Published in final edited form as:

J Pediatr. 2018 January ; 192: 66–72.e4. doi:10.1016/j.jpeds.2017.09.007.

Neonatal and Infant Mortality Risk Associated with Preterm and Small for Gestational Age Births in Tanzania: Individual Level Pooled Analysis Using the Intergrowth Standard

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Abstract

Objectives—To evaluate the risk of newborn and infant mortality associated with preterm, small for gestational age (SGA), and low birth weight (LBW) stratified by maternal HIV status and the location of birth.

Study design—We created a prospective cohort by pooling 5 individually randomized trials. We used Cox proportional hazard models to estimate the risk of mortality for SGA defined using the recently published Intergrowth standard, preterm, LBW, and gestational age and size for gestational age categories (preterm- appropriate for gestational age [AGA], term-SGA, and preterm-SGA). Effect modification by maternal HIV status and place of residence was assessed using the likelihood ratio test.

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The authors declare no conflicts of interest.

Results—Of the 31 988 infants, 15.3% were preterm, 16.6% were SGA, and 7.3% were LBW. The proportion of preterm and SGA births was higher among the HIV-infected cohort than in the uninfected cohort. Compared with term-AGA groups, infants born both preterm and SGA had a greater risk of neonatal mortality (hazard ratio [HR] 5.43, 95% CI 2.01–14.63) than preterm-AGA infants (HR 2.40, 95% CI 1.89–3.05) and term-SGA infants (HR 2.56, 95% CI 1.96–3.34). Maternal HIV infection modified the risk of infant mortality associated with being born preterm or LBW, with a higher relative risk among those born to HIV-uninfected women. Rural residence significantly modified the risk of neonatal mortality associated with being LBW (P for interaction = .005).

Conclusions—Preterm and SGA newborns had an increased risk of mortality during the first year of life. Interventions targeting these conditions, especially in HIV-exposed and rural populations, should be integrated into existing maternal and child health programs.

Neonatal and infant mortality related to preterm birth, low birth weight (LBW), and intrauterine growth restrictions are substantial in low- and middle-income countries.¹ In fact, complications from preterm births account for more than 14% of all deaths in children under 5 years of age.² The attributable mortality risk for small for gestational age (SGA) infants are high; worldwide an estimated 32.4 million babies are born SGA.³ The attributable risk is even higher when stillbirths are considered; SGA fetuses are up to 4 times more likely to be stillborn.⁴

The term SGA, defined as birth weight for gestational age below the tenth percentile of a standard population, is used as a proxy for fetal growth restriction. Although some SGA infants are constitutionally small, majority of SGA births in developing settings are results of growth restriction.⁵ The prevalence of SGA in a population and associated mortality risks, varies by the choice of reference populations.⁶ Recent estimates of mortality risks associated with preterm and SGA in low- and middle-income countries used the US population based standards to define SGA.¹ Some countries such as South Africa⁷ also used weight for gestational age standards based on local populations comprised of pregnant women with suboptimal health and nutritional status, and, thus, these standards may not reflect the full growth potential of the fetus. Recently, Papageorgiou et al⁸ published the Intergrowth standard, an international standard for fetal growth based on serial ultrasound measurements of fetuses born to healthy pregnant women at low risk of adverse perinatal outcomes from 8 geographically diverse populations. This standard is currently considered to be the most appropriate reference population to define SGA around the world.

The magnitude of risk of mortality because of preterm and SGA among vulnerable populations such as those living in rural areas or HIV-exposed infants needs evaluation. It is known that HIV-infected pregnant women experience an elevated risk of adverse birth outcomes and infant mortality.^{9–11} The high incidence of preterm and SGA births in HIV-infected women is partly attributed to HIV infection and the use of antiretroviral treatment (ART) in pregnancy to prevent mother-to-child transmission of HIV.^{12, 13} In general, infant survival and nutritional outcomes are thought to be better in urban areas, compared with rural areas, in low-income countries. However, an analysis including data from 47 countries found that the rates of stunting and child mortality are actually higher among the urban poor

compared with rural counterparts.¹⁴ As inequality declines between urban and rural cohorts, some research suggests this is partly accounted for by the declining health metrics for urban infants.¹⁵ The 2010 Tanzania Demographic and Health Survey estimated the infant mortality rate to be relatively higher in urban areas than in rural areas, 63 and 60 per 1000 live births, respectively.¹⁶ It is not known whether the risk associated with preterm birth and fetal growth restriction may help explain this “urban penalty.” The objective of this report was to evaluate the risk of mortality associated with adverse birth outcomes including preterm, LBW, and SGA defined using the Intergrowth standards in a pooled sample of 5 birth cohorts in Tanzania. Furthermore, we explored whether maternal HIV-status or rural residence modified the risk between adverse birth outcomes and child survival.

Methods

We created a prospective cohort by pooling data from five individually randomized trials of multivitamins in Tanzania. Fawzi et al¹⁷ enrolled 8430 HIV-uninfected pregnant women from 12–27 weeks of gestation and randomized women to multiple micronutrients or iron-folate supplementation. Another trial by Fawzi et al¹⁸ enrolled 1078 HIV-infected pregnant women from 12–27 weeks of gestation and randomized women to multiple micronutrients or iron-folate supplementation. Masanja et al¹⁹ enrolled 31 999 infants at birth who were randomized to receive a mega-dose of vitamin A (50 000 IU) or placebo. Duggan et al²⁰ randomized 2387 infants to receive daily oral supplements of multiple multivitamins or placebo from 6 weeks to 24 months.²⁰ McDonald et al²¹ randomized 2400 infants to zinc, multivitamin, or zinc and multivitamin supplementation. Subjects from these randomized trials were eligible for inclusion in this pooled prospective cohort if they were a singleton, live birth and had full information regarding child sex, gestational age at delivery, and birth weight (Figure 1; available at www.jpeds.com).

Outcomes of interest were early neonatal mortality (deaths < 7 days), neonatal mortality (deaths < 28 days), postneonatal mortality (deaths 29–365 days), and infant mortality (deaths < 365 days). Risk factors of interest included gestational age at birth (established based on the date of last menstrual period and categorized into early preterm [<34 weeks of gestation], preterm [34 to <37 weeks of gestation], and term [≥ 37 weeks of gestation]); SGA severity (severe SGA <3rd percentile, moderate SGA 3rd–10th percentile, appropriate for gestational age [AGA] >10th percentile); and gestational age and size for gestational age categorization (term-AGA, preterm-AGA, term-SGA, preterm-SGA).

Potential confounders included in the multivariate models included household wealth, years of maternal education, parity, whether the birth was by spontaneous vaginal delivery or by cesarean delivery, and maternal age. Household wealth was categorized into tertiles by reported daily food expenditure in three studies^{18, 20, 21} and using principle component analysis of assets in Masanja et al¹⁹ and Fawzi et al¹⁷ study. The level of education was based on the reported number of years of schooling, and this was categorized into no education, primary education (1–7 years), secondary (8–12 years), or more than secondary (>13 years) level. Parity was categorized as first birth or higher. Maternal age was categorized into 5-year age groups (<20 years, 20–<25 years, 25–<30 years, and ≥ 30 years).

Potential effect modifiers of interest were urban or rural residence and maternal HIV infection status. Women who were recruited and resided in Ilala, Temeke, or Kinondoni districts in Dar es Salaam Region were classified as urban, and those residing in Ulanga, Kilosa, and Kilombero districts in Morogoro Region were classified as rural. For studies Fawzi et al,¹⁸ Duggan et al,²⁰ and McDonald et al²¹ maternal HIV status was confirmed by 2 sequential enzyme-linked immunosorbent assays with the use of Murex HIV antigen/antibody (Abbott Murex) followed by the Enzygnost anti-HIV-1/2 Plus (Dade Behring)²² and the discordant results were resolved by the Western Blot test (Bio-Rad Laboratories). For Masanja et al,¹⁹ maternal HIV status was abstracted from the labor ward registers of a subsample of health facilities.

Statistical Analyses

Each study and those included in the cohort for this analysis were characterized using baseline data regarding household, maternal, and infant characteristics using means or proportions for continuous and categorical data, respectively. To examine the relationship between adverse birth outcomes and mortality, we used Cox proportional hazard regression models.²³ We also used Kaplan-Meier survival functions and corresponding log-rank tests to compare infant mortality, stratified by LBW. We assessed effect modification using the likelihood ratio test comparing the saturated model (including interaction terms) with the reduced model (without interaction terms). The missing indicator method was used for missing data to retain these observations in the model. All hypothesis tests were 2-sided, and a *P* value of <.05 was considered to be statistically significant. Analyses were performed using SAS software v 9.2 (SAS Institute, Cary, North Carolina).

Results

A total of 46 294 infants were enrolled in the 5 studies; 3% of infants (*n* = 1264) were twins and were excluded from the cohort. In addition, 13 042 (28%) were excluded from the cohort because of missing information regarding the child's sex, birth weight, or gestational age at delivery. The total number of infants included in the analysis was 31 988 (Figure 1). The majority (76.3%) of women across all studies attended primary school (1–7 years of education). The mean age of women in the cohort was 25.7 years (*SD* ± 5.6 years). Mothers in the study from Duggan et al²⁰ were, on average, older (Table I; available at www.jpeds.com). There were no differences between those included in the analysis compared with women excluded from the analysis (Table II; available at www.jpeds.com).

The early neonatal mortality rate was 9.9 per 1000 live births. The neonatal mortality rate was 13.4 per 1000 live births. The infant mortality rate was 38.8 per 1000 live births. More than 7% of the infants in the cohort were born with LBW, and 15% were born before 37 weeks of gestation. In addition, 16.6% of infants were born SGA (Table III). Of the LBW infants, 60% were SGA, 33% were preterm, and 4% were both preterm and SGA (data not shown). The proportion of preterm and SGA was higher among the HIV-exposed infants compared with HIV-unexposed infants, and similarly the proportion of infants with LBW was higher in rural areas compared with urban areas (Table IV).

Being born preterm was associated with an increased risk of early neonatal, neonatal, and infant mortality compared with term infants. Being an early preterm (<34 weeks) infant was associated with an even greater risk of mortality in all periods. Moderate SGA (3%–10%) was associated with an increased risk of mortality throughout infancy compared with infants AGA, and the risk was even greater for infants born with severe SGA. Infants born both preterm and SGA had a greater risk of neonatal mortality (hazard ratio [HR] 5.43, 95% CI 2.01–14.63) than term-AGA (reference group) and preterm-AGA infants (HR 2.40 95% CI 1.89–3.05). However, compared with term-AGA infants, the risk of death throughout infancy was not clearly different between preterm-AGA, term-SGA, and preterm-SGA infants. Compared with normal birth weight infants, LBW infants had 5-fold higher risk of early neonatal mortality (HR 5.41, 95% CI 4.24–6.90). Although the magnitude declined, there was an elevated risk of mortality among LBW infants throughout infancy (Table V).

Maternal HIV status did not significantly modify the risk of early neonatal or neonatal death associated with preterm and early preterm infants (*P* for interaction .85) (Figure 2).

However, there was evidence that maternal HIV status modified the risk associated with preterm and early preterm birth in the overall infant period (*P* for interaction <.01) (Figure 2). Early preterm infants born to HIV-infected women were twice as likely to die during infancy than full term infants born to HIV-infected women (HR 2.08, 95% CI 1.36–3.18); early preterm infants born to HIV-uninfected women were almost 5 times more likely to die during infancy than full term infants born to HIV-uninfected women (HR 4.86, 95% CI 3.52–6.71) (Figure 2). Maternal HIV status also modified the risk of infant mortality among LBW infants (*P* for interaction <.001) (Figure 2). However, maternal HIV status did not modify the risk of neonatal or infant mortality associated with being born SGA (neonatal mortality *P* for interaction =.29; infant mortality *P* for interaction =.76) (Figure 2).

Place of residence did not significantly modify the risk of neonatal or infant mortality associated with preterm status or SGA severity (Table VI; available at www.jpeds.com). However, rural residence did significantly modify the risk of neonatal and infant mortality associated with being LBW (*P* for interaction .005, .001) (Table VI).

Discussion

In a pooled cohort of Tanzanian infants, we evaluated the association between preterm and SGA births and mortality during infancy. We found that the risk of mortality was similar between preterm and SGA infants, but the highest risk was observed among infants that were born both preterm and SGA. The relative risk of neonatal death associated with SGA and preterm births were similar between HIV-exposed and HIV-unexposed infants. However, the association between preterm birth and infant mortality was significantly modified by maternal HIV status. We also observed effect modification by the location of birth for the effect of LBW on neonatal mortality.

Using the Intergrowth standard, the prevalence of SGA in our study was 17% among live births compared with 19% using the US population based standard (data not shown). Consistent with the prior reports from low- and middle-income countries, the majority (60%) of LBW infants in our study population were SGA, and only small proportion of

LBW infants were both preterm and SGA (4%).^{1, 24} Our study population had 15% preterm infants overall, and among them 3% were less than 34 weeks of gestation. The preterm prevalence in our study population was similar to the 2010 national estimates for Tanzania.²⁴ The high proportion of preterm births in our study population may have contributed to the difference in the prevalence of SGA. As the period of rapid intrauterine growth is cut short for preterm infants, they are less likely to be growth restricted and diagnosed SGA using a conventional birth weight standard.²⁵ In addition, we categorized all babies born before 33 weeks of gestation (n = 592) as AGA because the gestational age of the babies included in the Intergrowth studies ranged from 33 to 42 weeks of gestation.⁸

We observed higher prevalence of preterm and SGA births among the HIV-infected cohorts, which conforms to the prior body of literature reporting a high risk of adverse pregnancy outcomes among HIV-infected pregnant women.²⁶ Maternal HIV status modified the risk of infant mortality. Preterm infants born to HIV-infected mothers had a lower relative risk of infant mortality compared with preterm infants born to HIV-uninfected women. This is driven by the high mortality in all HIV-exposed infants; the infant mortality rate for term infants (the reference group) born to HIV-infected women is 97 per 1000 live births. The high infant mortality reported among HIV-exposed infants has been attributed to maternal health including high viral load, low CD4+ cell counts, advanced HIV disease status, and nonadherence to antiretroviral therapy.^{27, 28}

Our data included infants from both urban and rural areas in Tanzania, and this allowed us to estimate the relationship between adverse birth outcomes and infant mortality, stratified by place of residence. The risk of mortality overall was lower among the rural population, and the relative risk of infant mortality associated with LBW was lower among rural births compared with those living in urban areas. This may be some evidence that the “urban penalty” is driven in part by increased risk associated with LBW.²⁹ On the other hand, the relative risk may be a biased estimate, as the rural areas have a higher proportion of home births, which meant that LBW infants may have died at home before they were weighed, hence, were more likely to be excluded from the cohorts of our study. Prior studies reported that women of low socioeconomic background in rural areas are more likely to deliver at home and are at a higher risk of adverse birth outcomes like LBW and neonatal mortality.^{30–32}

Our study has few other limitations. HIV status was not known for all pregnant women in the Masanja et al¹⁹ cohort. We excluded pregnant women with missing information about their HIV status in the stratified analyses. Although the estimates we present were adjusted for some major confounders, we could not control for several potential confounders such as maternal nutritional status, birth spacing, and pregnancy complications as these data were not available across all cohorts.^{33, 34} The HIV-infected cohorts were enrolled over a long period of time during which the type and coverage of prenatal ART evolved, and we were not able to account for that variation in our analyses. In accordance with the current WHO recommendation, Tanzania now provides lifelong ART for pregnant women and in 2016 more than 85% women received ART during pregnancy. Although with increased coverage of prenatal ART, the incidence of adverse birth outcomes is decreasing, recent studies have reported an elevated risk of preterm and SGA associated with ART use.^{12, 35} Therefore, the

association of preterm and SGA with infant mortality among infants born to women receiving universal ART needs to be evaluated in future studies. Our estimates of preterm and SGA associated mortality risk may also be an underestimate, because of the measurement error introduced by calculation of gestational age based on date of last menstrual period and inclusion of large for gestational age infants in the AGA group.

A strength of our study was the use of large data from clinical trials that were conducted prospectively and collected quality data throughout infancy. Furthermore, this is one of the first studies to apply the Intergrowth standards to a large sample size ($n = 31\,988$) of infants selected from the general population in a sub-Saharan country. Although our findings are relevant in designing interventions to improve child survival in many similar populations, the results may not be generalizable as most of the study population was selected from women attending health facilities for antenatal checkup.

In conclusion, our study shows that preterm and SGA infants have an increased risk of mortality during infancy, and the risk elevation is consistent irrespective of their HIV exposure status or place of residence. Utilization of gestational age and weight for gestational age information can improve targeting of infants at high risk of mortality in resource limited settings. Implementation and scale-up of interventions aimed at lowering incidence and management of preterm and SGA birth is needed for reduction of infant mortality in this region.

Acknowledgments

Supported by the National Institutes of Health (5T32AI007358-27 [to E.R.S.] and T32AI114398 [to A.S.]). The parent studies were supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (R01 HD32257-05; R01 HD037701-03; NICHD R01 HD043688-01; K24HD058795) and by the Bill and Melinda Gates Foundation through the World Health Organization (Award Number 2011/133255-0).

Glossary

AGA	Appropriate for gestational age
ART	Antiretroviral treatment
HR	Hazard ratio
LBW	Low birth weight
SGA	Small for gestational age

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Figure 1.

Figure 2.

Characteristics of study populations, by study and overall (among all subjects) (n = 46 294)

	Fawzi et al 2007 ¹⁷ (n = 8430) n (%)	Fawzi et al 2007 ¹⁸ (n = 1078) n (%)	Masanja et al 2015 ¹⁹ (n = 31 999) n (%)	Duggan et al 2012 ²⁰ (n = 2387) n (%)	McDonald et al 2015 ²¹ (n = 2400) n (%)	Total (n = 46 294) n (%)
Infant sex						
Male	4073 (48.3)	499 (46.3)	16 783 (52.5)	1289 (54.0)	1221 (50.9)	23 865 (51.6)
Female	3808 (45.2)	484 (44.9)	15 211 (47.5)	1098 (46.0)	1173 (48.9)	21 774 (47.0)
Missing	549 (6.5)	95 (8.8)	5 (0.02)	0 (0)	6 (0.3)	655 (1.4)
Maternal education						
None	0 (0)	84 (7.8)	2656 (8.3)	158 (6.6)	36 (1.5)	2934 (6.3)
1–7 y	6563 (77.9)	886 (82.2)	24 428 (76.3)	1700 (71.2)	1731 (72.1)	35 308 (76.3)
8–12 y	1127 (13.4)	104 (9.7)	2775 (8.7)	450 (18.9)	543 (22.6)	4999 (10.8)
13 y	717 (8.5)	4 (0.4)	218 (0.7)	57 (2.4)	78 (3.3)	1074 (2.3)
Missing	23 (0.3)	0 (0)	1922 (6.0)	22 (0.9)	12 (0.5)	1979 (4.3)
Maternal age						
<20 y	1349 (16.0)	140 (13.0)	4483 (14.0)	53 (2.2)	167 (7.0)	6192 (13.4)
20–24 y	3349 (39.7)	435 (40.4)	9302 (29.1)	516 (21.6)	760 (31.7)	14 362 (31.0)
25–29 y	2269 (26.9)	328 (30.4)	8782 (27.4)	870 (36.5)	814 (33.9)	13 063 (28.2)
30 y	1437 (17.1)	175 (16.2)	8535 (26.7)	892 (37.4)	639 (26.6)	11 678 (25.2)
Missing	26 (0.3)	0 (0)	897 (2.8)	56 (2.4)	20 (0.8)	999 (2.2)
Mode of delivery						
Spontaneous vaginal delivery	7525 (89.3)	940 (87.2)	29 821 (93.2)	2021 (84.7)	2160 (90.0)	42 467 (91.7)
Cesarean delivery	659 (7.8)	56 (5.2)	1863 (5.8)	278 (11.7)	211 (8.8)	3067 (6.6)
Missing	246 (2.9)	82 (7.6)	315 (1.0)	88 (3.7)	29 (1.2)	760 (1.6)
Parity						
0	2394 (28.4)	266 (24.7)	7715 (24.1)	539 (22.6)	776 (32.3)	11 690 (25.3)
1	6008 (71.3)	707 (65.6)	18 536 (57.9)	1824 (76.4)	1612 (67.2)	28 687 (62.0)
Missing	28 (0.3)	105 (9.7)	5748 (18.0)	24 (1.01)	12 (0.5)	5917 (12.8)
Residence						
Urban	8430 (100)	1078 (100)	11 895 (37.2)	2387 (100)	2400 (100)	26 190 (56.6)
Rural	0 (0)	0 (0)	20 104 (62.8)	0 (0)	0 (0)	20 104 (43.4)

	Fawzi et al 2007 ¹⁷ (n = 8430) n (%)	Fawzi et al 2007 ¹⁸ (n = 1078) n (%)	Masanja et al 2015 ¹⁹ (n = 31 999) n (%)	Duggan et al 2012 ²⁰ (n = 2387) n (%)	McDonald et al 2015 ²¹ (n = 2400) n (%)	Total (n = 46 294) n (%)
Wealth						
0–25th percentile	1447 (17.2)	176 (16.3)	6807 (21.3)	639 (26.8)	373 (15.5)	9442 (20.4)
26–50th percentile	1617 (19.2)	217 (20.1)	7075 (22.1)	603 (25.3)	754 (31.4)	10 266 (22.2)
>50th percentile	4690 (55.6)	573 (53.2)	16 078 (50.3)	1145 (48.0)	1163 (48.5)	23 649 (51.1)
Missing	676 (8.0)	112 (10.4)	2039 (6.4)	0 (0)	110 (4.6)	2937 (6.3)

Characteristics of study populations, by study and overall (among those excluded from the cohort) (n = 14 306)

	Fawzi et al 2007 ¹⁷ (n = 1029) n (%)	Fawzi et al 2007 ¹⁸ (n = 262) n (%)	Masanja et al 2014 ¹⁹ (n = 12 632) n (%)	Duggan et al 2012 ²⁰ (n = 141) n (%)	McDonald et al 2015 ²¹ (n = 242) n (%)	Total (n = 14 306) n (%)
Infant sex						
Male	275 (26.7)	79 (30.2)	6784 (53.7)	69 (48.9)	121 (50.0)	7328 (51.2)
Female	205 (19.9)	88 (33.6)	5843 (46.3)	72 (51.1)	115 (47.5)	6323 (44.2)
Missing	549 (53.4)	95 (36.3)	5 (0.04)	0 (0)	6 (2.5)	655 (4.6)
Maternal education						
None	0 (0)	22 (8.4)	1210 (9.6)	10 (7.1)	2 (0.8)	1244 (8.7)
1–7 y	819 (79.6)	217 (82.8)	9729 (77.0)	102 (72.3)	164 (67.8)	11 031 (77.1)
8–12 y	127 (12.3)	23 (8.8)	907 (7.2)	23 (16.3)	64 (26.5)	1144 (8.0)
13 y	78 (7.6)	0 (0)	60 (0.5)	1 (0.7)	7 (2.9)	146 (1.0)
Missing	5 (0.5)	0 (0)	726 (5.8)	5 (3.6)	5 (2.1)	741 (5.2)
Maternal age						
<20 y	183 (17.8)	42 (16.0)	1714 (13.6)	3 (2.1)	23 (9.5)	1965 (13.7)
20–24 y	418 (40.6)	108 (41.2)	3458 (27.4)	30 (21.3)	72 (29.8)	4086 (28.6)
25–29 y	250 (24.3)	79 (30.2)	3668 (29.0)	36 (25.5)	75 (31.0)	4108 (28.7)
30 y	175 (17.0)	33 (12.6)	3449 (27.3)	35 (24.8)	65 (26.9)	3757 (26.3)
Missing	3 (0.3)	0 (0)	343 (2.7)	37 (26.2)	7 (2.9)	390 (2.7)
Mode of delivery						
Spontaneous vaginal delivery	708 (68.8)	167 (63.7)	11 355 (89.9)	55 (39.0)	232 (95.9)	12 517 (87.5)
Cesarean delivery	91 (8.8)	13 (5.0)	969 (7.7)	5 (3.6)	6 (2.5)	1084 (7.6)
Missing	230 (22.4)	82 (31.3)	308 (2.4)	81 (57.5)	4 (1.7)	705 (4.9)
Parity						
0	268 (26.0)	47 (17.9)	3040 (24.1)	34 (24.1)	81 (33.5)	3470 (24.3)
1	754 (73.3)	127 (48.5)	7561 (59.9)	101 (71.6)	156 (64.5)	8699 (60.8)
Missing	7 (0.7)	88 (33.6)	2031 (16.1)	6 (4.3)	5 (2.1)	2137 (14.9)
Residence						
Urban	1029 (100)	262 (100)	4007 (31.7)	141 (100)	242 (100)	5681 (39.7)
Rural	0 (0)	0 (0)	8625 (68.3)	0 (0)	0 (0)	8625 (60.3)

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	Fawzi et al 2007 ¹⁷ (n = 1029) n (%)	Fawzi et al 2007 ¹⁸ (n = 262) n (%)	Masanja et al 2014 ¹⁹ (n = 12 632) n (%)	Duggan et al 2012 ²⁰ (n = 141) n (%)	McDonald et al 2015 ²¹ (n = 242) n (%)	Total (n = 14 306) n (%)
Wealth						
>50th percentile	176 (17.1)	45 (17.2)	2723 (21.6)	37 (26.2)	26 (10.1)	3007 (21.0)
26–50th percentile	191 (18.6)	56 (21.4)	2962 (23.5)	49 (34.8)	61 (25.2)	3319 (23.2)
0–25th percentile	565 (54.9)	129 (49.2)	6017 (47.6)	55 (39.0)	140 (57.9)	6906 (48.3)
Missing	97 (9.4)	32 (12.2)	930 (7.4)	0 (0)	15 (6.2)	1074 (7.5)

Table III

Description of pooled studies

Authors	Year	Study site	Study design	Intervention	Size of original cohort	Size of analyzed cohort	Follow-up period	Maternal HIV status *	Prevalence per 1000 live births		
									LBW [†]	SGA [‡]	PTB [§]
Fawzi et al ¹⁷	2007	Dar es Salaam	Individually randomized placebo controlled trial	Maternal multivitamin supplementation	8430	7401	Enrollment (12–27 wk of pregnancy) –18 mo	Negative	67	102	153
Fawzi et al ¹⁸	2007	Dar es Salaam	Individually randomized placebo controlled trial	Maternal vit A, Multivitamin+vit A, Multivitamin, placebo	1078	816	Enrollment (12–27 wk of pregnancy)-through end of lactation	Positive	112	175	229
Masanja et al ¹⁹	2015	Dar es Salaam &	Individually randomized placebo controlled trial	Neonatal vitamin A supplementation	31 999	19 367	Enrollment (0–3 d)-12 mo	Positive and Negative	79	196	154
Morgan et al ²⁰	2012	Morogoro Region Dar es Salaam	Individually randomized placebo controlled trial	Infant multiple micronutrients supplementation (vitamins B, C, and E),	2387	2246	6 wk - 2 y	Positive	71	208	142
McDonald et al ²¹	2015	Dar es Salaam	Individually randomized placebo controlled trial	Infant zinc, Multivitamin+zinc, Multivitamin, placebo	2400	2158	6 wk - 2 y	Negative	36	75	127
Total					46 294	31 988			73	166	153

PTB, preterm birth.

* Among those in the analyzed cohort.

[†] LBW defined as <2500 g.[‡] SGA defined as weight for age <10th percentile using Intergrowth standards.[§] PTB defined as <37 weeks.

Table IV

Incidence of preterm, SGA, and LBW in study population (n = 31 988)

Risk factor	Total n (%)	Residence		HIV status		
		Urban n (%)	Rural n (%)	HIV-infected n (%)	HIV-uninfected n (%)	Unknown n (%)
LBW [*]	2349 (7.3)	1321 (6.4)	1028 (9.0)	269 (8.4)	875 (7.2)	1205 (7.2)
Term-AGA [†]	21 854 (68.3)	14 477 (70.6)	7377 (64.3)	2045 (63.9)	8887 (73.3)	10 922 (65.6)
Preterm-AGA [†]	4820 (15.1)	3213 (15.7)	1607 (14.0)	504 (15.8)	1694 (14.0)	2622 (15.7)
Term-SGA [‡]	5231 (16.4)	2771 (13.5)	2460 (21.4)	634 (19.8)	1531 (12.6)	3066 (18.4)
Preterm-SGA [‡]	83 (0.3)	48 (0.2)	35 (0.3)	17 (0.5)	16 (0.1)	50 (0.3)
Term [‡]	27 085 (84.7)	17 248 (84.1)	9837 (85.7)	2679 (83.7)	10 418 (85.9)	13 988 (84.0)
Preterm [‡]	3853 (12.1)	2498 (12.2)	1355 (11.8)	390 (12.2)	1316 (10.9)	2147 (12.9)
Early preterm [‡]	1050 (3.3)	763 (3.7)	287 (2.5)	131 (4.1)	394 (3.3)	525 (3.2)
AGA [§]	26 674 (83.4)	17 690 (86.3)	8984 (78.3)	2549 (79.7)	10 581 (87.2)	13 544 (81.3)
Moderate SGA [§]	2857 (8.9)	1582 (7.7)	1275 (11.1)	364 (11.4)	807 (6.7)	1686 (10.1)
Severe SGA [§]	2457 (7.7)	1237 (6.0)	1220 (10.6)	287 (9.0)	740 (6.1)	1430 (8.6)

^{*} LBW defined as <2500 g.

[†] SGA defined as weight for age <10th percentile using Intergrowth standards, Preterm defined as <37 weeks gestation.

[‡] Term defined as >37 weeks gestation. Preterm defined as 34 to <37 weeks gestation. Early preterm defined as <34 weeks gestation.

[§] AGA defined as >10th percentile, moderate SGA defined as 3rd-10th percentile, and severe SGA defined <3rd percentile using Intergrowth standards.

Risk of early neonatal and neonatal mortality stratified by birth weight, gestational age-size at gestational age category, preterm severity, and SGA severity (n = 31 988)

Table V

	Early neonatal mortality (0–7 d)				Neonatal mortality (0–28 d)				Infant mortality (0–12 mo)			
	Deaths n	Infants n	HR* (95% CI)	P value	Deaths	Infants	HR* (95% CI)	P value	Deaths	Infants	Hazard Ratio* (95% CI)	P value
All infants	318	31 988			430	31 988			1240	31 988		
Birth weight												
2500 g	224	29 639	1.00		298	29 639	1.00		999	29 639	1.00	
<2500 g	94	2349	5.41 (4.24,6.90)	<.01	132	2349	5.70 (4.64,7.01)	<.01	241	2349	3.23 (2.80,3.72)	<.01
GA-SGA category												
Term-AGA	149	21 854	1.00		198	21 854	1.00		668	21 854	1.00	
Preterm-AGA	79	4820	2.42 (1.84,3.19)	<.01	104	4820	2.40 (1.89,3.05)	<.01	266	4820	1.86 (1.61,2.14)	<.01
Term-SGA	88	5231	2.56 (1.96,3.34)	<.01	124	5231	2.68 (2.14,3.37)	<.01	301	5231	1.93 (1.68,2.21)	<.01
Preterm-SGA	2	83	3.61 (0.89,14.61)	.07	4	83	5.43 (2.01,14.63)	.001	5	83	2.02 (0.84,4.88)	.12
Preterm severity												
Term	237	27 085	1.00		322	27 085	1.00		969	27 085	1.00	
Preterm	46	3853	1.37 (1.00,1.88)	.05	66	3853	1.45 (1.11,1.88)	<.01	173	3853	1.27 (1.08,1.49)	<.01
Early preterm	35	1050	3.72 (2.61,5.32)	<.01	42	1050	3.31 (2.40,4.57)	<.01	98	1050	2.75 (2.23,3.38)	<.01
SGA severity												
AGA	228	26 674	1.00		302	26 674	1.00		934	26 674	1.00	
Moderate SGA	43	2857	1.82 (1.31,2.52)	<.01	55	2857	1.74 (1.30,2.32)	<.01	152	2857	1.54 (1.30,1.83)	<.01
Severe SGA	47	2457	2.30 (1.68,3.16)	<.01	73	2457	2.67 (2.06,3.45)	<.01	154	2457	1.82 (1.53,2.16)	<.01

* Model adjusted for study cohort, household wealth, maternal education, parity, mode of delivery, and maternal age.

Mortality outcomes by gestational age and size for gestational age categories in the neonatal and infancy periods, stratified by urban or rural population (n = 31 988)

Table VI

	Neonatal mortality (0–28 d)				Infant mortality (0–12 mo)			
	Deaths n	Infants N	HR* (95% CI)	P value	Deaths n	Infants n	HR* (95% CI)	P value
Birth weight								
Urban								
2500 g	216	19 188	1.00		718	19 188	1.00	
<2500 g	102	1321	7.06 (5.58,8.94)	<.01	177	1321	3.92 (3.32,4.62)	<.01
Rural								
2500 g	82	10 451	1.00		281	10 451	1.00	
<2500 g	30	1028	3.37 (2.19,5.17)	<.01	64	1028	2.27 (1.72,3.00)	<.01
P for interaction			.005				0.001	
Prem severity								
Urban								
Term	230	17 248	1.00		684	17 248	1.00	
Preterm	53	2498	1.6 (1.19,2.17)	<.01	129	2498	1.32 (1.09,1.59)	<.01
Early preterm	35	763	3.51 (2.46,5.03)	<.01	82	763	2.94 (2.33,3.70)	<.01
Rural								
Term	92	9837	1.00		285	9837	1.00	
Preterm	13	1355	0.98 (0.55,1.75)	.94	44	1355	1.10 (0.80,1.52)	.54
Early preterm	7	287	2.46 (1.14,5.32)	.02	16	287	1.94 (1.17,3.21)	.01
P for interaction			.36				.29	
SGA severity								
Urban								
AGA	242	17 690	1.00		711	17 690	1.00	
Moderate SGA	34	1582	1.61 (1.12,2.3)	.01	96	1582	1.51 (1.22,1.86)	<.01
Severe SGA	42	1237	2.50 (1.80,3.48)	<.01	88	1237	1.79 (1.43,2.23)	<.01
Rural								
AGA	60	8984	1.00		223	8984	1.00	

	Neonatal mortality (0–28 d)				Infant mortality (0–12 mo)			
	Deaths n	Infants N	HR* (95% CI)	P value	Deaths n	Infants n	HR* (95% CI)	P value
Moderate SGA	21	1275	2.42 (1.47,3.99)	<.01	56	1275	1.78 (1.33,2.39)	<.01
Severe SGA	31	1220	3.54 (2.28,5.51)	<.01	66	1220	2.16 (1.64,2.86)	<.01
P for interaction			.21				.35	

* Model adjusted for study cohort, household wealth, maternal education, parity, mode of delivery, and maternal age.