Telomere length and neurodevelopmental outcomes among children exposed and not exposed to HIV in Kenya

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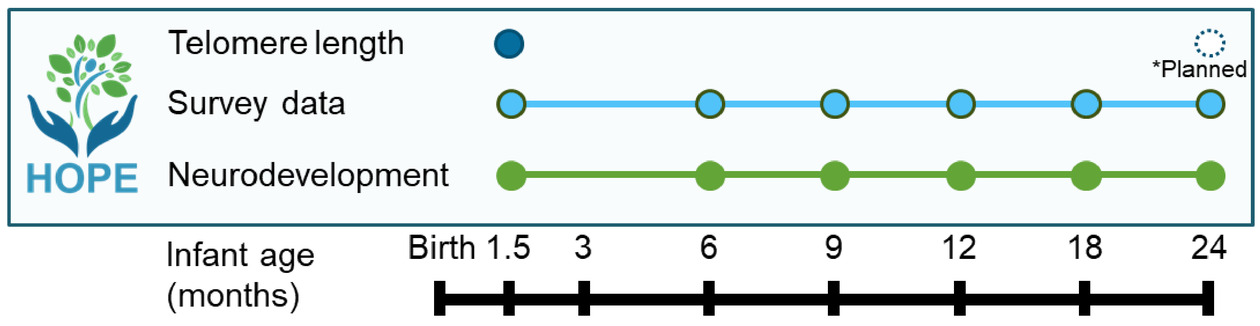
Background

- Telomere length (TL) is an important biomarker of biological aging.[1]
- TL shortens from cell division, inflammation, and oxidative stress.[2]
- Childhood is a time of increased telomere attrition[3] and changes in childhood TL are thought to persist into adulthood.[4]
- There is some evidence that CHEU may have shorter TL[5] and poorer neurodevelopmental outcomes compared to CHUU.[6]
- Shorter TL was associated with lower neurodevelopmental scores in some studies while others found no association.[7-9]

Objective: To determine the association between 6-week telomere length (TL) and repeated neurodevelopmental scores among children who are HIV exposed and uninfected (CHEU) and children who are HIV unexposed and uninfected (CHUU)

Methods

- **Parent study:** HOPE study enrolled 1,000 CHEU and 1,000 CHUU at 6 weeks and followed through 36 months of age
- **Population:** 250 CHEU and 250 CHUU in HOPE who were retained through 24 months from 6 clinics in Nairobi and Western Kenya
- **Design:** Prospective cohort study
- **Laboratory methods:** TL was measured from dried blood spots using a modified version[11] of the monochrome multiplex qPCR assay[12]
- **Exposure:** Relative infant TL, the ratio of the amount of telomeric DNA (T) to the single copy gene (S) z-score at 6 weeks
- **Outcomes:** Malawi Developmental Assessment Tool (MDAT) social, language, fine motor, and gross motor scores[13]



- **Statistical methods:**
  - Linear mixed effects models with clinic as a random effect
  - Adjusted for infant age, infant sex, maternal age and education
  - Benjamini-Hochberg approach to adjust for multiple comparisons
- Analysis plan was pre-registered prior to conducting the analysis

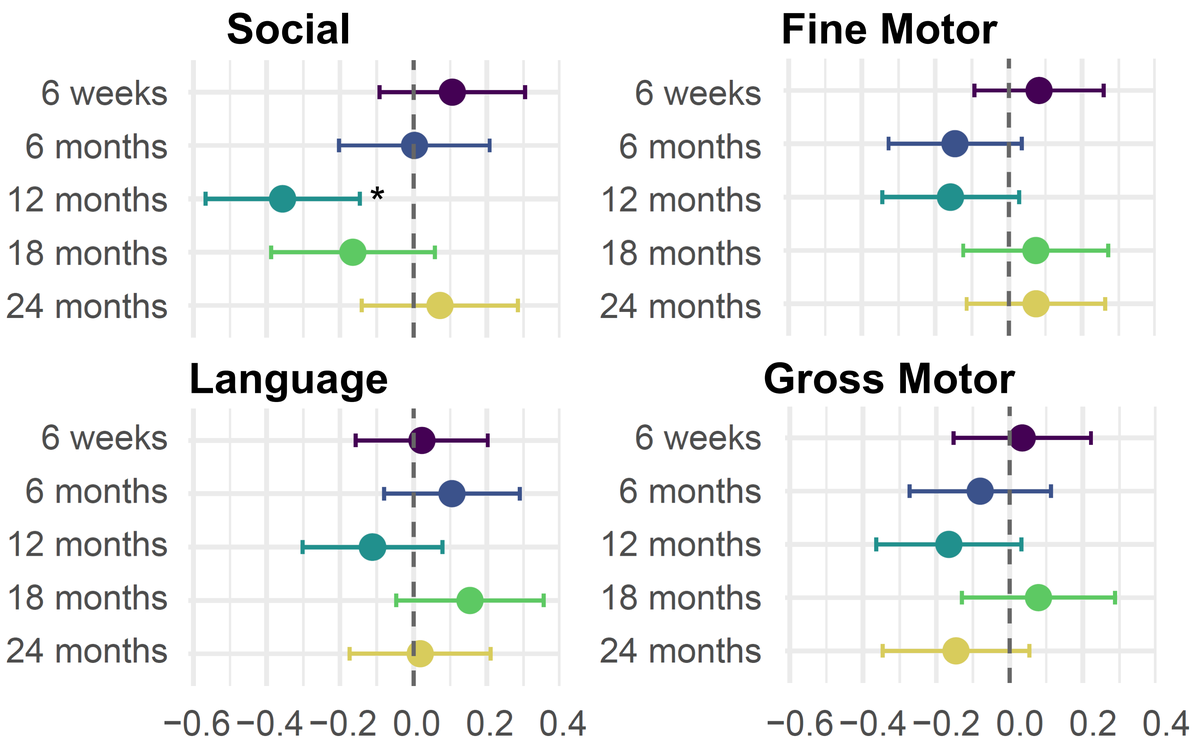
Results

Table 1. Characteristics of CHEU and CHUU with TL at 6 weeks

	n(%) or Median (IQR)	
	CHEU N=250	CHUU N=250
Age at sample collection (weeks)	6.6 (6.0, 7.9)	6.6 (6.0, 7.6)
Female (REF: Male)	130 (52%)	125 (50%)
Birth weight (kg)	3.2 (3.0, 3.5)	3.3 (3.0, 3.6)
Preterm birth (<37 weeks gestation)	7 (2.8%)	7 (2.8%)
Exclusively breastfed at 6 weeks	246 (99%)	238 (95%)
Maternal age (years)	31 (28, 36)	26 (23, 30)
Paternal age (years)	37 (32, 42)	31 (28, 35)
Maternal years of education	8 (8, 12)	12 (9, 12)
Moderate-to-severe food insecurity	63 (25%)	24 (10%)

- Compared to CHUU, CHEU were more frequently exclusively breastfed and had older parents, mothers with fewer years of education, and households with food insecurity (Table 1).
- Most mothers with HIV were on ART prior to and during pregnancy (88% and 99%, respectively).
  - During pregnancy, 76% of mothers of CHEU were on dolutegravir-based regimens.

Figure 1. Adjusted models evaluating the association between 6-week TL and neurodevelopmental outcomes



*p-value<0.05

- In stratified analyses of CHEU and CHUU, TL z-score was not correlated with neurodevelopmental scores

Conclusions

- In this large cohort of CHEU and CHUU, TL at 6 weeks was not significantly associated with neurodevelopmental outcomes measured at multiple timepoints.
- There is evidence that TL is associated with age-related health outcomes. Further analyses to assess whether TL decline between 6 weeks and 24 months or TL at 24 months correlate with child neurodevelopmental scores is warranted.

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References:

1. Vaiserman et al. *Front Genet* 2021; 2. Rizvi et al. *Curr Aging Sci* 2015; 3. Cowell et al. *Psychoneuroendocrinology* 2021; 4. Martens et al. *EBioMedicine* 2021; 5. Shiau et al. *J Acquir Immune Defic Syndr*. 2018; 6. McHenry *J Int AIDS Soc* 2019; 7. Wedderburn *Lancet Child Adolesc Health* 2022; 8. Pham et al. *Int J Mol Sci* 2022; 9. Naudé et al. *J Affect Disord* 2023; 10. Campos-Sánchez et al. *Eur Child Adolesc Psychiatry* 2024; 11. Rej et al. *American Journal of Human Biology* 2021; 12. Cawthorn et al. *Nucleic Acids Res* 2009; 13. Gladstone *PLoS Med* 2010