SGA alone, which was consistently associated with a 3-fold increased risk.[39] This seems plausible, as prematurity is one of the three largest causes of neonatal mortality worldwide.[40] In contrast, the longer-term growth consequences we report appear to indicate a stronger association between SGA and stunting than between preterm and stunting. Additionally, both SGA and preterm birth categories showed a dose-response relationship with stunting; SGA with low birthweight *vs.* not, and extremely or very preterm birth vs moderate or late preterm, were associated with a higher risk of stunting in childhood. This indicates that foetal growth restriction as assessed by SGA, and in the absence of low birthweight carries a lower, but still raised, risk of later stunting, suggesting a need for programmes to move toward measurement of SGA in addition to birthweight and preterm birth to identify newborns at risk.

Although there are many children who are growth restricted despite not being low birthweight and/or preterm, the co-occurrence of both preterm and SGA was remarkably low (1–2%), suggesting different aetiologies of SGA and preterm birth. The lower prevalence of the two conditions may also in part be due to the higher mortality in this group. Generally, preterm babies are less likely to be SGA because they have less time for growth and therefore growth restriction, especially as foetal growth is accelerated in the last few weeks of pregnancy.

Our data analysis and approach have several strengths and some limitations. Across 19 identified cohorts, we had a total sample of 44 374. We had good representation from different regions of the world. Deriving regional estimates from a limited number of countries may have its disadvantages for some regions, but the lack of heterogeneity in the risk estimates assures us that the relationship we observed was biologically plausible. Additionally, our sensitivity

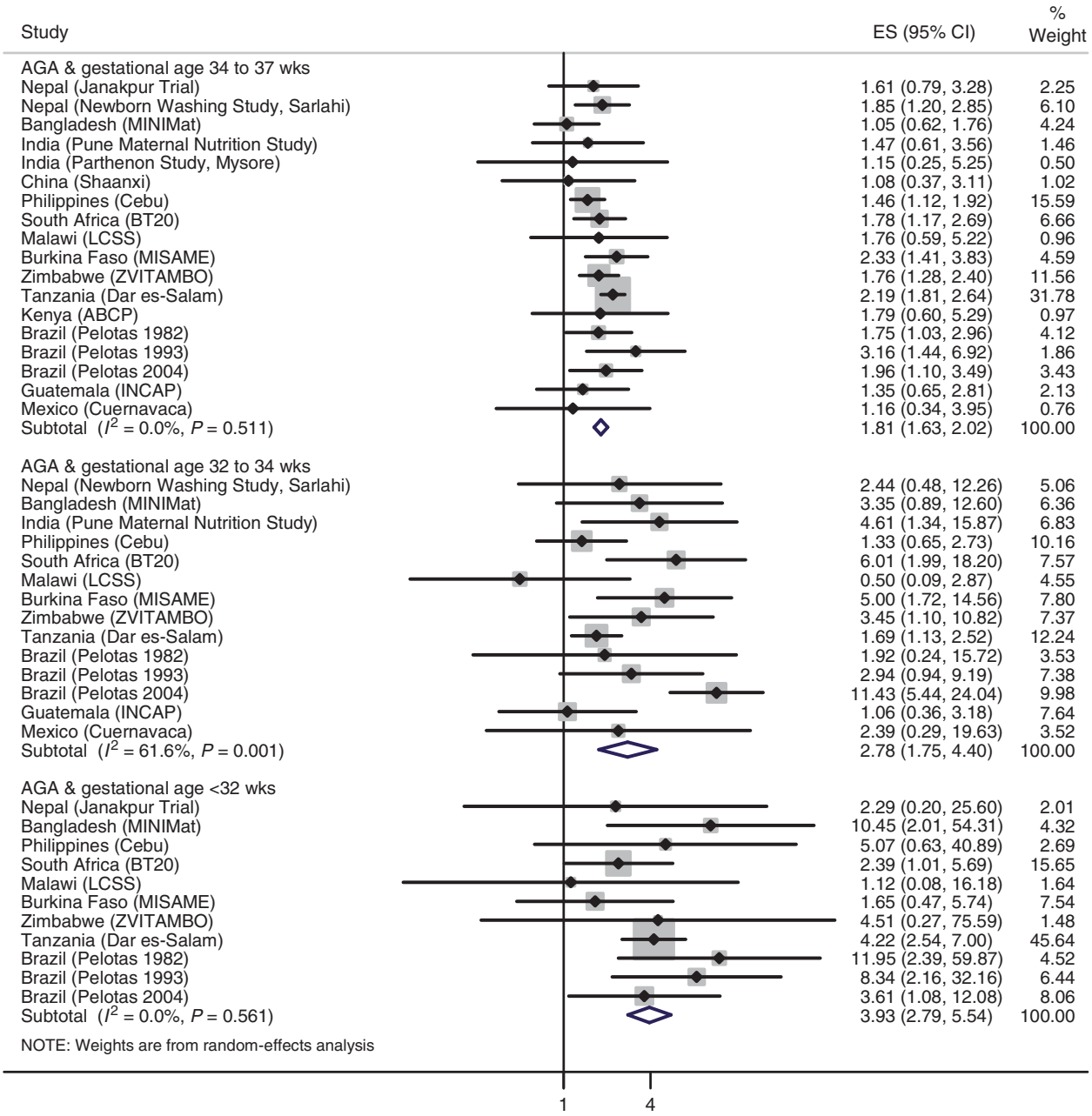

Figure 4 Random-effects model forest plot of odds ratios for childhood stunting at 12 to 60 months by gestational age categories in children born AGA and preterm. Reference group is children born AGA and term

analysis revealed no evidence of strong confounding and showed a dose-response relationship, indicating possible causal associations. One limitation, as expected in longitudinal studies, was the loss-to-follow up, especially due to mortality, which may result in a potential survival bias. A higher mortality in the SGA and especially in the preterm birth categories probably resulted in an underestimation of ORs rather than an overestimate, making our estimates of the risk relationship conservative. Other types of losses and missing values may have either attenuated or inflated the ORs, but we had limited information to determine whether the loss-to-follow-up differed by exposure categories. Another limitation was the lack of data on birth length in several cohorts, which we anticipate would be more strongly correlated with later stunting than SGA.[41] In a study among West Javanese infants, neonatal weight and length in multivariable analyses were the strongest positive predictors of nutritional status of infants and the strongest negative predictors of increases in weight and length during infancy.[42] This analysis will be

Table 5 Population attributable risk for childhood stunting and wasting at 12–60 months of age due to SGA and preterm birth categories, overall and by MDG regions

	SGA and term[a,b]			SGA and preterm[a,b]			AGA and preterm[a,b]		
MDG-regions [number of studies]	Prevalence (%)[c]	RR	PAR (95% CI)	Prevalence (%)[c]	RR	PAR (95% CI)	Prevalence (%)[c]	RR	PAR (95% CI)
Stunting									
Caucasus and Central Asia [19][d]	12.9	1.76	0.09 (0.07, 0.11)	2.1	2.68	0.03 (0.02, 0.05)	7.3	1.49	0.03 (0.02, 0.05)
Eastern Asia [2]	5.3	2.10	0.05 (0.03, 0.08)	1.7	7.27	0.09 (0.03, 0.16)	5.8	0.99	0.00 (−0.05, 0.05)
Southeastern Asia [6]	21.2	1.51	0.10 (0.06, 0.14)	3.0	1.85	0.03 (0.01, 0.04)	10.6	1.21	0.02 (0.01, 0.03)
Southern Asia [6]	41.5	1.51	0.18 (0.11, 0.24)	2.9	1.85	0.02 (0.01, 0.04)	10.3	1.21	0.02 (0.01, 0.03)
Western Asia [6]	19.6	1.51	0.09 (0.05, 0.13)	2.2	1.85	0.02 (0.01, 0.03)	7.7	1.21	0.02 (0.01, 0.02)
Oceania [19][d]	19.4	1.76	0.13 (0.10, 0.16)	1.6	2.68	0.03 (0.02, 0.04)	5.7	1.49	0.03 (0.02, 0.04)
Northern Africa [6]	8.5	1.65	0.05 (0.03, 0.08)	1.2	2.98	0.02 (0.02, 0.03)	6.2	1.62	0.04 (0.02, 0.05)
Sub-Saharan Africa [6]	23.5	1.65	0.13 (0.08, 0.19)	2.0	2.98	0.04 (0.03, 0.04)	10.3	1.62	0.06 (0.04, 0.08)
Latin America and the Caribbean [5]	10.7	2.45	0.13 (0.03, 0.24)	1.8	3.84	0.05 (0.01, 0.09)	6.7	1.88	0.06 (0.00, 0.11)
LMIC [19]	24.7	1.76	0.16 (0.12, 0.19)	2.3	2.68	0.04 (0.02, 0.05)	9.1	1.49	0.04 (0.03, 0.06)
Wasting									
Caucasus and Central Asia [19][d]	12.9	2.25	0.14 (0.12, 0.16)	2.1	3.55	0.05 (0.03, 0.07)	7.3	1.88	0.06 (0.03, 0.09)
Eastern Asia [2]	5.3	2.55	0.08 (0.02, 0.14)	1.7	1.00	0.00	5.8	2.61	0.08 (−0.09, 0.26)
Southeastern Asia [6]	21.2	2.19	0.20 (0.17, 0.24)	3.0	2.88	0.05 (0.02, 0.08)	10.6	1.53	0.05 (−0.02, 0.12)
Southern Asia [6]	41.5	2.19	0.33 (0.28, 0.38)	2.9	2.88	0.05 (0.02, 0.08)	10.3	1.53	0.05 (−0.02, 0.12)
Western Asia [6]	19.6	2.19	0.19 (0.16, 0.22)	2.2	2.88	0.04 (0.02, 0.06)	7.7	1.53	0.04 (−0.01, 0.09)
Oceania [19][d]	19.4	2.25	0.19 (0.17, 0.22)	1.6	3.55	0.04 (0.02, 0.06)	5.7	1.88	0.05 (0.02, 0.07)
Northern Africa [6]	8.5	2.26	0.10 (0.07, 0.12)	1.2	3.09	0.02 (0.01, 0.04)	6.2	2.11	0.06 (0.03, 0.10)
Sub-Saharan Africa [6]	23.5	2.26	0.23 (0.19, 0.27)	2.0	3.09	0.04 (0.02, 0.06)	10.3	2.11	0.10 (0.05, 0.15)
Latin America and the Caribbean [5]	10.7	3.69	0.22 (0.07, 0.38)	1.8	20.79	0.26 (0.08, 0.44)	6.7	3.20	0.13 (−0.06, 0.31)
LMIC [19]	24.7	2.25	0.24 (0.21, 0.26)	2.3	3.55	0.06 (0.03, 0.08)	9.1	1.88	0.07 (0.03, 0.11)

AGA, adequate-for-gestational age; SGA, small-for-gestational age; PAR, population attributable risk; LMIC, low- and middle-income countries.
[a]AGA defined as size ⩾10th percentile for gestational age; SGA defined as size <10th percentile for gestational age.
[b]Term defined as delivery at gestational age ⩾37 weeks; preterm defined as delivery at gestational age <37 weeks.
[c]Estimates of prevalence extracted from the concurrent CHERG working group.[8]
[d]No study from this region; RR for all LMIC used for PAR calculation.

Table 6 Population attributable burden[a] for childhood stunting and wasting by low birthweight, SGA and preterm birth

	LBW		SGA		Preterm	
MDG-region	**Stunting**	**Wasting**	**Stunting**	**Wasting**	**Stunting**	**Wasting**
Caucasus and Central Asia	78 199	26 128	172 679	57 045	96 794	33 493
Eastern Asia	328 108	184 427	1 117 785	152 087	701 034	169 982
Southeastern Asia	1 043 320	599 275	1 825 529	1 332 796	686 975	558 854
Southern Asia	93 42 401	5 971 181	13 604 176	10 677 979	3 069 295	2 907 789
Western Asia	281 569	84 066	482 464	183 505	150 424	63 847
Oceania	33 936	13 005	61 888	23 516	21 730	8 815
Northern Africa	149 313	86 705	255 232	144 422	204 120	106 770
Sub-Saharan Africa	5 897 206	2 203 385	9 492 042	3 535 281	5 450 969	1 884 386
Latin America and the Caribbean	670 169	259 594	1 149 626	386 248	650 828	309 578
Pooled (LMIC)	20 290 635	9 508 034	32 062 280	14 994 233	13 217 176	6 671 370

SGA, small-for-gestational age, defined as size <10th percentile for gestational age. LBW, defined as <2.5 kg measured within 72 h of birth; LMIC, low- and middle-income countries.
[a]Attributable burden calculated using estimated number of children stunted or wasted by MDG region, 2011.

pursued separately in cohorts which have data on birth length. Also, conditional growth analysis would have enabled us to account for the contribution of different periods of postnatal growth.

Nutritional interventions during pregnancy have been shown to be beneficial for foetal growth, but less so for increasing gestational age, except perhaps for prenatal zinc.[43] Recent meta-analyses of food (calorie and protein) supplementation during pregnancy showed a reduction of 34% in the risk of SGA (RR = 0.68, 95% CI: 0.51, 0.92),[44] and meta-analyses of randomized controlled trials of daily prenatal multiple micronutrient supplementation (without food) also show a significant reduction in SGA (pooled RR = 0.83, 95% CI: 0.73, 0.95).[45] Combining these nutritional intervention approaches in settings where maternal undernutrition is high, and multiple micronutrient deficiencies common,[46] would not only be important for addressing the huge burden of foetal growth restriction, but may also result in improved childhood nutritional status. Prenatal food supplementation has been shown to reduce stunting in children,[47] but not with multiple micronutrients,[47,18] although weight and circumferential measurements improved at 2 years of age.[18] Integration of prenatal and preschool balanced protein-calories with other public health programmes in a study in India was associated with improved height and healthier profiles of cardiovascular disease risk.[48]

Pre-pregnancy maternal height and BMI are strong determinants of low birthweight and SGA, in addition to maternal weight gain during pregnancy.[49] An inverse association between maternal height and child stunting has been found in a pooled analysis of DHS data,[50] although the data were cross-sectional.[51] Pre-pregnancy maternal height, an indicator of long-term nutritional status and other exposures, is linked to uterine volume and is a well-known predictor of foetal growth and birth size.[52] In many LMIC settings the intergenerational cycle of growth failure links small maternal size to the mother's size at birth and growth in childhood and adolescence. Thus, there is evidence that factors that well precede the pregnancy are strong and robust predictors of childhood undernutrition. Preconceptional interventions for improving maternal pre-pregnancy BMI, and interventions that can influence linear growth and attained adult height are therefore likely to benefit outcomes of foetal growth.

It is well recognized that postnatal growth tracks, although conventionally 'catch-up', is believed to occur among about 50% of children to achieve a normal pattern of growth and to meet genetic potential, at least in well-nourished environments.[53] In undernourished settings, our analyses allowed us to estimate the extent of tracking between the prenatal and postnatal periods. Factors and practices contributing to growth faltering in the first few years of life include: inadequate exclusive breastfeeding; frequency, energy density and micronutrient levels of complementary foods; and infectious morbidity. In many resource-poor settings, the basic and underlying causes of both foetal and childhood undernutrition are common and need to be uniformly addressed to improve growth and development in the first 1000 days of life.

Our analysis revealed an independent relationship, stronger for foetal growth restriction than preterm, with childhood stunting and wasting across regions, suggesting that child growth and nutritional status may be strongly linked to foetal life and in part prenatal in origin, suggesting a need to intervene during an earlier life stage with the focus on pregnancy nutrition.[52] Addressing the global problem of childhood stunting requires a life-stage approach, with interventions targeting the pregnancy period even as efforts

for improving breastfeeding and complementary feeding practices in the first 2 years of life are continued. The need for such a life-course approach to intervening is reflected in the emphasis on the first 1000 days.

Supplementary Data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- The extent to which stunting, common in low- and middle-income countries, is associated with foetal growth restriction and preterm birth—two causes of low birth weight—remains to be established.
- A meta-analysis of 19 longitudinal birth cohorts revealed small-for-gestational age (SGA) and preterm to be each associated with a 2.4 and 1.9 times increased odds of stunting, with both conditions being associated with a 4.5 times the risk.
- The population attributable risk for overall SGA for outcomes of childhood stunting and wasting was 20% and 30%, respectively.
- Childhood undernutrition is high in many settings; our analysis reveals that it may have its origins in part in the foetal period suggesting the need for early life interventions, especially during pregnancy.

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