Published in final edited form as:

J Pediatr. 2019 April ; 207: 71–79.e8. doi:10.1016/j.jpeds.2018.10.066.

Nutritional, Socio-Economic, and Delivery Characteristics are Associated with Neurodevelopment in Tanzanian Children

Mia M. Blakstad, MSc^a, Emily R. Smith, ScD, MPH^{a,b}, Analee Etheredge, PhD^b, Lindsey M. Locks, ScD, MPH^c, Christine M. McDonald, ScD^d, Roland Kupka, ScD^e, Rodrick Kisenge, MBBS^f, Said Aboud, MD, PhD^g, David Bellinger, PhD, MSc^h, Christopher R. Sudfeld, ScD^a, Wafaie W. Fawzi, MBBS, MPH, MS, DrPH^{a,c,i}, Karim Manji, MBBS, MMED, MPH[#], and Christopher P. Duggan, MD, MPH^{a,b,c}

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

^bDivision of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital

^cDepartment of Nutrition, Harvard TH Chan School of Public Health, Boston MA

^dUCSF Benioff Children's Hospital Oakland Children's Hospital Oakland Research Institute

^eUNICEF Headquarters, New York, NY

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

^gDepartment of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania

^hDepartment of Neurology, Boston Children's Hospital, Harvard Medical School

ⁱDepartment of Epidemiology, Harvard TH Chan School of Public Health, Boston MA

[#] These authors contributed equally to this work.

Abstract

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

Address Correspondence to: Christopher P. Duggan, MD, MPH, 333 Longwood Avenue, LO-418 Boston, MA 02115, christopher.duggan@childrens.harvard.edu, 617-355-7612.

Trial Registration [ClinicalTrials.gov](https://clinicaltrials.gov) NCT00197730 and NCT00421668

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 (SMD) = -0.41; CI: -0.74, -0.08) and lower gross motor scores (SMD = -0.32; CI: -0.61, -0.04) in HIV-exposed children. Among delivery characteristics, facility delivery predicted higher cognitive- (SMD = 1.36; CI: 0.26, 2.46); and oxytocin administration predicted lower fine motor scores (SMD = -0.48; CI: -0.87, -0.09) in HIV-exposed children. Higher length-for-age z-scores at 6 weeks predicted better cognitive (SMD = 0.15; CI: 0.01, 0.29) and expressive language scores (SMD = 0.16; CI: 0.02, 0.29) at 15 months in HIV-exposed infants.

Conclusion: 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 ECD at 15 months. In addition, several aspects of delivery (facility birth and oxytocin administration) were associated with ECD. Future intervention trials should focus on modifiable maternal, infant and obstetric factors to strengthen the evidence base concerning early childhood development.

Keywords

Early Childhood Development; Prospective cohort; Bayley Scales of Infant and Toddler Development 3rd edition; BSID-III

As rates of child survival continue to improve in low- and middle-income countries (LMICs) (1), more attention is being paid to early childhood development, school achievement, and lifetime earning potential. Improving ECD 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 socio-emotional development.(6–8) 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) which put children at risk for not reaching their developmental potential.(10, 11) Many studies have shown an association of maternal and child malnutrition with suboptimal ECD. For example, one 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 investigated associations between neonatal characteristics such as Kangaroo Mother Care, delayed cord clamping or hypoxic ischemic encephalopathy and direct measures of ECD.(14) In addition, few, if any, studies have

evaluated the potential role of obstetric interventions and delivery characteristics (e.g., oxytocin and ergometrine administration, state of amniotic fluid, delivery mode, or fetal distress) in ECD. Understanding these potential determinants may guide future ECD 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 two multivitamins supplementation clinical trials (of zinc and vitamins B complex, C and E); infants were born to HIV-infected women (i.e. HIV-exposed) (Child 1, [NCT00197730](#)) and to HIV-uninfected women (i.e. HIV-unexposed) (Child 2, [NCT00421668](#)). Details of the trials and main results were previously published.^(15, 16) Briefly, both studies randomized singleton infants at approximately 6 weeks; 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 reduced 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 reduced 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 ECD.^(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.

The outcome of interest, early childhood development (ECD), was assessed at 14–17 months of age. A sub-sample of 453 children from the parent trials was selected for neurodevelopment assessment from a single research site (Magomeni Hospital) due to training and space restrictions.⁽¹⁸⁾ The Bayley Scales of Infant and Toddler Development-third edition (BSID-III) was selected to evaluate neurodevelopment. A specialist in child neurology (DCB) 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 two 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 five ECD 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 below). Fetal distress was functionally defined as fetal distress as delivery by vacuum extraction, assisted breach, or emergency or elective cesarean section. Prolonged labor was defined as a time from labor onset to delivery greater than 20 hours if primiparous, and greater than 14 hours if multiparous. Non-spontaneous vaginal delivery included vacuum extraction, assisted breach, and emergency cesarean or elective cesarean. Length was measured using a length board, measured to the nearest 0.1 cm. Weight was measured using a SECA digital scale, measured to the nearest 0.1 kg. We used the 2006 WHO Child Growth Standards to calculate z-scores for weight-for-length (WLZ), length-for-age (LAZ), and weight-for-age (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 standard deviation (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 sub-score 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 $\geq .20$ in minimally adjusted models were retained for inclusion in multivariate models using robust regression. Given the potential for collinearity between variables (e.g., 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 due to co-linearity. Categorical anthropometry indicators (stunting, wasting and underweight) were evaluated in separate models.

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 three models: maternal socio-economic, 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 three models, our sample size did not allow for such assessments.

We analyzed the study populations from the two 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 1, 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 (e.g. maternal education and socioeconomic status) and adjusting for study would therefore likely bias our estimates towards 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 was missing for a linear variable. Whenever child anthropometric data

was missing, we excluded this observation from the analysis to perform a complete case analysis, as 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).

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 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 1. Delivery at age <20 was more frequent in HIV-uninfected mothers than in HIV-infected mothers. Most women had between one and seven years of education (i.e., primary level, standard I-VII). More than 60% of households were composed of three members or fewer. Oxytocin administration during 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 post-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 two 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 ECD (Figure 2, Figure 3, Table 2 [available at www.jpeds.com], and Table 3 [available at www.jpeds.com]) in both cohorts of children. HIV-exposed children born to mothers with one to seven 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 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 four or more members. Among HIV-unexposed children, a daily food expenditure below the median of 3000 Tanzanian shillings predicted lower fine motor and expressive language scores.

Among numerous delivery characteristics, we found that facility delivery, and oxytocin administration were all independently and significantly associated with ECD among HIV-exposed children (Figure 2, Figure 3, and Table 4 [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 ECD among HIV-unexposed infants (Table 5; 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 ECD 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, Table 6 (available at www.jpeds.com), and Table 7 (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 suggest inappropriate use of oxytocin in this cohort. However, the associations should be interpreted with caution, as the analysis was not able to control for maternal factors that may increase the likelihood of facility delivery. Lastly, stunting (or LAZ and WLZ) at 6 weeks was also independently associated with lower cognitive, language, and motor scores at 15 months.

Several independent risk factors were related to maternal nutrition and socio-economic 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 ECD.(13)(24) Similarly, infants born to mothers with higher 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 to ECD, a previous meta-analysis has shown links between shorter birth intervals and risk of child 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 socio-economic status, which may impact ECD during early infancy.(13)

Our study's novel findings include identification of several delivery characteristics that were related to ECD. Hospital delivery has been touted as one of the most important predictors of improved post-natal 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 ECD 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 post-delivery was common in order to prevent post-partum hemorrhage.(30) The apparent negative effect of oxytocin on motor development might be a result of confounding by indication (i.e., sicker mothers at risk of having infants with poorer ECD 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.(32)

Among both HIV-exposed and unexposed children, poor growth was associated with poorer performance in all five domains of 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 one year later. Our analysis is one of few studies that link nutritional status during early infancy with child development(34, 35), 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 unexposed infants, although we did not formally test these differences. Mothers in the HIV-infected cohort were poorer, had less education, were of shorter stature, 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 -unexposed cohorts was antiretroviral therapy (ART) 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(36), the effect of *in utero* exposure to HIV and ART on development of HIV-exposed uninfected children remains unclear.(37)

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, 38) In particular, caregiving and home environment stimulation are important predictors of developmental outcomes.(13, 38) 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 peri-urban Tanzania. Another limitation of this study is that our sample size did not allow us to perform mediation analyses including variables from all three 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.(39–41)

We found that maternal and delivery characteristics are important risk factors for suboptimal ECD. To our knowledge, this is the first study to link child delivery characteristics such as delivery outside a health facility and oxytocin administration to impaired neurodevelopment. We were also able to link poor early infant growth with developmental delays more than one 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 ECD 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.

Acknowledgements:

Roland Kupka is a UNICEF staff member. The opinions and statements in this article are those of the author and may not reflect official UNICEF policies. We thank the many people who have contributed to these studies, both in the field and otherwise.

Supported by the National Institutes of Health (NICHD R01 HD048969-01, NICHD R01 HD043688-01, K24DK104676, and 2P30 DK040561) and Aker Scholarship. Study sponsors had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication. No financial incentive was given for producing this manuscript. The authors declare no conflicts of interest.

Abbreviations:

BSID-III	Bayley Scales of Infant and Toddler Development 3 rd edition
LAZ	Length-for-age z-scores
SMD	Standardized mean difference
WAZ	Weight-for-age z-scores
WHO	World Health Organization
WLZ	Weight-for-length z-scores

References:

1. Global Burden of Disease Child Mortality Collaborators. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1725–74. [PubMed: 27733285]
2. Britto PR, Pérez-Escamilla R. No second chances? Early critical periods in human development. *Social Science & Medicine*. 2013;97:238–40. [PubMed: 24084209]
3. Richter LM, Daelmans B, Lombardi J, Heymann J, Boo FL, Behrman JR, et al. Investing in the foundation of sustainable development: pathways to scale up for early childhood development. *The Lancet*. 2017;389(10064):103–18.

4. Global Research on Developmental Disabilities Collaborators. Developmental disabilities among children younger than 5 years in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Global Health*. 2018.
5. Black MM, Lawn JE. Early childhood developmental disabilities—data still needed. *The Lancet Global Health*. 2018.
6. Sharma R, Gaffey MF, Alderman H, Bassani DG, Bogard K, Darmstadt GL, et al. Prioritizing research for integrated implementation of early childhood development and maternal, newborn, child and adolescent health and nutrition platforms. *Journal of global health*. 2017;7(1).
7. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *The Lancet*. 2008;371(9608):243–60.
8. Shonkoff JP, Garner AS. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1):e232. [PubMed: 22201156]
9. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities: Building a New Framework for Health Promotion and Disease Prevention. *JAMA*. 2009;301(21):2252–9. [PubMed: 19491187]
10. Walker SP, Wachs TD, Grantham-McGregor S, Black MM, Nelson CA, Huffman SL, et al. Inequality in early childhood: risk and protective factors for early child development. *Lancet*. 2011;378(9799):1325–38. [PubMed: 21944375]
11. Black MM, Walker SP, Fernald LCH, Andersen CT, Digirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. *The Lancet*. 2017;389(10064):77–90.
12. Sudfeld CR, McCoy DC, Danaei G, Fink G, Ezzati M, Andrews KG, et al. Linear growth and child development in low- and middle-income countries: a meta-analysis. *Pediatrics*. 2015;135(5):e1266–75. [PubMed: 25847806]
13. Prado EL, Sebayang SK, Apriatni M, Adawiyah SR, Hidayati N, Islamiyah A, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on Children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial. *The Lancet Global health*. 2017;5(2):e217–e28. [PubMed: 28104188]
14. Vaivada T, Gaffey MF, Bhutta ZA. Promoting Early Child Development With Interventions in Health and Nutrition: A Systematic Review. *Pediatrics*. 2017;140(2):e20164308. [PubMed: 28771408]
15. Duggan C, Manji KP, Kupka R, Bosch RJ, Aboud S, Kisenge R, et al. Multiple micronutrient supplementation in Tanzanian infants born to HIV-infected mothers: a randomized, double-blind, placebo-controlled clinical trial. *The American journal of clinical nutrition*. 2012;96(6):1437–46. [PubMed: 23134887]
16. McDonald CM, Manji KP, Kisenge R, Aboud S, Spiegelman D, Fawzi WW, et al. Daily Zinc but Not Multivitamin Supplementation Reduces Diarrhea and Upper Respiratory Infections in Tanzanian Infants: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *The Journal of nutrition*. 2015;145(9):2153–60. [PubMed: 26203094]
17. Manji KP, McDonald CM, Kupka R, Bosch RJ, Kisenge R, Aboud S, et al. Effect of Multivitamin Supplementation on the Neurodevelopment of HIV-Exposed Tanzanian Infants: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Journal of Tropical Pediatrics*. 2014;60(4):279–86. [PubMed: 24567309]
18. Locks LM, Manji KP, McDonald CM, Kupka R, Kisenge R, Aboud S, et al. The effect of daily zinc and/or multivitamin supplements on early childhood development in Tanzania: results from a randomized controlled trial. *Maternal & Child Nutrition*. 2016;13(2):910–8.
19. Cromwell EA, Dube Q, Cole SR, Chirambo C, Dow AE, Heyderman RS, et al. Validity of US norms for the Bayley Scales of Infant Development-III in Malawian children. *European Journal of Paediatric Neurology*. 2014;18(2):223–30. [PubMed: 24423629]
20. de Onis M WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva (Switzerland)2006.

21. World Health Organization. WHO child growth standards SAS macro (version 3.2.2) Geneva, Switzerland 2011 [2017 August 15]. Available from: <http://www.who.int/childgrowth/software/en/>.
22. Hoaglin DC. Wiley Series in Probability and Statistics : Exploring Data Tables, Trends, and Shapes (1). Mosteller FTJW, editor. Hoboken 2011.
23. Jeong J, McCoy DC, Fink G. Pathways between paternal and maternal education, caregivers' support for learning, and early child development in 44 low- and middle-income countries. *Early Childhood Research Quarterly*. 2017;41:136–48.
24. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *The Lancet*. 2013;382(9890):427–51.
25. Kozuki N, Lee ACC, Silveira M, Victora CG, Adair L, Humphrey J, et al. The associations of birth intervals with small-for-gestational-age, preterm, and neonatal and infant mortality: a meta-analysis. *BMC Public Health* 2013.
26. Tura G, Fantahun M, Worku A. The effect of health facility delivery on neonatal mortality: systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2013;13:18. [PubMed: 23339515]
27. United Republic Of Tanzania Tanzania demographic and health survey and malaria indicator survey final report. 2016.
28. Ounsted M, Moar VA, Cockburn J, Redman CW. Factors associated with the intellectual ability of children born to women with high risk pregnancies. *British Medical Journal (Clinical Research Edition)* 1984;288(6423):1038–41.
29. Ounsted M, Scott A, Moar V. Delivery and development: to what extent can one associate cause and effect? *Journal of the Royal Society of Medicine*. 1980;73(11):786–92. [PubMed: 6453995]
30. World Health Organization. WHO recommendations for the prevention and treatment of postpartum haemorrhage. Geneva, Switzerland; 2012.
31. Simpson KR, James DC. Effects of oxytocin-induced uterine hyperstimulation during labor on fetal oxygen status and fetal heart rate patterns. *American Journal of Obstetrics & Gynecology*. 2008;199(1):34 e1–5. [PubMed: 18342288]
32. Gonzalez-Valenzuela MJ, Lopez-Montiel D, Gonzalez-Mesa ES. Exposure to synthetic oxytocin during delivery and its effect on psychomotor development. *Developmental Psychobiology*. 2015;57(8):908–20. [PubMed: 26011378]
33. González-Valenzuela MJ, García-Forte P, Delgado-Ríos M, Cazorla-Granados O, Blasco-Alonso M, González-Mesa E. Effects of oxytocin used during delivery on development: A retrospective cohort study. *Journal of Clinical and Experimental Neuropsychology*. 2014:1–11.
34. Yang S, Tilling K, Martin R, Davies N, Ben-Shlomo Y, Kramer MS. Pre-natal and post-natal growth trajectories and childhood cognitive ability and mental health. *International Journal of Epidemiology*. 2011;40(5):1215–26. [PubMed: 21764769]
35. Pongcharoen T, Ramakrishnan U, Digirolamo AM, Winichagoon P, Flores R, Singkhornard J, et al. Influence of Prenatal and Postnatal Growth on Intellectual Functioning in School-aged Children. *Archives of Pediatrics & Adolescent Medicine*. 2012;166(5):411–6. [PubMed: 22566539]
36. Knight WG, Mellins CA, Levenson RL, Arpad SM, Kairam R. Effects of Pediatric HIV Infection on Mental and Psychomotor Development. *Journal of Pediatric Psychology*. 2000;25(8):583–7. [PubMed: 11085762]
37. Le Doaré K, Bland R, Newell M-L. Neurodevelopment in children born to HIV-infected mothers by infection and treatment status. *Pediatrics*. 2012;130(5):e1326. [PubMed: 23118140]
38. Sudfeld CR, McCoy DC, Fink G, Muhihi A, Bellinger DC, Masanja H, et al. Malnutrition and Its Determinants Are Associated with Suboptimal Cognitive, Communication, and Motor Development in Tanzanian Children. *The Journal of nutrition*. 2015;145(12):2705–14. [PubMed: 26446481]
39. Murray L, Cooper P, Artech A, Stein A, Tomlinson M. Randomized controlled trial of a home-visiting intervention on infant cognitive development in peri-urban South Africa. *Developmental Medicine & Child Neurology*. 2016;58(3):270–6. [PubMed: 26303135]
40. Spencer-Smith MM, Spittle AJ, Lee KJ, Doyle LW, Anderson PJ. Bayley-III Cognitive and Language Scales in Preterm Children. *Pediatrics*. 2015;135(5):e1258–65. [PubMed: 25896835]

41. Manno D, Kowa PK, Bwalya HK, Siame J, Grantham-McGregor S, Baisley K, et al. Rich micronutrient fortification of locally produced infant food does not improve mental and motor development of Zambian infants: a randomised controlled trial. *The British journal of nutrition*. 2012;107(4):556–66. [PubMed: 21733297]

Figure 1:

Directed Acyclic Graph displaying the hypothesized relationship between our three models and neurodevelopment at 15 months, represented by dashed pathways. Solid arrows represent relationships for which there is substantial evidence in the literature.

Figure 2: Standardized mean differences and associated confidence intervals for predictors of BSID-III z-scores in HIV-exposed infants. Adjusted models include all covariates with $p < 0.2$ in univariate regressions.

Figure 3: Standardized mean differences and associated confidence intervals for predictors of BSID-III z-scores in HIV-unexposed infants. Adjusted models include all covariates with $p < 0.2$ in univariate regressions.

Table 1:

Characteristics of Study Population

Maternal Characteristics	HIV-exposed cohort (N=206)	HIV-unexposed cohort (N=247)	p-value
	N (%)	N (%)	
	Mean (SD)	Mean (SD)	
Maternal age 18–19 vs 20 [n (%)] (n=452)	9 (4.4)	23 (9.3)	0.04
Married/cohabitating with partner [n (%)] (n=450)	182 (88.8)	217 (88.6)	0.87
Prior pregnancies [n (%)] (n=452)			
1	37 (18)	90 (36.6)	<0.01
3-Feb	117 (56.8)	132 (53.7)	0.47
4	52 (25.2)	24 (9.8)	<0.01
Height (cm) [n (%)] (n=452)			
Height < 150 cm	35 (17)	20 (8.1)	<0.01
Height between 150 and 155	59 (28.6)	96 (39)	0.02
Height > 155 cm	112 (54.4)	130 (52.8)	0.71
Body Mass Index at 6 weeks [n (%)] (kg/m ²) (n=386)			
<18.5	7 (3.4)	2 (0.8)	0.05
18.5- <25	118 (57.3)	136 (55.1)	0.64
25	81 (39.3)	107 (43.3)	0.39
Mid-upper arm circumference (cm) [Mean (SD)] (n=451)	26.40 (2.08)	26.48 (3.30)	0.82
Formal education [n (%)] (n=452)			
None	16 (7.8)	3 (1.2)	<0.01
1–7 yr.	149 (72.3)	189 (76.8)	0.31
8 yr. (ref)	41 (19.9)	54 (22)	0.61
Employment [n (%)] (n=450)			
Housewife without income	139 (67.5)	152 (62.3)	0.19
Housewife with small business	42 (20.4)	47 (19.3)	0.72
Formal job	25 (12.1)	45 (18.4)	0.07
Household less than 4 members [n (%)] (n=452)	125 (60.7)	161 (65.4)	0.32
Daily food expenditure 3000 TShs [n (%)] (n=430)	183 (91.5)	100 (43.5)	<0.01
Number of times meat eaten/wk [n (%)] (n=446)			
0 to 3 times per week	73 (36)	68 (28)	0.07
4 times per week	107 (52.7)	163 (67.1)	<0.01
5 or more times per week	23 (11.3)	12 (4.9)	0.01
Delivery and Child Characteristics			
Hospital delivery [n (%)] (n = 451)	203 (98.5)	244 (99.2)	0.82
Spontaneous vaginal delivery ¹ [n (%)] (n= 449)	171 (83.4)	215 (88.1)	0.23
Prolonged labor ² [n (%)] (n=422)	34 (16.5)	64 (25.9)	0.02
Fetal distress [n (%)] (n = 282)	34 (16.5)	29 (11.7)	0.15
Oxytocin administrated [n (%)] (n=291)	179 (89.5)	36 (39.6)	<0.01

Maternal Characteristics	HIV-exposed cohort (N=206)	HIV-unexposed cohort (N=247)	p-value
	N (%)	N (%)	
	Mean (SD)	Mean (SD)	
Ergometrine administrated [n (%)] (n=291)	10 (5)	44 (47.8)	<0.01
Amniotic fluid not clear ³ [n (%)] (n=268)	20 (10.3)	4 (5.5)	<0.01
Meconium in amniotic fluid [n (%)] (n=250)	19 (9.8)	-	-
Female sex [n (%)] (n=453)	106 (51.5)	125 (50.6)	0.86
Birth weight (kg) [Mean (SD)] (n=324)	3.12 (0.47)	3.15 (0.45)	0.2
Born < 37 weeks gestational age ⁴ [n (%)] (n=324)	34 (16.5)	15 (12.7)	<0.01
Apgar score 7 at 5 minutes [n (%)] (n=306)	4 (2.1)	1 (0.9)	0.83
Needed resuscitation at delivery [n (%)] (n=271)	60 (30.5)	6 (8.1)	<0.01
Child Anthropometrics at 6 weeks			
Weight-for-length Z-score ⁵ [Mean (SD)] (n=422)	0.00 (0.97)	0.10 (1.08)	0.28
Length-for-age Z-score ⁵ [Mean (SD)] (n=422)	-0.37 (1.00)	-0.31 (1.04)	0.54
Underweight [n (%)] (n=422)	13 (6.6)	8 (3.5)	0.14
Wasted [n (%)] (n=422)	9 (4.6)	13 (5.7)	0.62
Stunted [n (%)] (n=422)	11 (5.6)	12 (5.2)	0.87

¹ Vaginal delivery vs. vacuum extraction, assisted breach, emergency cesarean or elective cesarean

² Time from labor onset to delivery < 20 hours if primiparous, < 14 hours if multiparous (McGraw-Hill Concise Dictionary of Modern Medicine 2002)

³ Amniotic fluid bloody, foul smelling, or purulent or containing meconium vs. clear

⁴ Calculated from estimated date of last menstrual period

⁵ Number for complete analysis (dropping all observation with one or missing Z-scores)

Table 2:

Minimally adjusted and adjusted SMDs for maternal risk factors and the five domains of ECD as measured by BSID III z-score in HIV-exposed children.

Maternal Characteristics	N (%)	Outcome 1: Cognition Standardized Mean Difference ²		Outcome 2: Gross Motor Standardized Mean Difference ²		Outcome 3: Fine Motor Standardized Mean Difference ²		Outcome 4: Receptive Language Standardized Mean Difference ²		Outcome 5: Expressive Language Standardized Mean Difference ²	
		Minimally Adjusted ²	Adjusted ³	Minimally Adjusted ²	Adjusted ⁴	Minimally Adjusted ²	Adjusted ⁵	Minimally Adjusted ²	Adjusted ⁶	Minimally Adjusted ²	Adjusted ⁷
		SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹	SMD (95% CI) ¹
Maternal age 18–19 y	9 (4.4)	−0.07 (−0.70,0.57)		−0.11 (−0.66,0.43)		−0.09 (−0.65,0.47)		−0.10 (−0.75,0.56)		−0.71 (−1.34,−0.07) ^{**}	−0.78 (−1.44,−0.12) ^{**}
Married/cohabiting with partner	182 (88.3)	−0.16 (−0.58,0.25)		−0.10 (−0.46,0.25)		−0.03 (−0.39,0.34)		−0.04 (−0.47,0.39)		0.14 (−0.28,0.55)	
Prior pregnancies ⁸											
1 (ref)	37 (18)										
2–3	117 (56.8)	0.20 (−0.15,0.54)		−0.05 (−0.34,0.24)		0.29 (−0.02,0.60) [*]	0.21 (−0.08,0.50) ⁺	0.35 (−0.01,0.70) [*]	0.30 (−0.04,0.65) [*]	0.11 (−0.25,0.47)	0.05 (−0.31,0.42)
4	52 (25.2)	0.08 (−0.31,0.48)		0.07 (−0.26,0.41)		0.13 (−0.22,0.48)	0.00 (−0.35,0.35)	0.17 (−0.24,0.58)	0.03 (−0.38,0.44)	0.27 (−0.13,0.68) ⁺	0.24 (−0.20,0.68)
Height											
<150 cm	35 (17)	0.16 (−0.19,0.50)	0.22 (−0.12,0.57)	−0.23 (−0.54,0.09) ⁺	−0.20 (−0.52,0.13)	0.10 (−0.22,0.42)		0.21 (−0.16,0.57)		0.15 (−0.21,0.52)	0.11 (−0.26,0.49)
150–155 cm	59 (28.6)	−0.27 (−0.56,0.02) [*]	−0.21 (−0.50,0.08) ⁺	−0.05 (−0.31,0.21)	−0.11 (−0.38,0.15)	−0.14 (−0.41,0.13)		−0.11 (−0.42,0.20)		−0.22 (−0.52,0.09) ⁺	−0.24 (−0.55,0.07) ⁺
>155 cm (ref)	112 (54.4)										
Body Mass Index at 6 weeks (kg/m ²) ⁸											
<18.5	7 (3.4)	−0.49 (−1.22,0.24) ⁺	−0.36 (−1.04,0.33)	0.42 (−0.2,1.04) ⁺	0.44 (−0.19,1.08) ⁺	−0.35 (−0.98,0.29)		−0.19 (−0.94,0.57)		−0.37 (−1.10,0.36)	
18.5–<25 (ref)	118 (57.3)										
>25	81 (39.3)	0.13 (−0.14,0.40)	0.18 (−0.07,0.44)	0.11 (−0.12,0.34)	−0.03 (−0.34,0.28)	0.12 (−0.12,0.36)		0.07 (−0.21,0.35)		−0.15 (0.42,0.12)	
Mid-upper arm circumference (cm) ^{**}		0.03 (−0.02,0.07)		0.03 (0.00,0.07) [*]	0.03 (−0.02,0.08) ⁺	0.01 (−0.03,0.05)		0.01 (−0.04,0.05)		0.01 (−0.03,0.05)	
Formal education ⁸											
None	16 (7.8)	0.06 (−0.48,0.59)	0.01 (−0.52,0.54)	−0.22 (−0.69,0.24)	−0.28 (−0.76,0.20)	0.03 (−0.45,0.51)		0.35 (−0.22,0.91)		−0.07 (−0.62,0.48)	−0.07 (−0.64,0.50)
1–7 y	149 (72.3)	(−0.68,0.04) ^{**}	−0.41 (−0.74,0.08) ^{***}	−0.26 (−0.54,0.01) [*]	−0.32(−0.61,−0.04) ^{**}	−0.13 (−0.42,0.16)		−0.19 (−0.53,0.15)		−0.22 (−0.54,0.11) ⁺	−0.25 (−0.6,0.09) ⁺
>8 y (ref)	(19.9)										
Employment											
Housewife without income	139 (67.5)	0.13 (−0.27,0.53)		0.28 (−0.05,0.61) [*]	0.40 (0.05,0.76) ^{**}	0.34 (−0.01,0.69) [*]	0.32 (−0.01,0.65) [*]	0.42 (0.02,0.83) ^{**}	0.39 (−0.01,0.78) [*]	−0.11 (−0.52,0.29)	0.05 (−0.38,0.47)
Housewife with small business	42 (20.4)	−0.09 (−0.56,0.38)		0.20 (−0.20,0.59)	0.29 (−0.12,0.71) ⁺	0.35 (−0.07,0.76) [*]	0.40 (0.01,0.79) ^{**}	0.38 (−0.10,0.85) ⁺	0.32 (−0.15,0.78) ⁺	−0.37 (−0.84,0.10) ⁺	−0.25 (−0.74,0.24)
Formal job (ref)	25(12.1)										

Maternal Characteristics	N (%)	Outcome 1: Cognition Standardized Mean Difference ²		Outcome 2: Gross Motor Standardized Mean Difference ²		Outcome 3: Fine Motor Standardized Mean Difference ²		Outcome 4: Receptive Language Standardized Mean Difference ²		Outcome 5: Expressive Language Standardized Mean Difference ²	
		Minimally Adjusted ²	Adjusted ³	Minimally Adjusted ²	Adjusted ⁴	Minimally Adjusted ²	Adjusted ⁵	Minimally Adjusted ²	Adjusted ⁶	Minimally Adjusted ²	Adjusted ⁷
		SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I
Household less than 4 members	125 (60.7)	−0.30 (−0.56, −0.04) ^{**}	−0.31 (−0.57, 0.06) ^{**}	−0.01 (−0.24, 0.21)		−0.19 (−0.42, 0.04) ⁺	−0.14 (−0.38, 0.09)	−0.32 (−0.59, 0.05) ^{**}	−0.34 (−0.62, 0.06) ^{**}	−0.21 (−0.48, 0.06) ⁺	−0.1 (−0.39, 0.18)
Daily food expenditure 3000 TShs	183 (88.8)	−0.37 (−0.84, 0.10) ⁺	−0.05 (−0.53, 0.42)	0.07 (−0.33, 0.48)		−0.27 (−0.67, 0.13) ⁺	0.24 (−0.15, 0.64)	−0.19 (−0.67, 0.29)		−0.12 (−0.59, 0.34)	
Number of times meat eaten/ wk ⁸											
0–3	73 (35.4)	−0.10 (−0.38, 0.18)	−0.16 (−0.43, 0.11)	−0.01 (−0.25, 0.23)		0.14 (−0.11, 0.39)		−0.16 (−0.46, 0.13)		−0.04 (−0.33, 0.25)	
4 (ref)	23 (11.2)										
>4	107 (51.9)	0.29 (−0.13, 0.72) ⁺	0.14 (−0.28, 0.55)	0.14 (−0.22, 0.50)		−0.06 (−0.44, 0.33)		0.05 (−0.39, 0.48)		−0.14 (−0.57, 0.29)	

^I Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, child age, and BSID III examiner

³ Adjusted for maternal height, maternal BMI, maternal education, household size, meat consumption, child sex, child age, and BSID III examiner

⁴ Adjusted for maternal height, maternal BMI, maternal MUAC, maternal education, maternal employment status, child sex, child age, and BSID III examiner

⁵ Adjusted for prior pregnancies, maternal employment status, household size, daily food expenditure, child sex, child age, and BSID III examiner

⁶ Adjusted for prior pregnancies, maternal employment status, household size, child sex, child age, and BSID III examiner

⁷ Adjusted for maternal age, prior pregnancies, maternal height, maternal education, maternal employment status, household size, child sex, child age, and BSID III examiner

⁸ Percentages do not add up to 100 due to missing data

⁺ p<0.2

^{*} p<0.1

^{**} p<0.05

^{***} p<0.01

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3: Minimally adjusted and adjusted SMDs for maternal risk factors and the five domains of ECD as measured by BSID III z-score in HIV-unexposed children.

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 ² SMD(95% CI) ^I	Adjusted ³ SMD(95% CI) ^I	Minimally Adjusted ² SMD(95% CI) ^I	Adjusted ⁴ SMD(95% CI) ^I	Minimally Adjusted ² SMD(95% CI) ^I	Adjusted ⁵ SMD(95% CI) ^I	Minimally Adjusted ² SMD(95% CI) ^I	Adjusted ⁶ SMD(95% CI) ^I	Minimally Adjusted ² SMD(95% CI) ^I	Adjusted ⁷ SMD(95% CI) ^I					
Maternal age 18–19 y	23(9.3)	0.14(−0.30,0.58)		0.03(−0.20,0.25)		−0.05(−0.25,0.15)		−0.06(−0.32,0.20)		−0.16(−0.49,0.17)						
Married/cohabitating with partner	217(87.9)	−0.02(−0.41,0.38)		−0.01(−0.21,0.20)		−0.19(−0.39,0.01) [*]	−0.14(−0.36,0.08)	0.04(−0.19,0.27)		−0.13(−0.43,0.17)						
δ																
Prior pregnancies																
1 (ref)	90(36.4)															
2–3	132(53.4)	−0.39(−0.66,−0.12) ^{***}	−0.27(−0.54,−0.01) ^{**}	−0.08(−0.22,0.05)	−0.07(−0.21,0.07)	−0.05(−0.17,0.08)		−0.24(−0.41,−0.07) ^{***}	−0.25(−0.43,−0.08) ^{***}	−0.29(−0.49,−0.08) ^{***}	−0.26(−0.47,−0.06) ^{***}					
4	24(9.7)	−0.29(−0.74,0.16)	−0.12(−0.57,0.32)	0.16(−0.07,0.39) ⁺	0.18(−0.05,0.41) ⁺	0.07(−0.14,0.28)		0.03(−0.25,0.31)	−0.04(−0.35,0.27)	0.01(−0.33,0.35)	0.06(−0.28,0.40)					
Height																
<150 cm	20(8.1)	−0.48(−0.94,−0.01) ^{**}	−0.54(−1.01,−0.07) ^{**}	−0.09(−0.33,0.15)	−0.12(−0.36,0.12)	0.03(−0.19,0.26)	−0.04(−0.28,0.20)	−0.08(−0.37,0.20)	−0.19(−0.48,0.11)	−0.10(−0.46,0.26)	−0.19(−0.55,0.16)					
150–155 cm	96(38.9)	−0.45(−0.70,−0.19) ^{***}	−0.39(−0.65,−0.13) ^{***}	−0.16(−0.30,−0.03) ^{**}	−0.16(−0.29,−0.03) ^{**}	−0.12(−0.25,0.00) ^{**}	−0.14(−0.27,−0.01) ^{**}	−0.21(−0.36,−0.05) ^{***}	−0.19(−0.36,−0.03) ^{**}	−0.24(−0.44,−0.04) ^{**}	−0.22(−0.42,−0.03) ^{**}					
>155 cm (ref)	130(52.6)															
Body Mass Index at 6 weeks																
(kg/m ²) δ																
<18.5	20(8.1)	−0.63(2.03,0.78)	−0.77(−2.14,0.61)	−0.15(−0.87,0.58)		−0.22(−0.92,0.48)		−0.43(−1.26,0.39)	−0.54(−1.41,0.33)	−0.73(−1.79,0.34) ⁺	−0.90(−1.94,0.14) [*]					
18.5–<25 (ref)	136(55.1)															
25	107(43.3)	−0.27(−0.53,−0.02) ^{**}	−0.14(−0.40,0.11)	0.05(−0.08,0.18)		−0.07(−0.19,0.06)		−0.13(−0.28,0.02) [*]	−0.09(−0.25,0.07)	−0.22(−0.42,−0.03) ^{**}	−0.17(−0.37,0.02) [*]					
Mid-upper arm circumference																
(cm) δ																
Formal education																
None	3(1.2)	−0.19(−1.36,0.98)		0.18(−0.42,0.79)		−0.36(−0.90,0.17) ⁺	−0.13(−0.72,0.46)	−0.05(−0.74,0.64)	0.04(−0.68,0.76)	0.16(−0.73,1.05)						
1–7 y	189(76.5)	−0.01(−0.31,0.30)		0.00(−0.16,0.15)		0.04(−0.18,0.10)	0.06(−0.09,0.22)	0.15(−0.03,0.33) [*]	0.20(0.01,0.39) ^{**}	−0.07(−0.3,0.16)						
8 y (ref)	54(21.9)															
Employment																
Housewife without income	152(61.5)	0.12(−0.22,0.46)		0.07(−0.10,0.24)		−0.06(−0.23,0.12)		−0.04(−0.24,0.15)		0.12(−0.13,0.37)						
Housewife with small business	47(19)	0.05(−0.37,0.46)		0.02(−0.19,0.23)		−0.07(−0.28,0.15)		0.04(−0.28,0.20)		0.14(−0.17,0.46)						
Formal job (ref)	45(18.2)															
Household less than 4 members	161(65.2)	0.11(−0.15,0.38)		−0.07(−0.21,0.06)		−0.11(−0.24,0.01) [*]	−0.08(−0.22,0.06)	−0.13(−0.29,0.03) ⁺	−0.12(−0.31,0.07)	−0.06(−0.25,0.14)						

Outcome 1: Standardized Cognitive		Outcome 2: Standardized Gross Motor		Outcome 3: Standardized Fine Motor		Outcome 4: Standardized Receptive Language		Outcome 5: Standardized Expressive Language	
Maternal Characteristics	N(%)	Minimally Adjusted ² SMD(95% CI) ¹	Adjusted ³ SMD(95% CI) ¹	Minimally Adjusted ² SMD(95% CI) ¹	Adjusted ⁴ SMD(95% CI) ¹	Minimally Adjusted ² SMD(95% CI) ¹	Adjusted ⁵ SMD(95% CI) ¹	Minimally Adjusted ² SMD(95% CI) ¹	Adjusted ⁶ SMD(95% CI) ¹
Daily food expenditure TSHs	3000	−0.03(−0.29,0.23)		−0.02(−0.16,0.11)		−0.15(−0.28,−0.02)	−0.14(−0.28,0.00)	−0.21(−0.4,−0.01)	−0.25(−0.45,−0.06)
Number of times meat eaten/ wk ⁸									
0–3	68(27.5)	120.60**	0.31(0.03,0.59)**	0.07(−0.08,0.21)		−0.02(−0.16,0.12)		0.24(0.03,0.46)**	0.21(0.00,0.42)**
4 (ref)	12(4.9)								
>4	163(66)	0.57(−0.01,1.16)**	0.52(−0.05,1.09)*	0.08(−0.22,0.38)		0.08(−0.21,0.36)		0.08(−0.36,0.52)	−0.07(−0.50,0.37)

¹ Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, child age, and BSID III examiner

³ Adjusted for prior pregnancies, maternal height, maternal BMI, meat consumption, child sex, child age, and BSID III examiner

⁴ Adjusted for prior pregnancies, maternal height, child sex, child age, and BSID III examiner

⁵ Adjusted for marital status, maternal height, maternal education, household size, food expenditure, child sex, child age, and BSID III examiner

⁶ Adjusted for prior pregnancies, maternal height, maternal BMI, maternal education, household size, food expenditure, child sex, child age, and BSID III examiner

⁷ Adjusted for prior pregnancies, maternal height, maternal BMI, food expenditure, meatconsumption, child sex, child age, and BSID III examiner

⁸ Percentages do not add up to 100 due to missing data

⁹ Imputed median for missing values

⁺ p<0.2

^{*} p<0.1

^{**} p<0.05

^{***} p<0.01

Table 4:

Minimally adjusted and adjusted SMDs for delivery and child characteristics and the five domains of ECD as measured by BSID III z-score in HIV-exposed children.

Child Growth 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 ²		Adjusted ³	Minimally Adjusted ²		Adjusted ⁴	Minimally Adjusted ²		Adjusted ⁵	Minimally Adjusted ²		Adjusted ⁶	Minimally Adjusted ²		Adjusted ⁷
		SMD (95% CI) ¹		SMD (95% CI) ¹	SMD (95% CI) ¹		SMD (95% CI) ¹		SMD (95% CI) ¹		SMD (95% CI) ¹		SMD (95% CI) ¹		SMD (95% CI) ¹	
Hospital delivery	203(98.5)	0.98(−0.09,2.05) [*]		1.36(0.26,2.46) ^{**}	0.50(−0.42,1.43)		0.74(−0.21,1.69) ⁺		1.06(−0.12,2.24) ^{**}		0.28(−0.83,1.40)		0.81(−0.27,1.88) ⁺		0.79(−0.53,2.11)	
Not spontaneous vaginal delivery ^{8,9}	34(16.5)	0.04(−0.31,0.39)			−0.10(−0.40,0.20)		0.07(−0.24,0.39)				0.25(−0.11,0.61) ⁺		0.25(−0.10,0.6) ⁺			
Prolonged labor	34(16.5)	0.02(−0.33,0.37)			0.10(−0.20,0.40)		0.08(−0.24,0.39)				0.41(0.05,0.77) ^{**}		2(−0.05,0.70) [*]		0.17(−0.19,0.53)	
Fetal distress	34(16.5)	0.04(−0.31,0.39)			0.10(0.40,0.20)		0.07(−0.24,0.39)				0.25(−0.11,0.61) ⁺		0.10(−0.28,0.48)		0.12(−0.23,0.48)	
Oxytocin administered	179(86.9)	−0.30(−0.73,0.13) ⁺		−0.37(0.81,0.07) [*]	0.23(−0.13,0.60)		−0.39(−0.77,−0.01) ^{**}		−0.48(−0.87,−0.09) ^{**}		−0.33(−0.78,0.13) ⁺		−0.2(−0.66,0.27)		0.03(−0.41,0.46)	
Ergometrine administered	10(4.9)	0.36(−0.25,0.97)			0.31(−0.20,0.82)		0.19(−0.35,0.73)				0.10(−0.56,0.77)		0.29(−0.91,0.33)			
Amniotic fluid not clear	20(9.7)	−0.07(−0.51,0.36)			−0.16(−0.52,0.20)		−0.21(−0.60,0.18)				−0.17(−0.62,0.28)		−0.15(−0.58,0.29)			
Meconium in amniotic fluid	19(9.2)	−0.02(−0.47,0.44)			−0.20(−0.58,0.18)		−0.22(−0.62,0.19)				−0.17(−0.64,0.29)		0.11(−0.56,0.34)			
Female sex	106(51.5)	0.25(−0.01,0.50) [*]		0.19(−0.08,0.45) ⁺	0.21(−0.01,0.43)		0.17(−0.06,0.40)		0.09(−0.15,0.33)		0.14(−0.13,0.41)		0.07(−0.19,0.33)			
Birthweight (kg)		0.18(−0.11,0.46)			0.09(−0.15,0.34)0.3		0.21(−0.04,0.46) [*]		0.17(−0.08,0.42)		0.25(−0.04,0.55) [*]		0.17(−0.14,0.48)		0.35(0.06,0.65) ^{**}	
Born < 37 weeks gestational age	34(16.5)	−0.46(−0.93,0.01) ^{**}		−0.55(−1.02,−0.09) ^{**}	−0.3(−0.69,0.10) ⁺		−0.16(−0.57,0.26)				−0.07(−0.55,0.41)		−0.08(−0.55,0.40)			
Apgar score 7 at 5 minutes	4(1.9)	0.00(−0.93,0.94)			−0.54(−1.34,0.26) ⁺		0.22(−0.59,1.03)				0.18(−0.78,1.14)		0.02(−0.92,0.95)			
Needed resuscitation at delivery	60(29.1)	0.14(−0.15,0.43)			0.00(−0.24,0.25)		−0.1(−0.35,0.16)				0.12(−0.18,0.42)		0.27(0.00,0.55) ^{**}		0.31(0.01,0.61) ^{**}	

¹ Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, child age, and BSID III examiner

³ Adjusted for hospital delivery, oxytocin administration, gestational age, child sex, child age, and BSID III examiner

⁴ Adjusted for episiotomy performed, gestational age, apgar score, child sex, child age, and BSID III examiner

⁵ Adjusted for hospital delivery, fetal distress, oxytocin received in labor, birthweight, child sex, child age, and BSID III examiner

⁶ Adjusted for delivery mode, prolonged labor, fetal distress, oxytocin administration, birthweight, child sex, child age, and BSID III examiner

⁷ Adjusted for hospital delivery, delivery mode, fetal distress, birthweight, child resuscitation at delivery, child sex, child age, and BSID III examiner

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

This includes vacuum extraction, assisted breech, or emergency or elective cesarean
Percentages do not add up to 100 due to missing data
p<0.2
p<0.1
p<0.05
p<0.01

Table 5:

Minimally adjusted and adjusted SMDs for delivery and child characteristics and the five domains of ECD as measured by BSID III z-score in HIV-unexposed children.

Delivery and Child 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	
		Adjusted ³		Adjusted ⁴		Adjusted ⁴		Adjusted ⁵		Adjusted ⁶	
		Minimally Adjusted ²	SMD (95% CI) ¹	Minimally Adjusted ²	SMD (95% CI) ¹	Minimally Adjusted ²	SMD (95% CI) ¹	Minimally Adjusted ²	SMD (95% CI) ¹	Minimally Adjusted ²	SMD (95% CI) ¹
Hospital delivery	244 (98.8)	0.08 (−1.07,1.23)		−0.18 (−0.77,0.41)		0.07 (−0.46,0.60)		0.03 (−0.65,0.71)		−0.13 (−1.00,0.74)	
Not spontaneous vaginal delivery ^{7,8}	29 (11.7)	0.00 (−0.39,0.39)		−0.06 (−0.26,0.14)		−0.06 (−0.25,0.12)		−0.10 (−0.33,0.13)		−0.07 (−0.37,0.22)	
Prolonged labor	64 (25.9)	0.20 (−0.09,0.50) ⁺	0.24 (−0.05,0.54) ⁺	0.04 (−0.11,0.20)		0.04 (−0.10,0.18)		0.05 (−0.13,0.22)		0.08 (−0.14,0.30)	
Fetal distress	29 (11.7)	0.00 (−0.39,0.39)		0.06 (−0.26,0.14)		0.06 (−0.25,0.12)		0.10 (−0.33,0.13)		0.07 (−0.37,0.22)	
Oxytocin administered	36 (14.6)	0.28 (−0.15,0.71) ⁺	0.27 (−0.16,0.71)	0.14 (−0.08,0.36)		0.06 (−0.15,0.26)		0.20 (−0.05,0.45) ⁺	0.16 (−0.10,0.42)	0.29 (−0.03,0.62) [*]	0.20 (−0.29,0.70)
Ergometrine administered	44 (17.8)	−0.16 (−0.57,0.25)		0.08 (−0.14,0.29)		0.07 (−0.13,0.27)		−0.12 (−0.37,0.12)		−0.22 (−0.53,0.10) ⁺	−0.05 (−0.53,0.42)
Female sex	125 (50.6)	0.13 (−0.12,0.38)		0.01 (−0.12,0.14)		0.05 (−0.06,0.17)		0.05 (−0.10,0.20)		0.12 (−0.07,0.31)	
Birthweight (g) ⁹		0.15 (−0.25,0.56)		0.03 (−0.18,0.24)		0.06 (−0.14,0.26)		0.18 (−0.06,0.42) ⁺	0.15 (−0.10,0.40)	0.10 (−0.21,0.41)	
Born < 37 weeks gestational age	15 (6.1)	−0.33 (−0.88,0.22)		−0.19 (−0.48,0.09) ⁺	−0.20 (−0.49,0.08) ⁺	0.23 (−0.05,0.50) [*]	0.29 (0.03,0.56) ^{**}	−0.09 (−0.41,0.24)		−0.30 (−0.72,0.11) ⁺	−0.27 (−0.70,0.17)
Apgar score 7 at 5 minutes	1 (0.4)	−2.45 (−4.42,0.48) ^{***}	−2.58 (−4.58,0.59) ^{***}	0.01 (−1.02,1.04)	−0.17 (−1.11,0.77)			−1.27 (−2.43,−0.11) ^{**}	−1.16 (−2.38,0.05) [*]	−1.36 (−2.86,0.13) [*]	−1.39 (−2.90,0.11) [*]
Needed resuscitation at delivery	6 (2.4)	−0.50 (−1.33,0.34)		0.08 (−0.35,0.51)	−0.13 (−0.52,0.26)			−0.01 (−0.50,0.48)		0.14 (−0.50,0.78)	

¹ Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, child age, and BSID III examiner

³ Adjusted for prolonged labor, oxytocin administration, apgar score, child sex, child age, and BSID III examiner

⁴ Adjusted for gestational age, child sex, child age, and BSID III examiner

⁵ Adjusted for oxytocin administration, birthweight, apgar score, child sex, child age, and BSID III examiner

⁶ Adjusted for oxytocin administration, ergometrin administration, gestational age, apgar score, child sex, child age, and BSID III examiner

⁷ Vacuum extraction, assisted breech or emergency- or elective cesarean

⁸ Percentages do not add up to 100 due to missing data

10:0>d

50:0>d
**
1:0>d
*
2:0>d
+
median
6

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Minimally adjusted and adjusted SMDs for child growth characteristics and the five domains of ECD as measured by BSID III z-score in HIV-exposed children.

Table 6:

Child Growth 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 ²	Adjusted ³	Minimally Adjusted ²	Adjusted ³	Minimally Adjusted ²	Adjusted ³	Minimally Adjusted ²	Adjusted ³	Minimally Adjusted ²	Adjusted ³
		SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I	SMD (95% CI) ^I
Weight-for-lengthZ-score ⁴		0.00 (−0.14,0.13)	0.05 (−0.09,0.19)	0.09 (−0.03,0.21) ⁺	0.09 (−0.03,0.22) ⁺	0.06 (−0.06,0.18)	0.02 (−0.12,0.16)	0.05 (−0.10,0.20)	−0.01 (−0.14,0.13)	0.04 (−0.10,0.18)	
Length-for-age Z-score ⁴		0.12 (−0.01,0.26) [*]	0.15 (0.01,0.29) ^{**}	0.04 (−0.08,0.15)	0.05 (−0.07,0.17)	0.02 (−0.10,0.14)	0.09 (−0.05,0.23) ⁺	0.12 (−0.03,0.26) ⁺	0.16 (0.03,0.29) ^{**}	0.16 (0.02,0.29) ^{**}	
Underweight ²	9 (4.6)	−0.32 (−0.86,0.22)		−0.26 (−0.73,0.21)		−0.18 (−0.66,0.30)	−0.44 (−0.99,0.11) ⁺	−0.57 (−1.14,0.00) ^{**}	−0.57 (−1.10,−0.04) ^{**}	−0.66 (−1.19,−0.13) ^{**}	
Wasted ²	11 (5.6)	0.10 (−0.53,0.74)		−0.19 (−0.73,0.36)		0.05 (−0.54,0.64)	0.37 (−0.29,1.02)		0.12 (−0.52,0.75)		
Stunted ²	13 (6.6)	−0.25 (−0.83,0.34)		−0.19 (−0.69,0.30)		0.25 (−0.26,0.76)	−0.35 (−0.97,0.27)		−0.60 (−1.18,−0.02) ^{**}	−0.66 (−1.25,−0.08) ^{**}	

^I Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, child age, and BSID III examiner

³ Adjusted for maternal education, daily expenditure on food, child sex, child age, and BSID III examiner

⁴ Model includes weight-for-length Z-score, length-for-age Z-score, child sex, child age, and BSID III examiner

⁺ p<0.2

^{*} p<0.1

^{**} p<0.05

^{***} p<0.01

Minimally adjusted and adjusted SMDs for child growth characteristics and the five domains of ECD as measured by BSID III z-score in HIV-unexposed children.

Table 7:

Child Growth 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 ²	Adjusted ³	SMD(95%CI) ^I	Minimally Adjusted ²	Adjusted ³	SMD(95%CI) ^I	Minimally Adjusted ²	Adjusted ³	SMD(95%CI) ^I	Minimally Adjusted ²	Adjusted ³	SMD(95%CI) ^I	Minimally Adjusted ²	Adjusted ³	SMD(95%CI) ^I
		SMD(95%CI) ^I	SMD(95%CI) ^I		SMD(95%CI) ^I	SMD(95%CI) ^I		SMD(95%CI) ^I	SMD(95%CI) ^I		SMD(95%CI) ^I	SMD(95%CI) ^I		SMD(95%CI) ^I	SMD(95%CI) ^I	
Weight-for-length Z-score ⁴		−0.01(−0.13,0.11)		−0.01(−0.07,0.05)	0.02(−0.04,0.09)	0.02(−0.04,0.09)		−0.06(−0.11,0.00)	**	−0.05(−0.11,0.02) ⁺	−0.1(−0.17,−0.03) ^{***}	−0.08(−0.16,0.00) ^{**}	−0.15(−0.23,−0.06) ^{***}	−0.13(−0.23,−0.03) ^{***}		
Length-for-age Z-score ⁴		0.05(−0.07,0.17)		0.05(−0.01,0.11) ⁺	0.07(0.00,0.14) [*]	0.07(0.00,0.14) [*]		0.05(−0.01,0.11) [*]	*	0.06(−0.01,0.12) [*]	0.08(0.01,0.16) ^{**}	0.07(−0.02,0.15) ⁺	0.12(0.03,0.21) ^{***}	0.08(−0.02,0.18) ⁺		
Underweight	13(5.7)	−0.30(−0.99,0.40)		−0.09(−0.44,0.27)				0.18(−0.15,0.50)			0.22(−0.64,0.20)		0.13(−0.39,0.66)			
Wasted ²	12(5.2)	−0.03(−0.58,0.52)		0.00(−0.28,0.28)				0.10(−0.17,0.37)			0.24(−0.1,0.58) ⁺	0.29(−0.73,0.14) ⁺	0.24(−0.18,0.65)			
Stunted ²	8(3.5)	0.23(−0.34,0.80)		0.08(0.21,0.37)				−0.20(−0.46,0.05)		−0.31(−0.58,−0.03) ^{**}	−0.21(−0.56,0.14)		−0.16(−0.59,0.27)			

^I Standardized Mean Difference (SMD) and 95% Confidence Interval (CI) estimated by robust regression. Adjusted model includes all covariates with p<0.2 in univariate regressions

² Adjusted for child sex, age, and BSID III examiner

³ Adjusted for maternal education, daily expenditure on food, child sex, age, and BSID III examiner

⁴ Model includes weight-for-length Z-score, length-for-age Z-score, child sex, child age, and BSID III examiner

⁺ p<0.2

^{*} p<0.1

^{**} p<0.05

^{***} p<0.01