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Exploring Infant Size and Body Composition at 18 Months: An Ambidirectional Peri-Urban South African Cohort Study

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ABSTRACT

The first 1000 days of life lay the foundations for subsequent growth. This ambidirectional study, including prenatal, perinatal and postnatal factors, aimed to identify exposure variables affecting body size and composition and corresponding *Z*-score outcomes at age 18 months in infants born to women at low risk of adverse pregnancy outcomes in a peri-urban area of South Africa. Prenatal factors (maternal age, HIV status, anthropometry, parity, food insecurity and umbilical artery resistance index *Z*-score (UmA-RIAZ) as a measure of placental function, with higher UmA-RIAZ indicating poorer placental function); perinatal factors (infant sex, gestational age and birth anthropometry) and postnatal factors (infant feeding) were included as exposure variables, with infant anthropometry and body composition at 18 months as outcomes. Simple linear regression analysis was used to investigate associations between exposure variables and infant outcomes, and variables with $p < 0.10$ were included in the subsequent multiple regression analyses. Multiple regression analysis showed that higher UmA-RIAZ predicted lower birthweight [−0.11 kg (95% CI: −0.17, −0.04 kg)], birthweight-for-age *Z*-score [−0.24 (95% CI: −0.39, −0.09)] and 18-month infant length [−0.9 cm (95% CI: −1.4, −0.4 cm)] and length-for-age *Z*-score [−0.28 (95% CI: −0.45, −0.11)]. Maternal HIV infection predicted reduced 18-month infant length-for-age *Z*-score [−0.46 (95% CI: −0.83, −0.09)]. Household food insecurity predicted reduced fat-free mass-for-age *Z*-score at 18 months [−0.27 (95% CI: −0.51, −0.03)]. Infant anthropometry and body composition outcomes, therefore, are greatly affected by pre- and postnatal nutrition-related factors, such as placental insufficiency in utero and household food insecurity, with long-term consequences including stunting, which impact the individual, future generations and society.

1 | Introduction

The first 1000 days of life, from conception to the second birthday, constitute a period of immense growth and vulnerability, and the foundations laid during this period have lifelong effects on growth, development and health (Barker 2006; Cosmi et al. 2011; Cho and Suh 2016), even extending into subsequent generations (Martorell and Zongrone 2012).

Assessment of foetal growth is complex, and although *Z*-scores are available for foetal size measurements using conventional ultrasound biometry, foetal growth monitoring requires serial measurements and conventional ultrasounds are not routinely

Summary

- Prenatal (maternal height, multiparity, HIV exposure and placental function), perinatal (infant sex, gestational age and size at birth) and postnatal factors (6 months of exclusive breastfeeding and household food insecurity) contributed to suboptimal infant body size and body composition at 18 months.
- An impaired placental function was significantly associated with a reduced birthweight-for-age *Z*-score, suggesting in utero undernutrition.
- Maternal HIV infection and impaired placental function were independent predictors of reduced infant length-for-age *Z*-score at 18 months.
- Household food insecurity predicted reduced fat-free mass-for-age *Z*-score at 18 months.

available at primary health care clinics in resource-limited settings. In these situations, the first available measurements are taken at birth. Newborn size charts, such as the INTERGROWTH-21ST Newborn Size Standards, enable the calculation of birth size *Z*-scores according to sex and gestational age (GA) (Villar et al. 2014), but cannot reliably identify in utero growth faltering, especially in larger infants. For this reason, some researchers have proposed a personalised or customised growth index, the Gestation-Related Optimal Weight (GROW), which incorporates maternal factors such as height, weight, body mass index (BMI), parity and ethnic origin to determine an ideal birthweight in line with the newborn's genetic potential (Gardosi et al. 2018). A recent study illustrated the value of this approach: at higher maternal BMI, only GROW was able to identify foetal growth faltering as a predictor of stillbirth (Gardosi and Hugh 2023), highlighting how maternal overweight/obesity may obscure suboptimal foetal growth in otherwise appropriate-for-GA neonates.

Many factors influence foetal and postnatal growth, thereby affecting body size through infancy, childhood and beyond. These include maternal factors (e.g., age, parity, nutrition status, illness, medication and substance use), environmental factors (e.g., socioeconomic conditions, household food security, extreme heat, high altitude and exposure to pollutants and toxins) and pregnancy-specific conditions (e.g., pregnancy-related maternal illnesses, medications and placental function) (Hunter et al. 2023). Additionally, postnatal growth is affected by infant feeding practices and illness (Hunter et al. 2023). Several of these growth-limiting factors are prevalent in the South African setting, particularly, HIV infection and placental insufficiency.

In South Africa, an estimated 30.0% of pregnant women are HIV-infected, and the majority receive antiretroviral therapy (ART) during pregnancy (Woldesenbet et al. 2021). Thus, the approximately 1 million live births registered in South Africa in 2020 (Stats SA 2021) would have included approximately 300,000 HIV-exposed infants. Routine antenatal HIV testing and immediate initiation of ART have drastically reduced vertical transmission of HIV from 23% in 2003 to 0.7% in 2019 (Wessels et al. 2020). Thus, the majority of HIV-exposed infants remain HIV-uninfected. HIV-exposed-uninfected (HEU) neonates have been found to be smaller at birth (Evans, Jones, and Prendergast 2016), suggesting that exposure to HIV, ART or both may affect growth irrespective of HIV infection. This growth deficit persists postnatally: a study in Western Kenya has shown that, at least up to 24 months, HEU infants have lower length-for-age (LAZ), weight-for-length (WLZ) and weight-for-age (WAZ) *Z*-scores and higher rates of stunting ($LAZ < -2$) compared to HIV-unexposed-uninfected (HUU) infants (Rickman et al. 2023).

Recent South African studies revealed a high prevalence of placental insufficiency in healthy women with apparently low-risk pregnancies (Nkosi et al. 2019; Hlongwane et al. 2021; Vannevel et al. 2022), identified by Doppler screening of the umbilical artery at 28–34 weeks' gestation. Women with an elevated umbilical artery resistance index (UmA-RI) that was classified as abnormal, and indicative of placental insufficiency, were up-referred and this resulted in a significant reduction in the incidence of stillbirths (Nkosi et al. 2019). Infants with abnormal UmA-RI were smaller at birth (though many were appropriate-for-GA) (Nkosi et al. 2019; Hlongwane et al. 2021; Vannevel et al. 2022), and weight and fat-free mass (FFM) *Z*-scores remained lower up to 6 months of age in a repeated cross-sectional analysis (Feucht et al. 2021). At 24 months, these infants still had a lower weight and WAZ compared to infants with a normal UmA-RI, primarily due to lower FFM (Nel et al. 2023). Furthermore, Nyofane et al. (2022) showed that, although the anthropometry of infants with either HIV exposure or placental insufficiency did not significantly differ from infants without these exposures at 18 months, the simultaneous presence of both insults resulted in significantly poorer growth outcomes (particularly, stunting).

The role of maternal and infant dietary intake, including the mediating effect of household food insecurity, cannot be overlooked. A South African study reported household food insecurity as one of the factors influencing stunting in 4- to 55-month-old children (Harper et al. 2023). Food insecurity in breastfeeding women living with HIV may further compromise the growth of HEU infants (Widen et al. 2017). Postnatally, infant feeding practices affect infant body composition, with 6 months of exclusive breastfeeding (EBF) resulting in a lower infant fat mass percentage (%FM) at 12 months compared to mixed feeding (Mulol and Coutsoudis 2017). Furthermore, the breastfeeding degree and duration and timing of introduction and type of complementary foods, also affect infant growth (Saha et al. 2008).

Infant growth refers to a change in anthropometric measurements or *Z*-score over time, but this lacks important information about body composition (Wells 2019). Though commonly used, BMI has poor sensitivity for detecting excess adiposity in infants and children (Javed et al. 2014; Wells 2019). Differentiating FFM from fat mass (FM) is important, as body composition alterations (e.g., elevated or depleted FM) can affect long-term health (Wells 2019). A recent South African study found that reduced infant FM, and its associated index relative to infant weight/length, the FM index (FMI), were associated with infectious morbidity in infants, whereas LAZ and WLZ were not (Momberg et al. 2023). Body composition parameters can be reported as absolute values (FM, FFM), as percentage of weight (%FM) or relative to length (FMI and FFM index [FFMI], which are calculated in the same way as the BMI and add up to it) (Fabiansen et al. 2018). This helps clarify whether differences in FM and/or FFM stem from differences in the relative proportions of FM and FFM or differences in body size (i.e., differences in overall weight and/or length). With the use of appropriate method-specific reference data, age- and sex-specific *Z*-scores can be calculated for each of these parameters (Wells et al. 2020; Murphy-Alford et al. 2023).

Body composition can be estimated using various methods, including dual-energy x-ray absorptiometry, air displacement plethysmography, bioelectrical impedance analysis and stable isotope (deuterium) dilution. Deuterium dilution was used in this study, as it is appropriate from early infancy and was a more cost-effective alternative. The first paediatric reference charts based on deuterium dilution were published by Wells et al. (2020), based on healthy children (6 months to 5 years old) in the United Kingdom; their suitability for children from low- and middle-income countries (LMICs) and diverse ethnicities is unknown. Recently, the Multicenter Infant Body Composition Reference Study published reference charts for body composition using deuterium dilution in infants 3–24 months of age. This reference population included middle-income countries such as South Africa (Murphy-Alford et al. 2023), and may therefore be more appropriate for use in LMICs.

This ambidirectional cohort study aimed to investigate associations between maternal and prenatal factors and growth outcomes in HEU and HUU infants who were assessed for placental insufficiency in utero, as measured by (1) birth anthropometry and (2) anthropometry and body composition at 18 months, thus covering much of the important first 1000 days of life.

2 | Methods

2.1 | Study Design, Setting and Participants

This study reports data from the UmbiGodisa study, which aimed to investigate growth and developmental outcomes at 18 months in infants exposed to placental insufficiency and/or maternal HIV infection in utero. The study recruited infants from two concurrently running cohort studies in the same population in Tshwane District (Gauteng Province, South Africa): the Umbiflow International study (South African arm) and the Siyakhula study. The Umbiflow International study investigated the prevalence and related birth outcomes of abnormal UmA-RIs at 28–34 weeks' gestation in five LMICs (Ghana, India, Kenya, Rwanda and South Africa) using a low-cost portable continuous wave Doppler (Umbiflow) (Vannevel et al. 2022). Of the 1426 South African infants included in the Umbiflow International Study, 263 infants were available for follow-up at 18 months, of which 66 infants formed part of the ongoing longitudinal infant follow-up study from 6 weeks to 2 years postpartum (UmbiBaby study). The Siyakhula study investigated outcomes up to 2 years of age in 315 HEU and HUU infants. Ten HEU infants with placental insufficiency from Siyakhula were included in the UmbiGodisa study to provide adequate statistical power for comparative analyses. Siyakhula participants were recruited at 22 weeks' gestation, and UmA Doppler was performed at 28–34 weeks as part of full ultrasonography.

Mothers in both studies had low-risk pregnancies according to local basic antenatal care (BANC-Plus) guidelines (National Department of Health 2017), which follow the WHO recommendations for a positive pregnancy experience (WHO 2018), and in South Africa classify maternal HIV as a low-risk condition. Mothers who met the inclusion criteria for the UmbiGodisa study (i.e., any UmbiFlow International participants and Siyakhula participants who were both HIV-infected and had an abnormal UmA-RI at 28–34 weeks) were invited for a study visit at 18 months, and written informed consent was obtained from the mothers. Both studies excluded mothers < 18 years, multiple gestation and infants with severe medical conditions or chromosomal abnormalities. Additionally, preterm infants were excluded from this analysis, resulting in a total of 249 term-born infants in this study (Figure 1).

2.2 | Exposure Variables

Baseline data, placental function, maternal anthropometry, household food security and infant feeding practices were determined for adjustment purposes in the multiple regression models.

Baseline data collected at enrolment by trained research assistants included maternal sociodemographic data, HIV status, education, age, household food security, marital status, parity, gravidity and health data. Additional birth information, obtained from antenatal study records, included infant sex, GA and birth anthropometry.

Placental function according to the UmA-RI was assessed at 28–34 weeks' gestation for all participants, using the Umbiflow continuous wave Doppler device or conventional pulsed wave Doppler. The UmA-RI-for-GA *Z*-score (UmA-RIAZ) was calculated as a continuous variable using the published INTERGROWTH-21ST LMS values for UmA-RI (Drukker et al. 2020).

Maternal anthropometry was assessed at the 18-month visit. Height was measured in duplicate by a trained research nurse using a Seca 310 rigid stadiometer (Seca GmbH & Co. KG, Hamburg, Germany) to the nearest 0.1 cm and the mean recorded ($n = 245$). As pre-pregnancy maternal weights were unknown and it was impossible to determine whether 18-month postpartum weight was similar to pre-pregnancy weight, maternal weight was not included as an exposure variable for this analysis.

Household food security was assessed using the United States Household Food Security Survey Module (USDA Economic Research Service 2012), which comprises a set of 10 questions (including one screening question that is not scored) based on the past 4 weeks in both a Yes/No format as well as the frequency of occurrence (rarely/sometimes/often). A score of

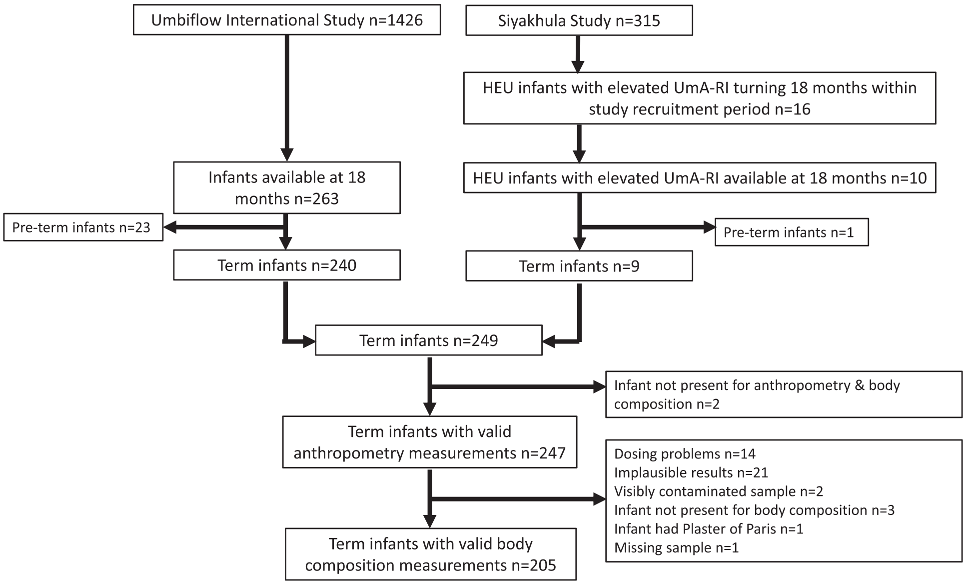

FIGURE 1 | Flow diagram of study participants. HEU = HIV-exposed and uninfected, UmA-RI = umbilical artery resistance index-for-GA *Z*-score.

3–5 indicates low household food security, whereas a score of 6–9 indicates very low household food security.

Infant feeding practices were determined using a questionnaire adapted from the WHO/UNICEF Infant and Young Child Feeding Questionnaire (WHO 2018). Mothers were asked whether the infant was ever breastfed or was breastfed or EBF at 6 months, per WHO recommendations (with EBF defined as only breast milk and medications if required) (WHO 2018). For infants participating in the longitudinal Siyakhula study, this information was collected from previous visits' infant feeding interviews. For infants only seen at 18 months, mothers were asked to recall the age of the first intake other than breast milk. The age at which protein-rich foods (e.g., meat, eggs, peanut butter, beans, cheese, yoghurt, fish) were introduced into the infant's diet was also recorded.

Birth anthropometry was included both as an exposure variable (to predict outcomes at 18 months) and as an outcome (predicted from pregnancy data). Birthweight, birth length and head circumference were obtained from routine labour ward measurements, and converted into the sex- and GA-specific *Z*-scores for birthweight (BWAZ), birth length (BLAZ) and head circumference (BHCAZ) using the INTERGROWTH-21ST Newborn Size Standards (Villar et al. 2014). Small-for-GA (SGA) was defined as a birthweight < 10th centile for GA and sex.

2.3 | Outcomes

Three infant outcomes were investigated: birth anthropometry (as described above), 18-month anthropometry and 18-month body composition.

Infant 18-month anthropometry was measured by a trained research nurse in duplicate and the mean was recorded. Infants were weighed without clothes, to 0.01 kg, using a Seca 354 electronic infant weighing scale (Seca GmbH & Co. KG, Hamburg, Germany). Recumbent length was measured to 0.1 cm using a Seca 416 rigid infantometer (Seca GmbH & Co. KG, Hamburg, Germany). Infant mid-upper arm circumference (MUAC) was measured on the left arm using a non-elastic measuring tape, midway between the acromion of the scapula and the olecranon of the ulna, to 0.1 cm. Head circumference was measured to 0.1 cm using a non-elastic tape around the widest part of the occiput.

Anthropometric *Z*-scores (WAZ, LAZ, WLZ and BMI-for-age [BAZ], head circumference-for-age [HCAZ] and MUAC-for-age [MUACZ]) were calculated according to the WHO Multicentre Growth Reference Study growth standards (De Onis et al. 2006) using the Stata ‘zanthro’ function (StataCorp, version 13.1, 2019). As all included infants were born at term, no correction for GA was necessary.

Infant body composition measurements were available in 205 infants using the deuterium dilution method, whereby an accurately measured 3 g (infant weight < 10 kg) or 6 g (infant weight ≥ 10 kg) dose of deuterium oxide was administered orally using a pre-weighed syringe (IAEA 2010). Spills were collected with pre-weighed tissues and the weight of the spill was subtracted from the dose consumed. Saliva samples were collected before dose administration and 2.5 h after. Fourier Transform Infrared Spectroscopy (IR-Prestige-21 FTIR Spectrophotometer; Shimadzu, Japan) was used to measure the deuterium enrichment in the post-dose sample compared to the baseline sample, from which the infant's total body water was calculated. Infant FFM was calculated as prescribed by the International Atomic Energy Agency (IAEA 2010) using Fomon's age- and sex-specific FFM hydration coefficients (Fomon et al. 1982). Infant FM was calculated by subtracting FFM from weight and %FM was calculated as FM/weight × 100. Infant length was used to calculate FFMI (FFM/length $(m)^2$) and FMI (FM/length $(m)^2$). Age- and sex-specific *Z*-scores were calculated for FFM, FM, FFMI, FMI and %FM using the recently published LMS values for infant body composition using the deuterium dilution method (Murphy-Alford et al. 2023).

2.4 | Statistical Analysis

Analyses were performed using Stata Statistical Software (version 13.1, StataCorp LLC, College Station, TX, US, 2013). Continuous variables were tested for normality using the Shapiro–Wilk test. Summary statistics were reported as means and standard deviations (normally distributed data), median and interquartile range (non-normally distributed data) or frequencies and proportions (categorical variables).

Simple linear regressions were carried out to identify significant associations ($p < 0.10$) between exposure variables and the outcomes of interest (birth anthropometry, infant anthropometry and infant body composition). Variables that were significantly associated with the outcome were included in multiple regression analyses, except where two variables showed significant collinearity (variance inflation factor > 5) or if the same variable was expressed in different ways (e.g., continuous variables that are also expressed categorically).

A backwards elimination multiple regression model was applied. Variables with $p < 0.10$ from the simple linear regression analyses were included in the model, and then removed one by one until only those with $p < 0.05$ remained. The final model was assessed to confirm that it met the assumptions of normality, linearity and homoscedasticity (constant variance of the error term).

2.5 | Ethics Statement

Ethical approval was obtained for the Umbiflow International Study (reference no. 228/2018) and its infant follow-up study (reference no. 283/2019) and the Siyakhula Study (reference no. 294/2017), from the University of Pretoria's Faculty of Health Sciences Research Ethics Committee.

3 | Results

Of the 249 term-born infants in the UmbiGodisa study, 205 had valid body composition results. Figure 1 shows the flow diagram of the study participants. None of the infants in the study tested positive for HIV by 18 months.

Maternal characteristics are shown in Table 1. Most mothers were multiparous (73.9%) and 20.1% were living with HIV. More than half (52.6%) reported a household monthly income below R 4000, comparable to the minimum monthly wage of R 3760 in 2021 (Department of Labour, South Africa 2021), equivalent to US$ 245 and US$ 231 at the time of data collection, respectively. Only one mother reported tobacco use (cigarette smoking) in pregnancy and no mothers reported using alcohol or recreational drugs during pregnancy.

Infant characteristics at birth and at 18 months are shown in Table 1, including anthropometric and body composition measurements with the associated *Z*-scores, and infant feeding practices. The mean birthweight was 3151 ± 461 g, with a mean BWAZ of -0.38 ± 1.04 and 16.9% SGA infants. At 18 months, the mean WAZ was -0.05 ± 1.18, the mean WLZ was 0.11 ± 1.22 and the mean BAZ was 0.20 ± 1.20, with 6.9% classified as overweight (both by WLZ > +2 and BAZ > +2) and 3.6% classified as wasted (WLZ < −2). The mean birth length was 50.5 ± 2.8 cm and the mean BLAZ was 0.60 ± 1.52. At 18 months, the mean LAZ had decreased to -0.28 ± 1.31, with 9.7% of the infants classified as stunted (LAZ < −2). More than half of the mothers (55.8%) reported that their infants were EBF at 6 months.

3.1 | Predictors of Infant Birth Anthropometry

Significant simple and multiple linear regression results for the association between the exposure variables and the birth anthropometry outcomes are shown in Table 2.

In multiple regression analysis, UmA-RIAZ significantly predicted lower birthweight and BWAZ, with each 1 *Z*-score increase in UmA-RIAZ predicting a −0.24 (95% CI: −0.39,−0.09) reduction in BWAZ. UmA-RIAZ was not significantly associated with birth length or BLAZ. Maternal height and GA were positively associated with birthweight and birth length. Maternal HIV infection and household food insecurity were not significantly associated with any of the birth anthropometry and associated *Z*-scores.

3.2 | Predictors of Infant Anthropometry at 18 Months

Table 3 shows significant simple and multiple linear regression associations between exposure variables and 18-month anthropometric outcomes. All birth anthropometry and associated *Z*-scores were positively associated with the corresponding 18-month outcomes in multiple regression analysis: for example, a 1 cm increase in birth length was associated with a 0.3 cm (95% CI: 0.1, 0.4 cm) increase in length at 18 months.

In the multiple regression analysis, UmA-RI was only significantly associated with length and LAZ, with a 1 unit increase in UmA-RIAZ predicting a reduction of infant length by −0.9 cm (95% CI: −1.4, −0.4 cm) and LAZ by −0.28 (95% CI: −0.45, −0.11).

Of the maternal factors, HIV infection was the strongest significant predictor of infant LAZ at 18 months, reducing infant LAZ by −0.46 (95% CI: −0.83, −0.09). Multiparity was significantly associated with a lower weight and WAZ, leading to a −0.59 kg (95% CI: −0.98, −0.19 kg) reduction in weight and a −0.42 (95% CI: −0.72, −0.11) reduction in WAZ. Maternal height was a significant predictor of infant weight, WAZ, length, LAZ and MUAC after multiple regression analysis; infant length at 18 months was increased by 0.2 cm (95% CI: 0.1, 0.3 cm) per 1 cm increase in maternal height.

Birth LAZ, UmA-RIAZ, maternal height, maternal HIV status and EBF at 6 months were significantly associated with LAZ at 18 months, showing the variety of variables influencing the infant's LAZ (Figure 2). WLZ and BAZ showed no significant associations with any of the exposure variables under investigation.

TABLE 1 | Maternal and infant background characteristics.

	N	
Maternal background characteristics		
Maternal age (years), median [IQR]	248	30 [26, 35]
UmA-RIAZ, median [IQR]	249	0.25 [−0.35, 0.64]
Gravidity, median [IQR]	249	2 [2, 3]
Parity, median [IQR]	249	2 [1, 3]
Parity (primiparous), *n* (%)	249	65 (26.1)
Maternal HIV infection, *n* (%)	249	50 (20.1)
Low/very low household food insecurity,[a] *n* (%)	249	55 (22.1)/65 (26.1)
Marital status (married or living with a partner)	249	146 (58.6)
Maternal education highest level (no education; any primary; any secondary; any tertiary), *n* (%)	249	4 (1.6); 15 (6.0); 179 (71.9); 51 (20.5)
Maternal employment, *n* (%)	249	101 (40.7)
Number of people earning an income in the household, median [IQR]	247	1 [1, 2]
Monthly household income < R 4000,[b] *n* (%)	247	130 (52.6)
Maternal smoker in pregnancy,[c] *n* (%)	249	1 (0.4)
Maternal alcohol consumption in pregnancy,[c] *n* (%)	249	0 (0.0)
Maternal recreational drug use in pregnancy,[c] *n* (%)	249	0 (0.0)
Maternal anthropometry at 18 months		
Maternal height (cm), median [IQR]	245	159.1 [155.6, 164.9]
Maternal weight (kg), median [IQR]	242	72.25 [60.00, 91.00]
Maternal MUAC (cm), median [IQR]	245	31 [28, 35]
Maternal BMI (kg/m^2), median [IQR]	242	27.9 [23.3, 35.5]
% BMI overweight (25.0–29.9 kg/m^2), *n* (%)	242	59 (24.4)
% BMI obese (≥ 30.0 kg/m^2), *n* (%)	242	100 (41.3)
Infant characteristics at birth		
Mode of delivery (vaginal; CS)	246	161 (65.5); 85 (34.5)
Apgar score at 5 min, median [IQR]	249	10 [9, 10]
Male sex, *n* (%)	249	121 (48.6)
Weight (g), mean ± SD	249	3151 ± 461
Length (cm), mean ± SD	241	50.5 ± 2.8
Head circumference (cm), mean ± SD	242	34.5 ± 1.5
BWAZ, mean ± SD	249	−0.38 ± 1.04
BLAZ, mean ± SD	241	0.60 ± 1.52
BHCAZ, mean ± SD	242	0.43 ± 1.24
GA (weeks), mean ± SD	249	39.9 ± 1.3
SGA, *n* (%)	249	42 (16.9)
Infant characteristics at 18 months		
Age (months), median [IQR]	249	18.2 [18.1, 18.6]
Weight (kg),[d] mean ± SD	247	10.75 ± 1.54
Length (cm), mean ± SD	247	81.2 ± 3.7
Head circumference (cm),[d] mean ± SD	242	48.1 ± 1.8
MUAC (cm),[d] mean ± SD	246	16.1 ± 1.5
BMI (kg/m^2),[d] mean ± SD	247	16.3 ± 1.7

(Continues)

TABLE 1 | (Continued)

	N	
WAZ, mean ± SD	247	−0.05 ± 1.18
LAZ,[d] mean ± SD	247	−0.28 ± 1.31
HCAZ, mean ± SD	241	0.85 ± 1.15
MUACZ,[d] mean ± SD	245	1.06 ± 1.09
BAZ, mean ± SD	246	0.20 ± 1.20
WLZ, mean ± SD	247	0.11 ± 1.22
Stunted (LAZ < −2), *n* (%)	247	24 (9.7)
Wasted (WLZ < −2), *n* (%)	247	9 (3.6)
Overweight (WLZ > +2), *n* (%)	247	17 (6.9)
Overweight (BAZ > +2), *n* (%)	246	17 (6.9)
TBW (L), mean ± SD	205	6.70 ± 0.90
FFM (kg), mean ± SD	205	8.54 ± 1.15
FFMAZ, mean ± SD	205	0.14 ± 0.96
FFMI (kg/m^2), mean ± SD	205	12.9 ± 1.3
FFMIAZ, mean ± SD	205	0.16 ± 0.99
%FFM, mean ± SD	205	79.0 ± 5.7
FM (kg),[d] mean ± SD	205	2.31 ± 0.81
FMAZ, mean ± SD	205	−0.07 ± 0.90
FMI (kg/m^2), mean ± SD	205	3.5 ± 1.1
FMIAZ, mean ± SD	205	−0.08 ± 0.88
%FM, mean ± SD	205	21.0 ± 5.7
%FMAZ, mean ± SD	205	−0.13 ± 0.83
Infant feeding practices		
Currently breastfeeding, *n* (%)	249	53 (21.3)
Ever breastfed, *n* (%)	249	239 (96.0)
Any breastfeeding at 6 months, *n* (%)	247	185 (74.9)
Exclusive breastfeeding at 6 months, *n* (%)	249	139 (55.8)
Duration of breastfeeding (months), median [IQR]	247	12.0 [5.5, 18.0]
Protein-rich foods introduced[e] (months), median [IQR]	243	9.0 [6.0, 12.0]
Infant illness		
Infant malnutrition/poor growth diagnosed, *n* (%)	248	22 (8.9)
Infant had diarrhoea, *n* (%)	248	77 (31.0)
Infant had visited a health care facility for illness, *n* (%)	248	79 (31.9)
Infant had been admitted to hospital, *n* (%)	247	23 (9.3)

Abbreviations: BAZ = BMI-for-age *Z*-score, BHCAZ = birth head circumference-for-gestational age *Z*-score, BLAZ = birth length-for-gestational age *Z*-score, BMI = body mass index, BWAZ = birthweight-for-gestational age *Z*-score, CS = Caesarean section, FFM = fat-free mass, FFMAZ = FFM-for-age *Z*-score, FFMI = fat-free mass index, FFMIAZ = FFMI-for-age *Z*-score, FM = fat mass, FMAZ = FM-for-age *Z*-score, FMI = fat mass index, FMIAZ = FMI-for-age *Z*-score, GA = gestational age, HCAZ = head circumference-for-age *Z*-score, HIV = human immunodeficiency virus, IQR = interquartile range, LAZ = length-for-age *Z*-score, MUAC = mid upper arm circumference, MUACZ = MUAC-for-age *Z*-score, SD = standard deviation, SGA = small-for-GA, TBW = total body water, UmA-RIAZ = umbilical artery resistance index for gestational age *Z*-score, WAZ = weight-for-age *Z*-score, WLZ = weight-for-length *Z*-score.

[a] Determined by the United States Household Food Security Survey Module score (3–5 = low food security; 6–9 = very low food security).

[b] R 4000 = US$ 245 at time of data collection.

[c] Based on maternal history.

[d] Non-normally distributed variables reported as mean ± SD for comparison.

[e] Protein-rich foods, for example, meat, eggs, peanut butter, beans, cheese, yoghurt and fish.

3.3 | Infant Body Composition at 18 Months

Birthweight/WAZ was positively associated with FFM, FM, FFMAZ and FMAZ at 18 months, as shown in Table 3 (other body composition outcomes have no comparable birth variables). Higher UmA-RIAZ was only associated with a lower infant FFM and FFMAZ at 18 months in the simple linear regression analysis, but this was no longer significant after the

TABLE 2 | Beta coefficients of significant associations between maternal/prenatal factors and infant birth anthropometry and associated *Z*-scores.

	Infant anthropometry at birth ($N = 249$)					
	Weight (kg)	**BWAZ**	**Length (cm)**	**BLAZ**	**HC (cm)**	**BHCAZ**
Simple linear regression[a]						
UmA-RIAZ	−0.147	−0.238	—	—	−0.291	—
Maternal height (cm)	0.013	0.020	0.075	0.026	0.031	—
Infant sex (M, F)	—	—	—	—	−0.471	—
GA (weeks)[b]	0.123	—	0.544	—	0.311	—
Parity (*n*, continuous)	—	—	—	—	0.218	0.194
Parity (primi, > 1)	—	—	—	—	0.414	0.408
Maternal age (years)	—	—	—	—	0.041	0.039
Multiple linear regression						
UmA-RIAZ	−0.106	−0.236			—	
Maternal height (cm)	0.009	—	0.060	—	—	
Infant sex (M, F)					−0.516	
GA (weeks)[b]	0.103		0.513		0.301	
Parity (*n*, continuous)					0.235	—
Maternal age (years)					—	0.039

Note: Empty cells in multiple regression analysis indicate that variable was not significant ($p \geq 0.10$) in the simple linear regression analysis and was, therefore, not included in the multiple regression analysis.

Abbreviations: BHCAZ = birth head circumference-for-GA *Z*-score, BLAZ = birth length-for-GA *Z*-score, BWAZ = birthweight-for-GA *Z*-score, GA = gestational age, HC = head circumference, HIV = human immunodeficiency virus, UmA-RIAZ = umbilical artery resistance index-for-GA *Z*-score.

—, Not significant ($p \geq 0.10$ in simple linear regression and $p \geq 0.05$ in multiple linear regression).

[a] Maternal HIV and household food insecurity (as determined by a score of 3–9 in the United States Household Food Security Survey Module) were not significant in any of the simple linear regression analyses ($p \geq 0.10$).

[b] Only term infants were included in the analysis.

multiple regression analysis. Infant sex was significantly associated with the FFM and FFMI, with female infants having −0.50 kg lower FFM (95% CI: −0.77, −0.22 kg) and −0.4 kg/m^2 lower FFMI (95% CI: −0.8, −0.1 kg/m^2).

Multiparity predicted a significant reduction in infant FFM of −0.40 kg (95% CI: −0.71, −0.10 kg) and FFMAZ of −0.31 (95% CI: −0.57, −0.04). Being EBF at 6 months was significantly associated with an FFM reduction of −0.36 kg (95% CI: −0.63, −0.09 kg) and FFMAZ reduction of −0.28 (95% CI: −0.52, −0.04). Household food insecurity was significantly associated with reduced FFMAZ of −0.27 (95% CI: −0.51, −0.03). No significant associations with body composition were seen for maternal HIV infection in the multiple regression analysis or the time of introduction of protein-rich foods into the diet in the simple regression analysis.

Breastfeeding at 18 months was the only factor significantly associated with %FFM and %FM at 18 months, predicting an increase in %FM (and equivalent decrease in %FFM) of 2.27% (95% CI: 0.32, 4.22%), with an associated increase in %FMAZ of 0.36% (95% CI: 0.07, 0.64%) (no *Z*-scores reference data are available for %FFMAZ). Other infant body fat components (FM, FMAZ, FMI and FMIAZ) were not significantly associated with infant sex, parity or food insecurity.

4 | Discussion

This study adds to the sparse body of evidence concerning outcomes in the first 1000 days of life in infants exposed to HIV and/or placental insufficiency in utero, with the goal of elucidating risk factors for poor growth. As infant body composition may influence body composition later in childhood (Admassu et al. 2018) and into adulthood (Li et al. 2003), identifying modifiable predictors of infant body composition in the first 1000 days of life could facilitate interventions to address suboptimal infant growth and promote lifelong health. Recent findings from the Multicenter Infant Body Composition Reference Study, which included South African infants, focussed on the longitudinal body composition changes according to sex (Norris et al. 2024; Santos et al. 2024) in infants that had no health, economic or environmental constraints on growth, thus presenting a standard for the ideal development of body composition from 3 to 24 months of life. In contrast, our study population included participants with a poor socioeconomic status and with known maternal medical conditions, for example, HIV infection.

Placental insufficiency, which impairs foetal nutrient and oxygen supply, is a major contributor to foetal growth restriction and stillbirth (Gardosi et al. 2013). The UmA-RIAZ is an important indicator of placental function that can be easily measured in pregnancy. Abnormal UmA-RI has been shown to affect growth into the postnatal period (Feucht et al. 2021; Nyofane et al. 2022; Nel et al. 2023). This current analysis utilised a larger sample size to identify which additional factor(s) contribute to suboptimal postnatal growth in these infants. Increases in the UmA-RIAZ had significant negative effects on the infant's birthweight and birth WAZ in multiple regression analysis, which extended to 18 months with a significant negative association with the infant's weight, WAZ, length, LAZ, HC, FFM and FFMAZ at 18 months in a simple linear regression analysis (though the association only remained significant for length and LAZ in the multiple regression analysis). These findings point to a foetus that was subject to insufficient nutrition in utero, resulting in a lower birthweight, but also foundations laid for further suboptimal growth, especially in terms of length growth. Stunting is a reflection of long-term undernutrition and a major concern in South Africa, with 27% of children under 5 years reported as stunted and 10% as severely stunted (Stats SA 2016). Stunting is associated with lower cognitive and motor development, higher morbidity and mortality and obesity, which is associated with a higher risk of chronic disease (De Onis and Branca 2016). The first 1000 days therefore provide an opportunity to improve the linear growth, both by identifying fetuses at risk of starvation in utero and by ensuring that infants are provided with optimal and adequate nutrition postpartum. Furthermore, this could reduce the intergenerational effects of poor growth (Martorell and Zongrone 2012).

The lack of association between UmA-RIAZ and WLZ/BMIZ could be due to the concurrent effect of UmA-RIAZ on weight and length, implying that the infants with an elevated UmA-RIAZ may be smaller, but proportionate. In the multiple regression analysis at 18 months, however, UmA-RIAZ only predicted infant length and LAZ, indicating that other important factors affect postnatal weight gain. UmA-RIAZ was significantly associated with the birth head circumference in the simple linear regression, but not after multiple regression analyses, and UmA-RIAZ was not significantly associated with HCAZ at birth and 18 months in simple linear regression analyses. This is concordant with the concept of brain-sparing growth described by the Developmental Origins of Health and Disease hypothesis, whereby the growth of the brain is prioritised and protected in situations of in utero nutrient scarcity (Barker 2006). Infants with placental insufficiency often catch up their growth postnatally, but this was not the case in this study population up to 2 years of life (Nel et al. 2023). Socioeconomic deprivation may be responsible for continued suboptimal growth postnatally, as suggested by the high rates of unemployment (59.3%), household food insecurity (48.2%) and monthly household income below R 4000, only slightly above the per-capita minimum wage (52.6%).

Maternal HIV infection was present in 20.1% of the study sample, which is below the 2019 South African national antenatal HIV prevalence of 30% (Woldesenbet et al. 2021), but typical of the region in which the study was carried out. Maternal HIV infection was not significantly associated with size at birth, but infant length and LAZ at 18 months were significantly reduced with maternal HIV infection in multiple regression analysis, pointing to long-term effects of exposure to HIV and/or ARTs in utero, even in the absence of vertical HIV transmission.

Previous research has associated multiparity with larger birthweights (Shah 2010), but this was not the case in our study, where parity was only associated with BHCAZ at birth. At 18 months, multiparity was significantly associated with reductions in infant weight, WAZ, FFM and FFMAZ at 18 months. This could be explained by the low socioeconomic status of the study population, which may result in insufficient household food budget and contribute to poor maternal and infant nutrition status. Additionally, poor complementary feeding practices are often reported in South Africa (Sayed and Schönfeldt 2020), which may further compromise infant growth beyond the EBF period.

Maternal height was significantly predictive of most of the infant anthropometric measurements at birth and 18 months and body composition at 18 months in simple and multiple regression analyses, showing the long-term influence of maternal body size on infant size. This is consistent with the GROW method of assessing birthweight, which takes into account not just the GA and sex of the infant but also the maternal height (Gardosi et al. 2018), as this is believed to reflect the infant's genetic potential. This relationship with maternal size was still significant at the infant age of 18 months. Although the magnitude of the differences associated with maternal height appears to be small, maternal heights in the study sample ranged over 42 cm (145–187 cm)—a difference that could have a considerable effect.

Reported breastfeeding practices, for example, EBF at 6 months of age, were much higher than the latest national survey, which reported 32% EBF rates from 0 to 5 months (Stats SA 2016). In multiple regression analysis, EBF was negatively associated with infant length, LAZ, FFM and FFMAZ at 18 months. This unexpected result may have been affected by social desirability bias, as reporting best practices even if they are not practising them is particularly common for the retrospective recall of EBF (Bland 2003; Li, Scanlon, and Serdula 2005; Greiner 2014). One South African study comparing an objective measure of EBF (dose-to-mother deuterium dilution) to reported EBF showed some correlation at 6 weeks but no correlation at 6 months in South Africa (Mulol and Coutsoudis 2018). In their study including healthy participants in the Multicenter Infant Body Composition Reference Study, Santos et al. 2024 found significantly reduced FM, FFM and FFMI in boys and girls who were still breastfed at 12 months, but did not report on EBF in the birth to 24-month cohort.

4.1 | Strengths and Limitations

The main strengths of this study were coverage of much of the critical first 1000 days of life (prenatally to 18 months), and the inclusion of data on a wide range of factors now known to affect postnatal body size and composition, including placental insufficiency, HIV exposure in utero, birth anthropometry, infant feeding, household food insecurity and maternal factors such as age, anthropometry and parity. We also believe that this is the first South African study to report results using data from the first 1000 days of life with the newly published body composition reference charts (Murphy-Alford et al. 2023).

The lack of pre-pregnancy maternal weight is an important limitation that should be addressed in future studies, especially given the high maternal BMIs and rate of overweight/obesity observed at 18 months postpartum. However, maternal height is constant across the time points and hence should be accurate in

TABLE 3 | Beta coefficients of significant associations between maternal/prenatal factors and infant anthropometry/selected body composition outcomes and associated *Z*-scores at 18 months.

	Infant anthropometry at 18 months ($N = 249$)									
	Weight (kg)	**WAZ**	**Length (cm)**	**LAZ**	**HC (cm)**	**HCAZ**	**MUAC (cm)**	**MUACZ**	**WLZ**	**BAZ**
Simple linear regression[a]										
Birth anthropometry/ *Z*-scores[b]	1.264	0.351	0.392	0.222	0.337	0.232				
UmA-RIAZ	−0.334	−0.239	−1.047	−0.315	−0.250	—	—	—	—	—
Maternal height (cm)	0.066	0.045	0.220	0.067	0.042	0.025	0.033	0.019	—	—
Maternal HIV (N, Y)	—	—	−1.527	−0.539	—	—	—	—		—
Infant sex (M, F)	−0.545	—	−1.137	—	−1.083	—	—	—	—	—
Household food insecurity[c] (N, Y)	−0.327	—	−0.970	−0.282	−0.468	−0.245	—	—	—	—
Parity (primi, > 1)	−0.495	−0.337	−1.241	−0.371	−0.460	—	—	—	—	—
Parity (*n*, continuous)	—	—	−0.547	−0.169	—	—	—	—	—	—
GA (weeks)[d]	0.206	0.154	0.500	0.160	—	—	0.116	0.099	0.106	—
EBF at 6 months (no EBF, EBF)	—	−0.264	−1.108	−0.419	—	—	—	—	—	—
BF at 6 months (no BF, BF)	—	—	—	—	—	—	—	—	—	—
BF at 18 months visit (N, Y)	—	—	—	—	0.647	—	—	—	—	—
Duration of BF (months)	—	—	—	—	—	—	—	—	—	—
Protein-rich foods introduced[e] (months)	—	—	—	—	0.068	—	—	—	—	—
Multiple linear regression[f]										
Birth anthropometry/ *Z*-scores[b]	1.149	0.338	0.287	0.171	0.302	0.231				
UmA-RIAZ	—	—	−0.875	−0.282	—					
Maternal height (cm)	0.051	0.034	0.194	0.062	—	—	0.033	—		
Maternal HIV (N, Y)			—	−0.458						
Infant sex (M, F)	—		—		−0.956					
Household food insecurity[c] (N, Y)	—		—	—	−0.509	—				
Parity (primi, > 1)	−0.590	−0.416	−1.125	—	—					
GA (weeks)[d]	—	0.131	—	—			—	—	—	
EBF at 6 months (no EBF, EBF)		—	−1.148	−0.400						
BF at 18 months visit (N, Y)					—					
Duration of BF (months)										

Note: Empty cells in the simple linear regression analysis indicate that there are no comparable birth measurements for this variable. Empty cells in multiple regression analysis indicate that the variable was not significant ($p \geq 0.10$) in the simple regression analysis and was therefore not included in the multiple regression analysis.
Abbreviations: BAZ = body mass index-for-age *Z*-score, BF = breastfeeding, BWAZ = birthweight-for-age *Z*-score, EBF = exclusive breastfeeding, FFM = fat-free mass, FFMAZ = FFM-for-age *Z*-score, FFMI = fat-free mass index, FFMIAZ = FFMI-for-age *Z*-score, FM = fat mass, FMAZ = FM-for-age *Z*-score, GA = gestational age, HC = head circumference, HCAZ = HC-for-age *Z*-score; HIV = human immunodeficiency virus, LAZ = length-for-age *Z*-score, MUAC = mid upper arm circumference, MUACZ = MUAC-for-age *Z*-score, UmA-RIAZ = umbilical artery resistance index-for-GA *Z*-score, WAZ = weight-for-age *Z*-score, WLZ = weight-for-length *Z*-score.
—, Not significant ($p \geq 0.10$ in simple linear regression and $p \geq 0.05$ in multiple linear regression).

[a] Maternal age and ever BF were not significant in the simple regression analysis ($p \geq 0.10$).

Infant body composition at 18 months ($N = 205$)										
FFM (kg)	FFMAZ	FFMI (kg/m^2)	FFMIAZ	% FFM	FM (kg)	FMAZ	FMI	FMIAZ	% FM	% FMAZ
0.934	0.332				0.383	0.152				
−0.235	−0.196	—	—	—	—	—	—	—	—	—
0.053	0.042	—	—	—	0.024	0.026	—	—	—	—
—		0.359	0.285		—	—		—	—	
−0.540	—	−0.405	—	—	—	—	—	—	—	—
−0.398	−0.370	—	—	—	—	—	—	—	—	—
−0.480	−0.366	—	—	—	—	—	—	—	—	—
−0.132	—	—	—	—	—	—	—	—	—	—
0.145	0.123	—	—	—	0.071	0.080	—	—	—	—
−0.357	−0.337	—	—	—	—	—	—	—	—	—
−0.350	−0.319	—	—	—	—	—	—	—	—	—
—	—	−0.410	−0.380	−2.273	0.326	0.372	0.375	0.298	2.273	0.356
−0.030	−0.026	−0.031	−0.024	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—
0.841	0.306				0.310	0.133				
—	—									
0.034	0.028				0.018	0.022				
		—	—							
−0.500		−0.424								
—	−0.273									
−0.404	−0.306									
—	0.141				—	—				
−0.359	−0.281									
				−2.273	0.273	0.324	—	—	2.273	0.356
		−0.032	−0.024							

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[b] Birthweight for weight, FFM and FM; birthweight-for-age *Z*-score for WAZ, FFMAZ and FMAZ; birth length for length; birth length-for-age *Z*-score for LAZ; birth head circumference for head circumference; birth head circumference-for-age *Z*-score for HCAZ; no birth equivalent for MUAC, MUACZ, WLZ, BAZ, FFMI, FFMIAZ, %FFM, FMI, FMIAZ, %FM, %FMAZ.

[c] Determined by a score of 3–9 in the United States Household Food Security Survey Module.

[d] Only term infants were included in the analysis.

[e] Protein-rich foods, for example, meat, eggs, peanut butter, beans, cheese, yoghurt and fish.

[f] Protein-rich foods introduced were not significant in the multiple regression analysis ($p \geq 0.05$).

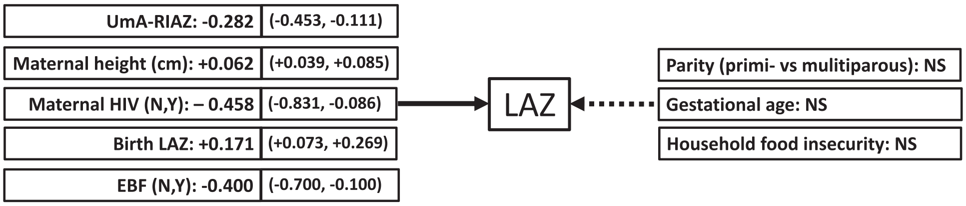

FIGURE 2 | Association of variables with infant LAZ at 18 months after multiple linear regression ($N = 249$).[a] Data shown are the *ß* coefficients (95% confidence intervals) of the significant associations. Only term infants were included in this analysis. [a]Maternal age, infant sex, ever breastfed, current breastfeeding, duration of breastfeeding and age of introduction of protein-rich foods into the infant's diet were not significant in the simple linear regression analysis ($p \geq 0.10$). EBF = exclusive breastfeeding at 6 months, HIV = human immunodeficiency virus, LAZ = length-for-age *Z*-score, NS = not significant, UmA-RIAZ = umbilical artery resistance index-for-gestational age *Z*-score.

all the analyses. Maternal dietary intake during pregnancy was not available and could also have affected the infant's size at birth (da Mota Santana et al. 2021) and subsequent anthropometry and body composition. In this study, the only available information related to food intake was obtained through a limited assessment of household food security; thus, recommendations for future work would include performing detailed dietary assessments. No information was collected on infant physical activity, which can also influence body size and composition (Prioreschi et al. 2022); it is recommended that future studies also include information on infant energy expenditure. Preterm infants were excluded from this analysis, and high-risk obstetric mothers did not form part of the study population but are at risk of placental insufficiency (e.g., with hypertension, pre-eclampsia); hence, larger future studies should include these. Birth measurements were collected as part of the routine health service, which may limit their accuracy. Finally, a limitation of the statistical analysis was that, despite adjusting for major factors affecting infant body size and composition, other already existing differences might still influence the results. Future studies should consider other additional potential confounders, for example, maternal pre-pregnancy BMI.

5 | Conclusion

Numerous multifactorial exposures predict suboptimal infant growth at 18 months, including prenatal factors (maternal height, multiparity, HIV exposure and placental function), perinatal factors (infant sex, GA and size at birth) and postnatal factors (6 months of EBF and household food insecurity). These may result in long-term consequences such as stunting. To prevent long-term consequences, at least the modifiable risk factors should be identified in a timely manner and included in holistic public health interventions of growth promotion in mother and child programmes.

Author Contributions

U.F. and H.M. designed the research study. H.M. performed the research, analysed the data and wrote the first draft of the paper. All authors reviewed and edited the draft manuscript and have read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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