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Original article

Growth, neurodevelopmental outcomes and micronutrient intake in 18-month-old children with exposure to maternal human immunodeficiency virus and placental insufficiency: The UmbiGodisa cross-sectional study

Mothusi Nyofane [a,b,c,d,*], Marinel Hoffman [a,c,d], Helen Mulol [c,d,e], Tanita Botha [f], Robert Pattinson [c,d,g], Ute Feucht [c,d,e]

[a] *Department of Consumer and Food Sciences, University of Pretoria, Pretoria, 0002, South Africa*
[b] *Department of Nutrition, National University of Lesotho, Maseru, 100, Lesotho*
[c] *Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies, University of Pretoria, Kalafong Provincial Tertiary Hospital, Pretoria, 0001, South Africa*
[d] *Maternal and Infant Health Care Strategies Research Unit, South African Medical Research Council, Pretoria, 0001, South Africa*
[e] *Department of Paediatrics, University of Pretoria, Pretoria, 0002, South Africa*
[f] *Department of Statistics, University of Pretoria, Pretoria, 0002, South Africa*
[g] *Department of Obstetrics and Gynaecology, University of Pretoria, Pretoria, 0002, South Africa*

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SUMMARY

Background and aim: Maternal human immunodeficiency virus (HIV) and intrauterine growth restriction (IUGR) are both associated with suboptimal childhood growth and neurodevelopment. This study assessed growth and neurodevelopmental outcomes and micronutrient intakes in children who are HIV-exposed-uninfected (CHEU), compared to HIV-unexposed-uninfected children (CHUU), stratified based on evidence of placental insufficiency.

Methods: Placental insufficiency, as proxy for IUGR, was identified using abnormal umbilical artery resistance indices (UmA-RI) on pregnancy Doppler ultrasound. At 18-months postpartum, 264 mother–child pairs were evaluated and categorized into four subgroups: CHUU with normal UmA-RI (control group), CHEU with normal UmA-RI (HIV exposure only), CHUU with abnormal UmA-RI (placental insufficiency only) and CHEU with abnormal UmA-RI (double-exposure). Dietary intake was assessed using a single 24-h dietary recall, and dietary intake of iron, zinc, and iodine was quantified by meal analysis on FoodFinder™ 3.0. Anthropometric data were collected and converted into z-scores. The Bayley Scales of Infant and Toddler Development (Bayley-III) assessed cognitive, language, and motor function. Statistical comparisons used t-test or Mann–Whitney U-tests; associations were analyzed with Spearman's correlation.

Results: Children with dual exposure (CHEU/AbN-RI) had significantly lower z-scores compared to the control group, including length-for-age z-score (-1.4 ± 1.4 vs 0.0 ± 1.3; $p = 0.001$), weight-for-age z-score (-0.6 ± 1.0 vs 0.0 ± 1.2; $p = 0.024$) and head circumference-for-age z-score (0.4 ± 0.7 vs 0.9 ± 1.2; $p = 0.035$). Mean cognitive scores were also lower in this group (93.9 ± 12.9 vs 100.1 ± 10.8; $p = 0.042$). Language composite scores were low across all groups. Higher zinc intake was positively associated with language scores ($r = 0.10$; $p = 0.042$) and weight-for-age z-scores were associated with motor outcomes ($r = 0.10$; $p = 0.028$). Among CHEU, better growth parameters were positively associated with cognitive and motor developmental domains.

Abbreviations: AbN-RI, Abnormal resistance index; ART, Antiretroviral therapy; CHEU, Children who are HIV-exposed-uninfected; CHUU, Children who are HIV-unexposed-uninfected; EAR, Estimated Average Requirement; GMCD, International Guide for Monitoring Child Development; HC, Head circumference; HCZ, Head circumference-for-age z-score; HIV, Human immunodeficiency virus; IUGR, Intrauterine growth restriction; LAZ, Length-for-age z-score; LMICs, Low-and middle-income countries; N-RI, Normal resistance index; PMTCT, Prevention of mother-to-child HIV transmission; UmA-RI, Umbilical artery resistance index; WAZ, Weight-for-age z-score; WLZ, Weight-for-length z-score.

* Corresponding author. Department of Consumer and Food Sciences, University of Pretoria, Pretoria 0002, South Africa.
E-mail address: mothusi.nyofane@tuks.co.za (M. Nyofane).

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Conclusion: Children exposed to both maternal HIV and placental insufficiency showed signs of suboptimal growth, particularly stunting, and delayed cognitive development, compared to unexposed controls. These findings highlight the need for early identification and targeted interventions for high-risk children within Child Health/Nutrition programmes.

1. Introduction

Nutrition plays a critical role in early growth and brain development, and nutritional deficiencies are major contributors to delayed neurodevelopment in low- and middle-income countries (LMICs) [1,2]. Suboptimal infant feeding practices are a leading cause of nutritional deficiencies [2]. The association between iron deficiency and neurodevelopment has been documented in the literature [3–8], with complementary diets fed to infants in developing countries previously found to contain suboptimal amounts of iron and zinc [9]. Inadequate iron, zinc and iodine intake during critical periods of rapid development is known to lead to impaired cognitive and motor development in animal model studies [5,10,11].

Child neurodevelopment is a global public health priority. Estimates are that almost half (43.0 %) of children under five years are at risk of not fully attaining their developmental potential, particularly in LMICs [2,12]. Child neurodevelopment is influenced by a multitude of pre- and post-natal maternal and child factors and exposures to environmental and biological risks, including human immunodeficiency virus (HIV) infection, placental insufficiency and suboptimal nutrition [4,13].

In South Africa, the prevalence of HIV infection in pregnant women is approximately 30.0 % [14]. The provision of antiretroviral therapy (ART) has resulted in improved maternal health, as well as the successful prevention of mother-to-child transmission (PMTCT) of HIV [12,15,16]. Therefore, the number of children who are HIV-exposed-uninfected (CHEU) is increasing, estimated at 15.4 million in 2020 globally [17] and 3.5 million in South Africa alone [18]. Pre- and postnatal exposure to maternal HIV infection and ART potentially affects growth and neurodevelopmental outcomes in CHEU [17], who have in several studies been shown to have poorer growth and neurodevelopmental outcomes, compared to children who are HIV-unexposed-uninfected (CHUU) [19–23]. Furthermore, Wedderburn and colleagues reported the risk of maternal HIV exposure on early structural brain development [24].

Placental insufficiency can be detected by an abnormal umbilical artery resistance index (UmA-RI) on Doppler ultrasound [25]. South African women, even those with seemingly low-risk pregnancies, have previously been found to have an unexpectedly high prevalence of abnormal UmA-RI of between 6 % and 13 % [26–28]. Placental insufficiency is associated with raised umbilical-placental vascular resistance and suboptimal blood flow, resulting in fetal starvation [29], and hence causes intrauterine growth restriction (IUGR) [25,30], which in turn is strongly associated with suboptimal child neurodevelopment due to intrauterine hypoxia [26–28]. Additionally, maternal HIV infection has been reported as a risk factor for IUGR [31,32], due to inflammation and dysregulation of placental vasculogenesis and angiogenesis, resulting in altered placental function [33–35].

The first 1000 days of life are a period of incredible potential and enormous vulnerability [36–38]. Despite the huge risks posed by HIV infection and placental insufficiency to early and late child development, the postpartum neurodevelopmental outcomes of children with both of these risk factors have been overlooked. Additionally, there is a lack of information on the effects of feeding practices, particularly iron, zinc and iodine intakes on neurodevelopment, especially in the context of HIV exposure and placental insufficiency. This study therefore assessed, compared and determined associations between iron, zinc and iodine intakes and growth and neurodevelopmental outcomes in CHEU and CHUU born with and without IUGR in the Tshwane District in the Gauteng Province of South Africa.

2. Materials and methods

2.1. Study setting

The UmbiGodisa study followed up children born to mothers recruited from the South African arm of the Umbiflow International study, which determined the prevalence of abnormal UmA-RI in unselected low-risk women at 28–34 weeks' gestation through a single screening with the low-cost Umbiflow™ Doppler device in South Africa, India, Ghana, Kenya and Rwanda. The cut-off centiles for normal and abnormal UmA-RI were <75th and ≥75th for the gestational age [39], respectively, previously linked to risk of suboptimal pregnancy outcomes like stillbirths. The South African study participants were screened from October 2018 to January 2020. To expand the study population of CHEU with abnormal UmA-RI, the current study enrolled additional participants from the Siyakhula study, carried out in the same locality, which assessed growth and neurodevelopment of CHEU, with similar study procedures and with pregnancy Doppler data available. The study participants were followed up at the University of Pretoria's Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies, located at Kalafong Provincial Tertiary Hospital in the Gauteng Province of South Africa.

2.2. Study design

UmbiGodisa was a cross-sectional study nested within two existing cohorts (Umbiflow and Siyakhula), designed to compare feeding practices, micronutrient intake, and developmental outcomes among children stratified by UmA-RI and HIV exposure. The case–control structure was applied retrospectively based on resistance index (RI) status, using data collected at a single time point. The study outcome for this manuscript was child neurodevelopment, namely cognitive, motor and language development, while the modifying factors included infant growth parameters, dietary iron, zinc and iodine intake and feeding practices. The mother–child pairs were only assessed once, at 18 months postpartum. Participants were classified into four subgroups according to HIV exposure and normal/abnormal UmA-RI: CHUU with normal UmA-RI (CHUU/N-RI; control group), CHEU with normal UmA-RI (CHEU/N-RI; single exposure), CHUU with abnormal UmA-RI (CHUU/AbN-RI; single exposure) and CHEU with abnormal UmA-RI (CHEU/AbN-RI; double exposure).

2.3. Study participants

Mothers with low-risk singleton pregnancies, with known HIV status and UmA-RI at 28–34 weeks, who delivered in local facilities with available pregnancy and birth information, were included in the study. Exclusion criteria included multiple pregnancies, lack of informed consent for any reason, minors, children with abnormalities or severe medical conditions and children aged above 21 months at time of study. Power analysis indicated that an overall sample size of 280 was sufficient with a split of 80/20 % for CHUU and CHEU groups. The anticipated sample size was 311 from the Umbiflow International cohort, however, 46 participants were not interested to join the study, others had aged above the set upper limit (n = 1), severe medical conditions (n = 2) or had withdrawn (n = 1). Therefore, 261 participants were recruited but 7 participants were excluded from analysis due to obvious developmental abnormalities such as encephalopathy (n = 3) and incomplete questionnaires or Bayley assessment (n = 4). Overall, 264 participants were included in the analysis, which included the additional 10 participants from the Siyakhula study. The subgroups size: CHUU/N-RI: n = 181; CHEU/N-RI: n = 50; CHUU/AbN-RI: n = 19; and CHEU/AbN-RI: n = 14 (Fig. 1).

2.4. Data collection

Mothers were booked telephonically for a study visit. The study staff were trained to administer the data collection tools. They obtained the informed consent and facilitated the data collection process from February to December 2021. The face-to-face maternal interviews and child growth and development assessments were conducted in local languages or English.

2.4.1. Sociodemographic, feeding practices and dietary intake data

A structured questionnaire was used to collect maternal-child sociodemographic variables and medical history. The household food security status was assessed using the adopted United States Household Food Security Survey Module [40]. The limitation of this tool is that it does not provide specific information on food security of children. The breastfeeding data over the first 6 months of life was collected using a standardized and previously used questionnaire based on maternal recall [41]. The previously validated, used and quantified single 24-h dietary recall method was employed to gather the children's dietary intake, as reported by the mother [42–44]. A detailed manual for administering a 24-hour dietary recall was available for guidance [45] and a standardized dietary kit was utilized. Breast milk substitutes and infant cereals were recorded per dry amount grams (g) [42,46].

2.4.2. Growth and neurodevelopmental assessment

Child weight, length and head circumference (HC) measurements were performed according to standard procedures, and measured twice and the mean value was used. We used calibrated digital scale (Seca 354); mechanical infantometer (Seca 416) and non-stretchable tape measure for weight, length and HC measurements, respectively. The developmental screening was performed using the International Guide for Monitoring Child Development (GMCD) at the corrected age for prematurity, which entails a series of open-ended questions, according to the child's age, on functional domains including expressive and receptive language, gross and fine movements, relating and response behavior, play, and self-help activities, that were answered by the child's caregiver [47]. The reliability and validity of GMCD have been reported by studies in Turkey and other LMIC settings [48]. An individually administered Bayley Scales of Infant and Toddler Development™ third edition (Bayley-III) was used to assess the cognitive, language (expressive and receptive) and motor (fine and gross) domains at the corrected age, using the Bayley-III kit. Bayley-III is a standardized and well-accepted tool that takes about 45–60 min to complete, and it may overestimate child performance [49,50]. GMCD was performed first, then Bayley-III, and they were completed using different trained study staff who were blinded to the results of the other test to avoid bias. Bayley-III was assessed when the child was in an alert state.

2.5. Data processing and statistical analysis

All data was managed using the Research Electronic Data Capture database v9.3.5. Outliers were examined for potential data entry errors and z-scores falling outside the reference population range (<−3 or >+3) were examined for plausibility. The reported household food intake measurements were converted to weight in grams [51]. South African based FoodFinder™ 3.0 was used for meal analysis of food intake, quantifying the dietary intake of iron, zinc, and iodine. FoodFinder™ 3.0 is programmed according to the use of iodized salt in South Africa. The Estimated Average Requirement (EAR) of 1–3 year old children for iodine, iron, and zinc are 65 mcg, 3.0 mg, and 2.5 mg per day, respectively [52]. The World Health Organization Anthro software was used to compute z-scores using corrected ages. Underweight, stunting, wasting and microcephaly were defined as weight-for-age z-score (WAZ), length-for-age z-score (LAZ), weight-for-length z-score (WLZ) and HC-for-age z-score (HCZ) of < -2, respectively, and the cut-off of < -3 was used as severe classifications. GMCD was classified as age-appropriate development if all milestones were attained; delay if one or more milestones were not attained in the appropriate age group and a significant delay if the child did not attain milestones in the appropriate age group and the previous age group. The Bayley-III composite score was calculated based on a comparison of the child to a normative age-matched sample established by the assessment and were interpreted as follows for any of the five domains, namely, a) mid-average functioning: composite score of 100 (15 SD standardized mean score); b) mild impairment/at risk of developmental delay: <85 (1 SD < mean); c) moderate impairment: composite score of <70 (2 SD < mean); d) severe impairment: composite score of <55 [53].

All statistical analysis was performed using R Statistical Software version 4.3.0. The Shapiro Wilk test was used to determine if the data was normally distributed. The four groups were compared for descriptive statistics using ANOVA tests for the normally distributed data and the Kruskal–Wallis H test for the non-normally distributed data, for all continuous variables. For each of the variables which were significantly different, a posthoc analysis which included the Bonferroni correction was performed to determine which groups differed from which and the adjusted p-values were used. The Chi-squared test and Fisher's exact test were used for categorical variables. For the micronutrient intake, anthropometry measurements and Bayley-III, the three exposure groups were compared against the control group, where the independent t-test was used for normally distributed variables and the Mann–Whitney U test was used for variables with a non-normal distribution. Groups with very low cell counts were excluded in the analysis as smaller groups lead to volatile results (presented as “n/a” in tables). Spearman's correlation was used to determine

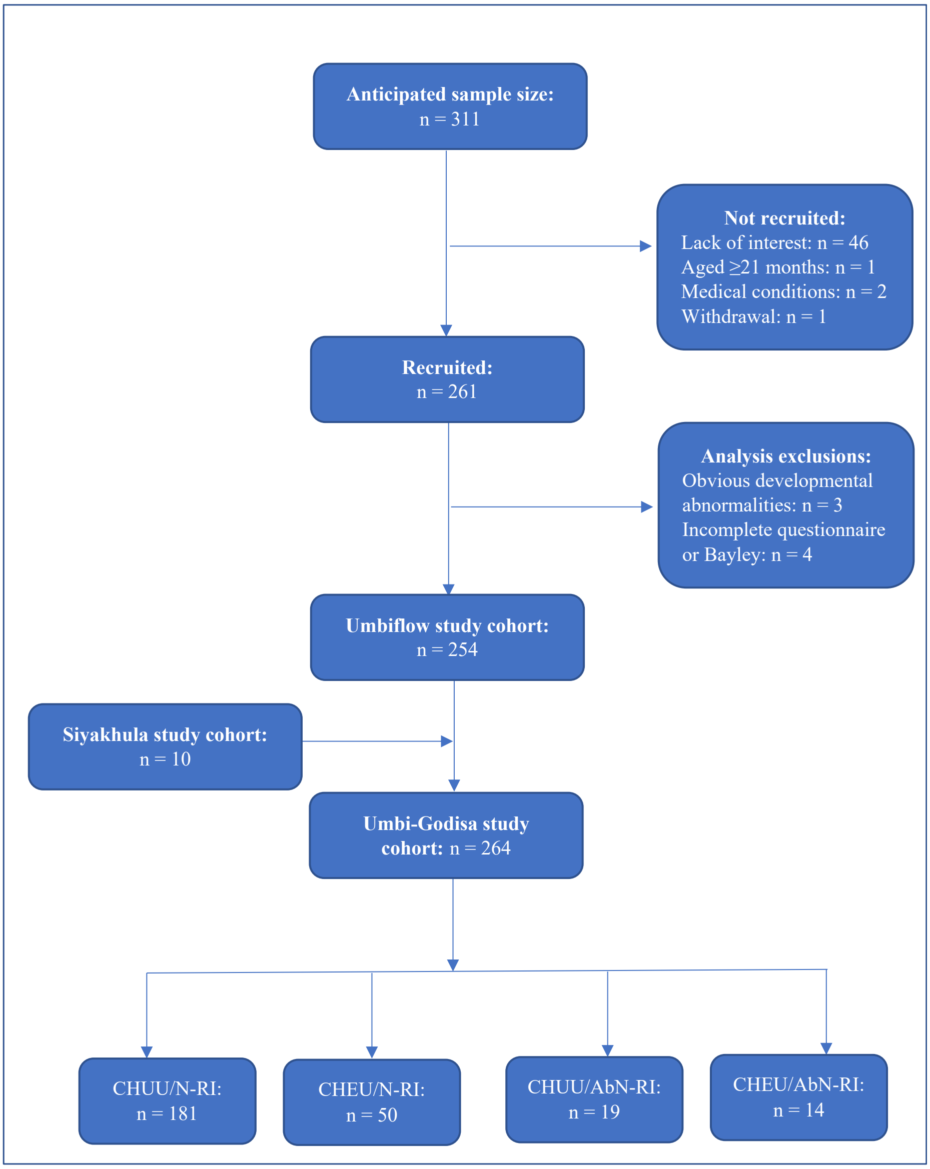

Fig. 1. Study cohort.

associations and their significances between Bayley-III and other variables. The correlation coefficient can be between −1 and +1, with stronger associations closer to the outer bounds (−1 and +1).

3. Results

About 36.8 % of CHUU/AbN-RI were born prematurely (<37 weeks' gestation) (Table 1). The mean birth weights were significantly different between the four groups ($p < 0.001$). A posthoc analysis indicated that CHUU/N-RI had a higher mean birth weight than CHEU/AbN-RI ($p = 0.004$) and CHUU/AbN-RI ($p < 0.001$). Furthermore, CHEU/N-RI had a higher mean birth weight compared to CHUU/AbN-RI ($p = 0.002$). A smaller mean HC was observed at birth in CHUU/AbN-RI when compared to CHUU/N-RI ($p = 0.004$) and CHEU/N-RI ($p = 0.009$). All CHEU were on ART prophylaxis and their mothers self-reported being on ART, with an overall latest mean CD4 count of 448 ± 298 cells/mm^3. Maternal mean age differed significantly between the four groups; $p < 0.001$. A posthoc analysis showed that mothers of the CHEU/AbN-RI were the oldest (37.1 ± 5.9 years) compared to mothers of the CHUU/AbN-RI (28.8 ± 4.2 years; $p < 0.001$), CHEU/N-RI (31.5 ± 5.4 years; $p = 0.007$) and the control group (30.1 ± 5.1 years; $p < 0.001$). Median gravidity and parity also differed significantly between the four groups; both were $p = 0.007$. Further analysis demonstrated that CHEU/AbN-RI had higher median gravidity ($p = 0.028$) and parity ($p = 0.010$) than the control group. More than 50 % of mothers of CHEU/AbN-RI delivered by caesarean section. Further, most mothers in all groups were single, unemployed, resided in formal townships and had attained some form of secondary schooling. Overall, 48.8 % of mothers were classified as being food insecure according to the US Household Food Security Survey Module. More than a quarter (30.0 %) of mothers of CHUU/N-RI were drinking alcohol after pregnancy and 4.0 % of mothers of CHEU/AbN-RI were smoking cigarettes after pregnancy.

On maternal recall, a high percentage of children (95.8 %) were ever breastfed across the groups (Table 2). Early initiation of breastfeeding within 1 h after birth was two-thirds or above in the

Table 1
Participant and maternal characteristics and medical history.

Measures	Subgroup	Statistic	CHUU/N-RI	CHEU/N-RI	CHUU/AbN-RI	CHEU/AbN-RI	P-value[a]
			(control group)	(single exposure)	(single exposure)	(double exposure)	
Sample size		N	181	50	19	14	
Age (months)		Mean ± SD	18.6 ± 0.9	18.5 ± 0.8	18.2 ± 0.2	18.8 ± 1.0	0.422
Sex	Female	*n* (%)	92 (50.8)	22 (44.0)	11 (57.9)	10 (71.4)	0.305
Premature birth		*n* (%)	15 (8.3)	2 (4.0)	7 (36.8)	1 (7.1)	n/a
Birth weight (g)		Mean ± SD	3194 ± 480	3108 ± 433	2650 ± 581	2742 ± 396	<**0.001**
Head circumference at birth (cm)			34.5 ± 1.7	34.5 ± 1.5	32.9 ± 1.9	34.0 ± 1.6	**0.006**
Birth weight z-score			−0.30 ± 1.16	−0.54 ± 0.96	−0.43 ± 1.08	−0.98 ± 0.75	0.105
Head circumference z-score			0.37 ± 1.32	0.35 ± 1.24	0.23 ± 0.97	0.50 ± 1.11	0.865
Apgar score at 5 min		Median [IQR]	10.0 [9.0, 10.0]	9.0 [9.0, 10.0]	9.0 [9.0, 9.0]	9.0 [9.0, 9.0]	**0.045**
Hospital admission during neonatal period		*n* (%)	33 (18.3)	6 (12.0)	6 (31.6)	1 (7.7)	n/a
HIV prophylaxis started[b]	NVP only	*n* (%)	N/A	41 (93.2)	N/A	6 (42.9)	n/a
	NVP and AZT		N/A	3 (6.8)	N/A	8 (57.1)	
Child ever had any form of malnutrition		*n* (%)	11 (6.1)	6 (12.0)	0 (0)	0 (0)	n/a
Child ever had diarrhoea			57 (31.5)	13 (26.0)	4 (21.1)	0 (0)	n/a
Child ever hospitalized for any illness			18 (9.9)	5 (10.0)	0 (0)	0 (0)	n/a
Maternal age (years)		Mean ± SD	30.1 ± 5.1	31.5 ± 5.4	28.8 ± 4.2	37.1 ± 5.9	<**0.001**
Obstetric history	Gravidity	Median [IQR]	2 [1, 3]	3 [2, 3]	2 [2, 3]	4 [3, 4]	**0.007**
	Parity		2 [1, 3]	2 [2, 3]	2 [2, 3]	3 [3, 3]	**0.007**
	Previous pregnancy losses		0 [0, 0]	0 [0, 1]	0 [0, 0]	0 [0, 1]	0.383
	Preeclampsia/ eclampsia	*n* (%)	2 (13.3)	0 (0)	0 (0)	0 (0)	n/a
	Postpartum complications		23 (12.7)	5 (10.0)	2 (10.5)	0 (0)	n/a
Umbilical artery Doppler	UmA-RI value at 28–34 weeks' gestation	Mean ± SD	0.64 ± 0.1	0.63 ± 0.0	0.75 ± 0.1	0.76 ± 0.0	**0.001**
	UmA-RI z-score		0.03 ± 0.7	−0.10 ± 0.6	1.81 ± 0.9	1.78 ± 0.7	<**0.001**
Mode of delivery	Vaginal delivery	*n* (%)	126 (69.2)	31 (62.0)	9 (47.4)	5 (35.7)	<**0.001**
	Cesarean section		54 (29.8)	19 (38.0)	10 (52.6)	9 (64.3)	
Latest CD4 count	Cells/mm^3	Mean ± SD	N/A	463 ± 310	N/A	416 ± 295	0.965
Latest HIV viral load	Copies/mL (log)	Median [IQR]	N/A	0.0 [0.0, 0.0]	N/A	0.0 [0.0, 0.0]	0.798
Current ART	TDF/FTC/EFV	*n* (%)	N/A	31 (62.0)	N/A	7 (50.0)	0.251
	Other ART		N/A	10 (20.0)	N/A	6 (42.9)	
	Not recorded		N/A	9 (18.0)	N/A	1 (7.1)	
Marital status	Single	*n* (%)	114 (63.0)	33 (66.0)	10 (52.6)	7 (50.0)	0.592
	Married/co-habiting		67 (37.0)	17 (34.0)	9 (47.4)	7 (50.0)	
Educational level	Any primary schooling	*n* (%)	13 (7.0)	4 (8.0)	3 (15.8)	2 (14.3)	0.221
	Any secondary schooling		124 (68.5)	40 (80.0)	12 (63.2)	11 (78.6)	
	Post-school education		44 (24.3)	6 (12.0)	4 (21.1)	1 (7.1)	
Maternal employment status	Unemployed	*n* (%)	110 (60.8)	29 (58.0)	10 (52.6)	10 (71.4)	0.736
	Employed		71 (39.2)	21 (42.0)	9 (47.4)	4 (28.6)	
Partner's employment status	Unemployed	*n* (%)	29 (16.9)	7 (14.3)	3 (15.8)	2 (14.3)	0.987
	Any type of employment		143 (83.1)	42 (85.7)	16 (84.2)	12 (85.7)	
Monthly household income (in ZAR)[c]	R 0 - R 2000	*n* (%)	36 (20.1)	7 (14.0)	0 (0)	4 (28.6)	n/a
	R 2001 - R 4000		42 (23.5)	15 (30.0)	8 (42.1)	0 (0)	
	R 4001 - R 6000		38 (21.2)	13 (26.0)	5 (26.3)	5 (35.7)	
	R 6001 - R 8000		11 (6.1)	5 (10.0)	1 (5.3)	2 (14.3)	
	R 8000 +		43 (24.0)	9 (18.0)	5 (26.3)	1 (7.1)	
	Don't know		9 (5.0)	1 (2.0)	0 (0)	2 (14.3)	
Household adult food security status	Food secure	*n* (%)	89 (49.2)	25 (50.0)	11 (57.9)	10 (71.4)	0.560
	Food insecure		92 (50.8)	25 (50.0)	8 (42.1)	4 (28.6)	
Description of neighborhood	Formal township	*n* (%)	114 (63.0)	27 (54.0)	14 (73.7)	7 (50.0)	0.348
	Informal settlement		67 (37.0)	23 (46.0)	5 (26.3)	7 (50.0)	
Postnatal lifestyle behavior	Any alcohol drinking[d]	*n* (%)	54 (30.0)	11 (22.4)	2 (12.2)	1 (7.7)	0.167
	Any cigarettes smoking[e]		3 (1.7)	2 (4.0)	0 (0.0)	1 (7.7)	n/a
Maternal mental health assessment[f]	Little interest or pleasure in doing things	*n* (%)	41 (22.9)	15 (30.0)	1 (5.9)	2 (15.4)	0.419
	Feeling down, depressed or hopeless		53 (29.6)	20 (40.0)	2 (11.8)	2 (15.4)	0.623
	Well	*n* (%)	165 (91.1)	44 (88.0)	18 (94.7)	14 (100.0)	n/a

Table 1 (*continued*)

Measures	Subgroup	Statistic	CHUU/N-RI	CHEU/N-RI	CHUU/AbN-RI	CHEU/AbN-RI	P-value[a]
			(control group)	(single exposure)	(single exposure)	(double exposure)	
Maternal self-assessed general heath rating	Fair		13 (7.2)	6 (12.0)	0 (0)	0 (0)	
	Poor		3 (1.7)	0 (0)	1 (5.3)	0 (0)	

Notes: AbN-RI: abnormal umbilical artery resistance index; ART: antiretroviral therapy; AZT: zidovudine; CD4: a cluster of differentiation 4; CHEU: children who are HIV-exposed-uninfected; CHUU: children who are HIV-unexposed-uninfected; IQR: interquartile range; n/a: Not applicable; N-RI: normal umbilical artery resistance index; NVP: nevirapine; SD: standard deviation; TDF/FTC/EFV: tenofovir/emtricitabine/efavirenz; UmA-RI: umbilical artery resistance index; ZAR: South African Rand.

[a] Comparison was made between the four groups. The ANOVA test was used for the normally distributed data and the Kruskal Wallis H test was used for the data that was not normally distributed, for continuous variables. The Chi-squared test and Fisher's exact test were used for categorical variables. All tests were performed at a 5 % level of significance. A significant difference is indicated by a bold p-value.

[b] CHEU/N-RI: n = 44.

[c] One South African Rand equates to 0.056 United States Dollars.

[d] Question asked: Since your baby was born, did you drink alcohol?.

[e] Question asked: Since your baby was born, did you smoke cigarettes?.

[f] CHUU/N-RI: n = 179; CHUU/AbN-RI: n = 17; CHEU/AbN-RI: n = 13.

Table 2

Child feeding practices based on maternal recall and micronutrient intake.

Measures	Subgroup	Statistic	CHUU/N-RI	CHEU/N-RI	CHUU/AbN-RI	CHEU/AbN-RI	P-value[a]
			(control group)	(single exposure)	(single exposure)	(double exposure)	
Sample size		N	181	50	19	14	
Ever breastfed	Yes	*n* (%)	173 (95.6)	47 (94.0)	19 (100.0)	14 (100.0)	0.601
Early initiation of breastfeeding after birth[b]	Within 1 h	*n* (%)	121 (78.1)	21 (48.8)	8 (50.0)	8 (66.7)	**0.001**
	After 1 h		34 (21.9)	22 (51.2)	8 (50.0)	4 (33.3)	
Feeding practices in the first 6 months	EBF	*n* (%)	58 (32.0)	20 (40.0)	7 (36.8)	6 (42.9)	n/a
	Formula feeding		11 (6.1)	3 (6.0)	0 (0)	0 (0)	
	Mixed feeding		105 (58.0)	20 (40.0)	10 (52.6)	3 (21.4)	
	Initially EBF, then formula feeding only		6 (3.3)	7 (14.0)	2 (10.5)	5 (35.7)	
Currently breastfeeding	Yes	*n* (%)	48 (26.7)	3 (6.1)	4 (23.5)	2 (15.4)	n/a
Age at weaning (in months)		Mean ± SD	11.4 ± 5.5	7.1 ± 5.1	8.8 ± 5.3	8.2 ± 5.2	<**0.001**
Introduction of food and timing of introduction							
Formula milk	Age (months)	Mean ± SD	5.6 ± 5.2	5.1 ± 3.8	6.1 ± 4.0	7.6 ± 8.3	0.815
Water			4.1 ± 2.1	4.6 ± 2.2	4.4 ± 1.8	4.6 ± 2.2	0.318
Tea, juice			9.7 ± 3.9	9.0 ± 4.0	8.9 ± 3.6	11.4 ± 4.3	0.235
Cow's milk			11.6 ± 3.4	12.7 ± 2.7	9.6 ± 5.5	10.4 ± 2.9	0.150
Semi-solids, e.g. cereals, porridge			5.2 ± 1.6	5.2 ± 1.7	5.5 ± 1.0	5.7 ± 1.7	0.388
Solids, e.g. vegetables, fruit			8.8 ± 3.5	8.3 ± 3.3	7.7 ± 2.2	10.1 ± 4.4	0.474
Protein rich foods, e.g. eggs			9.7 ± 3.4	8.9 ± 3.7	8.5 ± 2.6	11.2 ± 3.1	**0.048**
Dietary nutrients intake[c]	Iron (mg)	Mean ± SD	6.4 ± 5.1	6.9 ± 4.3	7.8 ± 7.3	6.3 ± 3.3	0.510
	Zinc (mg)		5.1 ± 5.2	5.5 ± 3.4	5.5 ± 2.8	4.6 ± 2.6	0.871
	Iodine (mcg)		26.2 ± 15.3	41.7 ± 23.9	45.4 ± 16.4	36.0 ± 18.5	0.094

Notes: AbN-RI: abnormal umbilical artery resistance index; EBF: exclusive breastfeeding; CHUU: children who are HIV-unexposed-uninfected; CHEU: children who are HIV-exposed-uninfected; mcg: micrograms; mg: milligrams; n/a: Not applicable; N-RI: normal umbilical artery resistance index; SD: standard deviation.

[a] Comparison was made between the four groups. The ANOVA tests was used for the normally distributed data and the Kruskal–Wallis H test was used for the data that was not normally distributed. The Chi-squared test and Fisher's exact test were used for categorical variables. All tests were performed at a 5 % level of significance. Significant difference is indicated by a bold p value.

[b] CHUU/N-RI: n = 155; CHEU/N-RI: n = 43; CHUU/AbN-RI: n = 16; CHEU/AbN-RI: n = 12.

[c] Comparison was made between CHUU/N-RI (control group) vs CHEU/AbN-RI (double exposure group). The Mann–Whitney U tests was used. All tests were performed at a 5 % level of significance. Dietary nutrients intake reported excludes any intake via breastmilk for the children who were still breastfed at the 18-month study visit.

CHEU/AbN-RI and CHUU/N-RI groups. The percentage of exclusive breastfeeding (EBF) in the first 6 months was high among CHEU/N-RI (40.0 %) and CHEU/AbN-RI (42.9 %) while percentage of mixed feeding was high in CHUU/N-RI (58.0 %) and CHUU/AbN-RI (52.6 %). CHEU/N-RI stopped breastfeeding earlier at mean 7.1 ± 5.1 months than CHEU/AbN-RI (8.2 ± 5.2 months), CHUU/AbN-RI (8.8 ± 5.3 months) and CHUU/N-RI (11.4 ± 5.5 months); p < 0.001. The mean introduction of cow's milk was earlier than the recommended twelve months of age in three of the groups (CHUU/N-RI: 11.6 ± 3.4, CHUU/AbN-RI: 9.6 ± 5.5 and CHEU/AbN-RI: 10.4 ± 2.9 months). CHEU/AbN-RI were introduced to protein-rich foods later at 11.2 ± 3.1 months than other groups; p = 0.048. There were no significant differences for the intake of iron, zinc and iodine between CHUU/N-RI vs CHEU AbN-RI. Iodine intake was lower among CHUU/N-RI when compared to CHEU/N-RI (p = 0.033) and CHUU/AbN-RI (p = 0.005). Generally, the iodine intake was below the EAR across all the groups.

In general, the CHEU/AbN-RI (double exposure) group had significantly lower anthropometric measurements and growth indices at age 18 months when compared to the CHUU/N-RI (control) group (Table 3). These include weight (kg) (9.9 ± 1.1 vs 10.9 ± 1.6; p = 0.015), length (cm) (78.1 ± 3.7 vs 81.9 ± 3.8; p = 0.001) and HC (cm) (47.3 ± 1.1 vs 48.1 ± 1.6; p = 0.024) and z-scores: WAZ (−0.6 ± 1.0 vs 0.0 ± 1.2; p = 0.024), LAZ (−1.4 ± 1.4 vs 0.0 ± 1.3; p = 0.001) and HCZ (0.4 ± 0.7 vs 0.9 ± 1.2; p = 0.035), while the WLZ were similar (0.0 ± 0.8 vs 0.1 ± 1.2; p = 0.843).

The findings of the GMCD screening indicated that 21.4 % of CHEU/AbN-RI (double exposure) and 10.0 % of CHEU/N-RI (CHEU single exposure) had a delay in gross movements. The Bayley-III assessment showed that the CHEU/AbN-RI (double exposure)

Table 3
Anthropometric measurements, GMCD screening and Bayley-III results at age 18 months.

Measures	Subgroup	Statistic	CHUU/N-RI	CHEU/N-RI	CHUU/AbN-RI	CHEU/AbN-RI	P-value[a]
			(control group)	(single exposure)	(single exposure)	(double exposure)	
Sample size		N	181	50	19	14	
Anthropometric measurements	Weight (kg)	Mean (SD)	10.9 ± 1.6	10.7 ± 1.8	10.8 ± 2.0	9.9 ± 1.1	**0.015**
	Length (cm)		81.9 ± 3.8	80.6 ± 3.3	81.0 ± 4.2	78.1 ± 3.7	**0.001**
	Head circumference (cm)		48.1 ± 1.6	48.1 ± 1.9	48.7 ± 1.7	47.3 ± 1.1	**0.024**
Growth indices[b]	Weight-for-age z-score	Mean (SD)	0.0 ± 1.2	−0.1 ± 1.3	0.0 ± 1.6	−0.6 ± 1.0	**0.024**
	Length-for-age z-score		0.0 ± 1.3	−0.6 ± 1.2	−0.2 ± 1.6	−1.4 ± 1.4	**0.001**
	Weight-for-length z-score		0.1 ± 1.2	0.2 ± 1.5	0.2 ± 1.3	0.0 ± 0.8	0.843
	Head circumference-for-age z-score		0.9 ± 1.2	0.8 ± 1.2	1.4 ± 1.4	0.4 ± 0.7	**0.035**
GMCD screening results, as reported by the caregiver[c]							
Had concerns about child's development		*n* (%)	6 (3.3)	4 (8.0)	3 (15.8)	2 (14.3)	n/a
Relating	Delay	*n* (%)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	n/a
	Significant delay		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Play activities	Delay	*n* (%)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	n/a
	Significant delay		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Self-help activities	Delay	*n* (%)	3 (1.7)	0 (0.0)	1 (5.6)	0 (0.0)	n/a
	Significant delay		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Expressive language	Delay	*n* (%)	5 (2.8)	0 (0.0)	1 (5.6)	1 (7.1)	n/a
	Significant delay		5 (2.8)	1 (2.0)	0 (0)	1 (7.1)	
Receptive language	Delay	*n* (%)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	n/a
	Significant delay		0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	
Gross movement	Delay	*n* (%)	12 (6.8)	5 (10.0)	1 (5.6)	3 (21.4)	n/a
	Significant delay		1 (0.6)	1 (2.0)	1 (5.6)	0 (0.0)	
Fine movement	Delay	*n* (%)	6 (3.6)	1 (2.2)	1 (5.6)	0 (0.0)	n/a
	Significant delay		2 (1.2)	2 (4.3)	0 (0.0)	0 (0.0)	
Bayley-III composite scores	Cognitive composite scores	Mean (SD)	100.1 ± 10.8	100.4 ± 10.3	98.2 ± 11.7	93.9 ± 12.9	**0.042**
	Language composite scores[d]		89.4 ± 12.5	88.7 ± 11.4	90.6 ± 10.6	90.9 ± 15.8	0.480
	Motor composite scores[d]		100.0 ± 11.7	99.4 ± 12.8	97.9 ± 11.6	95.6 ± 14.2	0.189
Cognitive domain	Normal development	*n* (%)	175 (97.2)	46 (92.0)	18 (94.7)	11 (78.6)	n/a
	Mild delay		4 (2.2)	4 (8.0)	0 (0)	3 (21.4)	
	Moderate delay		1 (0.6)	0 (0)	1 (5.3)	0 (0)	
Language domain[d]	Normal development	*n* (%)	108 (60.0)	31 (62.0)	14 (73.7)	10 (71.4)	n/a
	Mild delay		67 (37.2)	18 (36.0)	5 (26.3)	3 (21.4)	
	Moderate delay		5 (2.8)	1 (2.0)	0 (0)	1 (7.1)	
Motor domain[d]	Normal development	*n* (%)	170 (94.4)	44 (88.0)	18 (94.7)	13 (92.9)	n/a
	Mild delay		10 (5.6)	6 (12.0)	0 (0)	0 (0)	
	Moderate delay		0 (0)	0 (0)	1 (5.3)	1 (7.1)	

Notes: AbN-RI: abnormal umbilical artery resistance index; CHUU: children who are HIV-unexposed-uninfected; CHEU: children who are HIV-exposed-uninfected; cm: centimetre; GMCD: International Guide for Monitoring Child Development; kg: kilograms; n/a: Not applicable; N-RI: normal umbilical artery resistance index; SD: standard deviation.

[a] The results presented are for the comparison between CHUU/N-RI (control group) vs CHEU/AbN-RI (double exposure group). For normally distributed data, the independent t-test was used, and the Mann–Whitney U tests was used in the non-normally distributed data. All tests were performed at a 5 % level of significance. Significant differences are indicated by bolded p-values.

[b] Corrected for prematurity.

[c] No significance tests could be performed due to small cell counts.

[d] Language developmental measure comprises of expressive and receptive subdomains. Motor developmental measure includes fine and gross motor subdomains.

group had lower mean cognitive compared to the control group: 93.9 ± 12.9 vs 100.1 ± 10.8; p = 0.042. Overall, the mean language composite score was low in this population (overall mean was 89.4 ± 12.3) (Table 3). In the total study population, zinc intake was positively associated with the language domain (r = 0.10; p = 0.042), while WAZ was positively associated with the motor (r = 0.10; p = 0.028) developmental domain, and while statistically significant the correlations were not strong (Table 4). In this cohort, iron intake was not significantly associated with any developmental domains. In the CHEU group we found that cognitive development was significantly positively correlated with WAZ (r = 0.15; p = 0.021) and LAZ (r = 0.35; p = 0.009), while motor development was significantly positively correlated with WAZ (r = 0.32; p = 0.007), LAZ (r = 0.26; p = 0.017), WLZ (r = 0.27; p = 0.044) and HCZ (r = 0.24; p = 0.021). In the abnormal UmA-RI group, the motor developmental domain was significantly positively correlated with the HCZ (r = 0.43; p = 0.038).

4. Discussion

4.1. Participants characteristics

The present study successfully investigated the overlooked population of CHEU infants who additionally had been exposed to placental insufficiency in utero, and found that comparative to their unaffected counterparts, these children had lower growth indices and were at risk of delayed neurodevelopmental outcomes. This was a low-risk population in terms of the pregnancy history, apart from the exposure to maternal HIV in the CHEU group. Over a third of CHUU who had IUGR (as measured by an abnormal UmA-RI) were born premature, this being a risk factor for suboptimal growth and development. At birth, children who had IUGR had relatively lower mean birthweights, which is a well-known contributing factor for further poor growth and development. The higher maternal age in the CHEU/AbN-RI group may also have

Table 4
Associations between different measurements and Bayley-III composite scores.

Measures	Cognitive developmental domain		Language developmental domain		Motor developmental domain	
	Association[a]	P-value[b]	Association[a]	P-value[b]	Association[a]	P-value[b]
Total study population						
Daily iron intake (mg)	0.05	0.472	0.05	0.973	0.02	0.777
Daily zinc intake (mg)	0.08	0.062	0.10	**0.042**	0.08	0.128
Daily iodine intake (mcg)	−0.02	0.944	−0.05	0.400	0.01	0.567
Weight-for-age z-score	0.04	0.426	−0.05	0.759	0.10	**0.028**
Length-for-age z-score	0.05	0.284	0.00	0.797	0.07	0.133
Weight-for-length z-score	0.02	0.756	−0.05	0.596	0.10	0.063
Head circumference-for-age z-score	0.03	0.928	0.00	0.974	0.09	0.137
CHUU group						
Daily iron intake (mg)	0.03	0.844	0.00	0.679	0.01	0.726
Daily zinc intake (mg)	0.06	0.174	0.05	0.093	0.06	0.153
Daily iodine intake (mcg)	−0.05	0.177	−0.06	0.130	0.04	0.530
Weight-for-age z-score	−0.04	0.598	−0.11	0.247	0.02	0.426
Length-for-age z-score	−0.04	0.789	−0.03	0.919	−0.01	0.821
Weight-for-length z-score	−0.04	0.627	−0.11	0.148	0.06	0.376
Head circumference-for-age z-score	−0.02	0.499	−0.03	0.614	0.03	0.776
CHEU group						
Daily iron intake (mg)	0.12	0.088	0.19	0.389	0.04	0.977
Daily zinc intake (mg)	0.18	0.019	0.22	0.190	0.10	0.549
Daily iodine intake (mcg)	0.13	0.796	0.02	0.410	−0.04	0.801
Weight-for-age z-score	0.15	**0.021**	0.04	0.196	0.32	**0.007**
Length-for-age z-score	0.35	**0.009**	0.07	0.510	0.26	**0.017**
Weight-for-length z-score	0.21	0.166	0.14	0.185	0.27	**0.044**
Head circumference-for-age z-score	0.32	0.359	0.12	0.429	0.24	**0.021**
Normal UmA-RI group						
Daily iron intake (mg)	0.07	0.125	0.04	0.766	0.00	0.745
Daily zinc intake (mg)	0.11	**0.035**	0.08	**0.044**	0.06	0.123
Daily iodine intake (mcg)	0.00	0.598	−0.08	0.241	0.01	0.746
Weight-for-age z-score	0.01	0.407	−0.06	0.707	0.07	0.129
Length-for-age z-score	0.01	0.747	−0.01	0.738	0.02	0.458
Weight-for-length z-score	0.01	0.993	−0.06	0.497	0.10	0.152
Head circumference-for-age z-score	−0.01	0.879	−0.01	0.811	0.04	0.441
Abnormal UmA-RI group						
Daily iron intake (mg)	−0.23	0.203	0.03	0.441	0.04	0.935
Daily zinc intake (mg)	−0.13	0.488	0.14	0.737	0.15	0.931
Daily iodine intake (mcg)	−0.10	0.630	0.16	0.435	0.09	0.894
Weight-for-age z-score	0.16	0.237	0.01	0.837	0.26	0.077
Length-for-age z-score	0.16	0.252	0.06	0.916	0.35	0.126
Weight-for-length z-score	0.11	0.367	0.02	0.737	0.17	0.121
Head circumference-for-age z-score	0.31	0.093	0.03	0.657	0.43	**0.038**

Notes: CHUU: children who are HIV-unexposed-uninfected; CHEU: children who are HIV-exposed-uninfected; mcg: microgram; mg: milligram; UmA-RI: umbilical artery resistance index.

[a] The Spearman's correlation measure was used. The correlation can be between −1 and +1 with stronger associations closer to the outer bounds (−1 and +1).

[b] The significance test was performed to determine if the association was significantly different from 0, if this was not the case then there was no significant association. The p-values that are <0.05 have significant associations, indicated in bold font.

impacted their growth outcomes as advanced maternal age has previously been related to childhood stunting [54].

4.2. Child feeding practices and micronutrient intake

The percentage of EBF in the first six months reported in HIV-exposed groups is better than the previously reported percentage of 37.0 % in South African women living with HIV and this may indicate the success of ART programs in protecting, supporting and promoting breastfeeding [55]. In this cohort, water was, on average, given to children from as early as four months, similar to the finding reported in a South African review [56]. Also, cow's milk was introduced to children from nine months. Although the WHO 2023 guideline for complementary feeding of infants and young children recommends an intake of animal milk for non-breastfed infants aged 6–11 months, cow's milk interferes with iron absorption due to the high calcium and casein contents, increasing the risk of iron deficiency anemia [57]. Protein-rich foods, crucial for a children's optimal growth, were introduced late in the CHEU/AbN-RI group, at eleven months, placing these children at even higher risk of suboptimal growth and health. In the present study, the dietary intake of iron and zinc were adequate, while the iodine intake was lower than the EAR. Iodine deficiency is the preventable cause of irreversible neurodevelopmental deficits in children [58]. Salt fortification with iodine is the most effective intervention for addressing iodine deficiency. In South Africa, iodization of table salt is mandatory, however, iodization of salt used in food production is voluntary [59]. Therefore, with increasing nutrition transition, the low intake of iodine in this study population may be due to the declining consumption of discretionary salt and increasing consumption of non-discretionary salt [60].

4.3. Child growth and neurodevelopment

In this cohort, the double exposure (CHEU/AbN-RI) group had suboptimal growth, as indicated by the lowest mean LAZ, WAZ, and HCZ, with stunting predominating at 18 months of age. Similar findings for CHEU were reported in previous studies in Ethiopia, Malawi and Uganda that determined the growth of children exposed to maternal HIV infection and ART [61–63], although IUGR caused by placental insufficiency was not examined as a covariate in these studies.

In general, the findings from GMCD screening showed a cause for concern in children in terms of the gross movement subdomain and that the CHEU/AbN-RI group was most affected (21.4 %). Similarly, CHEU/AbN-RI had lower mean cognitive than the control group on the Bayley test, however, all groups had mean composite scores almost at mid-average functioning in the three developmental domains, indicating optimal neurodevelopment. These findings were in line with the Sacchi et al. report that children who had IUGR had lower cognitive scores [64], as well as De Beer et al. who found that CHUU and CHEU had similar developmental outcomes [65]. Nonetheless, additional categorical analysis of the Bayley test revealed that 21.4 % of CHEU/AbN-RI had mild delays in the cognitive domain. Moreover, we observed that mild delay in the language domain was common across the groups. Similar findings on language delays in CHEU have been reported in South Africa [19,66], potentially linked to the fact that South Africa is a multilingual country. Other causes of developmental delays include preventable causes such as inadequate nutrition and lack of an adequate care environment and stimulation [67]. Our findings suggesting adequate neurodevelopment among CHEU and children who had IUGR were different to the previously reported neurodevelopmental outcomes of CHEU vs CHUU [20,22,23,66,68] and children with a history of abnormal Doppler [69–71].

4.4. Associations between different measurements and child neurodevelopment

Additionally, our study determined associations between several variables and three neurodevelopmental domains, although only weak positive associations were found, likely because childhood growth and development are multifactorial. Zinc intake was significantly associated with language development in the total study population, in line with previously reported positive associations between zinc and neurodevelopment [2]. Furthermore, we observed positive associations between growth parameters and cognitive and motor development in CHEU. Similarly, studies have shown that stunting is associated with poor cognitive development [2,72]. Also, associations between LAZ and motor development were reported in South African children [73].

This study investigated the growth and neurodevelopment of an overlooked at-risk population born with a history of placental insufficiency and exposure to maternal HIV infection, also taking into account their micronutrient intake. The once-off investigation at 18 months is a limitation of the study as we could not determine changes in growth and neurodevelopmental outcomes over time for our study population. Also, the small sample size of children who had placental insufficiency (abnormal UmA-RI cohort as a proxy for IUGR) was a drawback.

5. Conclusion

CHEU are at risk of suboptimal growth outcomes, particularly stunting, which are worse when HIV exposure is compounded by IUGR attributed to placental insufficiency, as measured by an abnormal UmA-RI in pregnancy. This group of children is furthermore at risk of deficits in cognitive development. The study findings advocate for the large-scale implementation of antenatal Doppler screening, including on low-risk pregnant mothers at the primary health care level, to identify fetuses at risk of IUGR, in order to implement strategies, including early nutritional intervention and follow-up care, to enhance catch-up growth and address cognitive delays, especially in geographical areas with high maternal HIV prevalence. Future research should include large-scale longitudinal studies for a better understanding of the growth and neurodevelopmental trajectories in this vulnerable population. Also, we recommend the determination of iron, zinc and iodine status of children.

Author contributions

Ute Feucht, Robert Pattinson, Helen Mulol and Marinel Hoffman: funding acquisition, project design and administration, supervision, reviewing and editing the manuscript. Helen Mulol and Mothusi Nyofane: data curation and validation. Tanita Botha: formal analysis and visualizations. Mothusi Nyofane: writing original draft and editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for the study was obtained from the University of Pretoria Faculty of Natural and Agricultural Sciences and Faculty of Health Sciences Ethics Committees with reference number: NAS259/2021. The study was conducted in accordance with the Declaration of Helsinki. Informed and written consent was obtained from all study participants.

Data availability

The datasets generated during and analyzed during the current study are available in the University of Pretoria repository, https://doi.org/10.25403/UPresearchdata.24754485.v1.

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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