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Does Severity of HIV Disease in HIV-Infected Mothers Affect Mortality and Morbidity among Their Uninfected Infants?

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Abstract

Background—Rates of perinatal human immunodeficiency virus (HIV) transmission are higher among HIV-infected mothers with more advanced disease, but effects of maternal disease on HIV-uninfected offspring are unclear. We investigated the hypothesis that the severity of HIV disease and immune dysfunction among mothers is associated with increased morbidity and mortality among their uninfected infants.

Methods—In a birth cohort of 620 HIV-uninfected infants born to HIV-infected mothers in Lusaka, Zambia, we investigated associations between markers of more advanced maternal HIV disease and child mortality, hospital admissions, and infant weight through 4 months of age.

Results—Mortality in the cohort of uninfected infants was 4.6% (95% confidence interval [CI], 2.8–6.3) through 4 months of age. Infants of mothers with CD4⁺ T cell counts of <350 cells/μL were more likely to die (hazard ratio [HR], 2.87; 95% CI, 1.03–8.03) and were more likely to be hospitalized (HR, 2.28; 95% CI, 1.17–4.45), after adjusting for other factors, including maternal death and low birth weight. The most common cause of infant death and hospitalization was pneumonia and/or sepsis. A maternal viral load of >100,000 copies/mL was associated with significantly lower child weight through 4 months of age.

Conclusion—Children born to HIV-infected mothers with advanced disease who escaped perinatal or early breastfeeding-related HIV infection are nonetheless at high risk of mortality and morbidity during the first few months of life. HIV-related immunosuppression appears to have adverse consequences for the health of infants, in addition to risks of vertical transmission.

Infants born to HIV-infected mothers are at risk of acquiring HIV infection. The risk is serious, but it can be substantially reduced with antiretroviral drugs [1–3]. Yet, even in the absence of

interventions, the majority of infants born to HIV-infected mothers do not acquire infection. However, these infants risk losing their mother (and father) to HIV infection during childhood, with the social dislocation of orphanhood posing obvious dangers to their well-being [4–6]. But do HIV-uninfected children have other risks associated with having an HIV-infected mother?

There is surprisingly little known about morbidity and mortality among HIV-exposed, HIV-uninfected infants. Demographic studies estimate that mortality among children born to HIV-infected mothers is higher than that among children born to mothers without HIV infection, but interpretation is limited because the proportion of HIV-infected children is not known [6–9]. Factors affecting morbidity and mortality in general (e.g., lack of breastfeeding, unhygienic living conditions, and malaria exposure) are also likely to be important among HIV-exposed, HIV-uninfected infants. In addition, HIV exposure directly or indirectly in utero, intrapartum, and during breastfeeding may confer risks to infants, even in the absence of vertical transmission.

Perinatal transmission and disease progression among infected infants are higher among those born to mothers with more advanced HIV disease [10–12]. The effect, if any, on uninfected offspring is unclear. Here, we investigate whether advanced HIV disease and/or immune dysfunction among HIV-infected mothers increases mortality and morbidity among their uninfected infants. Any effect will have substantial public health consequences, because the absolute number of reproductive-aged women with HIV infection continues to increase.

SUBJECTS AND METHODS

Study design

We investigated risk factors for mortality, hospital admission, and lower weight through 4 months of age in a birth cohort of 620 HIV-uninfected infants born to HIV-infected mothers in Lusaka, Zambia. The cohort was recruited as part of a trial of early cessation of breastfeeding [13]. In brief, HIV-infected pregnant women who intend to breastfeed are recruited antenatally. They and their infants are given single-dose nevirapine for prevention of transmission. Women are counseled to breastfeed exclusively until the child is 4 months of age. Thereafter, women are randomized to 1 of 2 groups, in which breastfeeding is abruptly stopped when the infant is 4 months old or continued exclusively, with gradual weaning, until the infant is 6 months old. Randomization occurs no earlier than 1 week postpartum.

Diagnosis of HIV infection in infants

Clinic visits are scheduled at 1 and 5 weeks postpartum, at monthly intervals through 6 months of age, and at 3-monthly intervals thereafter. At each clinic visit, blood is collected from the infant by heel-stick onto filter paper. The dried blood specimens are tested by real-time PCR for HIV DNA [14]. β -Globulin amplification is included in each assay to ensure that samples are adequate.

Study population

This analysis was restricted to mothers who gave birth to live-born infants before December 2003. Within this birth cohort, there were 810 deliveries of 824 live-born infants (795 singletons, 14 sets of twins [2 cotwins were stillborn], and 1 set of triplets). Twenty-one infants (2.5%) died before a birth sample was collected, and 39 infants (4.7%) did not have a test result. Eight infants (1.0%), all of whom had a birth sample that tested negative for HIV, died before their first visit (the 4-day home visit), and 12 infants (1.6%) (3 with positive and 9 with negative results of HIV tests) withdrew or were lost to follow-up. These early losses were excluded from our analysis, to minimize the influence of nonviable births, early deaths due to prematurity or

birth complications, and incomplete data. Of the remaining 744 infants, 124 (16.6%) had at least 1 positive test result at ≥ 4 months of age. The analysis includes the remaining 620 uninfected infants (601 singletons, 7 twin pairs [14 infants], and 5 single infants from twin deliveries) born to 613 HIV-infected mothers.

Study outcomes

The primary outcomes were infant death, hospitalization, and growth through 4 months of age. Contact with the study cohort was intensive during the first 4 months (weekly during the first month and biweekly through 4 months). If visits were missed, home-visit teams were dispatched. New caretakers of children whose mothers died were encouraged to keep such children in the study, as were mothers of children who died. All deaths were investigated by interview and by review of health care records. Participants were asked about hospitalizations, and records were abstracted if admission occurred. Child weight was measured at each clinic visit. Trimethoprim-sulfamethoxazole prophylaxis was given from 5 weeks of age through the first year of life. Infant formula was provided for infants of mothers who died and for those whose mothers were unable or unwilling to breastfeed.

Risk factors

At enrollment, which occurred a median of 10 weeks (range, 0–32 weeks) before delivery, blood was drawn for determination of the CD4⁺ T cell count (FACSCCount system; BD Immunocytometry Systems) and the hemoglobin level (Hemocue system; Hemocue), and plasma was frozen for quantitative HIV RNA testing (Roche Amplicor, version 1.5; Roche), with a detection threshold of 400 copies/mL. Maternal weight and height were measured, and questions were asked about HIV-related illness. Body mass index at 1 month postpartum was calculated. Maternal deaths and hospitalizations were documented. Maternal antiretroviral treatment was not available at the time these data were collected.

Socioeconomic information, including maternal age, education level, employment status, marital status, availability of water and electricity in the home, cooking and refrigeration facilities, crowding, and food insecurity (number of days in the previous month when food was unavailable in the home), was collected at enrollment. Delivery circumstances and infant characteristics at birth, including birth weight, were recorded by midwives trained in completion of the study forms; if the child was born off-site, this information was collected after birth from records. Detailed information about feeding practices was collected during each visit.

Statistical analysis

Kaplan-Meier methods were used for univariate and Cox proportional hazards models for multivariable analysis of mortality and time to first hospitalization. All putative factors associated with the outcome ($P < .05$) in univariate analysis were entered and were retained in final models if they were significantly ($P < .05$) associated with the outcome or if their inclusion modified the hazard ratios (HRs) of the main factors of interest (i.e., markers of advanced maternal HIV disease) by $>10\%$. Breastfeeding was included as a categorical (i.e., “present” or “absent”), time-dependent variable lagged by 7 days. The lag was included to reduce the influence of child illness inflating associations between no breastfeeding and mortality and/or morbidity. The unit of analysis was the child. Results were unchanged if second twins were excluded. Child growth was analyzed by modeling all weight measurements as a linear function of age (in weeks) and sex using generalized estimating equations. Potential risk factors were examined singly with age and sex, and if $P < .05$, they were entered into a multivariable model. Breastfeeding was defined as absent if it had stopped >7 days before the weight measurement. Log transformations of age did not improve the model fit and were not used in final analyses. Analyses were undertaken using SAS, version 9.0 (SAS Institute).

RESULTS

Mortality

Among 620 HIV-exposed, HIV-uninfected infants who survived the immediate neonatal period, mortality was 1.8% (95% CI, 0.8%–2.9%) by 28 days (11 deaths) and 4.6% (95% CI, 2.8%–6.3%) cumulatively by 4 months (26 deaths). Ninety percent of survivors underwent 4 months of follow-up. Of 20 deaths of known cause, 10 were due to pneumonia, 4 to sepsis, 3 to prematurity, 2 to failure to thrive, and 1 to malaria. Thus, mortality due to pneumonia and/or sepsis ranged from 54% (14 of 26 infants) to 70% (14 of 20 infants).

In unadjusted analyses, infant mortality through 4 months was significantly associated with low CD4⁺ T cell count, low hemoglobin level, high viral load, maternal hospital admission, maternal death, low birth weight, and early cessation of breast-feeding. Multivariate analysis revealed that mortality continued to be significantly associated with a maternal CD4⁺ T cell count of <350 cells/ μ L (HR, 2.87; 95% CI, 1.03–8.03), a low maternal hemoglobin level of <10 g/dL (HR, 2.37; 95% CI, 1.04–5.41), maternal death within 4 months after delivery (HR, 6.84; 95% CI, 2.65–17.70), and birth weight of <2500 g (HR, 2.43; 95% CI, 1.05–5.65) (table 1). The univariate association between not breastfeeding and infant mortality was not significant after adjustment (HR, 3.13; 95% CI, 0.86–11.35).

Data on maternal mortality included only maternal deaths within 4 months of delivery. A weaker association with infant mortality was observed if later maternal deaths were also included. Infant mortality was 47.6% if mothers died within 4 months after giving birth, compared with 3.4% if mothers survived. Of 7 mother-infant pairs who died, 2 infant deaths preceded the death of the mother, 2 occurred within 4 days after the mother died, and 3 occurred >3 weeks after the mother died.

The hazard for infant death was reduced 0.70 (95% CI, 0.53–0.94) in a dose-dependent manner for each 100-cell/ μ L increase in the CD4⁺ T cell count, after adjusting for hemoglobin level, birth weight, and maternal death (figure 1). In this model, the association between hemoglobin level and mortality was reduced below significance. Relative to higher maternal CD4⁺ T cell counts, the adjusted risk for infant death was greater when the count was <200 cells/ μ L (HR, 4.90; 95% CI, 1.001–22.11), compared with 200–350 cells/ μ L (HR, 2.71; 95% CI, 0.57–12.94).

Hospitalization

Thirty-nine infants were admitted to the hospital at least once between 4 days and 4 months of life, and 2 of these infants were admitted twice. Most (31 of 39) admissions were for pneumonia and/or sepsis, 4 were for diarrhea, and 6 were for malaria (>1 cause could be given). Six admitted children (15.4%) died before discharge, and 10 (25.6%) died after discharge (6 of whom died during the 4-month period of this analysis). Of the 26 child deaths, 9 occurred without a previous hospital admission.

Time to the first hospital admission was significantly associated with low maternal CD4⁺ T cell count, delivery at the tertiary hospital, and no breastfeeding. Unadjusted analysis revealed a significantly lower risk of future hospitalization among children born at home, compared with children born at a hospital, but the difference did not remain significant in adjusted analysis (table 2). A maternal CD4⁺ T cell count of <350 cells/ μ L (HR, 2.28; 95% CI, 1.17–4.45) and no breastfeeding (HR, 3.41; 95% CI, 1.01–11.52) remained significantly associated with an increased risk of admission after adjustment. There was no clear dose-response gradient between maternal CD4⁺ T cell count and infant hospital admission (figure 1).

Possible misclassification of HIV infection status

We investigated whether the observed associations might be explained by undetected HIV infection. The median lag time between the last negative PCR result and death was 12 days among 26 deceased infants. Fifteen of 26 deaths occurred after 28 days of life, and when the analysis was restricted to infants surviving to 28 days, associations were of a similar magnitude but based on a smaller sample size. Specifically, low maternal CD4⁺ T cell count was associated with a 4.64-fold increased risk of infant mortality from 28 days through 4 months of age in unadjusted analysis (95% CI, 1.31–16.45) and with a 2.83-fold increase after adjusting for maternal death, which was the only variable significantly associated with mortality in this subgroup (95% CI, 0.73–10.96). Low maternal CD4⁺ T cell count remained significantly associated with an increased rate of infant hospitalization when analysis was restricted to infants >28 days of age who had negative test results (HR, 2.21; 95% CI, 1.13–4.32, after adjusting for breastfeeding).

Weight from week 1 through month 4 of age

Maternal death, maternal hospital admission, low maternal CD4⁺ T cell count, high HIV load, low hemoglobin level, and low body mass index were each (not adjusting for each other) associated with lower infant weight, adjusting for age and sex. Birth weight, having a twin, home birth, referral hospital birth, several socioeconomic indicators, and breastfeeding were also associated with lower infant weight (table 3). In multivariable analyses, maternal CD4⁺ T cell count and lower infant weight were no longer significantly associated, but other markers of advanced HIV infection, including high HIV load, low body mass index, and several other factors, continued to be significantly associated with lower infant weight (table 3). After adjustment, a maternal HIV load of >100,000 copies/mL was associated with an infant weight that was 150 g (95% CI, 50–250 g) less than that for infants whose mother had an HIV load of $\geq$ 100,000 copies/mL (similar to the sex differential) (figure 2).

DISCUSSION

We identify an overlooked population of children at high risk for mortality and morbidity. Early infant mortality and severe morbidity among uninfected infants born to HIV-infected mothers were more than double when maternal CD4⁺ T cell counts were low. The increase was not explained by maternal mortality, separation due to maternal hospitalization, lower birth weight, or any other factors we investigated. Infant growth was slower when the maternal HIV load was higher.

The magnitude of the population-attributable fraction of this association is not trivial. The HIV seroprevalence among pregnant women remains high in sub-Saharan Africa and has reversed decades of improvement in child survival rates in the world's poorest countries [15]. Good population coverage of programs to prevent mother-to-child HIV transmission should be able to offset some of this HIV-related child mortality. However, our data suggest that even complete eradication of vertical transmission will not be able to counteract the full negative impact of HIV infection in reproducing women on the health of their children.

Antiretroviral treatment programs are being implemented in low-resource settings, including the communities where our study was based. Ideally, drug treatment should be reaching mothers with low CD4⁺ T cell counts whose uninfected children we identified as having poor outcomes. Effective drug treatment typically results in rapid decrease in viral load, gradual increase in CD4⁺ T count to normal level, and partial correction of many other HIV-related immune dysfunctions [16]. Initiation of treatment during pregnancy may be too late to protect offspring from all the consequences of advanced HIV disease, but this hypothesis should be empirically tested. If effective, HIV treatment will not only improve maternal health and reduce

HIV transmission but may also allow HIV-infected women to have healthier HIV-uninfected children.

We can only speculate on mechanisms underlying the association. Maternal coinfections with opportunistic pathogens, such as cytomegalovirus, *Mycobacterium tuberculosis*, hepatitis C virus, and human herpesvirus 8, may be important [17–23]. Increased shedding and higher pathogen loads related to immunosuppression may cause increasing numbers of virulent congenital or maternally acquired neonatal infections. Passive immunity may be deficient among infants born to HIV-infected immunocompromised mothers, because reduced transplacental transfer of IgG antibodies to common infections has been observed [24]. Increased risk of early measles attributable to lower cord blood antibody titers among infants born to HIV-infected mothers has also been observed [25]. Immunological deficiencies in breast milk may play a role, because immunoglobulins and other components of breast milk are important in protecting infants against infections [26]. Viral exposure in utero and/or HIV-induced failure of the maternal immune system to adequately support development of competent infant immune capacity may result in diminished capacity of the infant to control common infections [27,28]. These vulnerabilities would not have been noticed in US and European cohorts, in which the background coinfection burden is considerably lower. Of concern in cases in which HIV exposure has compromised fetal immune development is that vaccines given in early childhood may not be immunogenic. A study from The Gambia found decreased bacille Calmette-Guérin scar formation among uninfected children born to HIV-infected mothers [29]. Nutritional or micronutrient deficiencies in breast milk [30] may be related to poor outcome in infants. Finally, social and psychological factors may also play a role. A physically or emotionally impaired mother may be less able to care for her newborn as well as a vigorous, healthy mother can.

It will be important to investigate whether the association persists in older children as the morbidity profile shifts to diarrheal diseases with the introduction of weaning foods and whether the association is only observed among breastfed infants. Too few infants were not breastfed in these early months to examine nonbreastfeeding infants separately. Another limitation is that markers of advanced maternal disease were measured at a single point during pregnancy. Given the strong predictive power of this measurement, we assume that maternal HIV disease status during pregnancy is most relevant but do not have postnatal maternal data to confirm the assumption. Inclusion of a sufficiently large and identically followed cohort of infants born to HIV-negative mothers would be informative to address whether HIV infection has adverse consequences in the absence of immunosuppression, but it is unlikely that such a cohort would have offered much additional insight into the association described here.

We cannot entirely rule out that unidentified HIV infection in the child is responsible for the association. The major constraint is the frequency of blood sampling among children. It does not seem reasonable to impose a protocol of blood sampling any more intensive than our own protocol; thus, some uncertainty about the HIV infection status of a deceased child is inevitable. If HIV transmission occurred during the interval between tests, it would also have to result in rapid disease progression. The relatively short lag between the last negative test result and the child's death (median interval, 12 days) suggests that this is an unlikely explanation. HIV RNA load may be more sensitive than HIV DNA load (our preferred method) for pediatric diagnosis, but differences in sensitivity between these 2 methods are small [31–35].

Maternal mortality and low birth weight were associated with infant mortality and morbidity, as shown elsewhere [4–8]. Morbidity risks attributable to lack of breastfeeding are also consistent with expectations [36]. These risks are the principal reason why avoidance of breastfeeding cannot simply be recommended for all HIV-infected women. Women who stopped breastfeeding early did so of their own volition. All had intended to breastfeed for at

least 4 months when initially enrolled. Formula was provided because this commodity is otherwise unaffordable. Stopping breastfeeding was associated with severity of maternal disease, but the association persisted even after adjusting for this variable.

Similar associations have been noted elsewhere [4,37,38]. We expand on these observations to demonstrate that the association between the severity of maternal HIV disease is robust across morbidity, mortality, and growth of HIV-exposed, HIV-uninfected children and remains strong even after adjustment for plausible confounders. Our results are also consistent with associations observed between maternal disease stage and the rapidity of disease progression among HIV-infected children [11,12].

In conclusion, we identify a group of children at high risk of mortality and morbidity who may not necessarily benefit from the HIV treatment and prevention interventions that are currently being implemented. Earlier recognition of immunosuppression in women before they become pregnant may be needed. Understanding of the biological and/or social bases of this association may help develop interventions that could complement programs to prevent mother-to-child HIV transmission and adult HIV treatment services to address the needs of this population of children.

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Potential conflicts of interest. All authors: no conflicts.

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Figure 1. Kaplan-Meier survival curves of infant mortality (A) and time to first hospital admission (B) among 620 HIV-uninfected infants born to HIV-infected mothers, by maternal CD4⁺ T cell counts of <200 cells/μL, 200–349 cells/μL, and >349 cells/μL.

Figure 2. Weights of infants between 1 week and 4 months of age born to HIV-infected mothers, by maternal HIV load. *Horizontal bars*, median values; *boxes*, interquartile ranges; *whiskers*, 10th and 90th percentiles.

Table 1
Predictors of mortality through 4 months of age among 620 uninfected infants born to HIV-infected women in Lusaka, Zambia.

Predictor	No. of infants	Hazard ratio ^a (95% CI)	
		Unadjusted analysis	Adjusted analysis ^b
Maternal CD4 ⁺ T cell count			
<350 cells/ μ L	295	4.81 (1.81–12.76)	2.87 (1.03–8.03)
$\geq$ 350 cells/ μ L	325	1.0 (Referent)	1.00 (Referent)
Maternal HIV load			
<100,000 copies/mL	444	1.0 (Referent)	...
$\geq$ 100,000 copies/mL	162	2.46 (1.14–5.31)	...
Maternal hemoglobin level			
<10 g/dL	167	3.84 (1.76–8.35)	2.37 (1.04–5.41)
$\geq$ 10 g/dL	453	1.0 (Referent)	1.00 (Referent)
Maternal survival			
Died within 4 months after delivery	16	16.19 (6.79–38.65)	6.84 (2.65–17.70)
Alive 4 months after delivery	604	1.0 (Referent)	1.00 (Referent)
Infant birth weight			
<2500 g	86	4.22 (1.92–9.31)	2.43 (1.05–5.65)
$\geq$ 2500 g	534	1.0 (Referent)	1.00 (Referent)
Early cessation of breastfeeding ^c			
Before 4 months	36	14.92 (5.44–40.91)	...
Still breastfeeding at 4 months of age	584	1.0 (Referent)	...
Maternal hospitalization			
At least once	48	6.55 (2.92–14.70)	...
None	572	1.0 (Referent)	...

^a Hazard ratios were calculated to indicate the magnitude of the association between mortality in the indicated stratum relative to the referent stratum.

^b Associations are adjusted simultaneously for all risk factors shown in the column.

^c Hazard ratio was calculated for no breastfeeding versus breastfeeding as a time-dependent covariate.

Predictors of time to first hospital admission through 4 months of age among 620 uninfected infants born to HIV-infected women in Lusaka, Zambia.

Predictor	No. of infants	Hazard ratio ^a (95% CI)	
		Unadjusted analysis	Adjusted analysis ^b
Maternal CD4 ⁺ T cell count			
<350 cells/ μ L	295	2.37 (1.22–4.60)	2.28 (1.17–4.45)
$\geq$ 350 cells/ μ L	325	1.00 (Referent)	1.00 (Referent)
Time of cessation of breastfeeding ^c			
Before 4 months of age	36	4.01 (1.18–13.6)	3.41 (1.01–11.52)
Still breastfeeding at 4 months of age	584	1.00 (Referent)	1.00 (Referent)
Child's place of birth			
Tertiary care hospital	88	2.25 (1.11–4.52)	..
Home	70	0.26 (0.04–1.88)	..
Primary care clinic maternity unit	462	1.00 (Referent)	..

^a Hazard ratios are calculated to indicate the magnitude of the association between hospital admissions in the indicated stratum relative to the referent stratum.

^b Associations are adjusted simultaneously for all risk factors shown in the column.

^c Hazard ratio was calculated for no breastfeeding versus breastfeeding as a time-dependent covariate.

Table 3

Predictors of weight from 1 week through 4 months of age among 582 uninfected infants (2498 weight measurements) born to HIV-infected women in Lusaka, Zambia.

Risk factor	Regression coefficient (95% CI)	
	Age- and sex-adjusted model ^a	Adjusted final model ^b
Female vs. male sex	−0.312 (−0.43 to −0.20)	−0.170 (−0.25 to −0.09)
Birth weight ^c	0.100 (0.09 to 0.11)	0.091 (0.08 to 0.10)
Twins vs. singletons	−1.261 (−1.88 to −0.64)	−0.417 (−0.73 to −0.10)
Born at home vs. at clinic	−0.237 (−0.40 to −0.07)	...
Born at hospital vs. at clinic	−0.223 (−0.43 to −0.02)	...
Maternal death	−1.251 (−1.76 to −0.74)	−0.540 (−0.89 to −0.19)
Maternal hospital admission	−0.538 (−0.83 to −0.25)	...
Maternal CD4 ⁺ T cell count of <350 cells/μL	−0.209 (−0.32 to −0.09)	...
Maternal HIV load of >100,000 copies/mL	−0.348 (−0.48 to −0.21)	−0.151 (−0.25 to −0.05)
Maternal hemoglobin level of <10 g/dL	−0.156 (−0.30 to −0.01)	...
Maternal body mass index of <18.5	−0.294 (−0.45 to −0.14)	−0.105 (−0.21 to −0.001)
Maternal HIV-related illnesses	−0.197 (−0.26 to −0.13)	...
Electricity in the home	0.258 (0.14 to 0.37)	0.090 (0.002 to 0.18)
Refrigerator in the home	0.400 (0.23 to 0.57)	...
Cook with a hotplate	0.277 (0.16 to 0.40)	...
Mother has some high school education	0.163 (0.05 to 0.28)	0.102 (0.02 to 0.19)
Mother married	0.208 (0.06 to 0.36)	...
Not breastfeeding	−0.418 (−0.55 to −0.28)	−0.252 (−0.35 to −0.16)

NOTE. Regression coefficients and 95% CIs are shown to indicate the magnitude of the associations between each risk factor and child weight from the generalized estimating equations models. The coefficient can be interpreted as the mean change in kilograms in child weight associated with each risk factor. Negative coefficients indicate a decrease in weight, and positive coefficients indicate an increase.

^a Coefficients are adjusted for age and sex only.

^b Associations are adjusted simultaneously for age and sex and all risk factors shown in the column.

^c Per 100-g increase.