Nutritional, Socioeconomic, and Delivery Characteristics Are Associated with Neurodevelopment in Tanzanian Children

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Objectives To evaluate the hypothesis that various maternal, socioeconomic, delivery, and infant nutritional characteristics are associated with early childhood development in young Tanzanian children.

Study design We performed a prospective cohort study among 206 HIV-exposed, uninfected and 247 HIV-unexposed Tanzanian infants who had been enrolled in 2 separate micronutrient trials (NCT00197730 and NCT00421668). Trained nurses administered culturally modified Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III), to evaluate cognitive, motor, and language development at 15 months of age. This analysis explored predictors of BSID-III z-scores using multivariable linear regression.

Results Among maternal determinants, we found that low maternal height predicted all BSID-III domains in HIV-unexposed children; low maternal education predicted lower cognitive (standardized mean difference, -0.41; 95% CI, -0.74 to -0.08) and lower gross motor scores (standardized mean difference, -0.32; 95% CI, -0.61 to -0.04) in HIV-exposed children. Among delivery characteristics, facility delivery predicted higher cognitive scores (standardized mean difference, 1.36; 95% CI, 0.26-2.46); and oxytocin administration predicted lower fine motor scores (standardized mean difference, -0.48; 95% CI, -0.87 to -0.09) in HIV-exposed children. Higher length-for-age z-scores at 6 weeks of age predicted better cognitive (standardized mean difference, 0.15; 95% CI, 0.01-0.29) and expressive language scores (standardized mean difference, 0.16; 95% CI, 0.02-0.29) at 15 months in HIV-exposed infants.

Conclusions This hypothesis-generating study found significant associations between nutritional status and health of the mother and child, and maternal educational attainment, with direct measures of early childhood development at 15 months of age. In addition, several aspects of delivery (facility birth and oxytocin administration) were associated with early childhood development. Future intervention trials should focus on modifiable maternal, infant, and obstetric factors to strengthen the evidence base concerning early childhood development. *(J Pediatr 2019;207:71-9).*

Trial registration ClinicalTrials.gov: NCT00197730 and NCT00421668.

As rates of child survival continue to improve in low- and middle-income countries,[1] more attention is being paid to early childhood development, school achievement, and lifetime earning potential. Improving early childhood development is considered a key component to achieving sustainable development.[2-5] The first 1000 days of life, including the pregnancy period and first 2 years of life, are critical for physical growth and broader cognitive, motor, and socioemotional development.[6-8] The fetal, infant, and early childhood periods represent windows of heightened developmental sensitivity, and modifiable insults incurred during these periods have potentially irreversible effects on growth and neurobehavioral development.[9]

There are a number of biological (eg, micronutrient and protein energy deficiencies, intrauterine growth restriction, infections, and toxicological exposures) and psychosocial risks (such as suboptimal caregiving, maternal depression, exposure to violence, and low maternal education) that put children at risk for not

BSID-III	Bayley Scales of Infant and Toddler Development, 3rd edition
LAZ	Length-for-age z-scores
WAZ	Weight-for-age z-scores
WLZ	Weight-for-length z-scores

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reaching their developmental potential.[10,11] Many studies have shown an association of maternal and child malnutrition with suboptimal early childhood development. For example, 1 meta-analysis showed strong evidence for positive associations between child height-for-age z-scores and cognitive ability and motor development,[12] and evidence has emerged about the importance of micronutrients in pregnancy for the development of child intellectual ability and procedural memory.[13] In a large systematic review of health and nutrition interventions promoting early childhood development, only a small number of studies have investigated associations between neonatal characteristics such as Kangaroo Mother Care, delayed cord clamping, or hypoxic ischemic encephalopathy and direct measures of early childhood development.[14] In addition, few, if any, studies have evaluated the potential role of obstetric interventions and delivery characteristics (eg, oxytocin and ergometrine administration, state of amniotic fluid, delivery mode, or fetal distress) in early childhood development. Understanding these potential determinants may guide future early childhood development research and policy.

We hypothesized that features of delivery, maternal health factors, and socioeconomic characteristics were related to early childhood neurodevelopment in Tanzanian children. In addition, we sought to identify predictors of poor neurodevelopment at 15 months of age among potential maternal, family, and child growth characteristics.

Methods

This prospective cohort study includes a subsample of infants enrolled in 2 multivitamin supplementation clinical trials (of zinc and vitamins B complex, vitamin C, and vitamin E); infants were born to HIV-infected women (ie, HIV exposed; Child 1, NCT00197730) and to HIV-uninfected women (ie, HIV unexposed; Child 2, NCT00421668). Details of the trials and main results have been published previously.[15,16] Briefly, both studies randomized singleton infants at approximately 6 weeks of age; children with major malformations or serious medical conditions were excluded. In the Child 1 trial, 2387 HIV-exposed infants were followed for 24 months to determine whether daily administration of multivitamins decreased the risk of mortality or infectious disease morbidity compared with placebo. In the Child 2 trial, 2400 HIV-unexposed infants were followed for 18 months to determine whether daily administration of the same regimen of multivitamins with or without zinc to infants decreased the risk of infectious disease morbidity compared with placebo. The children were tested for HIV infection at 6 weeks and 18 months of age.[15] Secondary endpoints of both studies included the evaluation of the effects of supplementation on neurodevelopment, but previous analyses found no treatment effect on early childhood development.[17,18] We included data from a convenience sample of 206 (Child 1) and 247 (Child 2) children attending a study clinic who were selected for neurodevelopmental testing and were HIV uninfected at 15 months of age.

The outcome of interest, early childhood development, was assessed at 14-17 months of age. A subsample of 453 children from the parent trials was selected for neurodevelopment assessment from a single research site (Magomeni Hospital) owing to training and space restrictions.[18] The Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III) was selected to evaluate neurodevelopment. A specialist in child neurology travelled to Dar es Salaam to train the BSID-III test administrators and conducted observational evaluations to address quality control. Tests were administered in Kiswahili by 2 trained Tanzanian nurses during the child's clinic visit. We elected to use raw, unstandardized scores because the BSID-III has not been validated in the Tanzanian context, and it may not be appropriate to compare our study population's scores with the US reference population used for standardization.[19] Each of the 5 early childhood development domains (cognitive, gross motor, fine motor, expressive language, and receptive language assessments) of the BSID-III score was analyzed independently as an outcome of interest.

Data collected in both trials included detailed demographic and socioeconomic characteristics (by maternal interviews, collected immediately after delivery whenever possible), delivery characteristics (by concomitant medical record review), and infant growth measures (methods noted elsewhere in this article). Fetal distress was functionally defined as delivery by vacuum extraction, assisted breach, or emergency or elective cesarean delivery. Prolonged labor was defined as a time from labor onset to delivery of more than 20 hours if primiparous and more than 14 hours if multiparous. Nonspontaneous vaginal delivery included vacuum extraction, assisted breach, and emergency cesarean or elective cesarean deliveries. Length was measured using a length board, measured to the nearest 0.1 cm. Weight was measured on a digital infant balance scale with a 10-g precision (Tanita, Arlington Heights, Illinois). We used the 2006 WHO Child Growth Standards to calculate weight-for-length z-scores (WLZ), length-for-age z-scores (LAZ), and weight-for-age z-scores (WAZ).[20] Stunting, wasting, and underweight were defined as LAZ, WLZ, or WAZ, respectively, of more than 2 standard deviations below the median. All extreme outliers ($-6 > WAZ > 5$, $-6 > LAZ > 6$, and $-5 > WLZ > 5$) were set to missing, per WHO recommendations.[21] We used the mean and SD or frequency and proportion to summarize demographic, delivery, child characteristics, anthropometrics, and standardized infant BSID-III scores. We evaluated the relationship between each risk factor and neurodevelopment subscore using minimally adjusted robust regression models to account for heteroskedastic errors.[22] Minimally adjusted models included infant age, sex, and BSID-III assessor. All risk factors with a P value of .20 or less in minimally adjusted models were retained for inclusion in multivariate models using robust regression. Given the potential for collinearity between variables (eg, maternal weight and body mass index), a representative variable was selected for inclusion in the multivariate model if both were individually significant in univariate analysis. Similarly, WAZ scores were not included in the same models as LAZ or WLZ owing to collinearity. Categorical anthropometry indicators (stunting, wasting and underweight) were evaluated in separate models.

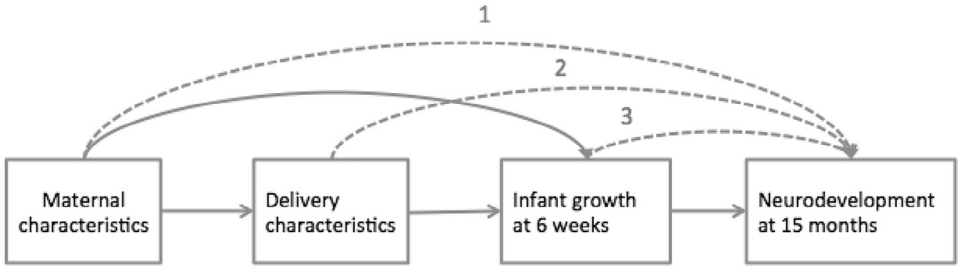

Figure 1. Directed acyclic graph displaying the hypothesized relationship between our 3 models and neurodevelopment at 15 months of age, represented by *dashed pathways*. *Solid arrows* represent relationships for which there is substantial evidence in the literature.

We used separate models for variables measured at different times in the study to avoid introducing bias into our analysis by adjusting for variables on the causal pathway between a risk factor and neurodevelopment (**Figure 1**). We created 3 models: maternal socioeconomic, demographic, and nutritional characteristics (**Figure 1**, pathway 1); delivery characteristics including location of delivery, birth weight, Apgar scores, and others (**Figure 1**, pathway 2); and child nutritional status at 6 weeks of age (**Figure 1**, pathway 3). Although we would have liked to perform mediation analyses including variables from all 3 models, our sample size did not allow for such assessments.

We analyzed the study populations from the 2 trials separately with the possibility of pooling, but we did not find clear, parallel effects in the individual studies. Additionally, as indicated by the descriptive statistics in **Table I**, the 2 cohorts were significantly different on several determinants of development. Furthermore, it is likely that maternal HIV status is a mediator of many of our associations (eg, maternal education and socioeconomic status) and adjusting for study would therefore likely bias our estimates toward the null. Thus, we present the results for each study separately here.

In the instance of missing covariate data for categorical variables, we used the missing indicator method in multivariate models for categorical variables. We imputed the median where covariate data were missing for a linear variable. Whenever child anthropometric data were missing, we excluded this observation from the analysis to perform a complete case analysis, because the number of missing observations was too small to allow adjustment by missing category. Because we have related outcomes and covariates, the Bonferroni adjustments for multiple comparisons were not appropriate. All analyses were conducted in SAS software version 9.4 (SAS Institute, Cary, North Carolina).

Results

We included 206 HIV-exposed and 247 HIV-unexposed infants in the models using maternal and delivery characteristics. The child growth analysis had fewer observations after excluding missing observations (missing n = 10 [4.9%] HIV-exposed and 21 [8.5%] HIV-unexposed infants) for a complete case analysis (n = 196 and 226, respectively). Descriptive statistics for HIV-exposed and HIV-unexposed mother–infant pairs, including baseline maternal and socioeconomic characteristics, delivery and child characteristics at birth, and child growth indices at 6 weeks, are presented in **Table I**. Delivery at less than 20 weeks of gestation was more frequent in HIV-uninfected mothers than in HIV-infected mothers. Most women had between 1 and 7 years of education (ie, primary level, standard I-VII). More than 60% of households were composed of 3 members or fewer. Oxytocin administration during the third stage labor was more common in HIV-infected (89.5%) than HIV-uninfected women (39.6%), likely because HIV-infected women were preferentially referred to a tertiary care center for delivery. In contrast, ergometrine administration after delivery was more common in HIV-uninfected (47.8%) than HIV-infected mothers (5.0%), because these women tended to deliver at district or other facilities. At infant age 6 weeks, the prevalence of wasting, stunting, and underweight was similar across the 2 studies.

In fully adjusted multivariate models, we found that maternal education, height and parity, the number of people in the household, and daily food expenditure were significantly and independently associated with early childhood development (**Figure 2**, **Figure 3**, **Table II** [available at www.jpeds.com], and **Table III** [available at www.jpeds.com]) in both cohorts of children. HIV-exposed children born to mothers with 1-7 years of education had lower cognitive scores and lower gross motor scores compared with children whose mothers had more than 7 years of education. Among HIV-unexposed children, children born to mothers with a height between 150 and 155 cm had lower cognitive, gross motor, fine motor, expressive language, and receptive language scores compared with children born to mothers taller than 155 cm. HIV-unexposed children born as the second or third child had significantly lower cognitive, receptive language, and expressive language scores compared with those born to primiparous mothers. HIV-exposed children born in households with 3 or fewer members had significantly lower cognitive scores and receptive language scores, compared with those born in households with 4 or more members. Among HIV-unexposed children, a daily food expenditure below the median of 3000

Table I. Characteristics of study population

Maternal characteristics	HIV-exposed cohort (n = 206)	HIV-unexposed cohort (n = 247)	*P* value
Maternal age 18-19 vs ≥20 y (n = 452)	9 (4.4)	23 (9.3)	.04
Married/cohabitating with partner (n = 450)	182 (88.8)	217 (88.6)	.87
Prior pregnancies (n = 452)			
1	37 (18)	90 (36.6)	<.01
2-3	117 (56.8)	132 (53.7)	.47
4	52 (25.2)	24 (9.8)	<.01
Height (n = 452), cm			
<150	35 (17)	20 (8.1)	<.01
150-155	59 (28.6)	96 (39)	.02
>155cm	112 (54.4)	130 (52.8)	.71
Body mass index at 6 weeks (n = 386), kg/m^2			
<18.5	7 (3.4)	2 (0.8)	.05
18.5-<25	118 (57.3)	136 (55.1)	.64
≥25	81 (39.3)	107 (43.3)	.39
Mid-upper arm circumference (n = 451), cm	26.40 ± 2.08	26.48 ± 3.30	.82
Formal education, y (n = 452)			
None	16 (7.8)	3 (1.2)	<.01
1-7	149 (72.3)	189 (76.8)	.31
≥8 (ref)	41 (19.9)	54 (22)	.61
Employment (n = 450)			
Housewife without income	139 (67.5)	152 (62.3)	.19
Housewife with small business	42 (20.4)	47 (19.3)	.72
Formal job	25 (12.1)	45 (18.4)	.07
Household <4 members (n = 452)	125 (60.7)	161 (65.4)	.32
Daily food expenditure of ≤3000 TShs (n = 430)	183 (91.5)	100 (43.5)	<.01
Number of times meat eaten per week (n = 446)			
0-3	73 (36)	68 (28)	.07
4	107 (52.7)	163 (67.1)	<.01
≥5	23 (11.3)	12 (4.9)	.01
Delivery and child characteristics			
Hospital delivery (n = 451)	203 (98.5)	244 (99.2)	.82
Spontaneous vaginal delivery* (n = 449)	171 (83.4)	215 (88.1)	.23
Prolonged labor† (n = 422)	34 (16.5)	64 (25.9)	.02
Fetal distress (n = 282)	34 (16.5)	29 (11.7)	.15
Oxytocin administrated (n = 291)	179 (89.5)	36 (39.6)	<.01
Ergometrine administrated (n = 291)	10 (5)	44 (47.8)	<.01
Amniotic fluid not clear‡ (n = 268)	20 (10.3)	4 (5.5)	<.01
Meconium in amniotic fluid (n = 250)	19 (9.8)	—	—
Female sex (n = 453)	106 (51.5)	125 (50.6)	.86
Birth weight, kg (n = 324)	3.12 ± 0.47	3.15 ± 0.45	.2
Born at <37 weeks gestational age§ (n = 324)	34 (16.5)	15 (12.7)	<.01
Apgar score ≤7 at 5 minutes (n = 306)	4 (2.1)	1 (0.9)	.83
Needed resuscitation at delivery (n = 271)	60 (30.5)	6 (8.1)	<.01
Child anthropometrics at 6 weeks			
WLZ¶ (n = 422)	0.00 ± 0.97	0.10 ± 1.08	.28
LAZ¶ (n = 422)	-0.37 ± 1.00	-0.31 ± 1.04	.54
Underweight (n = 422)	13 (6.6)	8 (3.5)	.14
Wasted (n = 422)	9 (4.6)	13 (5.7)	.62
Stunted (n = 422)	11 (5.6)	12 (5.2)	.87

Values are number (%) or mean ± SD.
*Vaginal delivery vs vacuum extraction, assisted breach, emergency cesarean, or elective cesarean delivery.
†Time from labor onset to delivery of <20 hours if primiparous, <14 hours if multiparous (McGraw-Hill Concise Dictionary of Modern Medicine, 2002).
‡Amniotic fluid bloody, foul smelling, or purulent or containing meconium vs clear.
§Calculated from estimated date of last menstrual period.
¶Number for complete analysis (dropping all observation with 1 or missing z-scores).

Tanzanian shillings predicted lower fine motor and expressive language scores.

Among numerous delivery characteristics, we found that facility delivery and oxytocin administration were independently and significantly associated with early childhood development among HIV-exposed children (**Figure 2**, **Figure 3**, and **Table IV** [available at www.jpeds.com]). HIV-exposed children delivered in a hospital had higher cognitive and fine motor scores. Oxytocin receipt was associated with lower fine motor scores. We did not find significant associations between delivery characteristics and early childhood development among HIV-unexposed infants (**Table V**; available at www.jpeds.com).

Among infant growth outcomes, we found that stunting, or alternatively LAZ and WLZ, at 6 weeks of age were independently associated with early childhood development across the cognitive (HIV-exposed only), language (both HIV-exposed and -unexposed), and motor domains (HIV-unexposed only) of the BSID-III. These results are reported in **Figure 2**, **Figure 3**,

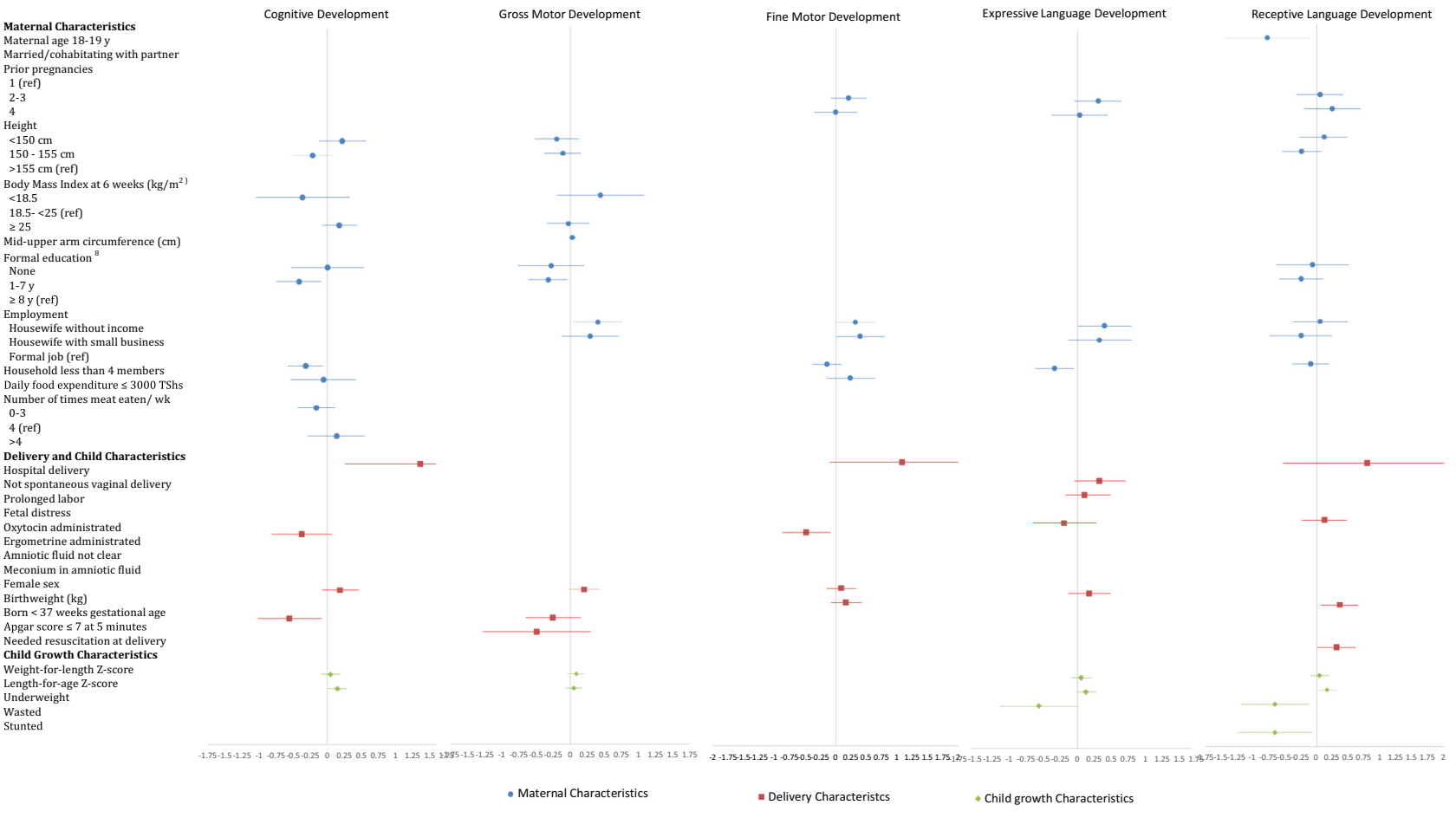

Figure 2. Standardized mean differences and associated CIs for predictors of BSID-III z-scores in HIV-exposed infants. Adjusted models include all covariates with $P < .2$ in univariate regressions.

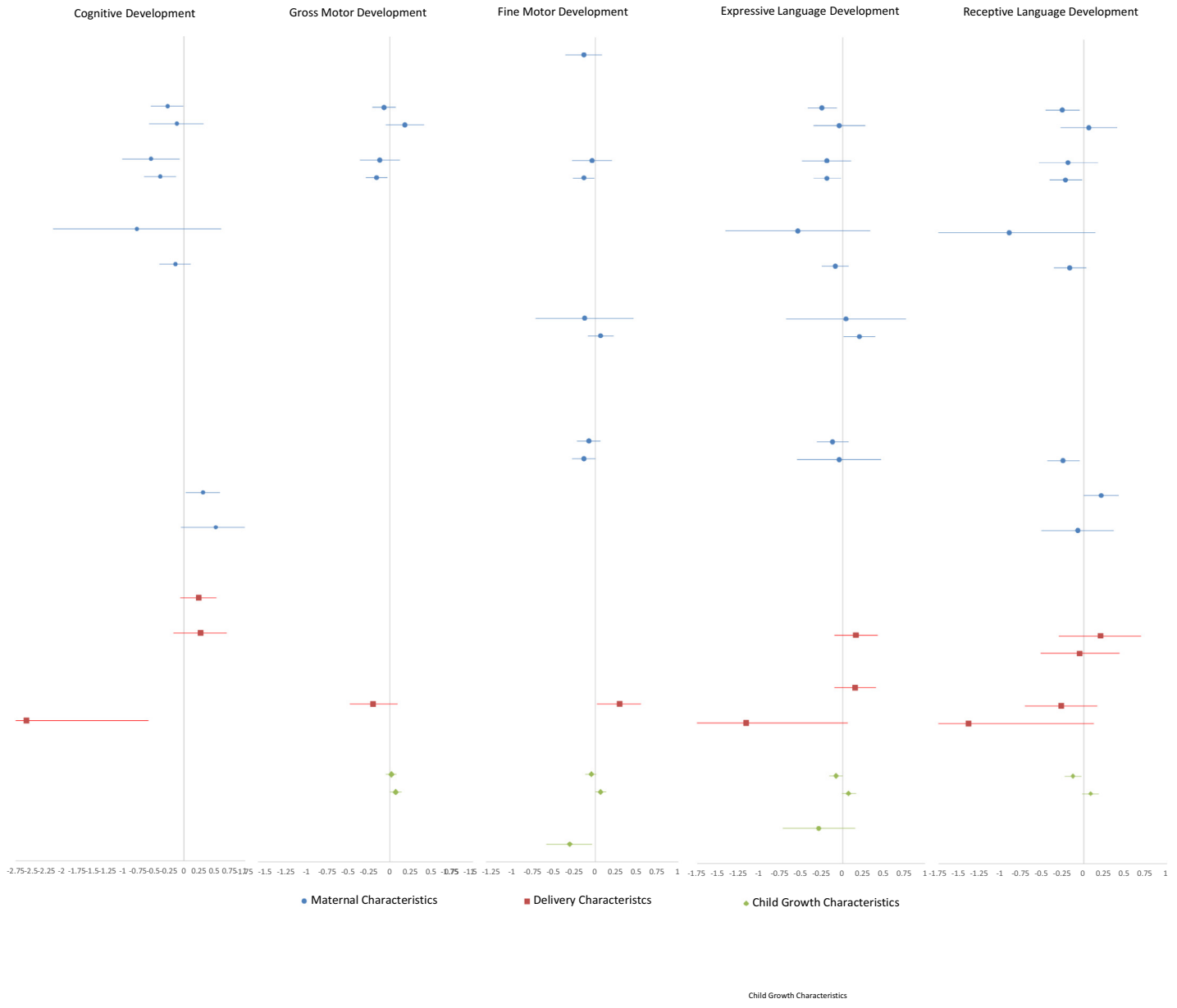

Figure 3. Standardized mean differences and associated CIs for predictors of BSID-III z-scores in HIV-unexposed infants. Adjusted models include all covariates with $P < .2$ in univariate regressions.

Table VI (available at www.jpeds.com), and **Table VII** (available at www.jpeds.com).

Discussion

In this observational cohort study of 453 young Tanzanian children, we identified several independent maternal, delivery-related, and infant growth risk factors for infant early childhood development. Maternal height, education level and parity, and household food expenditure were all independently associated with improved neurodevelopment. In addition, delivery characteristics such as delivery outside a health facility and oxytocin administration during delivery were independent risk factors of less optimal neurodevelopment. Although our risk factor was defined as oxytocin administered during the third stage of labor, we can speculate whether the association indicated inappropriate use of oxytocin in this cohort. However, this association should be interpreted with caution, because the analysis was not able to control for maternal factors that may increase the likelihood of facility delivery. Last, stunting (or LAZ and WLZ) at 6 weeks was also independently associated with lower cognitive, language, and motor scores at 15 months of age.

Several independent risk factors were related to maternal nutrition and socioeconomic conditions. Maternal education has commonly been linked to infant neurodevelopment, presumably via multiple biologic and social pathways.[10,23] Maternal height is thought to reflect the long-term nutritional conditions of the mother, and optimizing maternal nutrition has been proposed as an effective intervention for early childhood development.[13,24] Similarly, infants born to mothers with greater parity had significantly poorer cognitive and language development compared with those born to primiparous mothers. Although the authors are not aware of any studies directly linking parity with early childhood development, a previous meta-analysis has shown links between shorter birth intervals and the risk of a child being born small for gestational-age.[25] Low household food expenditure independently predicted poor motor and language scores. Estimates of food expenditure could be indicative of the food consumption patterns of the household, and also of the household socioeconomic status, which may impact early childhood development during early infancy.[13]

Our study's novel findings include the identification of several delivery characteristics that were related to early childhood development. Hospital delivery has been touted as one of the most important predictors of improved postnatal maternal and child health.[26] Our finding of a strong and positive association between facility delivery and cognitive and fine motor scores supports policy recommendations to encourage facility-based births. The causal pathway for this effect may be through avoiding birth complications and improving neonatal care. However, in Dar es Salaam, 94% of births are facility based,[27] and the observed association may also be related to precipitous delivery or the health-seeking behavior of the mother, which was not well-characterized in our cohort. Nonetheless, to our knowledge, our study is the first to demonstrate an association between hospital delivery and improved early childhood development outcomes. This is a hypothesis-generating study; thus, findings should be interpreted with caution and investigated in future studies.

Among HIV-exposed children, oxytocin use was a risk factor for poor cognitive and fine motor scores. During the period of our study, oxytocin administration after delivery was common to prevent postpartum hemorrhage.[28] The apparent negative effect of oxytocin on motor development might be a result of confounding by indication (ie, sicker mothers at risk of having infants with poorer early childhood development may receive oxytocin more frequently) rather than a causal relationship. Similar to our finding, a retrospective study on young children in Spain found that oxytocin administration was associated with delays in both gross and fine motor development.[29]

Among both HIV-exposed and HIV-unexposed children, poor growth was associated with poorer performance in all 5 domains of the BSID-III. These anthropometric measures suggest that both acute and chronic malnutrition are risk factors for impaired cognitive and motor development, consistent with many studies and a recent meta-analysis.[12] Notably, our findings suggest that anthropometric indices measured as early as at 6 weeks of age have a significant association with neurodevelopment measured more than 1 year later. Our analysis is one of few studies that link nutritional status during early infancy with child development[30,31] and provides further evidence to support the hypothesis that early infant nutrition is associated with longer term child health and development (**Figure 1**).[6]

Our analysis suggests that risk factors of impaired neurodevelopment might vary between HIV-exposed and HIV-unexposed infants, although we did not formally test these differences. Mothers in the HIV-infected cohort were poorer, had less education, were of shorter statue, and had fewer household resources than the HIV-negative mothers, which may account for some of the differences in findings between cohorts. Another important difference between the HIV-exposed and HIV-unexposed cohorts was antiretroviral therapy exposure in utero and during breastfeeding for some of the children born to HIV-positive mothers. Whereas infants infected with HIV are known to be at high risk for cognitive and motor development delays relative to uninfected children,[32] the effect of in utero exposure to HIV and antiretroviral therapy on the development of HIV-exposed uninfected children remains unclear.[33]

One limitation of our study was that we were not able to evaluate some factors (including responsive caregiving, maternal depression, and paternal education) that have previously been linked to neurodevelopment.[13,34] In particular, caregiving and home environment stimulation are important predictors of developmental outcomes.[13,34] We controlled for socioeconomic status by including measures of food expenditure and weekly meat consumption. Also, our convenience sample scheme may have limited our power to detect risk factors and the ability to generalize our findings beyond the context of infants in periurban Tanzania. Another limitation of this study is that our sample size did not allow us to

perform mediation analyses including variables from all 3 models. However, this analysis used longitudinal cohort data and collected data on risk factors prospectively. The sample size, 206 HIV-exposed and 247 HIV-unexposed children, was comparable with other studies evaluating cognition in low- and middle-income countries.[35-37]

We found that maternal and delivery characteristics are important risk factors for suboptimal early childhood development. To our knowledge, this is the first study to link child delivery characteristics such as delivery outside a health facility and oxytocin administration with impaired neurodevelopment. We were also able to link poor early infant growth with developmental delays more than 1 year later, a finding that has important implications for ensuring adequate fetal and postnatal growth. Facility-based births have been promoted for their immediate impact on maternal and neonatal outcomes, but our data support the possibility that longer term child outcomes are also improved. Although the associations demonstrated should be interpreted with caution, these data are useful to promote thinking more broadly about interventions to improve early childhood development through targeting risk factors. Future intervention trials should focus on modifiable maternal, infant, and obstetric factors to strengthen the evidence base concerning early childhood development. ■

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50 Years Ago in *The Journal of Pediatrics*

Thrombosis of the Superior Longitudinal Sinus during Infancy: Report of 2 Cases

Yang DC, Sohn D, Anand HK. J Pediatr 1969;74:570-5

In 1969, Yang described 2 cases of thrombosis of the superior longitudinal sinus in toddlers, one during an episode of acute gastroenteritis and one in a child with pneumonia. Both presented neurologic signs, rapid onset, and immediate systemic compromise. Yang suggested prompt diagnosis of cerebral sinus venous thrombosis (CSVT) can be suspected if high opening pressures and blood-stained spinal taps were present, as in both of their cases.

Nowadays, CSVT affects 0.34-0.67/100 000 children annually. Mortality is low but, neurologic sequelae are present in 62% of the survivors.[1] The etiology and clinical presentation are variable; however, prothrombotic disorders contribute to its presentation. Clinical findings include increased intracranial pressure secondary to venous drainage compromise, or focal brain injury from venous ischemia/infarction or hemorrhage.[2] The location of the thrombosis clinically differentiates CSVT from other vascular insults. Blood work is suggested for searching for prothrombotic states,[3] and unless meningitis is suspected, spinal tap is not recommended. Absence of an elevated cerebrospinal fluid opening pressure and high protein and cellularity counts should not rule out the diagnosis.[3] A venography is recommended when initial computed tomography or magnetic resonance imaging suggests CSVT.[3] Management suggested for nonhemorrhage CSVT (non-neonates) by the American Heart Association is the use of unfractionated heparin or low-molecular-weight heparin followed by warfarin for 3-6 months.[3] The American College of Clinical Pharmacy recommends the use of unfractionated heparin followed by low-molecular-weight heparin for 3 months.[2]

Today we know that CSVT is a rare pathology outside the neonatal period, with presumably primary hematologic diseases. New imaging modalities facilitate accurate diagnosis, and new guidelines for management are available.

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Table II. Minimally adjusted and adjusted SMDs for maternal risk factors and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-exposed children

		Outcome 1: cognition standardized mean difference*		Outcome 2: gross motor standardized mean difference*		Outcome 3: fine motor standardized mean difference*		Outcome 4: receptive language standardized mean difference*		Outcome 5: expressive language standardized mean difference*	
		Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶	Minimally adjusted*	Adjusted**
Maternal characteristics	n (%)	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††
Maternal age 18-19 y	9 (4.4)	−0.07 (−0.70 to 0.57)		−0.11 (−0.66 to 0.43)		−0.09 (−0.65 to 0.47)		−0.10 (−0.75 to 0.56)		−0.71 (−1.34 to −0.07)‡‡	−0.78 (−1.44 to −0.12)‡‡
Married/cohabitating with partner	182 (88.3)	−0.16 (−0.58 to 0.25)		−0.10 (−0.46 to 0.25)		−0.03 (−0.39 to 0.34)		−0.04 (−0.47 to 0.39)		0.14 (−0.28 to 0.55)	
Prior pregnancies§§											
1 (ref)	37 (18)										
2-3	117 (56.8)	0.20 (−0.15 to 0.54)		−0.05 (−0.34 to 0.24)		0.29 (−0.02 to 0.60)¶¶	0.21 (−0.08 to 0.50)***	0.35 (−0.01 to 0.70)¶¶	0.30 (−0.04 to 0.65)¶¶	0.11 (−0.25 to 0.47)	0.05 (−0.31 to 0.42)
4	52 (25.2)	0.08 (−0.31 to 0.48)		0.07 (−0.26 to 0.41)		0.13 (−0.22 to 0.48)	0.00 (−0.35 to 0.35)	0.17 (−0.24 to 0.58)	0.03 (−0.38 to 0.44)	0.27 (−0.13 to 0.68)***	0.24 (−0.20 to 0.68)
Height, cm											
<150	35 (17)	0.16 (−0.19 to 0.50)	0.22 (−0.12 to 0.57)	−0.23 (−0.54 to 0.09)***	−0.20 (−0.52 to 0.13)	0.10 (−0.22 to 0.42)		0.21 (−0.16 to 0.57)		0.15 (−0.21 to 0.52)	0.11 (−0.26 to 0.49)
150-155	59 (28.6)	−0.27 (−0.56 to 0.02)¶¶	−0.21 (−0.50 to 0.08)***	−0.05 (−0.31 to 0.21)	−0.11 (−0.38 to 0.15)	−0.14 (−0.41 to 0.13)		−0.11 (−0.42 to 0.20)		−0.22 (−0.52 to 0.09)***	−0.24 (−0.55 to 0.07)***
>155 (ref)	112 (54.4)										
Body mass index at 6 weeks, kg/m^2§§											
<18.5	7 (3.4)	−0.49 (−1.22 to 0.24)***	−0.36 (−1.04 to 0.33)	0.42 (−0.2 to 1.04)***	0.44 (−0.19 to 1.08)***	−0.35 (−0.98 to 0.29)		−0.19 (−0.94 to 0.57)		−0.37 (−1.10 to 0.36)	
18.5-<25 (ref)	118 (57.3)										
≥25	81 (39.3)	0.13 (−0.14 to 0.40)	0.18 (−0.07 to 0.44)	0.11 (−0.12 to 0.34)	−0.03 (−0.34 to 0.28)	0.12 (−0.12 to 0.36)		0.07 (−0.21 to 0.35)		−0.15 (−0.42 to 0.12)	
Mid-upper arm circumference, cm‡‡		0.03 (−0.02 to 0.07)		0.03 (0.00 to 0.07)¶¶	0.03 (−0.02 to 0.08)***	0.01 (−0.03 to 0.05)		0.01 (−0.04 to 0.05)		0.01 (−0.03 to 0.05)	
Formal education, y§§											
None	16 (7.8)	0.06 (−0.48 to 0.59)	0.01 (−0.52 to 0.54)	−0.22 (−0.69 to 0.24)	−0.28 (−0.76 to 0.20)	0.03 (−0.45 to 0.51)		0.35 (−0.22 to 0.91)		−0.07 (−0.62 to 0.48)	−0.07 (−0.64 to 0.50)
1-7	149 (72.3)	−0.36 (−0.68 to −0.04)‡‡	−0.41 (−0.74 to −0.08)†††	−0.26 (−0.54 to 0.01)¶¶	−0.32 (−0.61 to −0.04)‡‡	−0.13 (−0.42 to 0.16)		−0.19 (−0.53 to 0.15)		−0.22 (−0.54 to 0.11)***	−0.25 (−0.6 to 0.09)***
≥8 (ref)	41 (19.9)										

(*continued*)

Table II. Continued

Maternal characteristics	n (%)	Outcome 1: cognition standardized mean difference*		Outcome 2: gross motor standardized mean difference*		Outcome 3: fine motor standardized mean difference*		Outcome 4: receptive language standardized mean difference*		Outcome 5: expressive language standardized mean difference*	
		Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶	Minimally adjusted*	Adjusted**
		SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††
Employment											
Housewife without income	139 (67.5)	0.13 (–0.27 to 0.53)		0.28 (–0.05 to 0.61)¶¶	0.40 (0.05 to 0.76)‡‡	0.34 (–0.01 to 0.69)¶¶	0.32 (–0.01 to 0.65)¶¶	0.42 (0.02 to 0.83)‡‡	0.39 (–0.01 to 0.78)¶¶	–0.11 (–0.52 to 0.29)	0.05 (–0.38 to 0.47)
Housewife with small business	42 (20.4)	–0.09 (–0.56 to 0.38)		0.20 (–0.20 to 0.59)	0.29 (–0.12 to 0.71)***	0.35 (–0.07 to 0.76)¶¶	0.40 (0.01 to 0.79)‡‡	0.38 (–0.10 to 0.85)***	0.32 (–0.15 to 0.78)***	–0.37 (–0.84 to 0.10)***	–0.25 (–0.74 to 0.24)
Formal job (ref)	25 (12.1)										
Household <4 members	125 (60.7)	–0.30 (–0.56 to –0.04)‡‡	–0.31 (–0.57 to –0.06)‡‡	–0.01 (–0.24 to 0.21)		–0.19 (–0.42 to 0.04)***	–0.14 (–0.38 to 0.09)	–0.32 (–0.59 to –0.05)‡‡	–0.34 (–0.62 to –0.06)‡‡	–0.21 (–0.48 to 0.06)***	–0.1 (–0.39 to 0.18)
Daily food expenditure ≤3000 TShs	183 (88.8)	–0.37 (–0.84 to 0.10)***	–0.05 (–0.53 to 0.42)	0.07 (–0.33 to 0.48)		–0.27 (–0.67 to 0.13)***	0.24 (–0.15 to 0.64)	–0.19 (–0.67 to 0.29)		–0.12 (–0.59 to 0.34)	
Number of times meat eaten per week§§											
0-3	73 (35.4)	–0.10 (–0.38 to 0.18)	–0.16 (–0.43 to 0.11)	–0.01 (–0.25 to 0.23)		0.14 (–0.11 to 0.39)		–0.16 (–0.46 to 0.13)		–0.04 (–0.33 to 0.25)	
4 (ref)	23 (11.2)										
>4	107 (51.9)	0.29 (–0.13 to 0.72)***	0.14 (–0.28 to 0.55)	0.14 (–0.22 to 0.50)		–0.06 (–0.44 to 0.33)		0.05 (–0.39 to 0.48)		–0.14 (–0.57 to 0.29)	

SMD, standardized mean difference.
*Adjusted for child sex, child age, and BSID-III examiner.
†Adjusted for maternal height, maternal body mass index, maternal education, household size, meat consumption, child sex, child age, and BSID-III examiner.
‡Adjusted for maternal height, maternal body mass index, maternal mid-upper arm circumference, maternal education, maternal employment status, child sex, child age, and BSID-III examiner.
§Adjusted for prior pregnancies, maternal employment status, household size, daily food expenditure, child sex, child age, and BSID-III examiner.
¶Adjusted for prior pregnancies, maternal employment status, household size, child sex, child age, and BSID-III examiner.
**Percentages do not add up to 100 owing to missing data.
††Standardized mean difference (SMD) and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
‡‡$P < .05$.
§§Adjusted for maternal age, prior pregnancies, maternal height, maternal education, maternal employment status, household size, child sex, child age, and BSID-III examiner.
¶¶$P < .1$.
***$P < .2$.
†††$P < .01$.

Table III. Minimally adjusted and adjusted SMDs for maternal risk factors and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-unexposed children

		Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
	n (%)	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶	Minimally adjusted*	Adjusted**
Maternal characteristics		SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††
Maternal age 18-19 y	23 (9.3)	0.14 (−0.30 to 0.58)		0.03 (−0.20 to 0.25)		−0.05 (−0.25 to 0.15)		−0.06 (−0.32 to 0.20)		−0.16 (−0.49 to 0.17)	
Married/ cohabitating with partner	217 (87.9)	−0.02 (−0.41 to 0.38)		−0.01 (−0.21 to 0.20)		−0.19 (−0.39 to 0.01)‡‡	−0.14 (−0.36 to 0.08)	0.04 (−0.19 to 0.27)		−0.13 (−0.43 to 0.17)	
Prior pregnancies**											
1 (ref)	90 (36.4)										
2-3	132 (53.4)	−0.39 (−0.66 to −0.12)¶¶	−0.27 (−0.54 to −0.01)***	−0.08 (−0.22 to 0.05)	−0.07 (−0.21 to 0.07)	−0.05 (−0.17 to 0.08)		−0.24 (−0.41 to −0.07)¶¶	−0.25 (−0.43 to −0.08)¶¶	−0.29 (−0.49 to −0.08)¶¶	−0.26 (−0.47 to −0.06)¶¶
4	24 (9.7)	−0.29 (−0.74 to 0.16)	−0.12 (−0.57 to 0.32)	0.16 (−0.07 to 0.39)†††	0.18 (−0.05 to 0.41)†††	0.07 (−0.14 to 0.28)		0.03 (−0.25 to 0.31)	−0.04 (−0.35 to 0.27)	0.01 (−0.33 to 0.35)	0.06 (−0.28 to 0.40)
Height, cm											
<150	20 (8.1)	−0.48 (−0.94 to −0.01)***	−0.54 (−1.01 to −0.07)***	−0.09 (−0.33 to 0.15)	−0.12 (−0.36 to 0.12)	0.03 (−0.19 to 0.26)	−0.04 (−0.28 to 0.20)	−0.08 (−0.37 to 0.20)	−0.19 (−0.48 to 0.11)	−0.10 (−0.46 to 0.26)	−0.19 (−0.55 to 0.16)
150-155	96 (38.9)	−0.45 (−0.70 to −0.19)¶¶	−0.39 (−0.65 to −0.13)¶¶	−0.16 (−0.30 to −0.03)***	−0.16 (−0.29 to −0.03)***	−0.12 (−0.25 to 0.00)***	−0.14 (−0.27 to −0.01)***	−0.21 (−0.36 to −0.05)¶¶	−0.19 (−0.36 to −0.03)***	−0.24 (−0.44 to −0.04)***	−0.22 (−0.42 to −0.03)***
>155 (ref)	130 (52.6)										
Body mass index at 6 weeks, kg/m^2§§											
<18.5	2 (0.8)	−0.63 (−2.03 to 0.78)	−0.77 (−2.14 to 0.61)	−0.15 (−0.87 to 0.58)		−0.22 (−0.92 to 0.48)		−0.43 (−1.26 to 0.39)	−0.54 (−1.41 to 0.33)	−0.73 (−1.79 to 0.34)†††	−0.90 (−1.94 to 0.14)‡‡
18.5-<25 (ref)	136 (55.1)										
≥25	107 (43.3)	−0.27 (−0.53 to −0.02)***	−0.14 (−0.40 to 0.11)	0.05 (−0.08 to 0.18)		−0.07 (−0.19 to 0.06)		−0.13 (−0.28 to 0.02)‡‡	−0.09 (−0.25 to 0.07)	−0.22 (−0.42 to −0.03)***	−0.17 (−0.37 to 0.02)‡‡
Mid-upper arm circumference (cm)‡‡‡		−0.02 (−0.06 to 0.02)		−0.01 (−0.03 to 0.01)		−0.01 (−0.03 to 0.01)		−0.01 (−0.03 to 0.01)		−0.01 (−0.04 to 0.02)	
Formal education, y§§											
None	3 (1.2)	−0.19 (−1.36 to 0.98)		0.18 (−0.42 to 0.79)		−0.36 (−0.90 to 0.17)†††	−0.13 (−0.72 to 0.46)	−0.05 (−0.74 to 0.64)	0.04 (−0.68 to 0.76)	0.16 (−0.73 to 1.05)	
1-7	189 (76.5)	−0.01 (−0.31 to 0.30)		0.00 (−0.16 to 0.15)		−0.04 (−0.18 to 0.10)	0.06 (−0.09 to 0.22)	0.15 (−0.03 to 0.33)‡‡	0.2 (0.01 to 0.39)***	−0.07 (−0.3 to 0.16)	
≥8 (ref)	54 (21.9)										

(*continued*)

Table III. Continued

Maternal characteristics	n (%)	Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
		Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶	Minimally adjusted*	Adjusted**
		SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††
Employment											
Housewife without income	152 (61.5)	0.12 (–0.22 to 0.46)		0.07 (–0.10 to 0.24)		–0.06 (–0.23 to 0.12)		–0.04 (–0.24 to 0.15)		0.12 (–0.13 to 0.37)	
Housewife with small business	47 (19)	0.05 (–0.37 to 0.46)		0.02 (–0.19 to 0.23)		–0.07 (–0.28 to 0.15)		–0.04 (–0.28 to 0.20)		0.14 (–0.17 to 0.46)	
Formal job (ref)	45 (18.2)										
Household <4 members	161 (65.2)	0.11 (–0.15 to 0.38)		–0.07 (–0.21 to 0.06)		–0.11 (–0.24 to 0.01)‡‡	–0.08 (–0.22 to 0.06)	–0.13 (–0.29 to 0.03)†††	–0.12 (–0.31 to 0.07)	–0.06 (–0.25 to 0.14)	
Daily food expenditure ≤3000 TShs	100 (40.5)	–0.03 (–0.29 to 0.23)		–0.02 (–0.16 to 0.11)		–0.15 (–0.28 to –0.02)***	–0.14 (–0.28 to 0.00)***	–0.15 (–0.31 to 0.01)‡‡‡	–0.04 (–0.54 to 0.47)	–0.21 (–0.4 to –0.01)***	–0.25 (–0.45 to –0.06)¶¶
Number of times meat eaten/wk§§											
0-3	68 (27.5)	0.32 (0.04 to 0.60)***	0.31 (0.03 to 0.59)***	0.07 (–0.08 to 0.21)		–0.02 (–0.16 to 0.12)		0.03 (–0.14 to 0.20)		0.24 (0.03 to 0.46)***	0.21 (0.00 to 0.42)***
4 (ref)	12 (4.9)										
>4	163 (66)	0.57 (–0.01 to 1.16)***	0.52 (–0.05 to 1.09)‡‡	0.08 (–0.22 to 0.38)		0.08 (–0.21 to 0.36)		0.20 (–0.15 to 0.55)		0.08 (–0.36 to 0.52)	–0.07 (–0.50 to 0.37)

*Adjusted for child sex, child age, and BSID-III examiner.
†Adjusted for prior pregnancies, maternal height, maternal body mass index, meat consumption, child sex, child age, and BSID-III examiner.
‡Adjusted for prior pregnancies, maternal height, child sex, child age, and BSID-III examiner.
§Adjusted for marital status, maternal height, maternal education, household size, food expenditure, child sex, child age, and BSID-III examiner.
¶Adjusted for prior pregnancies, maternal height, maternal body mass index, maternal education, household size, food expenditure, child sex, child age, and BSID-III examiner.
**Adjusted for prior pregnancies, maternal height, maternal body mass index, food expenditure, meat consumption, child sex, child age, and BSID-III examiner.
††SMD and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
‡‡$P < .1$.
§§Percentages do not add up to 100 owing to missing data.
¶¶$P < .01$.
***$P < .05$.
†††$P < .2$.
‡‡‡Imputed median for missing values.

Table IV. Minimally adjusted and adjusted SMDs for delivery and child characteristics and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-exposed children

		Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
	n (%)	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶	Minimally adjusted*	Adjusted**
Delivery and child characteristics		SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††	SMD (95% CI)††
Hospital delivery	203 (98.5)	0.98 (−0.09 to 2.05)‡‡	1.36 (0.26 to 2.46)§§	0.50 (−0.42 to 1.43)		0.74 (−0.21 to 1.69)¶¶	1.06 (−0.12 to 2.24)§§	0.28 (−0.83 to 1.40)		0.81 (−0.27 to 1.88)¶¶	0.79 (−0.53 to 2.11)
Not spontaneous vaginal delivery***,†††	34 (16.5)	0.04 (−0.31 to 0.39)		−0.10 (−0.40 to 0.20)		0.07 (−0.24 to 0.39)		0.25 (−0.11 to 0.61)¶¶		0.25 (−0.10 to 0.6)¶¶	
Prolonged labor	34 (16.5)	0.02 (−0.33 to 0.37)		0.10 (−0.20 to 0.40)		0.08 (−0.24 to 0.39)		0.41 (0.05 to 0.77)§§	0.32 (−0.05 to 0.70)‡‡	0.17 (−0.19 to 0.53)	
Fetal distress	34 (16.5)	0.04 (−0.31 to 0.39)		−0.10 (−0.40 to 0.20)		0.07 (−0.24 to 0.39)		0.25 (−0.11 to 0.61)¶¶	0.10 (−0.28 to 0.48)	0.25 (−0.10 to 0.60)	0.12 (−0.23 to 0.48)
Oxytocin administrated	179 (86.9)	−0.30 (−0.73 to 0.13)¶¶	−0.37 (−0.81 to 0.07)‡‡	0.23 (−0.13 to 0.60)		−0.39 (−0.77 to −0.01)§§	−0.48 (−0.87 to −0.09)§§	−0.33 (−0.78 to 0.13)¶¶	−0.20 (−0.66 to 0.27)	0.03 (−0.41 to 0.46)	
Ergometrine administrated	10 (4.9)	0.36 (−0.25 to 0.97)		0.31 (−0.20 to 0.82)		0.19 (−0.35 to 0.73)		0.10 (−0.56 to 0.77)		−0.29 (−0.91 to 0.33)	
Amniotic fluid not clear	20 (9.7)	−0.07 (−0.51 to 0.36)		−0.16 (−0.52 to 0.20)		−0.21 (−0.60 to 0.18)		−0.17 (−0.62 to 0.28)		−0.15 (−0.58 to 0.29)	
Meconium in amniotic fluid	19 (9.2)	−0.02 (−0.47 to 0.44)		−0.20 (−0.58 to 0.18)		−0.22 (−0.62 to 0.19)		−0.17 (−0.64 to 0.29)		−0.11 (−0.56 to 0.34)	
Female sex	106 (51.5)	0.25 (−0.01 to 0.50)‡‡	0.19 (−0.08 to 0.45)¶¶	0.21 (−0.01 to 0.43)	0.20 (−0.02 to 0.42)‡‡	0.17 (−0.06 to 0.40)	0.09 (−0.15 to 0.33)	0.14 (−0.13 to 0.41)		0.07 (−0.19 to 0.33)	
Birthweight (kg)		0.18 (−0.11 to 0.46)		0.09 (−0.15 to 0.34)		0.21 (−0.04 to 0.46)‡‡	0.17 (−0.08 to 0.42)	0.25 (−0.04 to 0.55)‡‡	0.17 (−0.14 to 0.48)	0.37 (0.08 to 0.66)‡‡‡	0.35 (0.06 to 0.65)§§
Born at <37 weeks of gestation	34 (16.5)	−0.46 (−0.93 to 0.01)§§	−0.55 (−1.02 to −0.09)§§	−0.3 (−0.69 to 0.10)¶¶	−0.26 (−0.67 to 0.13)¶¶	−0.16 (−0.57 to 0.26)		−0.07 (−0.55 to 0.41)		−0.08 (−0.55 to 0.40)	
Apgar score of ≤7 at 5 minutes	4 (1.9)	0.00 (−0.93 to 0.94)		−0.54 (−1.34 to 0.26)¶¶	−0.49 (−1.28 to 0.30)	0.22 (−0.59 to 1.03)		0.18 (−0.78 to 1.14)		0.02 (−0.92 to 0.95)	
Needed resuscitation at delivery	60 (29.1)	0.14 (−0.15 to 0.43)		0.00 (−0.24 to 0.25)		−0.1 (−0.35 to 0.16)		0.12 (−0.18 to 0.42)		0.27 (0.00 to 0.55)§§	0.31 (0.01 to 0.61)§§

*Adjusted for child sex, child age, and BSID-III examiner.
†Adjusted for hospital delivery, oxytocin administration, gestational age, child sex, child age, and BSID-III examiner.
‡Adjusted for episiotomy performed, gestational age, Apgar score, child sex, child age, and BSID-III examiner.
§Adjusted for hospital delivery, fetal distress, oxytocin received in labor, birthweight, child sex, child age, and BSID-III examiner.
¶Adjusted for delivery mode, prolonged labor, fetal distress, oxytocin administration, birthweight, child sex, child age, and BSID-III examiner.
**Adjusted for hospital delivery, delivery mode, fetal distress, birthweight, child resuscitation at delivery, child sex, child age, and BSID-III examiner.
††SMD and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
‡‡$P < .1$.
¶¶$P < .2$.
§§$P < .05$.
***This includes vacuum extraction, assisted breech, or emergency or elective cesarean.
†††Percentages do not add up to 100 owing to missing data.
‡‡‡$P < .01$.

Table V. Minimally adjusted and adjusted SMDs for delivery and child characteristics and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-unexposed children

		Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
	n (%)	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted‡	Minimally adjusted*	Adjusted§	Minimally adjusted*	Adjusted¶
Delivery and child characteristics		**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****	**SMD (95% CI)****
Hospital delivery	244 (98.8)	0.08 (–1.07 to 1.23)		–0.18 (–0.77 to 0.41)		0.07 (–0.46 to 0.60)		0.03 (–0.65 to 0.71)		–0.13 (–1.00 to 0.74)	
Not spontaneous vaginal delivery††,‡‡	29 (11.7)	0.00 (–0.39 to 0.39)		–0.06 (–0.26 to 0.14)		–0.06 (–0.25 to 0.12)		–0.10 (–0.33 to 0.13)		–0.07 (–0.37 to 0.22)	
Prolonged labor	64 (25.9)	0.20 (–0.09 to 0.50)§§	0.24 (–0.05 to 0.54)§§	0.04 (–0.11 to 0.20)		0.04 (–0.10 to 0.18)		0.05 (–0.13 to 0.22)		0.08 (–0.14 to 0.30)	
Fetal distress	29 (11.7)	0.00 (–0.39 to 0.39)		–0.06 (–0.26 to 0.14)		–0.06 (–0.25 to 0.12)		–0.10 (–0.33 to 0.13)		–0.07 (–0.37 to 0.22)	
Oxytocin administrated	36 (14.6)	0.28 (–0.15 to 0.71)§§	0.27 (–0.16 to 0.71)	0.14 (–0.08 to 0.36)		0.06 (–0.15 to 0.26)		0.20 (–0.05 to 0.45)§§	0.16 (–0.10 to 0.42)	0.29 (–0.03 to 0.62)¶¶	0.20 (–0.29 to 0.70)
Ergometrine administrated	44 (17.8)	–0.16 (–0.57 to 0.25)		0.08 (–0.14 to 0.29)		0.07 (–0.13 to 0.27)		–0.12 (–0.37 to 0.12)		–0.22 (–0.53 to 0.10)§§	–0.05 (–0.53 to 0.42)
Female sex	125 (50.6)	0.13 (–0.12 to 0.38)		0.01 (–0.12 to 0.14)		0.05 (–0.06 to 0.17)		0.05 (–0.10 to 0.20)		0.12 (–0.07 to 0.31)	
Birthweight, g***		0.15 (–0.25 to 0.56)		0.03 (–0.18 to 0.24)		0.06 (–0.14 to 0.26)		0.18 (–0.06 to 0.42)§§	0.15 (–0.10 to 0.40)	0.10 (–0.21 to 0.41)	
Born at <37 weeks of gestation	15 (6.1)	–0.33 (–0.88 to 0.22)		–0.19 (–0.48 to 0.09)§§	–0.20 (–0.49 to 0.08)§§	0.23 (–0.05 to 0.50)¶¶	0.29 (0.03 to 0.56)†††	–0.09 (–0.41 to 0.24)		–0.30 (–0.72 to 0.11)§§	–0.27 (–0.70 to 0.17)
Apgar score ≤7 at 5 minutes	1 (0.4)	–2.45 (–4.42 to –0.48)‡‡‡	–2.58 (–4.58 to –0.59)‡‡‡	0.01 (–1.02 to 1.04)		–0.17 (–1.11 to 0.77)		–1.27 (–2.43 to –0.11)†††	–1.16 (–2.38 to 0.05)¶¶	–1.36 (–2.86 to 0.13)¶¶	–1.39 (–2.90 to 0.11)¶¶
Needed resuscitation at delivery	6 (2.4)	–0.50 (–1.33 to 0.34)		0.08 (–0.35 to 0.51)		–0.13 (–0.52 to 0.26)		–0.01 (–0.50 to 0.48)		0.14 (–0.50 to 0.78)	

*Adjusted for child sex, child age, and BSID-III examiner.
†Adjusted for prolonged labor, oxytocin administration, Apgar score, child sex, child age, and BSID-III examiner.
‡Adjusted for gestational age, child sex, child age, and BSID-III examiner.
§Adjusted for oxytocin administration, birthweight, Apgar score, child sex, child age, and BSID-III examiner.
¶Adjusted for oxytocin administration, ergometrine administration, gestational age, Apgar score, child sex, child age, and BSID-III examiner.
**SMD and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
††Vacuum extraction, assisted breech, or emergency or elective cesarean.
‡‡Percentages do not add up to 100 owing to missing data.
§§$P < .2$.
¶¶$P < .1$.
***Imputed median.
†††$P < .05$.
‡‡‡$P < .01$.

Table VI. Minimally adjusted and adjusted SMDs for child growth characteristics and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-exposed children*

		Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
	n (%)	Minimally adjusted†	Adjusted‡	Minimally adjusted†	Adjusted‡	Minimally adjusted†	Adjusted‡	Minimally adjusted†	Adjusted‡	Minimally adjusted†	Adjusted‡
Child growth characteristics		SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§	SMD (95% CI)§
WLZ¶		0.00 (–0.14 to 0.13)	0.05 (–0.09 to 0.19)	0.09 (–0.03 to 0.21)**	0.09 (–0.03 to 0.22)**	0.06 (–0.06 to 0.18)		0.02 (–0.12 to 0.16)	0.05 (–0.10 to 0.20)	–0.01 (–0.14 to 0.13)	0.04 (–0.10 to 0.18)
LAZ¶		0.12 (–0.01 to 0.26)††	0.15 (0.01 to 0.29)‡‡	0.04 (–0.08 to 0.15)	0.05 (–0.07 to 0.17)	0.02 (–0.10 to 0.14)		0.09 (–0.05 to 0.23)**	0.12 (–0.03 to 0.26)**	0.16 (0.03 to 0.29)‡‡	0.16 (0.02 to 0.29)‡‡
Underweight†	9 (4.6)	–0.32 (–0.86 to 0.22)		–0.26 (–0.73 to 0.21)		–0.18 (–0.66 to 0.30)		–0.44 (–0.99 to 0.11)**	–0.57 (–1.14 to 0.00)‡‡	–0.57 (–1.10 to –0.04)‡‡	–0.66 (–1.19 to –0.13)‡‡
Wasted†	11 (5.6)	0.10 (–0.53 to 0.74)		–0.19 (–0.73 to 0.36)		0.05 (–0.54 to 0.64)		0.37 (–0.29 to 1.02)		0.12 (–0.52 to 0.75)	
Stunted†	13 (6.6)	–0.25 (–0.83 to 0.34)		–0.19 (–0.69 to 0.30)		0.25 (–0.26 to 0.76)		–0.35 (–0.97 to 0.27)		–0.60 (–1.18 to –0.02)‡‡	–0.66 (–1.25 to –0.08)‡‡

*$P < .01$.
†SMD and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
‡Adjusted for child sex, child age, and BSID-III examiner.
§Adjusted for maternal education, daily expenditure on food, child sex, child age, and BSID-III examiner.
¶Model includes WLZ, LAZ, child sex, child age, and BSID-III examiner.
**$P < .2$.
††$P < .1$.
‡‡$P < .05$.

Table VII. Minimally adjusted and adjusted SMDs for child growth characteristics and the 5 domains of early childhood development as measured by BSID-III z-score in HIV-unexposed children

		Outcome 1: standardized cognitive		Outcome 2: standardized gross motor		Outcome 3: standardized fine motor		Outcome 4: standardized receptive language		Outcome 5: standardized expressive language	
	n (%)	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted†	Minimally adjusted*	Adjusted†
Child growth characteristics		SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡	SMD (95% CI)‡
WLZ§		–0.01 (–0.13 to 0.11)		–0.01 (–0.07 to 0.05)	0.02 (–0.04 to 0.09)	–0.06 (–0.11 to 0.00)¶	–0.05 (–0.11 to 0.02)**	–0.1 (–0.17 to –0.03)††	–0.08 (–0.16 to 0.00)¶	–0.15 (–0.23 to –0.06)††	–0.13 (–0.23 to –0.03)††
LAZ§		0.05 (–0.07 to 0.17)		0.05 (–0.01 to 0.11)**	0.07 (0.00 to 0.14)‡‡	0.05 (–0.01 to 0.11)‡‡	0.06 (–0.01 to 0.12)‡‡	0.08 (0.01 to 0.16)¶	0.07 (–0.02 to 0.15)*	0.12 (0.03 to 0.21)††	0.08 (–0.02 to 0.18)**
Underweight*	13 (5.7)	–0.30 (–0.99 to 0.40)		–0.09 (–0.44 to 0.27)		0.18 (–0.15 to 0.50)		–0.22 (–0.64 to 0.20)		0.13 (–0.39 to 0.66)	
Wasted*	12 (5.2)	–0.03 (–0.58 to 0.52)		0.00 (–0.28 to 0.28)		0.10 (–0.17 to 0.37)		0.24 (–0.1 to 0.58)**	–0.29 (–0.73 to 0.14)**	0.24 (–0.18 to 0.65)	
Stunted*	8 (3.5)	0.23 (–0.34 to 0.80)		0.08 (–0.21 to 0.37)		–0.20 (–0.46 to 0.05)**	–0.31 (–0.58 to –0.03)¶	–0.21 (–0.56 to 0.14)		–0.16 (–0.59 to 0.27)	

*Adjusted for child sex, age, and BSID-III examiner.
†Adjusted for maternal education, daily expenditure on food, child sex, age, and BSID-III examiner.
‡SMD and 95% CI estimated by robust regression. Adjusted model includes all covariates with $P < .2$ in univariate regressions.
§Model includes WLZ, LAZ, child sex, child age, and BSID-III examiner.
¶$P < .05$.
**$P < .2$.
††$P < .01$.
‡‡$P < .1$.