Mortality risk in preterm and small-for-gestational-age infants in low-income and middle-income countries: a pooled country analysis

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Summary

Background Babies with low birthweight (<2500 g) are at increased risk of early mortality. However, low birthweight includes babies born preterm and with fetal growth restriction, and not all these infants have a birthweight less than 2500 g. We estimated the neonatal and infant mortality associated with these two characteristics in low-income and middle-income countries.

Methods For this pooled analysis, we searched all available studies and identified 20 cohorts (providing data for 2 015 019 livebirths) from Asia, Africa, and Latin America that recorded data for birthweight, gestational age, and vital statistics through 28 days of life. Study dates ranged from 1982 through to 2010. We calculated relative risks (RR) and risk differences (RD) for mortality associated with preterm birth (<32 weeks, 32 weeks to <34 weeks, 34 weeks to <37 weeks), small-for-gestational-age (SGA; babies with birthweight in the lowest third percentile and between the third and tenth percentile of a US reference population), and preterm and SGA combinations.

Findings Pooled overall RRs for preterm were 6·82 (95% CI 3·56–13·07) for neonatal mortality and 2·50 (1·48–4·22) for post-neonatal mortality. Pooled RRs for babies who were SGA (with birthweight in the lowest tenth percentile of the reference population) were 1·83 (95% CI 1·34–2·50) for neonatal mortality and 1·90 (1·32–2·73) for post-neonatal mortality. The neonatal mortality risk of babies who were both preterm and SGA was higher than that of babies with either characteristic alone (15·42; 9·11–26·12).

Interpretation Many babies in low-income and middle-income countries are SGA. Preterm birth affects a smaller number of neonates than does SGA, but is associated with a higher mortality risk. The mortality risks associated with both characteristics extend beyond the neonatal period. Differentiation of the burden and risk of babies born preterm and SGA rather than with low birthweight could guide prevention and management strategies to speed progress towards Millennium Development Goal 4—the reduction of child mortality.

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Introduction

An estimated 20 million infants every year are born with low birthweight (LBW; <2500 g),[1] and these infants have an increased risk mortality in the first year of life. The primary causes of LBW are preterm birth, intrauterine growth restriction (IUGR), or a combination of the two. Of 135 million children born in low-income and middle-income countries (LMICs) in 2010, an estimated 29·7 million were born both term and small-for-gestational-age (SGA), 10·9 million were born preterm and appropriate-for-gestational-age, and 2·8 million were born preterm and SGA.[2] Risk factors and interventions to reduce the number of babies born SGA might differ from those to reduce the number of babies born preterm. The survival and growth patterns of preterm or growth-restricted newborn babies are not well described in LMICs and the contribution to mortality of non-LBW babies (≥2500 g) who are preterm or those with IUGR in such settings is unknown.

Few studies in LMICs have investigated differences in mortality by extent of prematurity, IUGR, or the two in combination,[3,4] or mortality risk in infants who are SGA stratified by gestational age.[5–10] Examination of the mortality risk by degree of prematurity and SGA as a proxy for IUGR might be crucial in understanding the attributable disease burden, especially because regions such as south Asia have a reported SGA prevalence of about 40%.[11,12] Such mortality risk estimates and attributable burden could enable the specific targeting of these disorders with appropriate interventions to more effectively save lives.

The Child Health Epidemiology Reference Group (CHERG) previously examined the risk of infant mortality associated with term-LBW as a proxy for IUGR.[13] However, term-LBW excludes growth-restricted infants weighing more than 2500 g and high risk infants born both preterm and SGA, and such

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associations between mortality and SGA-non-LBW or SGA-preterm have not been well described in LMICs. With more population-based studies in LMICs now collecting data for gestational age in addition to birthweight, the CHERG identified an opportunity to assess the mortality risk of SGA and preterm on early neonatal, late neonatal, neonatal, post-neonatal, and infant mortality.

Methods

Dataset identification

We searched Medline, WHO regional databases (African Index Medicus, LILAS, EMRO), bibliographies of sentinel articles and reviews, and grey literature to identify potential datasets from low-income and middle-income countries that recorded data for gestational age and birthweight, and systematically recorded vital status from delivery through at least 28 days of life. The most recent search was done on Feb 22, 2010. We applied no no date or language restrictions. Search terms included "preterm or SGA", "neonatal or infant mortality", and "developing country" (see appendix for detailed search terms). CHERG investigators also identified additional datasets that were not retrieved in our search. We excluded datasets for the following reasons: greater than 25% missing data for birthweight or gestational age, or loss to follow-up; measured weight only after the first week of life; did not have systematic follow-up of vital status in the first month of life; determined gestational age in months or by fundal height; or when we deemed gestational age determination inaccurate or poorly linked to birthweight (appendix). We aimed to include only datasets that were population-based, representing all deliveries arising from specific geographical or catchment areas, whether home-based or facility-based. We excluded stillbirths from the analyses of these cohorts. We approached principal investigators to do a set of standard analyses themselves, or to share their data with the CHERG working group to do the analyses. Datasets that were shared with the working group did not contain personal identifiers and were therefore deemed exempt by the Johns Hopkins Bloomberg School of Public Health institutional review board. Datasets analysed by the original study investigators were covered under existing institutional review board approvals.

Exposure definitions

If more than one gestational age measurement was available we used estimates in the following order of preference: ultrasound, best obstetric estimate (combination of ultrasound, date of last menstrual period, and neonatal clinical exam), last menstrual period, or clinical examination of the infant within 72 h of birth. Prematurity was defined as a gestational age of less than 37 completed weeks. We categorised prematurity into less than 32 weeks (early preterm), 32 weeks to less than 34 weeks

(moderate preterm), and 34 weeks to less than 37 weeks (late preterm).[14]

Weight was analysed if measured within 72 h. SGA was defined as birthweight below the tenth percentile of a standard optimal reference population for a given gestational age and sex. Appropriate-for-gestational-age (AGA) was defined as above the tenth percentile. WHO previously recommended data in a study by Williams and colleagues (collected in California from 1972 to 1976) as the reference.[15] We chose the more recent and commonly cited Alexander reference,[16] which includes 3 134 879 nationally representative, multi-ethnic births in the USA in 1991. Because that dataset provided data at only the tenth percentile, we identified another dataset (Oken and colleagues[17]) based on US data from 1999–2000 (6 690 717 births) that provided Z scores. We created two categories of SGA using a combination of these two reference populations:[16,17] the tenth percentile of Alexander[16] to the third percentile of Oken and colleagues,[17] and the lowest third percentile of Oken and colleagues. AGA included large-for-gestational-age (LGA) infants (≥90% birthweight for gestational age). However, in these datasets, the prevalence of LGA was very small and their inclusion in the reference population likely had very little effect on mortality risk.

We created four mutually exclusive exposures to capture interaction between preterm (<37 weeks) and SGA (<10%): term and appropriate-for-gestational-age (as reference), term-SGA, preterm and appropriate-for-gestational-age, and preterm and SGA. We defined mortality as early neonatal (birth to 7 days), late neonatal (8–28 days), neonatal (birth to 28 days), post-neonatal (29–365 days), and infant (birth to 365 days) mortality. For late neonatal and post-neonatal infant mortality, the denominators were infants alive at the start of the interval of interest with vital status available through the end of the interval.

Analysis of individual datasets

The same analysis was done on each dataset. We used an algorithm developed by Alexander and colleagues[16] to exclude infants with incompatible birthweight-gestational age combinations. Gestational ages of less than 24 weeks and more than 48 weeks were also excluded. We calculated the prevalence of LBW, preterm, SGA, and the overlap of these disorders for each dataset. We calculated relative risks (RRs) and risk differences (RDs) for early, late, neonatal, post-neonatal, and infant mortality associated with preterm and SGA categories.

RRs were adjusted for all confounders available in each dataset (including occupation of head of household, land ownership, years of maternal and paternal education or literacy, and maternal age and parity). We did adjusted analyses on 13 of the 20 datasets. Regression coefficients for the primary associations of interest were attenuated at less than 10% in all datasets except for one,[32] for which the parameters were not statistically significant.

Missing exposure data

All studies had few missing gestational age data (<10%). Analyses of mortality risk by preterm categories used all available gestational age data, irrespective of missing birthweight (full gestational age cohort). There were two main reasons for missing birthweight data (most of which were from home deliveries): some infants who died soon after delivery were not weighed, and infants who were weighed were measured at different times after delivery. For risk estimates associated with SGA, we included infants with weights taken within 72 h of birth (weighed cohort). For four Asian and two African studies with missing data for birthweight or that measured some weights after 72 h, we used multiple imputation[18] to impute birthweights (appendix). The imputed datasets were used to estimate the RRs and RDs.

Pooled analysis

Because multivariate adjustment did not substantially modify estimates of associations, we used the crude RRs and 95% CIs, and pooled data for the major UN Millennium Development Goal regions (Asia, Africa, and Latin America). We estimated overall and regional RRs of mortality for each exposure variable (preterm, SGA, and combinations). We used Stata (version 11) for all statistical analyses. Random effects models used the DerSimonian-Laird pooled RRs and 95% CIs, given between-study heterogeneity.[19]

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to most of the datasets, had access to all summary estimates from each dataset for meta-analysis, and had final responsibility for the decision to submit for publication.

Results

We included 20 datasets with 2 015 019 livebirths from sub-Saharan Africa, Latin America, and south and southeast Asia, with gestational age available for 2 008 675 babies and both gestational age and birth-weight available for 1 996 763 babies (table and appendix).[4,20–40] Study dates ranged from 1982 through to 2010. The Chilean national birth registry[35] provided much of these data. The prevalence of preterm birth (<37 weeks) in the study datasets ranged from 2·7% to 28%, with varying methods of gestational age determination (see appendix for specific study

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See Online for appendix

	Setting	Primary study design	Study population	N (original cohort)	N (analysed cohort for preterm/for SGA)	NMR (deaths per 1000 livebirths)	IMR (deaths per 1000 livebirths)	Systematic follow-up period	% LBW	% preterm	% SGA	% facility delivery
Asia												
Bangladesh (2005)[21]	Rural Sylhet	Cluster RCT of community sepsis treatment	Population-based recruitment of all pregnant women in study area	10 585	10 585/10 550*	31	..	1 month	30%	19%	50%	6%
India (2000)[26]	Rural Tamil Nadu	RCT of newborn vitamin A supplementation	Population-based recruitment of all pregnant women in study area	13 294	12 693/12 693*	38	..	6 months	33%	14%	62%	63%
Nepal (1999)[22]	Rural Sarlahi	Cluster RCT of multiple micronutrient supplementation	Recruitment of all pregnant women in study area	4130	4122/4094*	42	67	1 year	39%	22%	56%	6%
Nepal (2003)[25]	Peri-urban/rural Dhanusha	RCT of antenatal micronutrient supplementation	Antenatal clinic-based recruitment of pregnant women in study area	1106	1106/1052	25	..	1 month	22%	7%	53%	53%
Nepal (2004)[29]	Rural Sarlahi	Cluster RCT of newborn skin-umbilical cord cleansing with chlorhexidine	Population-based recruitment of all pregnant women in study area	23 662	23 650/22 723*	32	..	6 months	30%	18%	52%	10%
Pakistan (2003)[39]	Rural Sindh	Cluster RCT of maternal micronutrient supplementation	Population-based recruitment of all pregnant women in study villages	1548	1464/1434	18	..	1 month	19%	28%	28%	100%
Philippines (1983)[20]	Urban Cebu	Longitudinal health-nutritional survey of infant feeding patterns	Population-based, random cluster sample of census	3080	3050/2785	14	36	2 years	11%	18%	25%	34%
Thailand (2001)[24]	Urban Bangkok	Prospective follow-up of birth cohort	Longitudinal birth cohort of all births in four districts	4245	4032/3860	5	6	1 year	8%	9%	22%	99%

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(Continued from previous page)												
Sub-Saharan Africa												
Burkina Faso (2004)[27]	Rural Hounde	RCT of multiple micronutrient supplementation	Prospective, community-based cohort	1373	1311/1212*	21	67	1 year	17%	16%	35%	77%
Burkina Faso (2006)[36]	Rural Hounde	RCT of maternal fortified food supplementation	Prospective, community-based cohort	1316	1261/1067	20	..	1 month	16%	18%	29%	84%
South Africa (2004)[34]	Urban Soweto	RCT of birth canal and newborn skin cleansing with chlorhexidine	Facility-based delivery, tertiary-care hospital	8113	8113/8098	7	..	1 month	8%	4%	16%	100%
Tanzania (1998)[32]	Rural Mwanza	Maternal syphilis treatment, observational cohort	Facility-based recruitment; urban, antenatal clinics	1496	1425/1172	16	..	3 months	10%	3%	25%	98%
Tanzania (2001)[23]	Urban Dar es Salaam	RCT of mutivitamin supplementation	Facility-based, antenatal clinics	7752	7740/7557	28	..	6 weeks	8%	17%	20%	97%
Tanzania (2008)[38]	Rural Korogwe	Observational malaria study	Facility-based recruitment, antenatal clinics, community follow-up.	915	820/731	33	..	28 days	11%	5%	22%	88%
Uganda (2005)[37]	Rural Kabale district	RCT intermittent preventive malaria therapy and insecticide-treated nets	Facility-based recruitment ANC clinics; only include facility births	1561	1553/1477	17	..	1 month	7%	6%	10%	100%
Zimbabwe (1997)[33,40]	Urban Harare	RCT of maternal-neonatal vitamin A supplementation	Facility-based recruitment, 14 maternity clinics and hospitals	14 110	13 960/13 914	12†	93	1 year	14%	8%	33%	100%
Latin America												
Brazil (1982)[30]	Urban Pelotas city, Rio Grande do Sul, southern Brazil	Longitudinal birth cohort survey	Population-based, all births in Pelotas hospitals (100% facility delivery)	5914	4675/4670	11	28	1 year	7%	6%	17%	100%
Brazil (1993)[31]	Urban Pelotas city, Rio Grande do Sul, southern Brazil	Longitudinal birth cohort survey	Population-based, all births in Pelotas hospitals (100% facility delivery)	5279	4707/4632	7	14	1 year	9%	11%	19%	100%
Brazil (2004)[28]	Urban Pelotas city, Rio Grande do Sul, southern Brazil	Longitudinal birth cohort survey	Population-based, all births in Pelotas hospitals (100% facility delivery)	4287	3903/3837	10	17	1 year	11%	16%	15%	100%
Chile (2000)[35]	Chilean national birth registry	Birth registry	Population-based registry	1 901 611	1 898 250/1 898 250	5	..	1 month	6%	7%	7%	98%

RCT=randomised controlled trial. SGA=small for gestational age. NMR=neonatal mortality rate. IMR=infant mortality rate. LBW=low birthweight. *Weights imputed for datasets that met criteria described in appendix. †Enrolment of newborn babies occurred up to 96 h after birth, and the study might have missed neonatal deaths that happened before enrolment.

Table: Study characteristics of 20 included datasets

methods). The proportions of preterm births before 32 weeks of gestation ranged from 0% to 4% (appendix). Comparison of preterm prevalence by method of assessment was not possible because few studies used more than one method. The prevalence of SGA was generally higher than that of preterm births, ranging from 7% in the Chile national registry to 62% in a community-based trial in south India (appendix). The proportion of LBW infants who were SGA or preterm varied by region (figure 1). In the Asian cohorts, 83% of LBW infants were SGA and 33% were preterm (67% of LBW were term and SGA). In the African cohorts, 79% of LBW infants were SGA and 38% were preterm (62% of LBW were term and SGA). In the Latin American cohorts, 53% of LBW infants were SGA and 71% were preterm (29% of LBW were term and SGA). South Asia had the highest prevalence of preterm births and number of LBW and SGA infants. A substantial proportion of SGA infants did not have LBW in Asia (54%), Africa (65%), and Latin America (59%). The

proportion of children who were both SGA and preterm was small in these datasets (4% in Asia, 1% in Africa, and 2% in Latin America). In Africa and Asia, term infants were more often SGA than were preterm infants, but the opposite was true in Latin America (figure 1).

Neonatal mortality rates and relative risks increased with decreasing gestational age across studies and regions (figure 2). Although the highest relative risks (RRs) were seen in Latin America (mainly due to the very low mortality in the reference group), the risk differences were similar across regions. The overall pooled RRs across all regions were 6·82 (3·56–13·07) for neonatal mortality and 2·50 (1·48–4·22) for post-neonatal mortality. The overall pooled RRs across all regions for late preterm (34 weeks to <37 weeks), when most preterm births occur, were 3·05 (2·02–4·60; figure 2 and appendix). The RDs per 1000 livebirths for late preterm ranged from nine (95% CI 0–18) in Africa to 18 (9–28) in Asia, with an overall RD per 1000 livebirths of 13 (9–18; appendix). The overall pooled RRs for early preterm (<32 weeks) were 28·82 (15·51–53·56; figure 2 and appendix), although the RDs per 1000 livebirths ranged from 196 (95–297) in Asia to 350 (189–511) in Latin America, with an overall RD of 245 per 1000 livebirths (192–297; appendix). Early and late neonatal and post-neonatal infant mortality followed similar patterns, but the RRs were more attenuated the longer the follow-up period extended (appendix), except for early preterm in Latin America, when mortality risk decreased substantially across the early-post-neonatal to late-post-neonatal periods. However, a statistically significantly increased mortality risk persisted into the post-neonatal infant period in all regions for preterm compared to term.

Imputation of missing birthweights did not alter the prevalence of SGA, which was already high, although it did increase the risk of mortality associated with SGA (figure 3 and appendix). Neonatal mortality rates increased with severity of SGA (figure 3). The overall pooled RRs for SGA across all regions were 1·83 (1·34–2·50) for neonatal mortality and 1·90 (1·32–2·73) for post-neonatal mortality. The highest RR for SGA in neonates below the third percentile was in Latin America, compared with 1·91 (1·40–2·60) in Asia, although the CIs overlapped. The overall RR was 2·41 (1·66–3·50). Regional pooled RDs per 1000 livebirths for SGA below the third percentile ranged from 12 (10–15) in Asia to 23 (17–29) in Latin America, with an overall RD per 1000 livebirths of 14 (9–19; appendix). The RRs associated with SGA were of similar magnitude in the early-neonatal, late-neonatal, and post-neonatal periods across regions (appendix). The RRs associated with SGA were overall of smaller magnitude than preterm, and the association with increased mortality did not attenuate beyond the neonatal period and persisted through the first year of life.

Relative to term and AGA, the increased risk of neonatal mortality was lowest in those born term-SGA

(overall RR 2·44, 1·67–3·57) and highest in preterm-SGA infants (15·42, 9·11–26·12). RRs were similar for Asia and Africa, but higher in Latin America (figure 4).
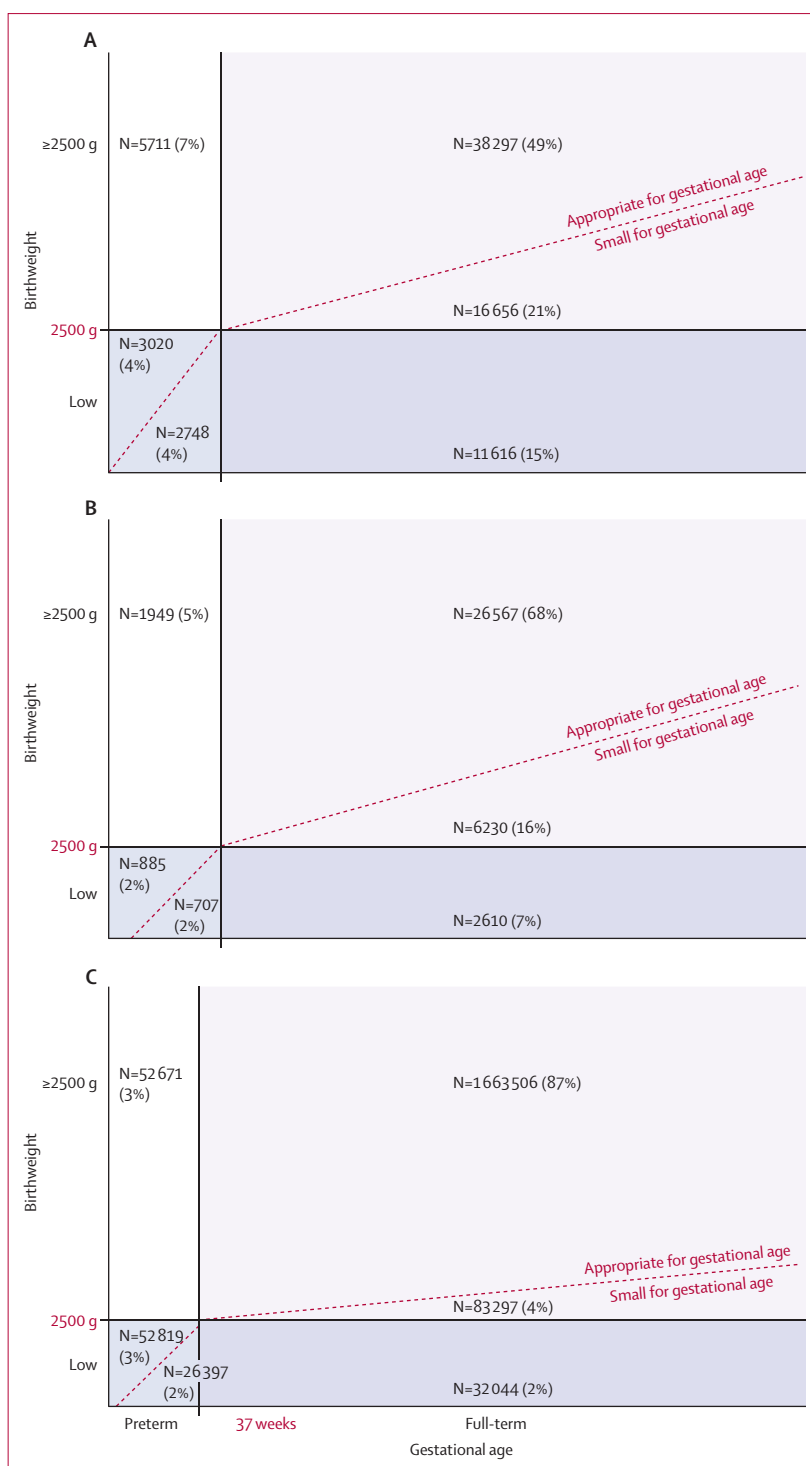

Figure 1: **The relation between birthweight and gestational age in Asia (A), Africa (B), and Latin America (C)**
For Asian cohorts (A), percentages are for 78 048 infants. For African cohorts (B), percentages are for 38 948 infants. For Latin American cohorts (C), percentages are for 1 910 734 infants.
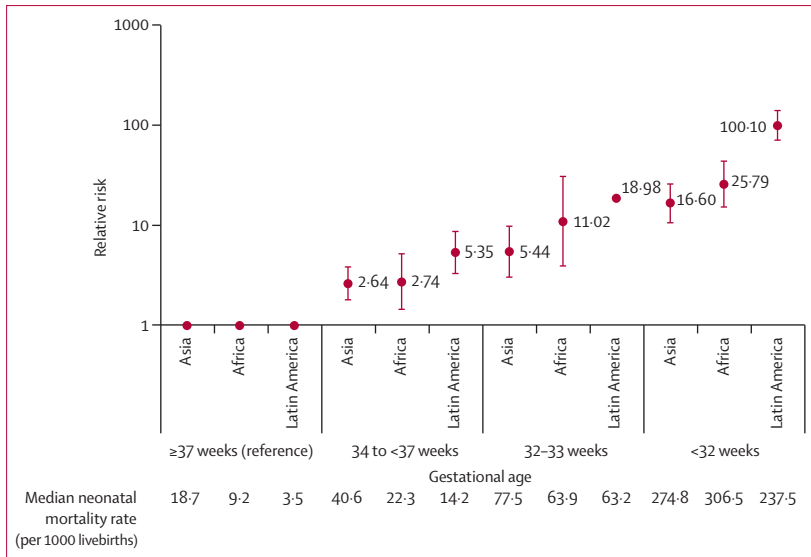
Figure 2: Relative risk of neonatal mortality associated with gestational age
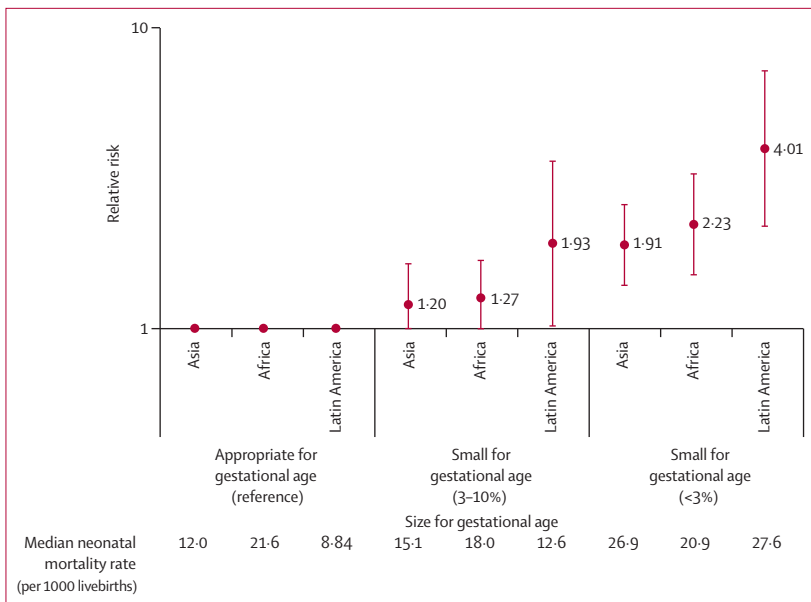Error bars are 95% CI.

Figure 3: Relative risk of neonatal mortality associated with small for gestational age

These higher RRs in Latin America were probably driven by the low mortality rate (2·4 per 1000) in the reference group. Pooled RDs were similar across regions (appendix). The RRs for term-SGA babies did not vary by timing of mortality (figure 5). For preterm-AGA and preterm-SGA babies, RRs were highest in the early neonatal period and lowest in the post-neonatal period, although the CIs largely overlapped (ie, no statistically significant between-group differences; figure 5 and appendix). This pattern of attenuated risk by length of follow-up was probably driven by prematurity and not SGA.

Discussion

We identified a large percentage of infants who were SGA but not LBW or preterm (21% in Asia, 16% in Africa, and 4% in Latin America), although their mortality rates were lower than preterm infants or SGA-LBW infants. Although most LBW was in term and SGA babies in Asia and Africa, the majority of babies with LBW in Latin America were preterm. Preterm mortality risk associations were generally higher at all gestational age categories (late, moderate, and early preterm) than SGA (3% to <10% or <3%). However, the attributable mortality risk for SGA infants is substantial, because many infants in LMICs are born SGA, especially in south Asia. The predominant increased mortality risk associated with preterm birth occurred in the first week of life, with statistically significant but attenuated risk remaining in the late-neonatal and post-neonatal periods. Although CIs overlapped, mortality risks associated with SGA were slightly higher in the late than early neonatal period, with persistent risk in the post-neonatal period.

The highest neonatal and infant mortality rates were detected in the Asian and African studies. The highest RRs for all exposures were seen in Latin America, although absolute risk differences were more comparable across regions. This higher RR in Latin America is due to very low mortality in the reference group in Latin America compared with Africa and Asia. In particular, the Latin America analysis was dominated by national registry data from Chile in which term neonatal mortality was 1·7 per 1000 livebirths. By comparison with these data, the average term neonatal mortality was 11 per 1000 livebirths in the African datasets and 19 per 1000 livebirths in the Asian ones. Alternately, preterm infants might be more severely preterm and survive delivery in Latin America but have delayed mortality.

Preterm birth was associated with an increased mortality risk compared with term birth. The proportion of infants born within 32 weeks of gestation was low but these infants had substantially higher mortality risks than did term infants in the first week of life. Late preterm birth comprised 50–96% of preterm births, and was associated with a smaller but statistically significant neonatal mortality risk ranging from 2·52 in Asia to 5·58 in Latin America (risk differences per thousand livebirths were nine in Africa, 11 in Latin America, and 18 in Asia). Evidence-based, low-cost interventions are feasible for LMICs and could reduce mortality related to preterm birth complications, such as antenatal corticosteroids for preterm labour, Kangaroo mother care, and treatment of neonatal infections.[41–43] Our findings suggest that simple interventions to target the improved care of late and moderate preterm infants could have a large effect on the reduction of mortality burden in preterm infants. In areas with a large proportion of facility deliveries and much post-delivery care, clinical interventions such as surfactant administration and continuous positive airway pressure might also improve survival.

Using a common US birthweight reference population, the prevalence of SGA and term-SGA babies was very high (higher than 50%) in many of the community-based South Asian cohorts.[11,12] In statistical modelling to estimate national and regional prevalences of SGA, we estimated that 42% of babies were term-SGA and that 3% of babies were preterm-SGA.[2] These findings contrast with a much lower prevalence of SGA in Africa, despite the high prevalence of risk factors such as malaria and HIV infection in pregnancy. SGA neonates had roughly double the mortality risk of appropriate-for-gestational-age infants, with slightly higher risk in those with more severe SGA. A large proportion of SGA infants weighed 2500 g or more, although their mortality risk was similar to that of term-AGA babies. The very high rates of SGA in South Asia might be explained by higher rates of adolescent pregnancy, chronic maternal malnutrition, low pre-pregnancy body-mass index, low weight gain in pregnancy, and low maternal height.[44–46]

The mortality risk associated with being preterm-SGA was substantially higher than for either alone. An estimated 2·8 million infants are born both preterm and SGA in LMICs annually[2] and these infants are at a 10–40 times increased risk of dying in the first month of life compared with term and appropriate-for-gestational-age infants. These children are key targets for public health interventions.

A strength of this analysis was the large number of representative livebirths analysed from a wide range of studies and geographical regions, producing internal validity and reduced variance of estimates. We adjusted for several covariates but noted that they did not alter the risk estimates. Although the cohort sizes varied substantially, with the Chilean national registry data dominating in absolute numbers, the use of random effects models to do meta-analyses downweights the effect of such large datasets. Although it constitutes 92% of the data, its contribution to the Latin American mortality risk estimate is about 50% and its contribution to the global estimate is 9·7%. While Chile is proably a good representation of a middle-income country in Latin America, it does not represent other low-income countries in the region. The earliest Brazilian cohort[30] might be more representative of such countries because it was done in a low-income setting.

We re-analysed individual data to estimate SGA prevalence and risk, applying a common SGA reference population. This reduced the variation associated with the use of different SGA reference populations commonly seen across studies. Although the use of a common reference population is a controversial issue, with arguments made about whether it is appropriate to apply one standard to all populations, we selected one reference population to be able to better compare our analyses across populations. Our use of a birthweight rather than fetal growth standard might have systematically under-represented SGA in preterm infants because preterm infants might have more
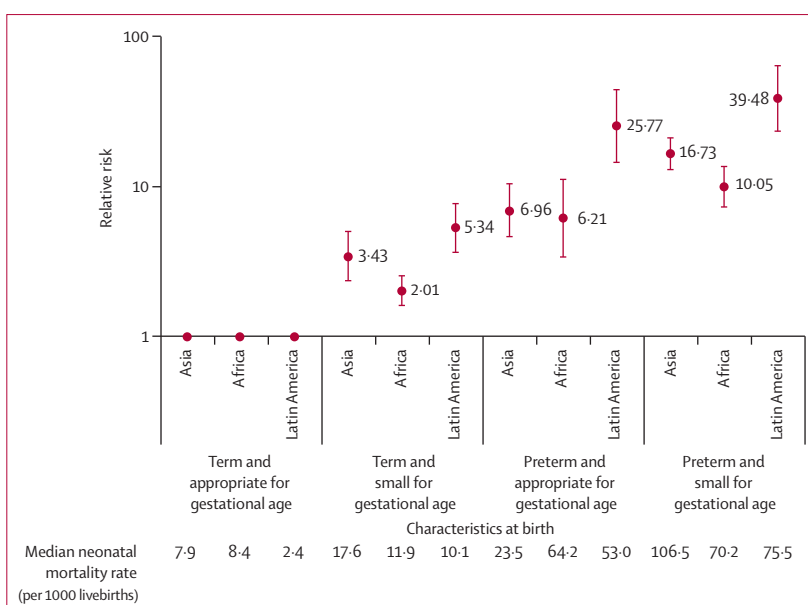

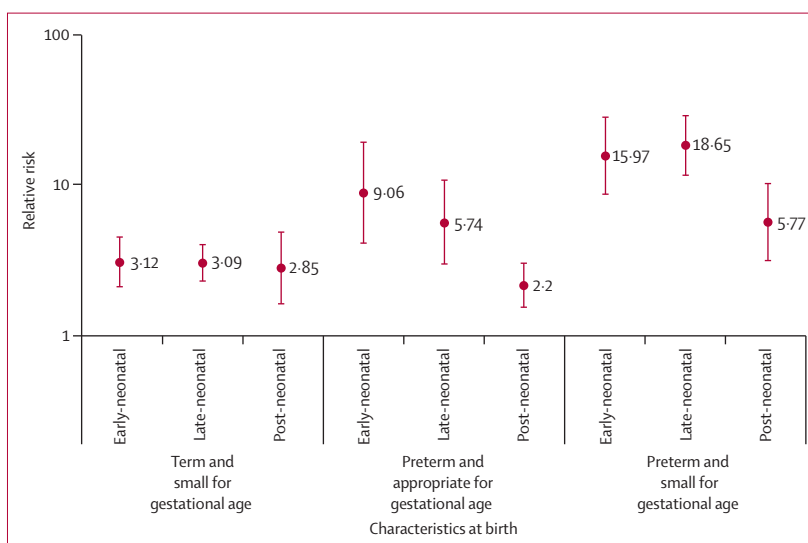Figure 4: Relative risk of neonatal mortality associated with preterm and size for gestational age

Figure 5: Relative risk of early-neonatal, late-neonatal, and post-neonatal infant mortality associated with preterm and size for gestational age

pathological IUGR than fetuses that remain in the womb for longer. The Intergrowth Study is collecting data for a common fetal growth reference using healthy populations from many countries. The use of this standard will help resolve this limitation in the future.

The large sample size allowed us to stratify preterm and SGA into severity categories and to pool mortality risk associated with each category by re-analysing primary data. Available covariates varied by study and residual confounding could have occurred. However, these findings might not be generalisable to countries or regions as a whole because they are derived from cohorts or randomised trials in which the geographical

For **The Intergrowth Study** see http://www.intergrowth21.org.uk

areas might have been selected for specific risk characteristics as evidenced by the range of preterm prevalence across studies (table). However, the use of meta-analyses with random effects of 20 cohorts probably reduced the bias and increased the precision of regional and global risk estimates. Although the prevalence of preterm and SGA births seemed quite variable across these datasets, the mortality differences associated with these characteristics were stable within regions. Hence these estimates are likely to be valid for use in attributable risk calculations if representative estimates of preterm and SGA prevalence are used and residual confounding was minimal.

A limitation of our community-based datasets was the exclusion of early deaths in infants who were not weighed. We used multiple imputation to address the potential effect on mortality associations. Nevertheless, we might have underestimated the mortality risks associated with SGA given that we were missing some covariate data with which to impute birthweight. Another limitation is the variability and accuracy of gestational age measurement between datasets. Nine studies included ultrasound dating, whereas the remainder relied on maternal recall of their last menstrual period or clinical exam. We used the best gestational age determination, excluding datapoints with improbable gestational age and birthweight combinations and datasets with poor gestational age measures. Gestational age categories might have been subject to some misclassification although these were probably minimised by the active, frequent pregnancy surveillance in many studies. Stillbirths were excluded from these analyses, but it is possible that there was misclassification of stillbirths and livebirths, especially in home deliveries that relied on maternal report, but the direction of this misclassification is unclear. Although assessment of cause of death by adverse pregnancy outcome is of interest, very few studies had cause of death, and most population-based studies that did, had cause assigned by physician via verbal autopsy. Assessing causes of death associated with SGA or preterm in these contexts would be a valuable future contribution to the design of appropriate mortality reduction interventions.

Many babies are born SGA in LMICs, especially in south Asia and sub-Saharan Africa, and such babies have increased risk of mortality and poor growth.[47] Preterm birth affects a smaller number of neonates but is associated with a higher mortality risk and seems to be a greater contributor to attributable risk in Latin America than in Asia. In both these regions, these risks extend beyond the neonatal period. Although few effective interventions to prevent preterm exist,[48] several interventions exist to improve preterm survival. Interventions shown to reduce SGA have focused mainly on increasing calories and protein during pregnancy, and more recently (during the past decade) maternal micronutrient supplementation.[48] As measurement of gestational age improves in LMICs, targeting interventions and tracking outcomes that reduce the incidence and improve the survival of babies born preterm and SGA rather than with a LBW might more clearly guide progress towards the reduction of child mortality.

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