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The contribution of preterm birth and intrauterine growth restriction to childhood undernutrition in Tanzania

Ayesha Sania, M.B.B.S. Sc.D., MPH^a, Donna Spiegelman, Sc.D.^{b,c}, Janet Rich-Edwards, Sc.D.^{b,e}, Ellen Hertzmark, MA^b, Ramadhani S Mwiru, MD, MS^d, Rodrick Kisenge, MD, PhD^f, and Wafaie W. Fawzi, M.B.B.S., Dr.P.H.^{a,b,d}

^aDepartment Global Health and Population, Harvard School of Public Health, Boston, MA

^bDepartment Epidemiology, Harvard School of Public Health, Boston, MA

^cDepartment Biostatistics, Harvard School of Public Health, Boston, MA

^dDepartment Nutrition, Harvard School of Public Health, Boston, MA

^eThe Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Boston, MA

^fDepartment of Pediatrics and Child Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

Introduction

Childhood undernutrition is a major public health problem in sub-Saharan Africa. Undernutrition, including stunting, wasting and underweight, has been identified as underlying cause of 35% of all deaths among young children (Black et al., 2008). Children suffering from undernutrition also experience the worst neurodevelopmental outcomes (Gutbrod et al., 2000). Tanzania is among the top ten countries with highest burden of childhood malnutrition, with a prevalence of 42% stunting, 17% underweight and 4% wasting among the under-five children (Unicef, 2009). Many studies have pointed out that malnutrition during childhood is actually a continuation of the malnutrition present at birth (Christian, 2009, Mukhopadhyay et al., 2012, Arifeen et al., 2000). Studies showed that, despite catch up growth, a large proportion of low birth weight (LBW) infants fail to attain

Address correspondence to: Ayesha Sania, Department of Global Health and Population, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, ays328@mail.harvard.edu, Phone- 6179975005, Fax- 6174326733.

Contributor's Statement:

Ayesha Sania conducted the data analysis, interpreted the results and wrote the first draft of the manuscript.

Donna Spiegelman and Janet Rich-Edwards contributed in data analysis and data interpretation, and provided critical inputs on the manuscript.

Rodrick Kisenge, and Ramadhani S Mwiru, participated in the study implementation and supervision of data collection.

Ellen Hertzmark participated in the data analysis and data interpretation.

Wafaie W. Fawzi is the principal investigator of the parent trial and contributed to the study design, implemented the study, and analyzed and interpreted the data.

All authors read and approved the final manuscript.

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the expected weight and height during infancy (Christian, 2009, Casey et al., 1990, Binkin et al., 1988). Compared to infants born with normal weight, LBW infants are also more prone to postnatal growth faltering (weight or height $<-2SD$ of reference) (Marks et al., 2006, Victora et al., 2001).

Prematurity and intrauterine growth restrictions are the two underlying biological factors leading to LBW. Preterm and growth restricted infants are vulnerable to infections, and infection leads to growth faltering- creating the vicious cycle of infection and undernutrition (Schaible and Kaufmann, 2007). Research conducted mostly in developed countries suggests that preterm and growth restricted infants follow different growth trajectories (Euser et al., 2008, Knops et al., 2005). Preterm infants who achieve catch up growth by three months display a normal growth pattern subsequently. whereas children born with growth restriction remain smaller and gain less weight compared to appropriate size and preterm children (Finken et al., 2006). Due to paucity of gestational age-specific longitudinal growth data, the pattern of growth among the preterm and growth restricted infants and their contribution to childhood undernutrition in developing country settings has not been adequately explored.

Reduction of childhood undernutrition is needed to achieve the MDGs, particularly the MDGs 1, 2 and 4. By targeting high risk infants during the immediate postnatal period, a large proportion of growth faltering during childhood can be prevented. Therefore, it is important to examine patterns of growth among preterm and growth restricted infants separately to identify which infants are at greatest risk. In the present study, we examined patterns of growth among preterm and growth restricted infants, and their association with stunting, wasting and underweight during the first 18 months of life in a cohort of infants born to HIV-negative mothers in Dar es Salaam, Tanzania.

Materials and methods

Study design and population

Infants included in this analysis were part of a randomized, double blind, placebo controlled trial designed to evaluate the benefits of daily administration of multiple micronutrients (Vitamin B, C and E) on adverse pregnancy outcomes including prematurity, low birth weight, and fetal death. The details of the study design and findings were published earlier (Fawzi et al., 2007). From August 2001 to July 2004, pregnant women were enrolled in the trial from four antenatal clinics in Dar es Salam, Tanzania. Women were eligible for the trial if they tested negative for HIV infection, had an estimated gestational age at enrolment between 12 and 27 weeks according to the date of the last menstrual period (LMP), and if they planned to stay in the city until delivery and for 1 year thereafter. Women were then followed up once a month until the 32nd week of pregnancy, then every two weeks until the 36th week and then weekly until delivery. Women who did not come to the clinic within 3 days of expected delivery date were visited at home to assess the outcome of pregnancy. Following delivery mothers and children were asked to return to the study clinics for follow-up visits every month until 18 months of age.

Information on sociodemographic characteristics and obstetric history of current and previous pregnancies was collected at baseline. A study nurse obtained height and weight and a study physician performed a complete clinical examination of the pregnant women. Birth weight of the babies was measured to 10 grams precision by fulltime research midwives who attended the woman at delivery. Gestational age at birth was calculated based on the mother's date of LMP as reported at baseline. At the monthly follow-up visits, study nurses performed anthropometric measurements, the infant's weight was measured to the nearest 10 g using a digital infant balance (TANITA, Arlington Heights, IL, USA), and length was measured to the nearest 1 mm using a rigid length board with a movable foot piece (Shorr Productions, Olney, MD, USA). The anthropometric measurement equipment was calibrated regularly. The study nurses underwent training and standardization in anthropometric techniques. During the monthly visits, a morbidity assessment of the infants was conducted by the study nurse. The study nurse also inquired about breastfeeding practices during those visits.

The parent trial was approved by the institutional review boards of Muhimbili University of Health and Allied Sciences in Dar es Salaam and Harvard School of Public Health in Boston. Written informed consent was obtained from all participants.

Statistical Methods

For this study, we included all singleton infants for whom we had complete information on birth weight and gestational age and who had at least one set of anthropometric measurements taken after birth and before 18 months of age (n=6664 of 7752 total). Using a recent US population based standard of birth weight for gestational age, developed by Oken et al. (Oken et al., 2003) we classified the infants as small for gestational age (SGA, birth weight <10th percentile for gestation week) and appropriate for gestational age (AGA, birth weight >10th percentile for gestation week). Preterm was defined as birth before 37 weeks of gestational age. We then classified the infants based on their gestational age and size at gestation into four groups: term-AGA (reference group), preterm-AGA, term-SGA and preterm-SGA. Growth indicators, length-for-age (LAZ), weight-for-length (WLZ), and weight-for-age (WAZ) Z-scores during each follow up visits were calculated using the 2006 WHO Child Growth Standards (Who, 2004). Using the gender and age specific Z scores, stunting was defined as length-for-age Z score <-2 SD, wasting was defined as weight-for-height <-2 SD, and underweight was defined as weight-for-age <-2 SD. Children with Z-scores below -2 for any of the growth indicators were considered to have growth faltering.

We used mixed effects models to compare estimated average weight and height at 6 months, 12 months and 18 months of age for the gestational age- size at gestation categories using the term-AGA as the reference category (Fitzmaurice et al., 2011). We constructed curves that depicted all infants' LAZ, WLZ, and WAZ (in continuous form), by age, over the entire follow-up period, and stratified these by gestational age and weight for gestational age categories using stepwise restricted cubic spline models (Durrleman and Simon, 1989, Govindarajulu et al., 2007).

Hazard ratios and 95% CI for each of the three exposure groups compared to the reference group were obtained from Cox proportional hazards models, with time to first episode of

stunting, wasting, or underweight as the outcome and age in months as the time scale. To control for confounding, we adjusted for maternal body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), height, and haemoglobin level measured between 12 and 27 week of gestation, marital status, smoking during pregnancy, education, number of household possessions, multivitamin intake during pregnancy, infant's gender, exclusive breastfeeding status, diarrhoea and respiratory infections. The covariates were selected based on prior knowledge of the risk factors of childhood undernutrition (Black et al., 2008, Mcdonald et al., 2012, Meshram Ii, 2012, Rahman A, 2007). We used missing indicator terms in the multivariate models for covariates with missing data.

Results

The analysis included 6664 singletons with complete gestational age and birth weight information who survived beyond the neonatal period and for whom at least one (2.6% had only one visit) anthropometric measurement was obtained. Median number of visits was 12 (inter quartile range 9-17) and only 11% of children had 3 visits or fewer. During follow up 2851 (42.7%) infants became stunted, 1496 (22.4%) became wasted and 1519 (22.7%) became under underweight. Median time to stunting, wasting and underweight was 5.1 months, 5.8 months and 6.2 months, respectively.

Table 1 shows baseline maternal, socioeconomic, and infant characteristics. More than half of the mothers were 25 years of age or younger, over 60% were currently married, and more than half of the women had had at least one prior pregnancy. About 67% of mothers had 5-7 years of formal education and about half of the families owned more than three common household possessions. Of the infants, 48% were female, 6% were born with birth weight <2500 g, and 14% were preterm. 93% of infants experienced 1 or more episodes of respiratory infection, and 38% experienced diarrhoea during the study period.

Table 2 shows the estimated mean weight and length among the groups and the differences in estimated weight and length compared to the term-AGA group over the follow up period. Preterm-SGA infants had significantly lower mean weight than term AGA infants at all ages. The estimated mean weights of the preterm-AGA infants were not significantly different from the term-AGA infants at 18 months of age. However, all three groups of infants had statistically significantly smaller length than term-AGA infants throughout the first 18 months.

Figures 1-3 depict an overall decline in the nutritional status of the infants over time compared to the WHO growth standards. There was steep decline in LAZ among all groups except the preterm-SGA group which experienced a rapid gain until 5 months of age (figure 1). Despite some catch up growth, the mean Z-scores among the preterm-SGA infants remained the lowest of all groups, preterm-AGA infants were slightly better off than the term-SGA infants, and the gap in average Z-scores among the groups remained similar throughout the follow-up (figures 1-3). The mean WLZ score increased among term infants until 4 months before declining consistently until 18 months, while preterm infants experienced a rapid decline in the WLZ score throughout the entire period (figure 3). Mean WAZ declined gradually over time, although the preterm-AGA and term-SGA infants had

similar mean WAZ at the beginning of the follow up, the term-SGA group experienced a steeper decline (figure 2).

The risk ratios for stunting, wasting and underweight among groups defined by birth weight categories and by gestational age and weight for gestational age categories are given in table 3. Among the low birth weight infants, the risk ratios of stunting, wasting and underweight were significantly elevated compared to normal birth weight infants. Compared to term-AGA infants, preterm-AGA infants were twice as likely to be stunted and underweight. A more than two-fold higher risk of stunting and an approximately three fold higher risk of underweight were observed among term-SGA infants compared to term-AGA infants. Very high relative risks of stunting (RR 7.58, 95% CI 5.41-10.64) and underweight (RR 7.78, 95% CI 6.13-9.86) were observed among preterm-SGA infants. The results were similar when analysed for multivitamin and placebo group separately (supplemental table 1). When we analysed the data with incident outcome (i.e infants who presented with the outcome in any subsequent visits who did not have the outcome in the first visit) only, the magnitude of the association among the preterm-AGA and term-SGA groups was slightly attenuated but the overall conclusion remained similar (figure 4). However, among the preterm-SGA group, the hazard ratios were greatly diminished (RR of stunting decreased from 7.58 to 2.87), as the majority of these infants had growth faltering at birth.

The risk ratios of stunting, wasting and underweight among early preterm, late preterm, moderately (birth weight 3-10% of standard) and severely (birth weight <3% of standard) growth restricted infants are shown in table 4. Compared to appropriately sized infants, severe SGA infants were 3 times more likely and moderate SGA infants were 2 times more likely to be stunted. Compared to term infants, early preterm was associated with a threefold higher risk of stunting and late preterm infants had double the risk of stunting. A similar elevation of risk of being underweight was observed among the early and late preterm infants and also among the severe and moderate SGA infants. However, the risk ratios for wasting were much lower in all groups.

Discussion

Our study evaluated the risk of stunting, wasting and underweight among groups of infants defined by gestational age and weight for gestational age in an urban sub-Saharan African setting with a high prevalence of undernutrition. All four groups of infants experienced a decline in nutritional status during follow-up. Preterm-AGA infants had a slightly better nutritional status than the term-SGA infants and, despite some catch up growth during the first six months of life, the preterm-SGA infants had the poorest nutritional status. Compared with term-AGA infants, the risk of being stunted, wasted and underweight was elevated in all the three groups, with the highest magnitude of risk among the babies who were both preterm and SGA.

Our observation that LBW infants were at a high risk of being stunted, wasted and underweight is consistent with reports from both developing and developed countries (Mukhopadhyay et al., 2012, Mcdonald et al., 2012, Christian, 2009, Vitolo et al., 2008). The standard definition of LBW (birth weight <2500 gm), however, leaves out a large group

of normal birth weight infants who were preterm-AGA (12%) or term-SGA (18%) (Sania et al., 2013) and also have a higher risk of becoming undernourished. Our study found term-SGA infants to be 2 times as likely to be stunted and 3 times as likely to be wasted compared to term-AGA infants during first 18 months of life. We found that the magnitude of the risk of the outcomes were slightly higher than the preterm-AGA infants, suggesting intrauterine growth restriction has a greater impact on undernutrition during infancy than gestational age. We also found the estimated mean height and weight of the term-SGA infants were lower than that of the preterm-AGA infants. To the best of our knowledge, this is the first study to report the magnitude of association between undernutrition and SGA in sub-Saharan Africa. But similar observations have been made in several studies conducted in developed settings (Knops et al., 2005, Ford et al., 2000), which together suggest that compared to the preterm infants, the SGA children are born with lower intrinsic potential for growth because of the persistent effect of growth restriction *in utero*. Preterm infants, however, experienced a higher risk of neonatal and infant mortality compared to SGA infants (Katz et al., 2013, Sania et al., 2013).

Our results show that compared to term-AGA infants the adjusted risk ratios for stunting, wasting and underweight for the preterm-SGA group were 7, 3 and 10 times higher, respectively. This group of infants (less than 1% of the study population) had significantly lower mean weight and height than the other three groups throughout the follow up. Literature about the growth patterns of preterm-SGA infants is limited. Consistent with our observations, the 143 preterm-SGA infants followed up in the Infant Health and Development Program (IHDP) also had poorer weight gain compared to AGA infants (Strauss and Dietz, 1997). In the IHDP study, the preterm-SGA infants had limited catch up weight gain until the age of 4 months. After that their growth paralleled that of the preterm-AGA infants. In our study, they experienced a catch up gain in weight until age of 5 months. Then the curve started to decline and the gap with the reference group remained until 18 months of age when the study ended. Several studies with longer follow up conducted in developed countries showed that a large proportions of these infants (17.5%) failed to attain full catch up growth (Hokken-Koelega et al., 1995) and they had shorter stature compared to the AGA infants during childhood and adult life (Carrascosa et al., 2006, Pilling et al., 2008, Hack et al., 2003).

A few studies have examined the association between preterm birth and stunting, wasting and underweight in developing countries. Results of a community-based study in rural Malawi among a cohort of 840 infants found that preterm infants were at a significantly higher risk of being wasted and underweight compared to the term infants (Gladstone et al., 2011). Another study conducted in Brazil, a middle income country, reported that at the age of one year the odds ratios for stunting, wasting and underweight among the late preterm infants were 2.35, 3.98 and 2.57, respectively. (Santos et al., 2009) These estimates are higher than our estimates (table 3). The prevalences of stunting (8.7%), wasting (1.1%) and underweight (3.4%) are however, much lower in Brazil compared to Tanzania. In our study, although the mean weight and height of the preterm-AGA infants were not much different from that of the term-AGA infants, the WAZ and LAZ curves of the preterm-AGA infants were always lower than the term-AGA infants and there was a declining trend parallel to

that of the term-SGA infants. Studies with longer follow up suggest that if preterm-AGA infants experience postnatal growth restraint, they are likely to experience similar growth as the term-SGA infants (Euser et al., 2008) and this parallelism may extend until adulthood (Finken et al., 2006, Saigal and Doyle, 2008).

Our study has both strengths and limitations. We estimated gestational age based on the reported date of last menstrual period, which is subject to measurement error as it depends on the recall ability of the women. Also, we excluded the infants for whom we did not have birth weight because they were born at home (182, 2.3%), and the infants with improbable birth weight and gestational age combinations (72, 0.93%). Studies have shown that mothers with low socioeconomic status have the poorest LMP recall, (Alexander and Allen, 1996, Dipietro and Allen, 1991), are likely to deliver at home, and babies born to these women are more likely to be undernourished. (McDonald et al., 2012) The misclassification of preterm birth due to measurement error in gestational age estimations and the selection bias due to the exclusion of infants without are likely to have led to an underestimate in the true risk of undernutrition due to preterm birth. We lost some infants (291, 4.3%) due to infant mortality (details in Sania et al., 2013). The percent lost to follow-up because of infant death is very low and is unlikely to be an important source of bias. The study duration was 18 months and enrolment was staggered, therefore follow up for some infants ended between 15-18 months. Follow up until 15 months age is more than 90%. But the percent without follow-up data after the age of 15 months was higher and perhaps could be associated with some bias. However this loss was uniform across four study groups (supplemental table 2). Since no recent birth weight standard based on African children is available, we used a US population based standard to classify the SGA infants which may not be a suitable reference for the Tanzania children. The growth of the prematurely born infants until the term occurs outside the uterus under a non-physiologic situation and therefore may not be comparable with the growth of infants born at term (Diekmann et al., 2005, Tudehope et al., 2012). Hence, the WHO growth standard may not be the appropriate standard to classify postnatal growth faltering among the preterm infants.

The strengths of our study include a large sample size and frequent repeated anthropometric measurements. Gestational age-specific longitudinal growth data on such large sample (n=6664) from sub-Saharan Africa is unique. Birth weight and the subsequent length and weight of the infants were measured by trained research staff. The repeated monthly collection of anthropometric data allowed us to perform precise time to event analysis and also to plot trajectories of nutritional status over the follow up. We had detailed information on many potential confounders.

In conclusion, preterm and SGA babies born to HIV-negative women in Tanzania had substantially increased risks of stunting, wasting and underweight. A marked reduction in childhood undernutrition, and consequent morbidity and mortality, can be achieved by promoting interventions such as micronutrient and balanced protein energy supplementation during pregnancy to prevent SGA births (Imdad and Bhutta, 2012). Furthermore, targeting interventions with proven efficacy, e.g. the promotion of early and exclusive breastfeeding, proper management of ARI and diarrhoea, and micronutrient supplementation to high risk infants is likely to result in a major reduction in undernutrition in Tanzania and other low

income countries (Bhutta Z.A., 2013). Incorporating gestational age and birth weight for gestational age information in routine newborn assessment will help to identify infants at high risk of growth faltering in resource limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AGA	appropriate for gestational age
BW	birth weight
GA	gestational age
IUGR	intrauterine growth restriction
LBW	low birthweight
LAZ	length-for-age Z-score
LMP	last menstrual period
SGA	small for gestational age
WAZ	weight-for-age Z-score
WLZ	weight-for-length Z-score

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Key Messages

The pattern of growth among the preterm and growth restricted infants and their contribution to childhood undernutrition in developing country settings has not been adequately explored.

A large proportion of malnutrition during infancy is a continuation of the malnutrition present at birth

Intrauterine growth restriction has a greater impact on undernutrition during infancy than preterm birth.

Incorporating gestational age and birth weight for gestational age information in routine newborn assessment will help to identify infants at high risk of growth faltering in resource limited settings.

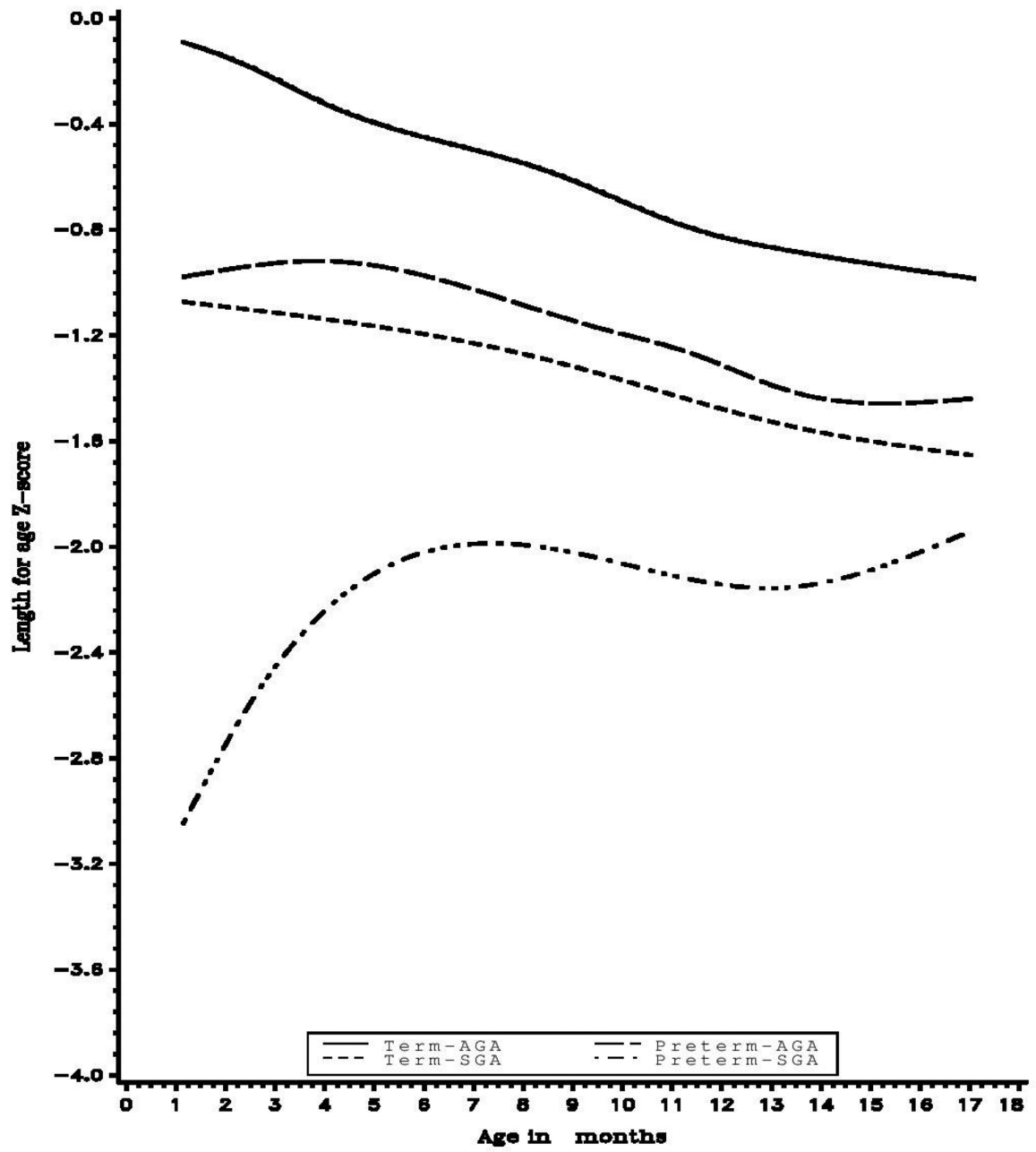


Figure 1. Length for age Z score by gestational age and weight for gestational age

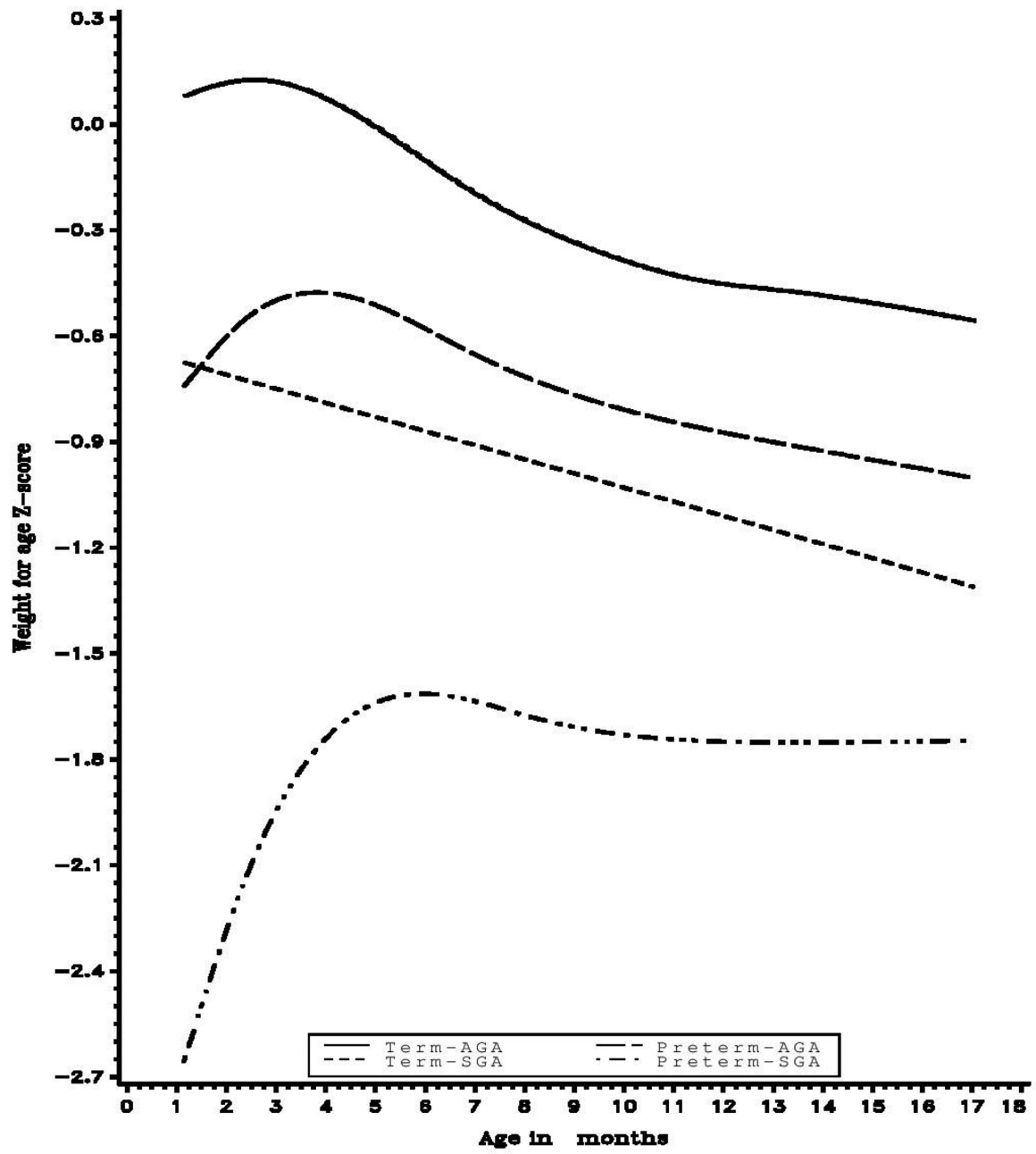


Figure 2. Weight for age Z score by gestational age and weight for gestational age

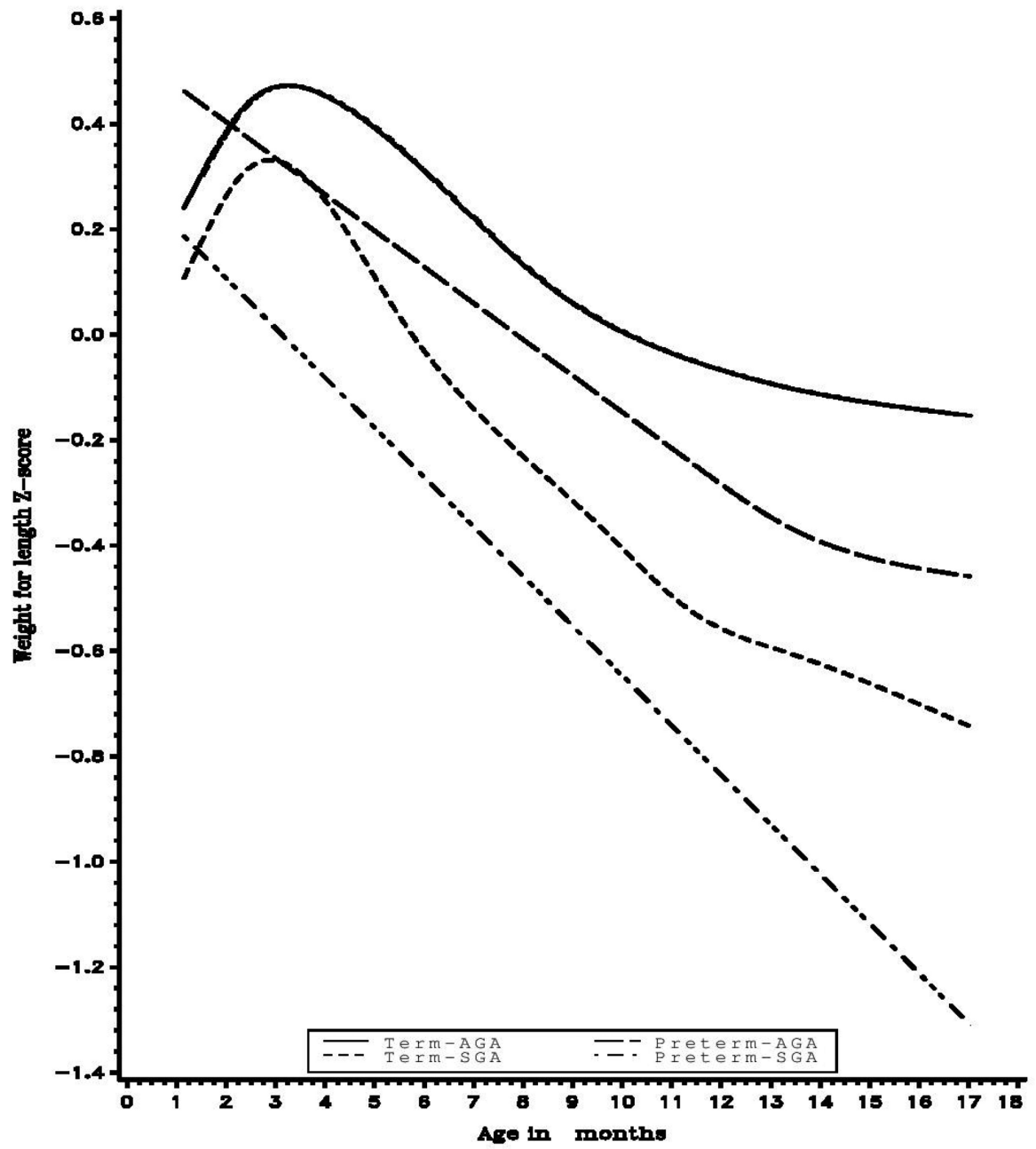


Figure 3. Weight for length Z score by gestational age and weight for gestational age categories

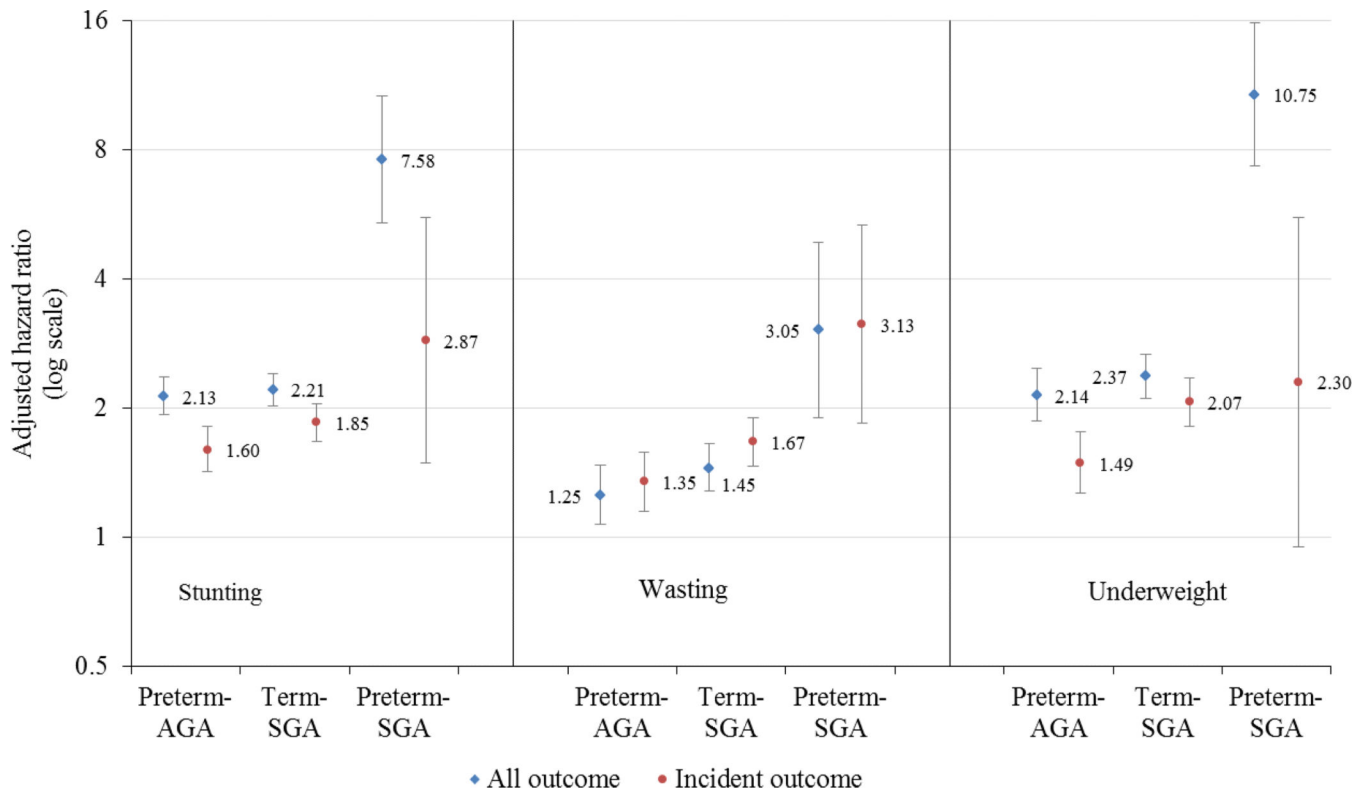


Figure 4. Adjusted hazard ratios of stunting wasting and underweight by gestational age-weight at gestational age groups for all outcomes and incident outcome

Table 1

Characteristics of the study participants (N=6664)

	N ^a (%) or mean ± s.d.
<i>Maternal characteristics</i>	
<i>Marital status</i>	
Married	4242 (64.0)
Cohabiting	1386 (20.9)
Polygamous	262 (3.9)
Unmarried	736 (11.1)
<i>Years of education</i>	
0-4	725 (10.9)
5-7	4453 (67.0)
8-11	1137 (17.1)
>12	331 (4.98)
<i>Household Possessions^b</i>	
0	415 (6.3)
1-3	2784 (41.9)
3	3444 (51.8)
<i>Age, years</i>	
<20	1023 (15.4)
20-24	2604 (39.2)
25-29	1852 (27.9)
30	1161 (17.5)
<i>BMI in early pregnancy, kg/m²</i>	
<18.5	132 (2.2)
18.6-<25	3505 (59.5)
25-<30	1692 (28.7)
30	563 (9.6)
<i>Height, cm</i>	
<145	206 (3.4)
145-149	730 (12.0)
150-154	1768 (29.2)
155	3362 (55.4)
<i>Current smoker</i>	
Yes	20 (0.3)
No	7605 (99.7)
<i>Parity</i>	
0	2897 (43.7)
1	1878 (28.3)
2	1021 (15.4)
3	832 (12.6)
<i>Hemoglobin level in early pregnancy</i>	

	N ^a (%) or mean ± s.d.
<8.5g/dl	676 (11.8)
8.5-<11 g/dl	3148 (54.8)
11 g/dl	1915 (33.4)
<i>Multivitamin intake</i>	
Multivitamin with iron and folate	3331 (49.9)
Iron and folate only	3333 (50.0)
<i>Child characteristics</i>	
<i>At birth</i>	
Female sex	3575 (48.3)
Birth weight <2500 g	373 (5.6)
Birth <37 weeks of gestation	960 (14.4)
Birth weight (g)	3149.41 ± 481
Gestational age (weeks)	39.6 ± 2.8
Term-AGA	4335 (65.1)
Preterm-AGA	919 (13.8)
Term-SGA	1369 (20.5)
Preterm-SGA	41 (0.62)
<i>Morbidity during the follow up</i>	
Diarrhoea 1 episode	2549 (38.2)
Acute respiratory infection ^c 1 episode	6212 (93.2)

Abbreviations: AGA, Appropriate for gestational age; SGA, Small for gestational age

^aTotals may not add up to 6664 due to missing data

^bFrom a list that includes fan, refrigerator, radio, television, and sofa

^cCough plus difficulty breathing, rapid respiratory rate or refusal to eat

Estimated mean height and weight by gestational age-weight at gestational age categories during first 18 months of life

Table 2

Weight (kg) ^d		Age			
		3 months	6 months	12 months	18 months
Term-AGA	Mean (SE)	6.19(0.03)	7.75 (0.03)	9.02 (0.04)	10.21 (0.05)
	Mean (SE)	5.81 (0.08)	7.43 (0.09)	8.66 (0.10)	9.98 (0.22)
	Differences ^a (SE)	-0.38 (0.09) ^b	-0.31 (0.10) ^c	-0.36 (0.11) ^c	-0.23 (0.22)
Term-SGA	Mean (SE)	5.74 (0.07)	7.23 (0.08)	8.51 (0.10)	9.73 (0.17)
	Differences ^a (SE)	-0.45 (0.08) ^b	-0.52 (0.09) ^b	-0.50 (0.11) ^b	-0.47 (0.18) ^b
	Mean (SE)	4.67 (0.11)	6.34 (0.13)	7.56 (0.17)	8.77(0.23)
Preterm-SGA	Differences ^a (SE)	-1.51 (0.12) ^b	-1.41 (0.14) ^b	-1.46 (0.18) ^b	-1.44 (0.25) ^b
	<hr/>				
	Length (cm)^e				
Term-AGA	Mean (SE)	59.71 (0.03)	65.74 (0.04)	72.63 (0.04)	78.69 (0.07)
	Mean (SE)	58.38 (0.09)	64.73 (0.09)	71.52 (0.10)	77.51 (0.18)
	Differences ^a (SE)	-1.34 (0.10) ^b	-1.01 (0.10) ^b	-1.12 (0.11) ^b	-1.17 (0.19) ^b
Term-SGA	Mean (SE)	57.99 (0.06)	64.16 (0.07)	71.12 (0.07)	77.02(0.11)
	Differences ^a (SE)	-1.72 (0.07) ^b	-1.57 (0.08) ^b	-1.51 (0.09) ^b	-1.67 (0.13) ^b
	Mean (SE)	54.57 (0.58)	61.98 (0.44)	69.40 (0.52)	76.27 (0.72)
Preterm-SGA	Differences ^a (SE)	-5.14 (0.59) ^b	-3.75 (0.44) ^b	-3.24 (0.49) ^b	-2.42 (0.73) ^c

Abbreviations: AGA, Appropriate for gestational age; SGA, Small for gestational age

Reference group: term-AGA

^aFrom individual mixed effects regression models for repeated measurements in which height or weight is the dependent variable and the predictors include time since birth, gestational age-weight for gestational age groups, and their interaction terms.

^b p <0.0001

^c p<0.001

Table 3

Risk of stunting, wasting and underweight by birth weight, gestational age-weight at gestational age category during first 18 months of life

GA-SGA category	Children followed	Stunting				Wasting				Underweight	
		Events (n)	Hazard Ratio(95% CI) ^a		Events (n)	Hazard Ratio(95% CI) ^a		Events (n)	Hazard Ratio(95% CI) ^a		
			Crude	Adjusted ^b		Crude	Adjusted ^b		Crude	Adjusted ^b	
Term-AGA	4335	1479	1.00 (Ref)	1.00 (Ref)	864	1.00 (Ref)	1.00 (Ref)	705	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Preterm-AGA	919	513	2.27 (2.05–2.51)	2.13 (1.93–2.36)	216	1.27 (1.09–1.80)	1.25 (1.07–1.47)	283	1.96 (1.85–2.07)	2.14 (1.86–2.47)	
Term-SGA	1369	824	2.43 (2.23–2.64)	2.21 (2.02–2.41)	398	1.53 (1.36–1.72)	1.45 (1.28–1.65)	503	3.03 (2.85–3.21)	2.37 (2.11–2.67)	
Preterm-SGA	41	35	7.11 (5.08–9.94)	7.58(5.41–10.64)	18	2.96 (1.85–4.72)	3.05 (1.90–4.87)	28	7.78 (6.13–9.86)	10.75 (7.34–15.77)	
Birth weight											
2500 g	6291	2554	1.00 (Ref)	1.00 (Ref)	1367	1.00 (Ref)	1.00 (Ref)	1297	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
<2500 g	373	297	4.41 (3.90–4.97)	4.28(3.78–4.85)	129	1.80 (1.50–2.15)	1.76 (1.46–2.11)	222	5.08 (4.34–5.78)	4.78 (4.12–5.54)	

Abbreviations: AGA, Appropriate for gestational age; SGA, Small for gestational age

^aHazard Ratios and 95% CIs were obtained from Cox proportional hazards models

^bAdjusted for maternal age (<20, 20-24, 25-29, and 30 years), BMI (<18.5, 18.6-24.99, 25-29.99 and >30 kg/m²), maternal height (<145, 145-149, 150-154, and 155 cm), maternal hemoglobin level (<8.5, 8.5-11 and 11g/dl), maternal marital status (married, cohabiting, poly married and unmarried), parity (0, 1, 2, and 3), maternal smoking (ever and never smoker), maternal education (0-4, 5-7, 8-11 and 12 years), household possessions (0, 1-3, and 3) and multivitamin intake (iron and folate only, multivitamin with iron and folate) and infant gender, exclusive breast feeding (yes, no), respiratory infections (0, 1episodes) and diarrhea (0, 1episodes)

Table 4 Risk of stunting, wasting and underweight by gestational age, and weight for gestational age during first 18 months of life

	Children followed	Events (n)	Stunting		Wasting		Underweight	
			Hazard Ratio(95% CI) ^a		Hazard Ratio(95% CI) ^a		Hazard Ratio(95% CI) ^a	
			Crude	Adjusted ^b	Crude	Adjusted ^b	Crude	Adjusted ^b
Gestational Age								
37 wks	5704	2303	1.00	1.00	1.00	1.00	1.00	1.00
Late preterm ^c (34- <37 weeks)	729	395	2.10(1.88-2.34)	2.00(1.79-2.24)	1.28(1.09-1.50)	1.27(1.08-1.49)	2.17(1.86-2.52)	2.03(1.74-2.36)
Early preterm ^c (<34 weeks)	231	153	3.31(2.8-3.91)	3.13(2.82-3.70)	1.45(1.11-1.89)	1.44(1.10-1.87)	3.74(3.02-4.64)	3.51(2.82-4.36)
Weight for gestational age								
AGA (10%)	5254	1992	1.00	1.00	1.00	1.00	1.00	1.00
Moderate SGA ^d (3-<10%)	878	492	2.04(1.84-2.26)	1.89(1.71-2.10)	1.37(1.19-1.58)	1.31(1.14-1.52)	2.12(1.84-2.43)	1.96(1.7-2.26)
Severe SGA ^d (<3%)	532	367	3.49(3.11-3.91)	3.18(2.82-3.58)	1.91(1.63-2.24)	1.84(1.56-2.17)	4.16(3.61-4.79)	3.67(3.16-4.27)

Abbreviation: SGA, Small for gestational age

^aHazard Ratios and 95% CIs were obtained from Cox proportional hazards models

^bAdjusted for maternal age (<20, 20-24, 25-29, and 30 years), BMI (<18.5, 18.6-24.99, 25-29.99 and >30 kg/m²), maternal height (<145, 145-149, 150-154, and 155 cm), maternal hemoglobin level (<8.5, 8.5-11 and 11g/dl), maternal marital status (married, cohabiting, poly married and unmarried), parity (0, 1, 2, and 3), maternal smoking (ever and never smoker), maternal education (0-4, 5-7, 8-11 and 12 years), household possessions (0, 1-3, and 3) and multivitamin intake (iron and folate only, multivitamin with iron and folate) and infant gender, exclusive breast feeding (yes, no), respiratory infections (0, 1episodes) and diarrhea (0, 1episodes)

^cAdjusted for SGA

^dAdjusted for prematurity