Exploring Cognitive Disparities: Cognitive Outcomes in HIV Exposed Uninfected Children In Kenya

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Abstract

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Background

Recent studies suggest that children exposed to HIV (CHEU) have poorer neurocognitive outcomes than those who are not exposed to HIV (CHUU). However, evidence is limited to neurodevelopmental outcomes among children under the age of 5 years. Few studies have examined outcomes at school age, and evidence for poor outcomes is mixed.

Methods

In a cross-sectional study, we recruited Kenyan CHEU and CHUU aged 7 to 18 years. Using the NIH Toolbox African Languages cognitive battery, we assessed memory, attention and inhibitory control, cognitive flexibility, and processing speed. Assessments were administered in either Kiswahili or Dholuo. We compared domain scores between groups and determined correlates of lower scores using linear regression, with models adjusted for age and socio-demographic factors that differed in the 2 groups.

Results

Overall, 219 and 209 CHEU and CHUU, respectively, were enrolled. The median age was 12 years (IQR: 9.1, 14.0) for CHEU and 12.8 (IQR: 9.2, 15.0) for CHUU. CHEU were more likely to be orphaned and vulnerable children (OVC) and to have mild food insecurity.

Compared to CHUU, CHEU had significantly lower scores in working memory (age adjusted coefficient 1.3, 95% CI 0.5, 2.1, $p = 0.001$), and processing speed (age adjusted coefficient 4.65, 95% CI 2.3, 7.0, $p < 0.001$). These differences persisted in separate models adjusted for age and food security as well as age and OVC status. There were no differences in the other domains assessed (episodic memory, attention and inhibitory control, and cognitive flexibility).

Among CHEU, male sex was linked to higher episodic memory scores, while food insecurity was associated with lower processing speed scores. Older maternal age and higher years of maternal education were each associated with higher processing speed scores.

Conclusion

Our findings suggest that CHEU may experience deficits in working memory and processing speed. Biological and sociodemographic factors were each associated with cognitive outcomes. These findings highlight the need to address socio-economic factors to improve neurodevelopment and to better understand mechanisms that lead to neurodevelopment compromise in CHEU.

Introduction

HIV remains a significant global health crisis with about 39 million people living with HIV in 2022, including 1.5 million children aged 0-14 years globally.[1] [2] As a result of successful use of antiretroviral therapy (ART) to prevent vertical transmission of HIV, 14.8 million children have been exposed to HIV, 90% of whom reside in sub-Saharan Africa.[3] Exposure to HIV and ART especially during the developmentally sensitive period from conception to the 2 years of life,[4] elevates the risk of adverse health outcomes including poor growth (small for gestational age), prematurity, congenital abnormalities and increased morbidity and mortality. [4] [5]

Neurodevelopmental deficits in CHEU may occur directly through ART toxicity, exposure to HIV virions and/or viral proteins or may occur indirectly as a result of poor growth and higher morbidity during critical windows of brain development in infancy and early childhood. Biological factors during pregnancy and the post-partum period, such as intrauterine infections, preterm birth, and sub-optimal breastfeeding practices, in addition, social factors that disproportionately impact pregnant women living with HIV, such as alcohol or substance misuse and food insecurity may each in turn contribute to poorer outcomes. These different factors may ultimately converge through shared mechanisms leading to adverse outcomes.[6]

Deficits in language development, and fine motor function have consistently been identified in CHEU.[7] However, there is mixed evidence regarding executive function and gross motor deficits in CHEU. Some brain imaging studies have found differences in regional brain volume and microstructure between younger CHEU and CHUU[8]. However evidence regarding cognitive outcomes in CHEU is inconsistent with some studies reporting deficits among HEU[9] and others not finding differences.[10] These differences in study findings may be attributed to timing of the

maternal infection and exposure, breastfeeding, difference in ART regimens, socioeconomic and environmental factors and differences in assessment tools used to measure neurocognitive outcomes.[11]

In studies conducted among children aged 7 -13 years, lower scores in global cognitive ability, memory, attention, processing speed and academic performance have been seen in CHEU compared to CHUU.[12] [13] [14] However, other studies have reported similar scores in other domains (mental processing, sequential processing and learning) when comparing CHEU and CHUU at school age.[15] [16] Similar to younger children, imaging studies have found smaller white matter across various brain regions among CHEU.[17] Differences in results could be associated with different assessment tools as well as sociodemographic differences. These findings emphasize the need for additional studies among school-aged CHEU.

The National Institutes of Health Toolbox for Assessment of Neurological and Behavioral Function (NIH Toolbox) is a collection of standardized validated neurocognitive assessment tools that has been adapted for the Kenya Setting. [18] [19] [20] In this study, we assessed working memory, attention, processing speed, episodic memory and cognitive flexibility among school age Kenyan CHEU and CHUU.[21]

Methods

Study design and setting: This is a cross-sectional study using data collected from the HEU outcomes: population-evaluation and screening strategies (HOPE) study that aims to compare neurodevelopmental and mental health outcomes of Kenyan CHEU and CHUU from infancy to adolescence (age 3-18 years). Data from the cross-sectional component of the HOPE Study were collected from Kisumu county in Kenya.

Data collection: Data was collected using questionnaires that included questions on socio-demographics, pregnancy, medical history and HIV testing and test results. Inclusion criteria included being healthy and HIV negative, maternal HIV status known during pregnancy/breastfeeding and if HIV negative, had a recent HIV test (1 year ago). Cognitive assessments were done among children and youth aged 7-18 years using the NIH Toolbox Cognitive Battery, African Languages Adaptation, by trained study staff.[22] Before administering the cognition battery assessments, participants completed a practice tutorial that required successful completion before test administration.

Outcomes: Outcomes of interest were domain specific assessments scores. Specific domains assessed included working and episodic memory using the List Sorting Working Memory Test and the Picture Sequence Memory Test, respectively, attention and inhibitory control assessed using the Flanker Inhibitory Control and Attention Test, cognitive flexibility assessed using the Dimensional Change Card Sort Test (DCCS), and processing speed assessed using the Pattern Comparison Test.

Exposures: The primary exposure of interest was exposure to HIV infection which was determined by combination of maternal report, medical records and HIV testing to determine HIV status of mothers and children. Other exposures of interest included maternal education level, marital status, employment status, household food insecurity, gestation, birthweight and orphaned and vulnerable child (OVC) status defined as a child, 0-17 years old, who have lost one or both parents, been abandoned, or live in hardship.

Data Analysis

Descriptive statistics, including proportions, medians, and interquartile ranges (IQR) were used to summarize socio-demographic characteristics of caregiver and children/youth. The Student's

t-tests and Chi-squared tests, were used to assess differences in characteristics between the CHEU and CHUU at $\alpha \leq 0.05$

Cognitive domain scores were compared between groups and the correlates of lower scores and 95% confidence intervals (Cls) determined using linear regression. Models were adjusted for age and sociodemographic factors that varied between groups.

Among CHEU, we further examined the associations between poorer neurodevelopmental scores and various cofactors including prematurity, low birthweight, breastfeeding, education level, household food insecurity, maternal age, OVC status and sex using linear regression. All models were adjusted for age. All analysis was conducted using R version 4.3.2.

Results

Overall, 219 and 209 CHEU and CHUU respectively, were enrolled. The median age was 12 years (IQR: 9.1, 14.0) for CHEU and 12.8 (IQR: 9.2, 15.0) for CHUU, a majority of children/youth (98%) were born at term and a majority (96%) were breastfed. There were no significant differences in sex, maternal age, marital status and employment status between CHEU and CHUU. CHEU were more likely to be orphaned and vulnerable children (37% vs 22%, p = 0.001), and to live in households with mild food insecurity (42% vs 56%, p = 0.05) than CHUU. Median breastfeeding duration was longer among CHUU (18 vs 6 months) but not statistically significantly different (Table 2).

CHEU had significantly lower mean scores in the List Sorting Memory Test (mean scores 12.3 [SD = 2.7]) versus 13.6 [SD = 4.3] among CHUU, age adjusted coefficient -1.1, 95% Cl -1.7, -0.4; p = 0.002). This difference persisted after adjusting for both child's age and food security

(adjusted coefficient -1.1, 95% CI -1.7, -0.4, p = 0.002) as well as age and OVC status (adjusted coefficient -1.03, 95% CI -1.7, -0.3, p = 0.003).

CHEU also had significantly lower mean scores in the Pattern Comparison Processing Speed Test (mean scores 30.8 [SD = 10.8] versus 33 [SD = 12.2] among CHUU, age adjusted coefficient -4.2, 95% Cl -6.3. -2.1, p < 0.001). This difference persisted after adjusting for both the child's age and food security (adjusted coefficient -4.8, 95% CI -6.9, -2.7; p <0.001) as well as age and OVC status (adjusted coefficient of -4.1 (95% CI -6.3, -2; p < 0.001).

There were no differences in scores comparing CHEU and CHUU for the Flanker and Inhibitory Control and Attention Test, Picture Sequence Memory Test and Dimensional Change Card Sort Test. (Table 3)

Correlates of Cognitive Outcomes

Among CHEU, male sex was significantly associated with higher picture sequence memory test scores (age-adjusted coefficient = 1.6, 95% Cl 0.04, 2.9; p = 0.03). Increased maternal age and higher number of years of education were associated with increased pattern comparison processing speed test scores (age-adjusted coefficient = 0.6, 95% Cl 0.14, 0.62; p < 0.001, and 0.5, 95% Cl 0.1, 1; p = 0.03, respectively). Higher number of years of education was also significantly associated with increased flanker inhibitory control and attention scores (age-adjusted coefficient = 0.02, 95% Cl -9.9, 0.03; p = 0.05). Mild and severe food insecurity were significantly associated with lower pattern comparison processing speed test scores and (age-adjusted coefficient = -8.9, 95% Cl -15.7, -2.2; p = 0.01 and -7.5, 95% Cl -14.3, -0.6; p = 0.03, respectively). (Table 4a)

Among CHUU, male sex was significantly associated with higher picture sequence memory test scores (age-adjusted coefficient = 1.6, 95% Cl 0.6, 2.6; $p < 0.001$). OVC status was significantly associated with higher dimensional change card sort test scores (age-adjusted coefficient = 1, 95% Cl 0.2, 1.8; $p = 0.01$) and picture sequence memory score test scores (age-adjusted coefficient = 2.7, 95% Cl 0.7, 4.7; $p = 0.01$). Older maternal age and higher years of education were significantly associated with higher list sorting working memory scores (age-adjusted coefficient = 0.1, 95% Cl -0.001, 0.2; $p < 0.001$ and 0.2, 95% Cl 0.04, 0.4; $p = 0.01$, respectively). (Table 4b)

Discussion

CHEU had significantly lower scores in list sorting working memory and pattern comparison processing speed test with differences persisting after adjusting for age and food security as well as age and OVC status. Male sex was significantly associated with increased picture sequence memory test scores. Increased maternal age and higher number of years of education were associated with increased pattern comparison processing speed test scores. Higher number of years of education was also significantly associated with increased flanker inhibitory control and attention scores. Mild and severe food insecurity were significantly associated with lower pattern comparison processing speed test scores.

Our findings are similar to studies done in Kenya and South Africa that found significantly lower scores for processing speed, working and delayed memory among CHEU.[12] [23] However, other studies in Thailand and Cambodia, found no differences in working memory and processing speed in CHEU compared to CHUU.[14] We did not observe differences in other cognitive domains

including attention that has previously been observed in other studies.[12] Differences in results between these different cohorts could be explained by variations in socioeconomic factors and cognitive assessment tests, across regions that might impact cognitive outcomes.

The mechanisms for poorer neurodevelopment among CHEU are multifactorial.[4 24] Despite effective maternal combination antiretroviral therapy, chronic inflammation and immune dysfunction may influence fetal brain development.[25] Exposure to HIV, viral proteins and infant immune response to HIV may all impact neurodevelopment. Studies on CHEU and whose mothers received ART during pregnancy have shown mixed results. While some reported lower scores in language, motor and cognitive outcomes for CHEU[7 9 26] ,others found no differences between the groups.[10] Rapid changes in HIV treatment guidelines challenge determining associations of ART exposure on cognitive outcomes among CHEU, and studies assessing newer safer current regimens are needed. In our study, most children in the 7 - 18 age range studies were exposed to dolutegravir (DTG), efavirenz (EFV) and nevirapine (NVP) maternal antiretrovirals.

We found that male sex was significantly associated with higher episodic memory scores in both CHEU and CHUU. While some studies have reported lower neurodevelopmental scores among males,[27] results have been inconsistent.[28] Findings suggest that females excel in auditory memory tasks, while males perform better in visual episodic and working memory tests. However, the impact of gender on cognitive performance varies across different age groups.[29] The range of cognitive differences between each gender group is extensive and shaped by factors beyond biology as socio-cultural and environmental interactions substantially contribute to these discrepancies.

We found that CHEU children/youth living in households with food insecurity had significantly lower episodic memory scores. Our findings contribute to evidence demonstrating that inadequate diet and lack of food access are associated with cognitive deficits. Food insecurity during pregnancy and early childhood has been linked to adverse birth outcomes and morbidity and poor growth and neurodevelopment that could be linked to micronutrient deficiencies.[30] Household food insecurity frequently coexists with HIV infection and is associated with increased HIV-related illnesses, lower adherence to antiretroviral therapy, and poor access to treatment and care services that may impact child growth and development.[31]

Our study had a large sample size and a homogenous population. Neurocognitive outcomes were assessed using a tool that was adapted to the local setting. The cross-sectional design is limited in its ability to establish causal relationships. Missing data and inaccurate assessments may have occurred if participants were fatigued, uncomfortable answering sensitive questions or did not pass practice items. Recall bias may have resulted in misclassification of exposures.

Overall, we found that CHEU exhibited deficits in processing speed and memory. Maternal and socio-demographic factors influenced cognitive outcomes providing opportunities for targeted interventions for optimal growth and development. Long-term follow up of CHEU will continue to be important to understand the impact of HIV exposure on neurocognitive functioning.

REFERENCES

1. Global HIV & AIDS statistics — Fact sheet | UNAIDS. Accessed October 27, 2023. https://www.unaids.org/en/resources/fact-sheet
2. HIV. Accessed December 7, 2023. https://www.who.int/data/gho/data/themes/hiv-aids
3. Slogrove AL, Powis KM, Johnson LF, Stover J, Mahy M. Estimates of the global population of children who are HIV-exposed and uninfected, 2000–18: a modelling study. *Lancet Glob Health*. 2020;8(1):e67-e75. doi:10.1016/S2214-109X(19)30448-6
4. Evans C, Jones CE, Prendergast AJ. HIV-exposed, uninfected infants: new global challenges in the era of paediatric HIV elimination. *Lancet Infect Dis*. 2016;16(6):e92-e107. doi:10.1016/S1473-3099(16)00055-4
5. Decreased growth among antiretroviral drug and HIV-exposed u... : AIDS. Accessed October 28, 2023. https://journals.lww.com/aidsonline/fulltext/2020/02010/decreased_growth_among_antiretroviral_drug_and.7.aspx
6. Growth and Neurodevelopment of HIV-Exposed Uninfected Children: a Conceptual Framework | Current HIV/AIDS Reports. Accessed November 23, 2023. https://link.springer.com/article/10.1007/s11904-019-00459-0
7. R N, J C, C E, et al. Early child development in children who are HIV-exposed uninfected compared to children who are HIV-unexposed: observational sub-study of a cluster-randomized trial in rural Zimbabwe. *J Int AIDS Soc*. 2020;23(5). doi:10.1002/jia2.25456
8. Cj W, Na G, A R, et al. Early structural brain development in infants exposed to HIV and antiretroviral therapy in utero in a South African birth cohort. *J Int AIDS Soc*. 2022;25(1). doi:10.1002/jia2.25863
9. Roux SL, Donald K, Brittain K, et al. Neurodevelopment of breastfed HIV-exposed uninfected and HIV-unexposed children in South Africa: a prospective cohort. *AIDS Lond Engl*. 2018;32(13):1781. doi:10.1097/QAD.0000000000001872
10. Chaudhury S, Williams PL, Mayondi GK, et al. Neurodevelopment of HIV-Exposed and HIV-Unexposed Uninfected Children at 24 Months. *Pediatrics*. 2017;140(4). doi:10.1542/peds.2017-0988
11. Bulterys MA, Njuguna I, King'e M, et al. Neurodevelopment of children who are HIV-exposed and uninfected in Kenya. *J Int AIDS Soc*. 2023;26:e26149. doi:10.1002/jia2.26149
12. Benki-Nugent SF, Yunusa R, Mueni A, et al. Lower neurocognitive functioning in HIV-exposed uninfected children compared with HIV-unexposed children. *J Acquir Immune Defic Syndr 1999*. 2022;89(4):441. doi:10.1097/QAI.0000000000002881
13. Powis KM, Lebanna L, Schenkel S, et al. Lower academic performance among children with perinatal HIV exposure in Botswana. *J Int AIDS Soc*. 2023;26:e26165. doi:10.1002/jia2.26165
14. Sj K, T P, Km M, et al. Increased Risk of Executive Function and Emotional Behavioral Problems Among Virologically Well-Controlled Perinatally HIV-Infected Adolescents in Thailand and Cambodia. *J Acquir Immune Defic Syndr 1999*. 2019;82(3). doi:10.1097/QAI.0000000000002132
15. P D, F BL, E P, et al. Neurodevelopmental outcomes in HIV-infected and uninfected African children. *AIDS Lond Engl*. 2018;32(18). doi:10.1097/QAD.0000000000002023
16. Mj B, L BM, Mc C, et al. Neuropsychological performance in African children with HIV

enrolled in a multisite antiretroviral clinical trial. *AIDS Lond Engl*. 2018;32(2). doi:10.1097/QAD.0000000000001683
17. Sk Y, Rk G, S H, et al. Brain microstructural changes support cognitive deficits in HIV uninfected children born to HIV infected mothers. *Brain Behav Immun - Health*. 2020;2. doi:10.1016/j.bbih.2020.100039
18. McHenry MS, Roose A, Abuonji E, et al. A Psychometric Evaluation of the NIH Toolbox Fluid Cognition Tests Adapted for Swahili and Dholuo Languages in Kenyan Children and Adolescents. *J Int Neuropsychol Soc JINS*. 2023;29(10):933. doi:10.1017/S1355617723000632
19. Mm D, D A, G A, et al. Translation and Cultural Adaptation of NIH Toolbox Cognitive Tests into Swahili and Dholuo Languages for Use in Children in Western Kenya. *J Int Neuropsychol Soc JINS*. 2022;28(4). doi:10.1017/S1355617721000497
20. Hackett K, Krikorian R, Giovannetti T, et al. Utility of the NIH Toolbox for assessment of prodromal Alzheimer's disease and dementia. *Alzheimers Dement Diagn Assess Dis Monit*. 2018;10:764. doi:10.1016/j.dadm.2018.10.002
21. Njuguna I, King'e M, Moraa H, et al. Longitudinal and population comparison of children who are HIV exposed uninfected and children who are HIV unexposed in Kenya (HOPE study). *Bmjopen-2023-081975R1*.
22. Duffey MM, Ayuku D, Ayodo G, et al. Translation and Cultural Adaptation of NIH Toolbox Cognitive Tests into Swahili and Dholuo Languages for Use in Children in Western Kenya. *J Int Neuropsychol Soc*. 2022;28(4):414-423. doi:10.1017/S1355617721000497
23. Milligan R, Cockcroft K. Working Memory Profiles in HIV-Exposed, Uninfected and HIV-Infected Children: A Comparison with Neurotypical Controls. *Front Hum Neurosci*. 2017;11:279324. doi:10.3389/fnhum.2017.00348
24. Dirajlal-Fargo S, Mussi-Pinhata MM, Weinberg A, et al. HIV-exposed uninfected infants have increased inflammation and monocyte activation. *AIDS Lond Engl*. 2019;33(5):845. doi:10.1097/QAD.0000000000002128
25. Klatt NR, Chomont N, Douek DC, Deeks SG. Immune activation and HIV persistence: implications for curative approaches to HIV infection. *Immunol Rev*. 2013;254(1):326-342. doi:10.1111/imr.12065
26. Mj B, L MS, Lw O, et al. Neurodevelopmental effects of ante-partum and post-partum antiretroviral exposure in HIV-exposed and uninfected children versus HIV-unexposed and uninfected children in Uganda and Malawi: a prospective cohort study. *Lancet HIV*. 2019;6(8). doi:10.1016/S2352-3018(19)30083-9
27. Bulterys MA, Njuguna I, King'e M, et al. Neurodevelopment of children who are HIV‐exposed and uninfected in Kenya. *J Int AIDS Soc*. 2023;26(Suppl 4). doi:10.1002/jia2.26149
28. R S, Al C, S N, et al. Growth Faltering and Developmental Delay in HIV-Exposed Uninfected Ugandan Infants: A Prospective Cohort Study. *J Acquir Immune Defic Syndr 1999*. 2021;87(1). doi:10.1097/QAI.0000000000002626
29. Pauls F, Petermann F, Lepach AC. Gender differences in episodic memory and visual working memory including the effects of age. *Memory*. Published online October 1, 2013. Accessed May 20, 2024. https://www.tandfonline.com/doi/abs/10.1080/09658211.2013.765892
30. Ad J, Aj M. Associations Between Household Food Insecurity in Early Childhood and Children's Kindergarten Skills. *Child Dev*. 2018;89(2). doi:10.1111/cdev.12764

31. Anema A, Vogenthaler N, Frongillo EA, Kadiyala S, Weiser SD. Food Insecurity and HIV/AIDS: Current Knowledge, Gaps, and Research Priorities. *Curr HIV/AIDS Rep*. 2009;6(4):224. doi:10.1007/s11904-009-0030-z

Table 1: Summary of NIH toolbox tests assessed

Test	Ages:	Time to administer:	Scoring Scale	Domains measured:
Dimensional Change Card Sort Test	7–85 yrs	4 minutes	0–10	Cognitive flexibility
Flanker Test	7–85 yrs	3 minutes	0-3*	Attention and inhibitory control
List Sorting	7–85 yrs	7 minutes	0–26	Working Memory
Pattern Comparison	7–85 yrs	3 minutes	0–130	Processing Speed
Picture Sequence Memory	7–85 yrs	7 minutes	0–31	Episodic Memory

*rate adjusted score

Table 2: Sociodemographic characteristics of participants

	HEU n= 219 (n/% or Median/IQR)	**HUU** n=209 (n/% or Median/IQR)	**Overall** N=428 (n/% or Median/IQR)	**p-value**
Child Characteristics				
Age (years)	12 (9.13-14.04)	12.8 (9.39 -15)	12 (9.23, 15)	0.5
Male	111 (50.7)	101 (48.3%)	212 (49.5%)	0.63
Child OVC status	82 (37.4%)	46 (22%)	128 (29.9%)	**0.001**
Gestational Age				
Full term (37-41 weeks)	216 (98.6%)	204 (97.6%)	420 (98.1%)	0.35
Pre-term (<37 weeks)	3 (1.4%)	3 (1.4%)	6 (1.4%)	
Post-term (>42 weeks)	0 (0.0%)	2 (1.0%)	2 (0.5%)	
Breastfeeding				0.11
Yes	214 (97.7%)	197 (94.3%)	411 (96%)	
No	5 (2.3%)	12 (5.7%)	17 (4%)	
Breastfeeding Duration	6 (6-12)	18 (12-24)	12 (6-24)	0.5
Parent characteristics				
Education (years)	8 (7-12)	10.5 (8-12)	8 (8-12)	0.5
Mother's age (years)	37 (33-42)	35 (31-39)	36 (32 - 40)	0.5
Mother's Marital status				0.17
Married (reference)	164 (74.9%)	165 (78.9%)	329 (76.9%)	
Separated/widowed	55 (25.1%)	42 (20.1%)	97 (22.7%)	
Single	0 (0%)	2 (1%)	2 (0.5%)	
Employment status				0.59
Professional (reference)	33 (15.1%)	33 (15.8%)	66 (15.4%)	
Casual	34 (15.5%)	29 (13.9%)	63 (14.7%)	

Unemployed	57 (26%)	72 (34.4%)	129 (30.1%)	
Other	95 (43.4%)	95 (35.9%)	170 (39.7%)	
Household food insecurity				
Food Secure	14 (6.4%)	6 (2.9%)	20 (4.7%)	
Mild	91 (41.6%)	116 (55.5%)	207 (48.4%)	0.045
Moderate	31 (14.2%)	30 (14.4%)	61 (14.3%)	0.22
Severe	83 (37.9%)	57 (27.3%)	140 (32.7%)	0.50
ART Exposure				
After pregnancy	95 (43.4%)	NA	NA	
Before pregnancy	124 (56.0%)	NA	NA	

Table 3: Cognitive Domain scores and differences comparing CHEU and CHUU

NIH TOOLBOX CONSTRUCT	**HEU N = (Mean/SD)**	**HUU N = (Mean/SD)**	**Coefficient** (95% Cl)	**Adjusted coefficient** (95% Cl) *	**Adjusted coefficient** (95% Cl)**	**Adjusted coefficient** (95% Cl) ***
Flanker Inhibitory Control and Attention Test.	0.68 (0.4)	0.75 (0.42)	-0.07 (-0.1, 0.01)	-0.06 (-0.13, 0.02)	-0.1 (-0.12, 0.02)	-0.06 (-0.14, 0.01)
Dimensional Change Card Sort	4.98 (2.6)	5.2 (2.7)	-0.1 (-0.6, 0.4)	0.1 (-0.4, 0.5)	0.12 (-0.3, 0.6)	-0.06 (-0.5, 0.4)
List Sorting Working Memory	12.3 (3.75)	13.6 (4.3)	**-1.2** (-1.9, -0.5)	**-1.1** (-1.7, -0.4)	**-1.1** (-1.7, -0.4)	-1.03 (-1.7, -0.3)
Picture Sequence Memory	9.16 (6.3)	9.1 (6.7)	-0.2 (-1.4, 0.9)	0.03 (-1.1, 1.1)	0.08 (-1.5, 0.9)	0.09 (-1.1, 1.2)
Pattern Comparison Processing speed	30.8 (10.8)	33 (12.2)	**-4.63** (-6.8, -2.4)	**-4.2** (-6.3, -2.1)	**-4.8** (-6.9, -2.7)	**- 4.1** (-6.3, -2)

*Model adjusted for child's age

**Model adjusted for child's age and food security

***Model adjusted for age and ovc status[1]

[1] Bold: p-value less than 0.05

Table 4a: Correlates of higher neurodevelopmental scores among HEU

VARIABLE	Flanker Inhibitory Control and Attention Test.	Dimensional Change Card Sort	List Sorting Working Memory	Picture Sequence Memory	Pattern Comparison Processing speed
	Adjusted r (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)
Child characteristics					
Male	0.01 (-0.1, 0.1)	0.25 (-0.4, 0.9)	**1.1** (0.2, 2)	**1.6** (-0.04, 2.9)	-1.9 (-4.6, 0.8)
Female	*Ref*				
OVC status	-0.001 (-0.1, 0.1)	0.2 (-0.5, 0.84)	-0.3 (-1.25, 0.6)	-0.9 (-2.5, 0.6)	-1.69 (-4.4, 1.05)
Breastfed	0.2 (-0.2, 0.6)	1.3 (-0.7, 3.4)	**-3.5** (-6.9, -0.01)	-2.1 (-7.2, 3.1)	1.7 (-7.6, 11.1)
Pre-term <37 weeks	-0.3 (-0.8, 0.1)	-0.6 (-3.8, 2.7)	-1.2 (-6.2, 3.7)	-6.23 (-14.3, 1.8)	-12.8 (-27.4, 1.8)
Birthweight <2500g	-0.3 (-1.0, 0.4)	0.18 (-5.5, 5.8)	0.27 (-5.5, 6)	3 (-14.9, 21)	0.95 (-28.3, 30.2)

Caregiver characteristics					
Maternal Age	0.003 (-0.01, 0.01)	0.05 (-0.004, 0.1)	0.07 (-0.02, 0.15)	0.1 (-0.02, 0.2)	**0.6** (0.1, 0.6)
Education (years)	**0.02** (-9.9, 0.03)	0.09 (-0.01, 0.2)	0.1 (-0.03, 0.3)	0.02 (-0.24, 0.3)	**0.5** (0.1, 1)
Food secure	Ref				
Mild	0.07 (-0.2, 0.3)	-0.5 (-2.07, 1.05)	-1.4 (-3.7, 0.88)	0.98 (-2.8, 4.8)	**-8.9** (-15.7, -2.2)
Moderate	0.03 (-0.2, 0.3)	-0.4 (-2.14, 1.31)	-0.6 (-3.11, 1.99)	1.9 (-2.3, 6.1)	-5.7 (-13.2, 1.9)
Severe	0.08 (-0.2, 0.3)	-1.4 (-2.9, 0.19)	-1.15 (-3.5, 1.16)	0.2 (-3.6, 4.1)	**-7.5** (-14.3, -0.6)

*Model adjusted for child's age

Table 4b: Correlates of higher neurodevelopmental scores among HUU

VARIABLE	Flanker Inhibitory Control and Attention Test.	Dimensional Change Card Sort	List Sorting Working Memory	Picture Sequence Memory	Pattern Comparison Processing speed
	Adjusted r (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)	*Adjusted r* (95% CI)
Child characteristics					
Male	0.1 (-0.02, 0.2)	0.5 (-0.2, 1.1)	**1.6** (0.6, 2.6)	1.2 (-0.5, 2.8)	-0.5 (-3.8, 2.9)
Female	*Ref*				
OVC status	0.12 (-0.02, 0.26)	**1** (0.2, 1.8)	0.15 (-1.1, 1.4)	**2.7** (0.7, 4.7)	0.9 (-3.2, 4.9)
Breastfed	0.01 (-0.2, 0.25)	-0.3 (-1.6, 1.1)	0.5 (-1.65, 2.75)	-1.2 (-4.7, 2.2)	4.3 (-2.7, 11.3)
Pre-term <37 weeks	-0.01 (-0.5, 0.5)	0.7 (-2.2, 3.6)	-0.8 (-5.4, 3.8)	-0.5 (-8.1, 7.2)	-3.4 (-18.6, 11.8)
Birthweight <2500g	0.9 (-2.6, 4.3)	-3.7 (-124.3, 117)	-0.4 (-41.9, 41.1)	-6.4 (-37.7, 25)	-27 (-236.1, 182.05)
Caregiver characteristics					

Maternal Age	0.01 (-0.004, 0.02)	0.04 (-0.04, 0.1)	**0.1** (-0.001, 0.2)	0.1 (-0.08, 0.3)	0.3 (-0.1, 0.6)
Education (years)	0.01 (-0.01, 0.03)	0.02 (-0.1, 0.1)	**0.22** (0.04, 0.4)	0.06 (-0.2, 0.4)	0.6 (-0.04, 1.2)
Food secure	Ref				
Mild	0.2 (-0.1, 0.6)	-0.67 (-2.9, 1.7)	-0.2 (-3.6, 3.2)	-2.1 (-7.6, 3.4)	-6.5 (-17.3, -4.2)
Moderate	0.2 (-0.2, 0.5)	-1.11 (-3.5, 1.3)	-0.01 (-3.6, 3.5)	-2.4 (-8.2, 3.4)	-6.4 (-17.7, 4.9)
Severe	0.2 (-0.2, 0.5)	-1.1 (-3.5, 1.3)	0.2 (-3.3, 3.7)	-2.6 (-8.2, 3.1)	1.2 (-9.9, -12.2)

*Model adjusted for child's age