South African Journal of Clinical Nutrition 2025; 38(4):173–181
https://doi.org/10.1080/16070658.2025.2538402

SAJCN
ISSN 1607-0658 EISSN 2221-1268

RESEARCH ARTICLE

Associations of maternal HIV infection, anaemia and placental insufficiency with neurodevelopment and anaemia in South African children: a cross-sectional study

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

[a]*Department of Consumer and Food Sciences, University of Pretoria, Pretoria, South Africa*
[b]*Department of Nutrition, National University of Lesotho, Maseru, Lesotho*
[c]*Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies, University of Pretoria, Kalafong Provincial Tertiary Hospital, Pretoria, South Africa*
[d]*Maternal and Infant Health Care Strategies Unit, South African Medical Research Council, Pretoria, South Africa*
[e]*Department of Pediatrics, University of Pretoria, Pretoria, South Africa*
[f]*Biostatistics Research Unit, South African Medical Research Council, Pretoria, South Africa*
[g]*Department of Obstetrics and Gynecology, University of Pretoria, Pretoria, South Africa*
**Correspondence: mothusi.nyofane@tuks.co.za*

Objective: To determine associations between maternal anaemia and child neurodevelopment and anaemia among 18-month-old children exposed to maternal HIV infection and placental insufficiency.
Design: A cross-sectional study was conducted. Placental insufficiency was detected by an abnormal umbilical artery resistance index (UmA-RI) on Doppler ultrasound during gestation.
Setting: Kalafong Provincial Tertiary Hospital.
Subjects: In total, 260 mother–child pairs grouped into HIV-unexposed-uninfected children (CHUU): $n = 198$ vs. HIV-exposed-uninfected children (CHEU): $n = 62$, and normal UmA-RI (N-RI): $n = 225$ vs. abnormal UmA-RI (AbN-RI): $n = 35$ were investigated. Also, CHUU/N-RI (control): $n = 178$ was compared with CHEU/AbN-RI (dual exposure): $n = 15$.
Outcome measures: Haemoglobin concentrations were tested using the HemoCue® Hb 201$^+$. Bayley-III assessed children's cognitive, motor, and language development at the corrected age.
Results: More than one-third of children across the groups were mildly anaemic. Some 25.7% of mothers in AbN-RI group were mildly anaemic, significantly more than the N-RI mothers (9.8%); $p = 0.027$. In the CHEU group, maternal haemoglobin concentrations were associated with child haemoglobin concentrations: $\beta = 0.19$, 95% confidence interval (CI) (0.02,0.36); $p = 0.028$. The AbN-RI group had significantly lower mean cognitive composite scores compared with the N-RI group: 96.4 ± 12.2 vs. 100.0 ± 10.5; $p = 0.017$. Significantly lower mean cognitive scores were observed in CHEU/AbN-RI compared with CHUU/N-RI: 93.9 ± 12.9 vs. 100.0 ± 10.6; $p < 0.001$. There was no evidence to suggest an association between haemoglobin concentration and child neurodevelopment; however, in CHEU, cognitive development was associated with LAZ: $\beta = 3.34$, 95% CI (1.13,5.54), $p = 0.004$.
Conclusions: Child health and nutrition-sensitive programmes need to prioritize CHEU and children with placental insufficiency as at-risk groups for cognitive delays.

Keywords: maternal HIV-exposure, anaemia, placental insufficiency, neurodevelopment

Introduction

Anaemia is a primary global health concern, particularly affecting women and young children. Globally, it affects 30.0% of women of childbearing age, 37.0% of pregnant women, and 40.0% of young children.[1,2] Low- and middle-income countries (LMICs) are heavily affected, with 106 million women and 103 million children being anaemic in Africa.[2] In South Africa, the prevalence of anaemia in women and children has been reported as 28.1% and 61.3%, respectively.[3,4] It has been associated with impaired physical health, stunting, and delayed neurodevelopment in 6- to 24-month-old children.[1,4,5]

Nutrient deficiencies including vitamin A, B_{12}, C, iron, and folate, resulting from inadequate diet, are causes of nutritional anaemia. In South Africa, iron deficiency is a common nutritional cause of anaemia.[3,6] Other risk factors of anaemia include infections such as HIV and tuberculosis, which cause anaemia of chronic diseases, as well as side effects of therapy.[7]

Nutrient deficiencies are most common in people living with HIV as they are prone to food and nutrition insecurity. South Africa is a country highly burdened by HIV infection, particularly among women and girls (53.0%).[4] Estimates showed that 30.0% of South African pregnant women are living with HIV, with an anaemia prevalence of 60.6% to 71.3%.[4,8] Nonetheless, these women give birth to HIV-free infants due to the successes of the prevention of vertical transmission of HIV programmes.[9,10] Notwithstanding the fact that the population of HIV-free children born to women living with HIV, referred to as children who are HIV-exposed-uninfected (CHEU), are classified as at-risk for inadequate nutrition, poor growth, and neurodevelopment. Delicio et al.[11] reported a significant prevalence of anaemia (25.7%) in CHEU in Brazil.

Another factor affecting child neurodevelopment and growth is placental insufficiency. Placental insufficiency is one of the immediate causes of intrauterine growth restriction (IUGR) and can be detected by an abnormal umbilical artery resistance index (UmA-RI) on Doppler ultrasound during pregnancy.[12] Lower neurodevelopmental scores have previously been described in children with a history of IUGR.[13,14] Child neurodevelopment is a public health concern; estimates are that over one-third of children aged under five years are at risk of not attaining their full developmental potential, particularly in LMICs.[15] Placental insufficiency may additionally expose children to anaemia.

It is of great importance to better understand the associations between maternal and child anaemia and neurodevelopmental outcomes of children who had placental insufficiency in the context of high maternal HIV prevalence in the LMIC setting.

Materials and methods

Study setting, design, and population

The study is a follow-up to the South African arm of the Umbiflow International study that determined the prevalence of abnormal UmA-RIs as a marker for placental insufficiency in unselected, low-risk obstetric populations at 28–34 weeks' gestation in Ghana, India, Kenya, Rwanda, and South Africa.[16] Abnormal UmA-RIs were defined as resistance indices ≥ 75th centile-for-gestational age, previously described to indicate a high risk of suboptimal clinical outcomes, including stillbirths and lower birthweights-for-gestational age, linked to placental insufficiency.[17] To expand the study population of children with both placental insufficiency and maternal HIV exposure, the present study also enrolled participants from the Siyakhula study, which longitudinally investigated growth and neurodevelopment in CHEU from birth to two years, in the same geographical area, population, and with similar procedures.[18]

The cross-sectional UmbiGodisa study was conducted in 2021 among 18-month-old CHEU and HIV-unexposed-uninfected children (CHUU) with normal or abnormal UmA-RI, with available pregnancy and birth data, at the University of Pretoria's Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies at Kalafong Provincial Tertiary Hospital. Children with chromosomal or structural abnormalities or other severe medical conditions known to impact child neurodevelopment were excluded. The anticipated sample was 311 from the Umbiflow International study. However, 46 participants did not attend the planned study visit, two participants subsequently withdrew, and two children had severe medical conditions. A total of 271 participants were recruited, including 10 participants from the Siyakhula study. Eleven participants were excluded from the current analysis, as they had incomplete questionnaires ($n = 4$), had an obvious developmental disability ($n = 1$), had acute medical conditions resulting in an inadequately alert state ($n = 2$), or had missing haemoglobin concentrations as they were not tested due to the temporary malfunctioning of the instrument on the day of their study visit ($n = 4$). We therefore investigated 260 mother–child pairs, grouped based on HIV-exposure status (CHUU: $n = 198$; CHEU: $n = 62$) and normal ($n = 225$) or abnormal UmA-RI ($n = 35$) during pregnancy. In further analysis, the grouping was as follows: CHUU with normal UmA-RI (CHUU/N-RI; control group; $n = 178$), CHEU with normal UmA-RI (CHEU/N-RI; single exposure; $n = 47$), CHUU with abnormal UmA-RI (CHUU/AbN-RI; single exposure; $n = 20$) and CHEU with abnormal UmA-RI (CHEU/AbN-RI; dual exposure; $n = 15$).

Questionnaires

The face-to-face maternal interviews were conducted by trained study staff in either English or local languages, using structured and previously used questionnaires to collect maternal and child sociodemographic data and medical history, as well as descriptive quantitative breastfeeding data over the first 18 months of life, which was based on maternal recall.

Measurements

The haemoglobin concentration is used as an indicator of anaemia and by proxy for iron deficiency, with anaemia defined by the World Health Organization (WHO) as a haemoglobin concentration of <11 g/dL in children aged 6–59 months and <12 g/dL in non-pregnant women.[19] Maternal and child haemoglobin concentrations were measured using the HemoCue® Hb 201$^+$ System Analyzer (https://hemocue.com/en/products/hematology/hemocue-hb-201plus-system/). About 10 µL of blood was drawn using a HemoCue sterile safety lancet (2.25 mm depth) and Hb 201 micro cuvettes. This system has been reported to be the standard haemoglobin point-of-care test, which provides laboratory accuracy for determining haemoglobin in whole blood with a measuring range of 0–25.6 g/dL and delivers results within 1 minute.[20] Further, the system is easy to use and has outstanding lot-to-lot reproducibility. The International Council for Standardization in Hematology (ICSH) calibrates it from the factory for determining haemoglobin.[18,20]

Child neurodevelopment outcomes were measured using the Bayley Scales of Infant and Toddler Development™ third edition (Bayley-III), which is a standardized and well-accepted tool for developmental assessment of children aged 1–42 months and assesses children in terms of cognitive, motor, and language domains.[21] The Bayley-III assessment was conducted at the corrected age, with the motor domain including the fine and gross motor domains and expressive and receptive language included in the language domain.

The anthropometric measurements of the mother–child pairs were performed following standardized WHO procedures.[22] Two trained assessors carried out measurements two consecutive times, and if the measurements were similar the mean value was recorded.[23] A third measurement was done if two measurements differed by 0.5 cm or 0.05 kg. There were missing anthropometric measurements for seven mothers because of repeat pregnancies ($n = 5$) or because children were brought by the caregivers ($n = 2$).

Data processing and statistical analyses

Data were managed and independently double-entered on the online electronic platform, Research Electronic Data Capture (REDCap) v9.3.5 (https://project-redcap.org/). Missing or inaccurate data were dealt with immediately upon completing the interviews. The study classified the haemoglobin concentration into the following categories for children: severe anaemia (< 7.0 g/dL); moderate anaemia (7.0–9.9 g/dL); mild anaemia (10.0–10.9 g/dL) and normal (≥ 11.0 g/dL). Haemoglobin concentration classification for non-pregnant women was as follows: severe anaemia (< 8.0 g/dL); moderate anaemia (8.0–10.9 g/dL); mild anaemia (11.0–11.9 g/dL) and normal (≥ 12.0 g/dL).[7]

Bayley-III composite scores were defined as 100 for mid-average functioning, < 85 for mild impairment, < 70 for moderate impairment and < 55 for severe impairment. Maternal body mass index (BMI) was computed, with subsequent classification as follows: underweight: < 18.5 kg/m^2; normal: 18.5–24.9 kg/m^2; overweight: 25–29.9 kg/m^2; obese: ≥ 30 kg/m^2. The child birth anthropometric z-scores were computed using the INTERGROWTH-21st Newborn Size tool (International Fetal and Newborn Growth Consortium for the 21st Century, Oxford, UK), and the WHO Anthro Survey Analyzer (https://www.who.int/tools/child-growth-standards/software) was used to compute childhood z-scores: weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), head circumference-for-age (HCZ), and mid-upper arm circumference-for-age (MUACZ). Premature births were corrected for age. The study utilized WHO guidelines to define stunting, underweight, wasting, and moderate acute malnutrition as LAZ, WAZ, WLZ, and MUACZ < −2 SD. The z-scores < −3 were classified as a severe condition. The anthropometrical z-scores outside the range of the reference population (<−3 and >+3) were reviewed and corrected in the event of an error in data capturing.

R statistical software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria) was used for descriptive statistical analysis. The variables were assessed for normality using the Shapiro–Wilk test. Frequencies and percentages were reported for categorical data and significances were determined using the chi-square test, and Fisher's exact test as an alternative where group counts were less than five. For continuous data, means and standard deviations were reported and significances were determined using the independent t-test. Associations were determined using univariable and multivariable linear regression models. Multivariable models were adjusted for UmA-RI status, maternal HIV status, sex, LAZ, and WLZ. The *p*-values < 0.05 were considered to be statistically significant.

Ethical considerations

Ethical approvals were obtained from the Faculty of Natural and Agricultural Sciences and Faculty of Health Sciences Ethics Committees with ethics reference numbers NAS259/2021 and 283/2019, respectively, in accordance with Declaration of Helsinki guidelines. Participants were given relevant information concerning the follow-up study, and participation was voluntary. Mothers provided consent on behalf of themselves and their infants. There were minimal risks for participation in the study. Mothers were reimbursed for transport costs and given light refreshments.

Results

Baseline characteristics

A total of 260 mother/caregiver–child pairs participated in this study, and their baseline characteristics are presented in Table 1. In terms of the birth outcomes, we observed that the percentage of premature births was significantly higher among children who had abnormal UmA-RI (AbN-RI), as a marker for placental insufficiency (22.9%), in comparison with their normal UmA-RI (N-RI) counterparts (7.1%); $p = 0.007$. Also, children who had AbN-RI had significantly lower mean length ($p = 0.049$) and mean head circumference (HC) at birth ($p = 0.034$) than N-RI children. Furthermore, CHEU had a lower mean birth length ($p = 0.037$) and birthweight z-score ($p = 0.031$) than CHUU.

For the feeding practices during the first six months, percentages of exclusive breastfeeding were significantly higher in CHEU than in CHUU (43.5% vs. 34.3%; $p = 0.004$) and in children who had AbN-RI than in N-RI children (42.9% vs. 36.0%; $p = 0.015$). More than 50% of CHUU and N-RI children were mixed-fed. Current or continued breastfeeding was found in 26.8% of CHUU and 11.3% in CHEU; $p = 0.038$. When comparing maternal factors between the groups, it was observed that mothers of CHEU ($p = 0.004$) and children who had AbN-RI ($p = 0.015$) were significantly older than their counterparts.

Haemoglobin concentrations and Bayley-III developmental composite scores

Table 2 presents the findings on child anthropometric outcomes, maternal and child haemoglobin, and Bayley-III findings between the CHUU vs. CHEU as well as the N-RI vs. AbN-RI groups. The comparisons between groups indicated significantly lower LAZ among CHEU vs. CHUU (−0.7 ± 1.2 vs. −0.1 ± 1.3; $p = 0.014$) and in children who had AbN-RI vs. N-RI children (−0.7 ± 1.5 vs. −0.1 ± 1.3; $p = 0.020$). Significantly lower cognitive composite scores were observed among children who had AbN-RI when compared with their N-RI counterparts: 96.4 ± 12.2 vs. 100.0 ± 10.5; $p = 0.017$. More than a third of children across the compared groups presented with mild anaemia, while around one-quarter (25.7%) of mothers of AbN-RI children were mildly anaemic when compared with mothers of N-RI children (9.8%); $p = 0.027$.

Further analysis included participants grouped into CHUU/N-RI, CHEU/N-RI, CHUU/AbN-RI,and CHEU/AbN-RI. Table 3 presents child anthropometric outcomes, indices, haemoglobin, and neurodevelopmental findings among CHUU/N-RI (control) vs. CHEU/AbN-RI (dual exposure) groups. Results on anthropometric measurements and indices showed that the CHEU/AbN-RI (dual exposure) group had lower anthropometric measurements and z-scores than the control group. Findings of the Bayley-III test demonstrated that CHEU/AbN-RI had a significantly lower mean cognitive composite score than the control group (93.9 ± 12.9 vs. 100.0 ± 10.6; $p < 0.001$). About 44.7% of CHEU/N-RI and 40.0% of CHUU/AbN-RI were mildly anaemic.

No statistically significant differences existed between the mean child haemoglobin values and haemoglobin classifications when comparing the exposure groups with the control group. However, CHUU/AbN-RI had a mean haemoglobin value of 10.9 ± 1.4 g/dL, indicating mild anaemia in these children. Mothers of CHEU/AbN-RI had significantly lower mean haemoglobin concentrations than mothers of CHUU/N-RI (12.0 ± 1.3 vs. 12.8 ± 1.5; $p = 0.024$). The findings on the maternal haemoglobin classification differences between the control and dual exposure groups were not statistically significant.

However, it was observed that more mothers of CHEU/AbN-RI were mildly (20.0%) or moderately anaemic (20.0%), compared with mothers of the control group (9.6% and 12.4%, respectively). Further comparative analysis showed that a significantly higher percentage (30.0%) of mothers of CHUU/AbN-RI were mildly anaemic compared with control group mothers (9.1%); $p = 0.020$. Also, mothers of CHEU/N-RI had significantly lower mean haemoglobin values than their counterparts in the control group: 12.4 ± 1.7 g/dL vs. 12.8 ± 1.5 g/dL; $p = 0.022$, and more (21.7%) of these mothers were moderately anaemic compared with mothers in the control group (12.0%), although this was not statistically significant.

Table 1: Participants' baseline characteristics and birth information based on HIV exposure and normal or abnormal umbilical artery resistance index

Variables	CHUU	CHEU	*p*-value	N-RI	AbN-RI	*p*-value
Sample size (*n*)	198	62		225	35	
Child factors:						
Child age (months), mean ± SD	18.5 ± 0.8	18.6 ± 0.8	0.180	18.6 ± 0.9	18.5 ± 0.7	0.930
Child sex: Female, *n* (%)	101 (51.0)	33 (53.2)	0.770	114 (50.7)	20 (57.1)	0.590
Premature birth, *n* (%)	20 (10.1)	4 (6.5)	0.460	16 (7.1)	8 (22.9)	**0.007**
GA at birth (weeks), mean ± SD	39.0 ± 2.0	39.2 ± 1.7	0.720	39.2 ± 1.8	38.3 ± 2.5	**0.045**
Birthweight (g), mean ± SD	3073 ± 482	3183 ± 558	0.090	3107 ± 469	3048 ± 682	0.860
Birth length (cm), mean ± SD	50.4 ± 3.1	49.6 ± 2.3	**0.037**	50.4 ± 2.9	49.2 ± 3.1	**0.049**
Birth HC (cm), mean ± SD	34.3 ± 1.7	34.3 ± 1.5	0.780	34.4 ± 1.6	33.5 ± 2.2	**0.034**
Birthweight z-score, mean ± SD	−0.4 ± 1.1	−0.7 ± 1.0	**0.031**	−0.4 ± 1.1	−0.7 ± 1.0	0.420
Birth length z-score, mean ± SD	0.6 ± 1.6	0.2 ± 1.3	0.058	0.5 ± 1.6	0.5 ± 1.2	0.150
Birth HC z-score, mean ± SD	0.4 ± 1.3	0.3 ± 1.2	0.440	0.4 ± 1.3	0.4 ± 1.0	0.240
Child received multivitamins or supplements, n (%)	42 (21.2)	9 (14.5)	0.350	47 (20.9)	4 (11.4)	0.300
The child was ever breastfed, n (%)	190 (96.0)	59 (95.2)	0.730	214 (95.1)	35 (100.0)	0.370
Infant feeding from birth to 6 months, *n* (%)			**0.004**			**0.015**
EBF	68 (34.3)	27 (43.5)		81 (36.0)	15 (42.9)	
Formula feeding	10 (5.1)	4 (6.6)		14 (6.2)	0 (0.0)	
Mixed feeding	112 (56.6)	20 (32.3)		118 (52.4)	14 (40.0)	
Formula feeding but previously EBF	8 (4.0)	11 (17.7)		12 (5.3)	6 (17.1)	
Continued breastfeeding	53 (26.8)	7 (11.3)	**0.038**	53 (23.6)	7 (20.0)	0.900
Maternal factors at 18 months postpartum:						
Age (years), mean ± SD	30.0 ± 5.1	32.5 ± 5.8	**0.004**	30.3 ± 5.2	32.1 ± 6.5	**0.015**
UmA-RI z-score, mean ± SD	0.2 ± 0.9	0.3 ± 1.0	0.320	0.0 ± 0.6	1.7 ± 0.8	**0.012**
Gravidity, median [IQR]	2 [2, 3]	3 [2, 3]	0.054	2 [2, 3]	2 [2, 3]	0.770
Parity, median [IQR]	2 [1, 3]	2 [2, 3]	**0.040**	2 [2, 3]	2 [2, 3]	0.830
Previous pregnancy losses, n (%)	40 (20.2)	19 (30.6)	0.110	54 (24.0)	5 (14.3)	0.440
Weight (kg), mean ± SD [a]	76.9 ± 19.8	75.6 ± 23.9	0.430	78.1 ± 20.8	67.1 ± 18.1	**0.002**
Height (cm), mean ± SD [a]	159.9 ± 6.1	161.3 ± 8.1	0.200	160.6 ± 6.8	158.0 ± 5.2	0.090
BMI (kg/m^2), mean ± SD [a]	30.1 ± 7.7	28.8 ± 8.1	0.470	30.3 ± 7.9	26.8 ± 6.5	**0.009**
MUAC (cm), mean ± SD [a]	32.0 ± 5.0	31.1 ± 5.7	0.530	32.1 ± 5.2	29.6 ± 4.6	**0.009**
Iron supplementation [b], *n* (%)	24 (12.1)	24 (38.7)	< **0.001**	34 (15.1)	10 (28.6)	0.096
Folic acid supplementation [c], n (%)	18 (9.1)	19 (30.6)	< **0.001**	27 (12.0)	10 (28.6)	**0.022**
Maternal TB status, *n* (%):			0.410			0.580
Previously had TB	2 (1.0)	2 (3.2)		4 (1.8)	0 (0.0)	
Never had TB	187 (94.4)	53 (85.5)		208 (92.4)	32 (91.4)	
Unknown	9 (4.6)	7 (11.3)		13 (5.8)	3 (8.6)	
Latest CD4 count (cells/mm^3), mean ± SD	n/a	429 ± 294	n/a	455 ± 311	336 ± 232	0.510
Latest viral load (copies/mL),median [IQR]	n/a	0 [0, 0]	n/a	0 [0, 0]	0 [0, 0]	0.540
Drinks alcohol [d], *n* (%)	51 (25.8)	16 (25.8)	> 0.999	65 (28.9)	2 (5.7)	**0.008**
Smokes cigarettes[e], *n* (%)	4 (2.0)	2 (3.2)	0.950	6 (2.7)	0 (0.0)	0.720
Marital status, *n* (%)			0.490			0.260
Single	82 (41.4)	23 (37.1)		95 (42.2)	10 (28.6)	
Married/cohabiting	116 (58.6)	39 (62.9)		130 (57.8)	25 (71.4)	
Education level, *n* (%)			0.570			0.310
Any primary level	19 (9.6)	5 (8.1)		22 (9.8)	2 (5.7)	
Any secondary level	133 (67.2)	46 (74.2)		151 (67.1)	28 (80.0)	
Any tertiary level	46 (23.2)	11 (17.7)		52 (23.1)	5 (14.3)	
Employment status, *n* (%)			0.880			> 0.999
Any employment	79 (39.9)	24 (38.7)		89 (39.6)	14 (40.0)	
Unemployed	119 (60.1)	38 (61.3)		136 (60.4)	21 (60.0)	

Abbreviations: AbN-RI: abnormal umbilical artery resistance index; BMI: body mass index; CHUU: HIV-unexposed-uninfected children; CHEU: HIV-exposed-uninfected children; cm: centimetre; EBF: exclusive breastfeeding; HC: head circumference; IQR: interquartile range; GA: gestational age; kg: kilogram; n/a: not applicable; N-RI: normal umbilical artery resistance index; MUAC: mid-upper arm circumference; SD: standard deviation; TB: tuberculosis.

Notes: A *p*-value less than 0.05 indicates that the results were statistically significant, and such *p*-values are in bold.

[a]Anthropometry measurements were carried out on 253 mothers: CHUU: $n = 192$; CHEU: $n = 61$; N-RI: $n = 219$; and AbN-RI: $n = 34$. [b]Antenatal supplementation of iron supplements. [c]Antenatal supplementation of folic acid. [d]Question asked: Since your baby was born, did you drink alcohol? [e]Question asked: Since your baby was born, did you smoke cigarettes?

Table 2: Comparisons of gestational age-corrected anthropometry and Bayley-III mean composite scores as well as haemoglobin concentrations in HIV-exposed vs. HIV-unexposed children and children with normal vs. abnormal umbilical artery resistance index in utero, and their mothers

Measures, mean ± SD	CHUU	CHEU	*p*-value	N-RI	AbN-RI	*p*-value
Sample size (*n*)	198	62		225	35	
Children's anthropometric measurements and indices						
Weight (kg)	10.9 ± 1.6	10.5 ± 1.7	0.130	10.8 ± 1.6	10.4 ± 1.7	**0.045**
Length (cm)	81.8 ± 3.8	80.2 ± 3.4	**0.023**	81.7 ± 3.7	79.8 ± 4.1	**0.006**
MUAC (cm)	16.1 ± 1.5	16.2 ± 1.6	0.900	16.1 ± 1.5	16.2 ± 1.6	0.740
HC (cm)	48.1 ± 1.6	47.9 ± 1.8	0.240	48.1 ± 1.7	47.9 ± 1.7	0.460
Weight-for-age z-score	0.0 ± 1.2	−0.2 ± 1.3	0.170	0.0 ± 1.2	−0.3 ± 1.3	0.110
Length-for-age z-score	−0.1 ± 1.3	−0.7 ± 1.2	**0.014**	−0.1 ± 1.3	−0.7 ± 1.5	**0.020**
Weight-for-length z-score	0.1 ± 1.2	0.1 ± 1.3	0.950	0.1 ± 1.3	0.0 ± 1.1	0.770
MUAC-for-age z-score	1.1 ± 1.1	1.1 ± 1.2	0.790	1.1 ± 1.1	1.2 ± 1.2	0.570
HC-for-age z-score	0.9 ± 1.2	0.7 ± 1.2	0.230	0.9 ± 1.2	0.8 ± 1.3	0.700
Children's Bayley composite scores, mean ± SD						
Cognitive development	99.8 ± 10.7	98.5 ± 11.1	0.910	100.0 ± 10.5	96.4 ± 12.2	**0.017**
Language development	89.5 ± 12.2	88.8 ± 12.4	0.120	89.1 ± 12.2	90.7 ± 12.8	0.660
Motor development	99.7 ± 11.7	98.4 ± 13.5	0.180	99.7 ± 12.0	96.9 ± 12.6	0.530
Children's haemoglobin concentration and classification						
Haemoglobin value (g/dL)	11.0 ± 1.2	11.0 ± 1.1	0.800	11.0 ± 1.2	11.0 ± 1.3	0.170
Haemoglobin level classification, *n* (%)						
Normal haemoglobin concentration (≥ 11.0 g/dL)	100 (50.5)	33 (53.2)	0.920	115 (51.1)	18 (51.4)	0.210
Mild anaemia (10.0–10.9 g/dL)	87 (43.9)	26 (41.9)		100 (44.4)	13 (37.1)	
Moderate anaemia (7.0–9.9 g/dL)	11 (5.6)	3 (4.8)		10 (4.4)	4 (11.4)	
Maternal haemoglobin concentration and classification						
Haemoglobin value (g/dL)	12.8 ± 1.5	12.3 ± 1.6	0.081	12.7 ± 1.5	12.4 ± 1.4	0.430
Haemoglobin level classification, *n* (%)						
Normal haemoglobin concentration (≥ 12.0 g/dL)	152 (76.8)	40 (64.5)	0.100	171 (76.0)	21 (60.0)	**0.027**
Mild anaemia (11.0–11.9 g/dL)	22 (11.1)	9 (14.5)		22 (9.8)	9 (25.7)	
Moderate anaemia (8.0–10.9 g/dL)	24 (12.1)	13 (21.0)		32 (14.2)	5 (14.3)	

Abbreviations: AbN-RI: abnormal umbilical artery resistance index; CHUU: HIV-unexposed-uninfected children; CHEU: HIV-exposed-uninfected children; g/dL: grams per decilitre; HC: head circumference; MUAC: mid-upper arm circumference; N-RI: normal umbilical artery resistance index; SD: standard deviation.
Note: A *p*-value less than 0.05 indicates that results were statistically significant, and such *p*-values are in bold.

Association between maternal and child haemoglobin concentration and child neurodevelopment

In univariable regression analysis of the total population, maternal haemoglobin was not significantly associated with child haemoglobin (β = 0.08 [95% confidence interval (CI): −0.02,0.17]; $p = 0.113$), but further analysis showed that in the CHEU group, a significant association was found (β = 0.19 [0.02,0.36]; $p = 0.028$). This significant association remained on multivariable regression analysis, adjusted for umbilical artery resistance index status, maternal HIV status, sex, LAZ, and WLZ (β = 0.19 [0.01,0.37]; $p = 0.035$).

In univariable and multivariable regression analysis, we found no indications to suggest an association between the child or maternal haemoglobin and child neurodevelopment. In particular, we observed no evidence of the association between haemoglobin concentration and cognitive development in the AbN-RI and CHEU/AbN-RI groups. As a result, we further determined the association between child neurodevelopment, LAZ, and stunting. In the CHEU group, the univariable and multivariable regression analysis indicated a significant positive association between cognitive and motor development and increasing LAZ, and a significant negative association between cognitive development and stunting (Table 4 and Table 5).

Discussion

Our study aimed to determine an association between maternal/child haemoglobin levels, exposure to maternal HIV infection, and placental insufficiency in utero and child neurodevelopment. Findings indicated lower cognitive scores among children with a history of placental insufficiency, a leading cause of IUGR, and even lower cognitive scores in the dual exposure group (CHEU/AbN-RI). However, there was no evidence that lower cognitive scores were associated with either child or maternal haemoglobin.

Nearly a quarter of children who had AbN-RI were born prematurely; a similar finding has previously been reported.[24] The high number of premature births may be attributed to the fact that, once the clinicians had identified the abnormal Doppler, the mothers were referred for obstetric management, and if the risk of stillbirth was deemed to be too high then the pregnancy was delivered. Many of these premature births were therefore iatrogenic.

Regarding breastfeeding practices, a high percentage of CHEU and children who had AbN-RI were reported to be exclusively breastfed during the first six months of life. In children who had AbN-RI, a high percentage of exclusive breastfeeding may be due to the fact that many of these children were born prematurely, and their mothers were counselled and supported on breastfeeding through the Kangaroo Mother Care programme

Table 3: Gestational age-corrected anthropometry and Bayley-III composite scores as well as haemoglobin concentrations and classifications at the 18-month study visit: control vs. dual exposure infant groups, as well as their mothers

Measures, mean ± SD	CHUU/N-RI (control)	CHEU/AbN- RI (dual exposure)	*p*-value
Sample size (*n*)	178	15	
Children's anthropometric measurements and indices			
Weight (kg)	10.9 ± 1.6	9.9 ± 1.0	**0.009**
Length (cm)	81.9 ± 3.8	78.2 ± 3.5	**0.017**
MUAC (cm)	16.1 ± 1.4	16.0 ± 1.4	0.540
HC (cm)	48.1 ± 1.6	47.1 ± 1.2	**0.011**
Weight-for-age z-score	0.0 ± 1.2	−0.6 ± 0.9	**0.019**
Length-for-age z-score	−0.1 ± 1.3	−1.3 ± 1.3	**0.001**
Weight-for-length z-score	0.1 ± 1.2	0.0 ± 0.8	0.800
MUAC-for-age z-score	1.1 ± 1.1	1.0 ± 1.0	0.330
HC-for-age z-score	0.9 ± 1.2	0.3 ± 0.7	**0.020**
Maternal anthropometric measurements			
Age (years)	30.1 ± 5.1	36.6 ± 6.1	**<0.001**
Weight (kg)	77.5 ± 19.7	63.1 ± 15.4	**0.004**
Height (cm)	160.1 ± 6.2	158.3 ± 5.3	0.490
BMI (kg/m^2)	30.3 ± 7.7	25.1 ± 5.2	**0.009**
MUAC (cm)	32.0 ± 5.1	28.0 ± 4.0	**0.003**
Children's Bayley composite scores			
Cognitive development	100.0 ± 10.6	93.9 ± 12.9	**<0.001**
Language development	89.4 ± 12.4	90.9 ± 15.8	0.250
Motor development	99.9 ± 11.7	95.6 ± 14.2	0.230
Children's haemoglobin concentration and classification			
Haemoglobin value (g/dL)	11.0 ± 1.2	11.1 ± 1.1	0.350
Haemoglobin level classification, *n* (%)			0.690
Normal haemoglobin concentration (≥ 11.0 g/ dL)	91 (51.1)	9 (60.0)	
Mild anaemia (10.0–10.9 g/dL)	79 (44.4)	5 (33.3)	
Moderate anaemia (7.0–9.9 g/dL)	8 (4.5)	1 (6.7)	
Maternal haemoglobin concentration and classification			
Haemoglobin value (g/dL)	12.8 ± 1.5	12.0 ± 1.3	**0.024**
Haemoglobin level classification, *n* (%)			0.230
Normal haemoglobin concentration (≥ 12.0 g/dL)	139 (78.0)	9 (60.0)	
Mild anaemia (11.0–11.9 g/dL)	17 (9.6)	3 (20.0)	
Moderate anaemia (8.0–10.9 g/dL)	22 (12.4)	3 (20.0)	

Abbreviations: AbN-RI: abnormal umbilical artery resistance index; BMI: body mass index; CHEU: HIV-exposed-uninfected children; CHUU: HIV-unexposed-uninfected children; cm: centimetre; HC: head circumference; kg: kilogram; MUAC: mid-upper arm circumference; N-RI: normal umbilical artery resistance index; g/dL: gramd per decilitre; SD: standard deviation.
Note: A *p*-value less than 0.05 indicates that results were statistically significant, and such *p*-values are in bold.

in the local geographic area. The high percentage of exclusive breastfeeding in CHEU on the other hand may be attributed to the success in the promotion of breastfeeding in the context of HIV.[25,26] Furthermore, a similar high percentage of exclusive breastfeeding has recently been reported in South African CHEU.[27] On the other hand, current or continued breastfeeding percentages were low in all groups, despite the known importance of promoting growth and development during the critical period of transitioning from exclusive breastfeeding to complementary feeding.[27]

Across all the groups, the reported percentage of mothers who received antenatal iron and folic acid supplementation was very low. Nonetheless, a significant percentage of mothers of CHEU had antenatal iron and folic acid supplementation. Micronutrient deficiencies, including iron deficiency, are known to be common in pregnant women living with HIV due to increased requirements as a result of pregnancy and HIV infection. Still, irrespective of maternal HIV status, all pregnant women should be given nutrient supplementations as a standard of care for prevention and treatment.[28]

The study found that there were no statistical significances in terms of haemoglobin levels (except for mothers of CHEU/AbN-RI vs. CHUU/N-RI) and classification between groups for mothers (except for mothers in N-RI vs. AbN-RI groups) and their children. Observations were that, across the groups, mothers and children had mean haemoglobin values on or above the standard cut-off values except for CHUU/AbN-RI children, who were mildly anaemic. Also, above a quarter of mothers of AbN-RI were mildly anaemic. These findings of mild anaemia in children who had AbN-RI and their mothers were in line with the literature that maternal anaemia is related to the occurrence of childhood anaemia.[29] Another

Table 4: Univariable linear regression findings for the association between child LAZ and stunting and Bayley-III composite scores at 18 months

	LAZ		Stunting	
Item	**Univariable model β (95% CI)**	*p*-value	**Univariable model β (95% CI)**	*p*-value
Total population:				
Cognitive domain	0.67 (−0.33,1.67)	0.190	−6.15 (−10.75,−1.55)	**0.009**
Language domain	0.30 (−0.84,1.44)	0.608	−2.83 (−8.10,2.43)	0.290
Motor domain	0.57 (−0.09,2.16)	0.072	−7.26 (−12.43,−2.10)	**0.006**
CHUU:				
Cognitive domain	−0.13 (−1.29,1.03)	0.830	−1.92 (−8.83,4.99)	0.585
Language domain	0.13 (−1.18,1.44)	0.840	−0.34 (−8.16,7.48)	0.931
Motor domain	0.21 (−1.05,1.47)	0.739	−2.23 (−9.74,5.28)	0.559
CHEU:				
Cognitive domain	3.34 (1.13,5.54)	**0.004**	−9.10 (−16.78,−3.20)	**0.005**
Language domain	0.82 (−1.84,3.47)	0.541	−4.87 (−12.95,3.20)	0.232
Motor domain	3.53 (0.80,6.26)	**0.012**	−10.64 (−19.04,−2.23)	**0.014**
N-RI:				
Cognitive domain	0.32 (−0.77,1.42)	0.560	−6.05 (−11.55,−0.55)	**0.031**
Language domain	0.40 (−0.86,1.66)	0.531	−2.51 (−8.92,3.91)	0.442
Motor domain	0.68 (−0.57,1.93)	0.284	−6.74 (−13.05,−0.44)	**0.036**
AbN-RI:				
Cognitive domain	1.60 (−1.19,4.40)	0.252	−4.28 (−14.42,5.87)	0.397
Language domain	0.16 (−2.85,3.16)	0.916	−5.25 (−15.88,5.38)	0.321
Motor domain	2.20 (−0.66,5.04)	0.126	−7.18 (−17.49,3.13)	0.166
CHEU/AbN-RI:				
Cognitive domain	1.44 (−4.48,7.36)	0.605	−1.04 (−16.81,14.73)	0.888
Language domain	−2.49 (−9.65,4.68)	0.464	−1.63 (−20.93,17.68)	0.858
Motor domain	1.34 (−5.23,7.90)	0.665	−6.08 (−23.10,10.93)	0.451

Abbreviations: AbN-RI: abnormal umbilical artery resistance index; CHUU: HIV-unexposed-uninfected children; CHEU: HIV-exposed-uninfected children; n/a: not applicable; CI: confidence interval; LAZ: length-for-age z-score; N-RI: normal umbilical artery resistance index.
Note: A *p*-value less than 0.05 indicates that results were statistically significant, and such *p*-values are in bold.

possible risk factor for mild anaemia in children with previous in utero growth restriction may be a high percentage of premature birth in this group, with prematurity known to be a risk factor for childhood anaemia.[29] Further, more than a quarter of children across all the groups were mildly anaemic. However, the reported percentages were lower than the 61.3% prevalence of childhood anaemia previously reported in a South African systematic review by Turawa et al.[4]

CHEU who had AbN-RI had low anthropometric measurements and indices, particularly mean LAZ, indicating a risk of stunting. Similar poorer growth parameters have been reported in South African CHEU compared with CHUU.[27] Other researchers have shown that IUGR does not impact anthropometric measurements;[30] these may, perhaps, depend on the type of anthropometric measurement used.

Furthermore, children who had AbN-RI and CHEU/AbN-RI had significantly lower Bayley-III mean cognitive composite scores. Lower cognitive scores were reported among children who had IUGR by Sacchi et al.[13] in their systematic review and meta-analysis involving 60 studies that included 52 822 children, as well as by von Beckerath et al.[24] There was no significant difference in mean cognitive scores between CHEU vs. CHUU, similar to previous studies in South Africa and Botswana, in which similar cognitive development was described in CHEU and CHUU.[31,32]

Our univariable and multivariable regression analyses indicated that no associations existed between maternal or child haemoglobin and child neurodevelopment. These findings align with many reports in the literature.[33] However, the findings differed from those of Olney et al.[34] and a systematic review and meta-analysis by Larson et al.[35], which showed an association between child haemoglobin and motor development. Nonetheless, studies in the literature did not focus on the dual exposures of HIV and placental insufficiency.

The lower cognitive scores among children who had AbN-RI and CHEU/AbN-RI were not associated with child or maternal haemoglobin concentrations, and the findings differed from another report, although HIV exposure and UmA-RI were not investigated.[36] Observations were that these children who were HIV-exposed and had AbN-RI also had lower LAZ; however, further investigations showed a significant association between cognitive and motor development and LAZ among CHEU only. This may suggest that poor linear growth is not a risk factor for cognitive deficit in children who had UmA-RI. We assume the cognitive domain was mainly affected due to its reliance on brain structures highly sensitive to prenatal disruptions like oxygen and nutrient deprivation.

Limitations of the study include the lack of a full blood count for assessing anaemia. Also, the maternal haemoglobin at 18 months postpartum may not fully indicate the maternal haemoglobin during pregnancy/early postpartum, which is likely more important in terms of its impact on child neurodevelopment. Another limitation was that we had a small dual-exposure group sample size. Nonetheless, this study investigated the overlooked population of children exposed to HIV and placental insufficiency.

Table 5: Multivariable linear regression findings for the association between child LAZ and stunting and Bayley-III composite scores at 18 months

	LAZ		Stunting	
Item	**Multivariable model β (95% CI)**	*p*-value	**Multivariable model β (95% CI)**	*p*-value
Total population:				
Cognitive domain	0.26 (−0.93,1.45)	0.667	−4.40 (−9.37,0.57)	0.083
Language domain	0.43 (−0.62,1.47)	0.421	−2.04 (−7.72,3.65)	0.481
Motor domain	0.72 (−0.44,1.88)	0.221	−4.62 (−10.16,0.92)	0.101
CHUU:				
Cognitive domain	−0.19 (−1.34,0.97)	0.751	−1.08 (−7.95,5.79)	0.757
Language domain	0.14 (−1.18,1.47)	0.830	0.03 (−7.84,7.90)	0.994
Motor domain	0.08 (−1.17,1.34)	0.895	−1.16 (−8.61,6.29)	0.760
CHEU:				
Cognitive domain	2.93 (0.49,5.37)	**0.019**	−9.53 (−17.36,−1.69)	**0.018**
Language domain	0.92 (−1.10,3.84)	0.529	−5.25 (−14.55,4.06)	0.263
Motor domain	3.39 (0.41,6.38)	**0.027**	−9.23 (−18.97,0.52)	0.062
N-RI:				
Cognitive domain	0.22 (−0.90,1.35)	0.698	−5.19 (−11.09,0.70)	0.084
Language domain	0.30 (−0.99,1.59)	0.647	−0.92 (−7.70,5.87)	0.790
Motor domain	0.41 (−0.86,1.68)	0.527	−3.92 (−10.60,2.75)	0.248
AbN-RI:				
Cognitive domain	1.02 (−1.93,3.98)	0.484	0.48 (−10.32,11.29)	0.928
Language domain	0.07 (−3.38,3.51)	0.969	−6.22 (−18.47,6.03)	0.307
Motor domain	2.28 (−0.80,5.35)	0.141	−5.58 (−16.99,5.83)	0.324
CHEU/AbN-RI:				
Cognitive domain	0.26 (−8.96,9.48)	0.951	1.49 (−18.41,21.39)	0.869
Language domain	−4.67 (−16.82,7.49)	0.408	−3.64 (−30.87,23.58)	0.769
Motor domain	2.30 (−9.38,13.98)	0.667	−7.84 (−32.67,17.00)	0.494

Abbreviations: AbN-RI: abnormal umbilical artery resistance index; CHUU: HIV-unexposed-uninfected children; CHEU: HIV-exposed-uninfected children; n/a: not applicable; CI: confidence interval; LAZ: length-for-age z-score; N-RI: normal umbilical artery resistance index.

Note: Multivariable models were adjusted for umbilical artery resistance index status/placental insufficiency, HIV status, child sex, prematurity, and maternal haemoglobin. A *p*-value less than 0.05 indicates that the results were statistically significant, and such *p*-values are in bold.

Conclusions

The prevalence of anaemia remains alarmingly high among South African children irrespective of their medical backgrounds. This study's findings add to the existing knowledge that children who had placental insufficiency, as measured by Doppler ultrasound in pregnancy in otherwise low-risk pregnancies, have lower cognitive scores, with the dual-exposure group with added in utero HIV exposure having the lowest cognitive scores. The findings indicate that maternal HIV exposure and placental insufficiency are risk factors for impaired cognitive neurodevelopment. However, there was no evidence to suggest that child neurodevelopment was associated with maternal haemoglobin concentration in HIV- and placental insufficiency-exposed groups. Child health and nutrition-sensitive programmes should prioritize CHEU and children with placental insufficiency as at-risk groups for cognitive delays.

Acknowledgements – The authors would like to thank the study staff for their assistance, and mother-and-child pairs for participating. This article forms part of the PhD thesis of Nyofane.[18]

Funding – The research study was funded by the UNDP-UNFPAUNICEF-WHO-World Bank Special Program of Research, Development and Research Training in Human Reproduction (HRP), the South African Medical Research Council (SAMRC), and Collaborative Initiative for Pediatrics HIV Education and Research (CIPHER) funding: grant ID: 2017/560_FEU.

Author contributions – MN, UF, MH, HM: Conceptualization, methodology and investigation. MN and HM: Data curation. QN, HM and MN: Formal analysis and validation. UF and RP: Funding acquisition. HM, UF and RP: Project administration and resources. UF, HM and MH: Supervision. MN: Writing – original draft. UF, HM, MH and MN: Writing – review and editing.

Disclosure statement – No potential conflict of interest was reported by the authors.

Data availability – The data used to support the findings of this study are available from the corresponding author upon request.

ORCID

Mothusi Nyofane http://orcid.org/0000-0001-7738-3511

References

1. Juul SE, Derman RJ, Auerbach M. Perinatal iron deficiency: implications for mothers and infants. Neonatol. 2019;115(3):269–74. https://doi.org/10.1159/000495978
2. World Health Organisation. Anaemia. Geneva: World Health Organisation; 2023; Available at: https://www.who.int/news-room/fact-sheets/detail/anaemia [accessed on 9 January 2024].
3. Tunkyi K, Moodley J. Anemia and pregnancy outcomes: a longitudinal study. J Matern Fetal Neonatal Med. 2018;31(19):2594–8. https://doi.org/10.1080/14767058.2017.1349746

4. Turawa E, Awotiwon O, Dhansay MA, et al. Prevalence of anaemia, iron deficiency, and iron deficiency anaemia in women of reproductive age and children under 5 years of age in South Africa (1997–2021): A systematic review. Int J Environ Res Public Health. 2021;18(23):12799. https://doi.org/10.3390/ijerph182312799
5. Malako BG, Asamoah BO, Tadesse M, et al. Stunting and anemia among children 6–23 months old in damot sore district, southern Ethiopia. BMC Nutr. 2019;5(1):3. https://doi.org/10.1186/s40795-018-0268-1
6. Dorsamy V, Bagwandeen C, Moodley J. The prevalence, risk factors and outcomes of anaemia in South African pregnant women: a systematic review and meta-analysis. Syst Rev. 2022;11(1):16. https://doi.org/10.1186/s13643-022-01884-w
7. Tunkyi K, Moodley J. Prevalence of anaemia in pregnancy in a regional health facility in South Africa. S Afr Med J. 2015;106(1):101–4. https://doi.org/10.7196/samj.2016.v106i1.9860
8. South African National AIDS Committee. Let our actions count: National Strategic Plan on HIV, TB and STIs (2017-2022); 2018; Available at: https://sanac.org.za/wpcontent/uploads/2018/09/NSP_FullDocument_FINAL.pdf [accessed on 9 January 2024].
9. Chandna J, Ntozini R, Evans C, et al. Effects of improved complementary feeding and improved water, sanitation and hygiene on early child development among HIV-exposed children: substudy of a cluster randomised trial in rural Zimbabwe. BMJ Glob Health. 2020;5(1):e001718. https://doi.org/10.1136/bmjgh-2019-001718
10. Neary J, Langat A, Singa B, et al. Higher prevalence of stunting and poor growth outcomes in HIV-exposed uninfected than HIV-unexposed infants in Kenya. AIDS. 2022;36(4):605–10. https://doi.org/10.1097/qad.0000000000003124
11. Delicio AM, Lajos GJ, Amaral E, et al. Adverse effects in children exposed to maternal HIV and antiretroviral therapy during pregnancy in Brazil: a cohort study. Reprod Health. 2018;15(1):76. https://doi.org/10.1186/s12978-018-0513-8
12. Pardi G, Marconi AM, Cetin I. Placental-fetal interrelationship in IUGR fetuses—a review. Placenta. 2002;23(Suppl A):S136–S41. https://doi.org/10.1053/plac.2002.0802
13. Sacchi C, Marino C, Nosarti C, et al. Association of intrauterine growth restriction and small for gestational Age status With childhood cognitive outcomes: A systematic review and meta-analysis. JAMA Pediatr. 2020;174(8):772–81. https://doi.org/10.1001/jamapediatrics.2020.1097
14. Al-Qashar F, Sobaih B, Shajira E, et al. Impact of intrauterine growth restriction and birth weight on infant's early childhood neurodevelopment outcome. JCN. 2018;7(1):1–6. https://doi.org/10.4103/jcn.JCN_16_17
15. John CC, Black MM, Nelson CA. Neurodevelopment: the impact of nutrition and inflammation during early to middle childhood in low-resource settings. Pediatrics. 2017;139(Suppl 1):S59–S71. https://doi.org/10.1542/peds.2016-2828h
16. Vannevel V, Vogel JP, Pattinson RC, et al. Antenatal Doppler screening for fetuses at risk of adverse outcomes: a multicountry cohort study of the prevalence of abnormal resistance index in low-risk pregnant women. BMJ Open. 2022;12(3):e053622. https://doi.org/10.1136/bmjopen-2021-053622
17. Pattinson RC, Theron GB, Thompson ML, et al. Doppler ultrasonography of the fetoplacental circulation-normal reference values. S Afr Med J. 1989;76(11):623–5.
18. Nyofane M. Growth and Neurodevelopmental Outcomes of Children with in Utero Growth Restriction Due to Placental Insufficiency and Modification by Maternal HIV Status (Doctoral thesis). South Africa: University of Pretoria; 2024. Available at: https://repository.up.ac.za/items/de828e41-e479-40a5-8dc2-e269a5f10b1d [accessed on 08 May 2025].
19. World Health Organisation. *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity*. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization. 2011; Available at: http://www.who.int/vmnis/indicators/haemoglobin. [accessed 23 July 2021].
20. Hemocue. *HemoCue® Hb 201+ System. 2021*; Available at: https://www.hemocue.com/en/solutions/hematology/hemocue-hb-201plus-system. [accessed on 22 March 2021].
21. Ballot DE, Ramdin T, Rakotsoane D, et al. Use of the bayley scales of infant and toddler development, to assess developmental outcome in infants and young children in an urban setting in South Africa. Int Sch Res Notices. 2017;2017:1631760. https://doi.org/10.1155/2017/1631760
22. World Health Organisation. Physical status: The use of and interpretation of anthropometry, report of a WHO expert committee. Geneva: World Health Organization; 1995.
23. Stomfai S, Ahrens W, Bammann K, et al. Intra- and inter-observer reliability in anthropometric measurements in children. Int J Obes Lond. 2011;35(Suppl 1):S45–S51. https://doi.org/10.1038/ijo.2011.34
24. von Beckerath A-K, Kollmann M, Rotky-Fast C, et al. Perinatal complications and long-term neurodevelopmental outcome of infants with intrauterine growth restriction. Am J Obstet Gynecol. 2013;208(2):130.e1-6. https://doi.org/10.1016/j.ajog.2012.11.014
25. Budree S, Goddard E, Brittain K, et al. Infant feeding practices in a South African birth cohort—A longitudinal study. Matern Child Nutr. 2017;13(3):e12371. https://doi.org/10.1111/mcn.12371
26. Nyofane M, Hoffman M, Mulol H, et al. Early childhood growth parameters in South African children with exposure to maternal HIV infection and placental insufficiency. Viruses. 2022;14(12):2745. https://doi.org/10.3390/v14122745
27. Tshiambara P, Hoffman M, Legodi H, et al. Comparison of feeding practices and growth of urbanized African infants aged 6-12 months old by maternal HIV status in gauteng province, South Africa. Nutrients. 2023;15(6):1500. https://doi.org/10.3390/nu15061500
28. Khondakar NR, Finkelstein JL. Iron and HIV/AIDS. In: Mehta S, Finkelstein JL, editors. Nutrition and HIV: epidemiological evidence to public health. New York: CRC Press; 2018. pp 89–151. https://doi.org/10.1201/9781351058193-3
29. Mou J, Zhou H, Feng Z, et al. A case-control study of the factors associated with anemia in Chinese children aged 3–7 years Old. Anemia. 2023;23(1):8316658. https://doi.org/10.1155/2023/8316658
30. Calek E, Binder J, Palmrich P, et al. Effects of intrauterine growth restriction (IUGR) on growth and body composition compared to constitutionally small infants. Nutrients. 2023;15(19):4158. https://doi.org/10.3390/nu15194158
31. Wedderburn CJ, Weldon E, Bertran-Cobo C, et al. Early neurodevelopment of HIV-exposed uninfected children in the era of antiretroviral therapy: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2022;6(6):393–408. https://doi.org/10.1016/s2352-4642(22)00071-2
32. De Beer CC, Krüger E, Van der Linde J, et al. Developmental outcomes of HIV-exposed infants in a low-income South African context. Afr Health Sci. 2020;20(4):1734–41. https://doi.org/10.4314/ahs.v20i4.25
33. Ahun MN, Aboud FE, Aryeetey R, et al. Child development in rural Ghana: associations between cognitive/language milestones and indicators of nutrition and stimulation of children under two years of age. Can J Public Health. 2018;108(5-6):e578–e585. https://doi.org/10.17269/cjph.108.5875
34. Olney DK, Kariger PK, Stoltzfus RJ, et al. Development of nutritionally at-risk young children is predicted by malaria, anemia, and stunting in pemba, zanzibar. J Nutr. 2009;139(4):763–72. https://doi.org/10.3945/jn.107.086231
35. Larson LM, Kubes JN, Ramírez-Luzuriaga MJ, et al. Effects of increased hemoglobin on child growth, development, and disease: a systematic review and meta-analysis. Ann NY Acad Sci. 2019;1450(1):83–104. https://doi.org/10.1111/nyas.14105
36. Wainstock T, Walfisch A, Sergienko R, et al. Maternal anemia and pediatric neurological morbidity in the offspring – results from a population based cohort study. Early Hum Dev. 2019;128:15–20. https://doi.org/10.1016/j.earlhumdev.2018.11.002

Received: 8-05-2025 Accepted: 20-07-2025