Association of prenatal placental function with anthropometry and body composition through two years of age in South African infants: the UmbiBaby study.

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Abbreviations:

- AEDF = absent end-diastolic flow

- BC: body composition
- BMIZ = body mass index-for-age z-score
- FFM = fat-free mass
- %FFM = percentage fat-free mass percentage
- FFMI = fat-free mass index
- FGR = fetal growth restriction
- FM = fat mass
- %FM = percentage fat mass
- FMI = fat mass index
- HC = head circumference
- HCZ = HC-for-age z-score
- LAZ = length-for-age z-score
- MUAC = mid-upper arm circumference
- MUACZ = MUAC-for-age z-score
- SGA = small for gestational age
- TBW = total body water
- UmA-RI = umbilical artery resistance index
- WAZ = weight-for-age z-score
- WLZ = weight-for-length z-score

UF and HM designed research; HM conducted data collection; UF and FW supervised research and analysis; SN, UF and FM planned statistical analysis; SN and HM performed statistical analysis; SN wrote paper; FW, HM and UF edited paper; SN had primary responsibility for final content.

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ABSTRACT

Background: Placental insufficiency negatively impacts fetal growth and body composition (BC), potentially affecting lifelong health. Placental insufficiency, detectable as an abnormal umbilical artery resistance index (UmA-RI) on Doppler ultrasonography, is highly prevalent in otherwise healthy South African pregnant women. Appropriate intervention reduces stillbirth and perinatal death, but research on long-term outcomes of surviving infants is lacking.

Objective: To describe and compare anthropometry and BC during the first two years of life in a cohort of term-born infants with normal and abnormal prenatal UmA-RI.

Methods: Term-born infants (N=81; n=55 normal, n=26 abnormal UmA-RI on third trimester Doppler screening) were followed up at eight time points until age two years. Anthropometric measurements were taken, and fat-free mass (FFM) and fat mass (FM) assessed by deuterium dilution. Age- and sex-specific z-scores were calculated for anthropometric indices, FM, FFM, FM index (FMI) and FFM index (FFMI) using appropriate reference data. Anthropometry and BC of infants with normal and abnormal UmA-RI were compared using independent t-test or Mann-Whitney test.

Results: At most ages, group mean z-scores were <0 for length-for-age and FM, and >0 for weight-for-length and FFM. Compared to infants with normal UmA-RI, infants with abnormal UmA-RI had significantly lower weight-for-age z-scores at birth (-0.77±0.75 vs -0.30±1.10, *P*=0.026), ages 10 weeks to 9 months (-0.4±0.87 to -0.2±1.12 vs 0.3±0.85 to 0.6±1.09; *P*=0.007-0.017) and 18 months (-0.6±0.82 vs 0.1±1.18; *P*=0.037); length-for-age z-scores at ages ≤14 weeks (-1.3±1.25 to -0.9±0.87 vs -0.2±1.04 to -0.1±1.00; *P*=0.004-0.021); and FFM-for-age z-scores at ages ≤9 months (-0.1±0.82 to 0.7±0.71 vs 0.7±1.00 to 1.3±0.85; *P*=0.002-0.028). FFMI, %FFM, FM, %FM and FMI showed no consistent significant differences.

Conclusions: Infants with abnormal UmA-RI had lower weight-for-age and length-for-age z-scores, particularly at younger ages, with proportionally lower FFM but no consistent differences in %FFM and FFMI. These findings merit further investigation in larger cohorts.

KEYWORDS

Fetal growth restriction; placental insufficiency; Doppler ultrasound; body composition; anthropometry

INTRODUCTION

The first 1000 days of life, from conception through the second year of life, are widely regarded as a critical developmental period. Nutritional, environmental, and other health-related conditions during this period can have life-long effects (1). Growth and development start *in utero*, and are affected by many of these factors (2), including placental function. The placenta is the fetus's life-support system (3, 4), and any impairment in placental blood flow or transfer can negatively affect fetal growth and survival (5). Placental function can be assessed using Doppler ultrasonography of the umbilical artery (UmA), with an increase in resistance index (RI; [peak systolic velocity – end diastolic velocity]/ peak systolic velocity) or pulsatility index (PI; [peak systolic velocity – end diastolic velocity]/ mean velocity) indicating impaired placental function (3, 6). This implies decreased nutrient and oxygen transfer to the fetus, increasing risk of fetal growth restriction (FGR) and perinatal complications (4, 7-9).

In South Africa, like most low- and middle-income countries, ultrasound examination is largely restricted to women with high-risk pregnancies, yet half of small-for-gestational age (SGA) stillbirths occur in otherwise healthy women with no clinical reason for ultrasonography referral (10). To improve early detection of increased risk of stillbirth in low-risk women, the South African Medical Research Council and the Council for Scientific and Industrial Research developed the Umbiflow™ device, a low-cost mobile continuous-wave Doppler apparatus intended for use in resource-limited settings (11). The Umbiflow™ device

has been extensively tested and shows good agreement with commercial pulsed-wave Doppler ultrasound performed by an expert clinician (12, 13).

South African studies using Umbiflow™ for third-trimester screening of healthy, low-risk pregnant women have found an unexpectedly high prevalence of abnormally elevated umbilical artery RI (UmA-RI), as a marker of placental insufficiency. One study conducted in Tshwane District detected abnormal UmA-RI in 11.3% of the study sample, including end-stage placental insufficiency (absent end-diastolic flow, AEDF) in 1.3% (13). Likewise, a multi-site nationwide study found abnormal UmA-RI in 13.0% of the study sample, with AEDF in 1.2% (14). The reason for the high prevalence of impaired placental functioning remains unknown, since the study cohorts consisted only of otherwise healthy women with no known risk factors for adverse pregnancy outcomes (13, 14). Crucially, appropriate referral significantly reduced stillbirths by up to 45% without increasing neonatal mortality (13, 14). Thus, fetuses who may otherwise have been stillborn can now survive to infancy and childhood. The UmbiBaby study was subsequently designed to investigate the neurodevelopment and growth (including body composition (BC)) of a sub-sample of infants recruited from the South African arm of the Umbiflow™ International study.

It is plausible that impaired placental functioning may affect fetal BC, since fetal fat deposition occurs mainly in the third trimester of pregnancy (15). Late-onset placental insufficiency could therefore limit fat accumulation, resulting in lower fat mass (FM) at birth. Likewise, muscle wasting due to fetal starvation could deplete fat-free mass (FFM), particularly with more severe placental insufficiency. Preliminary data from the UmbiBaby cohort revealed that infants with abnormal UmA-RI antenatally had significantly lower FFM and %FFM and higher %FM at six weeks of age (16). Whether these differences normalize postnatally or persist throughout childhood and beyond could have important health implications, particularly as %FM is positively associated with risk of longer-term adverse metabolic outcomes (17).

Little research has been published regarding the long-term BC outcomes of infants with placental insufficiency; most published research comparing fetal growth to later outcomes in infancy rely on birth weight as a summative descriptor of intrauterine growth (and, by implication, fetal nutrition) rather than utilizing a measure of placental function such as Doppler examination. However, relying on birth weight alone can be misleading, since it risks misclassifying both the constitutionally small fetus (with normal placental function and consistent intrauterine growth), and the fetus with placental insufficiency and faltering growth who remains above commonly used cut-offs for small-for-gestational age (SGA), like the 10th percentile, at birth (7). Studies using Umbiflow^{TM} confirm that, while fetuses with abnormal UmA-RI are smaller and more likely to be born SGA or with low birth weight (<2500g), the vast majority of fetuses with abnormal UmA-RI are still appropriate-for-gestational age and normal birth weight (13, 14, 16). Thus, birth weight cannot reliably be used to identify a prenatal history of placental insufficiency after the fact. Apart from the preliminary UmbiBaby results (16), no published studies could be found comparing BC in infancy or childhood with prenatal placental function. Likewise, studies investigating infant BC in relation to fetal growth assessed by antenatal ultrasound are rare: a 2022 meta-analysis identified only two such studies, conducted in Spain and the Netherlands, both of which showed lower FM and FFM up to 6 months of age in infants with FGR (18). No published research of this type could be found for African infants beyond 6 months of age. It should be noted that results from high-income, predominantly Caucasian populations cannot necessarily be extrapolated to the South African setting, since ethnicity and socioeconomic factors have been shown to significantly affect BC in early infancy (19). Considering the high prevalence of Abnormal placental function and the early-life alterations in BC described in South African studies, research extending into infancy and early childhood is of great importance. The researchers hypothesized that the growth and BC of infants with and without a history of abnormal UmA-RI would remain different throughout the first two years of life.

AIM

This research aimed to describe and compare the anthropometry and BC of infants with and without a history of placental insufficiency (defined as an abnormally elevated UmA-RI) at up to eight time points during in the first two years of life, in a cohort of term-born infants from Tshwane District, South Africa.

METHODS

STUDY POPULATION AND SAMPLING

The UmbiBaby study is an observational, longitudinal cohort study. Study participants were recruited from the South African arm of the Umbiflow™ International Study, as previously described, and included mostly low-income urban Black African women who accessed public health care facilities in the Gauteng Province of South Africa (11). The Umbiflow™ International Study recruited pregnant women classified as low risk according to local antenatal care guidelines: in the South African arm, the 2015 Guidelines for Maternity Care in South Africa (20) were used, which do not classify HIV infection as a high-risk condition. Thus, women with other pre-existing or pregnancy-induced medical conditions (including hypertensive disorders and diabetes) were excluded from the study. Doppler screening with the Umbiflow™ device was performed at 28-34 weeks' gestation. Study participants were invited to participate in the UmbiBaby study after delivery. Women aged <18 years, multiple pregnancies, and infants with severe medical conditions or chromosomal/structural abnormalities were excluded.

DATA COLLECTION

Antenatal and birth data (including UmA-RI value, date of birth, sex, gestational age, and birth weight) were obtained from the Umbiflow™ International Study records. Infant follow-up study visits were conducted at a dedicated research unit based at a tertiary academic hospital in Tshwane District, Gauteng Province. Visits were scheduled for 6, 10 and 14

weeks and 6, 9, 12, 18 and 24 months of age to coincide with routine well child/ immunization visits.

Anthropometric measurements were taken by two trained research nurses. Weight was measured naked to the nearest 0.01 kg using electronic infant weighing scales (Seca 354; Seca, Birmingham, UK). Length was measured recumbent to the nearest 0.1 cm using a rigid infantometer (Seca 416; Seca, Birmingham, UK). Head circumference (HC) was measured above the eyebrows, around the widest part of the occiput, using a non-elastic measuring tape, and recorded to the nearest 0.1 cm. Mid-upper arm circumference (MUAC) was measured on the left arm, midway between the acromion of the scapula and the olecranon of the ulna, using a non-elastic measuring tape, and recorded to 0.1 cm.

Deuterium dilution was used to assess BC according to the methodology described by the International Atomic Energy Agency (21). Saliva samples were collected using a dental cotton swab, held in the infant's mouth until saturated, and then transferred to a clean 20 mL disposable syringe and the plunger depressed to expel the saliva. A minimum sample volume of 2 mL was collected. Pre-dose samples were collected ≥15 minutes after the infant's last food or beverage intake. A pre-measured dose of deuterium-labelled water (D_2O; Sercon, 99.8%; dose of 3 g for infants <10 kg and 6 g for infants >10 kg) was administered using a syringe. Deuterium doses were administered undiluted to minimize the volume consumed and avoid disruption of exclusive breastfeeding in young infants, in alignment to the baby-friendly hospital policy of the institution. To ensure accurate calculation of the consumed deuterium dose, each dosing syringe was weighed before and after administration of the D_2O. Spillage was caught on a pre-weighed tissue, and the difference in tissue weight subtracted from the administered dose. Post-dose saliva samples were collected 2.5 hours after D_2O administration. Deuterium enrichment in the saliva samples was measured by Fourier transform infrared spectrometry (IR-Prestige-21 FTIR Spectrophotometer; Shimadzu, Japan; calibrated according to standard procedures). A calibration curve was constructed with D_2O samples of known concentrations (100-2000

ppm) to ensure linearity, accuracy, and precision of measurements. The measured deuterium enrichment of saliva samples was compared to a calibration standard using isotope.exe software (UK Medical Research Council; Cambridge, UK). Total body water (TBW) was calculated from deuterium enrichments (incorporating a factor to account for non-aqueous hydrogen exchange), and fat-free mass (FFM) estimated using age- and sex-specific hydration constants described by Fomon *et al* (22), as recommended by the International Atomic Energy Agency (21). Fat mass was calculated as the difference between body weight and FFM.

DATA MANAGEMENT AND PREPARATION FOR ANALYSIS

Measurements were recorded on paper forms before being entered into an electronic database (REDCap v9.3.5; 2021; SAMRC/Vanderbilt University) in duplicate by two separate data capturers; discrepancies and implausible values were resolved by referring to original records. Data were exported to Microsoft Excel for further processing.

Doppler UmA-RI results were classified by the Umbiflow^{TM} device software, based on South African reference data published by Pattinson *et al* (23), with an UmA-RI >75th percentile considered abnormal. The reference curves were compiled using data from a high-risk obstetric population, and validation studies found an UmA-RI >75th percentile to be associated with increased perinatal mortality in otherwise healthy women (24). We calculated z-scores for UmA-RI using the INTERGROWTH-21ST reference values, which were compiled based on a multi-ethnic, multi-country sample of healthy women with uncomplicated pregnancies (25).

Sex- and GA-specific birth weight z-scores and percentiles were calculated according to the INTERGROWTH-21ST Newborn Size Standards electronic calculator. (https://intergrowth21.tghn.org/newborn-size-birth/) (26). For each visit, sex-specific z-scores were calculated for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), body mass index-for-age (BMIZ), HC-for-age (HCZ) and MUAC-for-age (MUACZ, from 3

months of age), according to the WHO Growth Standards (27, 28) using WHO Anthro software (http://www.who.int/childgrowth/software/en/). As all included infants were born at term, no age correction was performed.

Indices of BC was expressed as absolute values of FM and FFM (in kg), as well as in terms of percentage FM (%FM), percentage FFM (%FFM), FM index (FMI=FM(kg)/[length(m)]^2), and FFM index (FFMI=FFM(kg)/[length(m)]^2). Sex- and age-specific z-scores for TBW, FM, FFM, FMI and FFMI were calculated using the LMS method and reference data published by Wells *et al*, since this is the only available reference for the study sample age group based on isotope dilution (29). The median (M) and some coefficient of variation (S) values in the reference data vary with age; thus, where participant age did not match the given reference data age exactly, values were interpolated using a linear equation between the age points preceding and following the actual age of the participant. Infants with %FM <7.0% were excluded as biologically implausible values.

STATISTICAL ANALYSIS

Data were analysed using R (v 4.1.2, 2020; R Foundation for Statistical Computing, Vienna, Austria). Continuous data were assessed for normality using the Shapiro Wilk test. Baseline characteristics and anthropometric and BC parameters of infants with normal and abnormal (elevated) UmA-RI at each age were compared using, as appropriate, independent t-test (normally distributed continuous data), Mann-Whitney/Wilcoxon rank-sum test (continuous data not normally distributed) and chi-squared or Fisher's exact test (categorical variables). All comparative analyses were performed with two-sided probabilities and α=0.05.

ETHICAL CONSIDERATIONS

Permission to conduct the study was obtained through the University of Pretoria Faculty of Health Sciences Research Ethics Committee (protocol 283/2019), as well as from the institutions and health services involved. Informed consent was obtained from all parents/legal guardians at enrolment.

RESULTS

SAMPLE DESCRIPTION

The UmbiBaby study included 91 infants (n=62 normal UmA-RI, n=29 abnormal UmA-RI). For this analysis, 10 preterm-born infants were excluded (n=7 normal UmA-RI, n=3 abnormal UmA-RI), leaving a total of N=81 term-born infants (n=55 normal UmA-RI, n=26 abnormal UmA-RI), described in Table 1.

No significant difference was found in the age, gravidity, parity, formal education level, employment status, or height of mothers with normal and abnormal UmA-RI, or in the sex of the infants (all $P>0.2$). The sample had an HIV infection rate typical for South Africa(30), with non-significantly lower rates in the abnormal UmA-RI group (19.2% vs 36.4%; $P=0.13$). Infants in the abnormal UmA-RI group had significantly lower mean gestational age (38.7±1.1 vs 39.7±1.0 weeks; $P<0.001$), although all infants included were born at ≥37 weeks. Abnormal UmA-RI infants also had significantly lower birth weight (2.82±0.36 vs 3.17±0.49 kg; $P=0.002$) and birth weight z-score (-0.7±0.75 vs -0.30±1.10; $P=0.026$), although similar numbers of infants in both groups were classified as SGA (26.9% vs. 21.8%; $P=0.61$). In each group, all but one mother initiated breastfeeding ($P>0.99$).

INFANT ANTHROPOMETRY AND BODY COMPOSITION FOLLOW-UP

Table 2 describes the number of BC datasets available for each time point, as well as the completeness of individual participants' datasets. Missing BC data can be attributed to COVID-19 lockdown regulations precluding saliva sample collection (35 samples), unsuccessful dosing or sample collection (31 samples) or excluded due to implausible results (%FM <7.0; 34 samples over the entire study period). The number of participants with available BC measurements at each visit ranged from 51 to 72 (Abnormal UmA-RI n=11 to 20; Normal UmA-RI n=31 to 47). The largest percentage of participants had five (n=20; 24.7%) or six (n=22; 27.2%) BC measurements; with eight (9.9%) participants having a full set of eight measurements. A comparison of the infants with valid BC measurements

available to the entire group attending each visit revealed no significant differences in age, sex, or anthropometry, suggesting that the infants with BC data were similar to the overall study sample.

Table 3 describes the anthropometry and BC for the whole sample at each visit, and Figures 1-4 compare the anthropometry and BC of participants with normal and abnormal UmA-RI at each time point (Supplementary Tables 1-2). The data presented at each age includes only those infants for whom both anthropometry and BC were available at that study visit.

For most visits, the mean study sample LAZ was <0 (except at 6 and 9 months, where the mean LAZ was 0.07 and 0.04 respectively) and the mean WAZ >0 (except at 18-24 months, where mean WAZ was <0). Similarly, mean WLZ and BMIAZ were >0 for all visits except 24 months. Mean MUACZ (only calculated from 3 months onward) and HCZ were >0 at all visits. Mean z-scores for TBW, FFM and FFMI displayed similar patterns to weight-related indices: mean TBW and FFM z-scores were >0 for all visits except 18 and 24 months, whilst FFMI z-score was only <0 at the 24 months visit. Conversely, mean FM and FMI z-scores were <0 for all visits except 6 months. Breastfeeding rates were high (>85%) up to 14 weeks, declining thereafter; no infants were still breastfeeding at 24 months.

Comparing the normal and abnormal UmA-RI groups, weight was significantly lower (P=0.004 to 0.033) in the Abnormal UmA-RI group at all visits except 6 weeks (P=0.12), while WAZ was significantly lower (P=0.007 to 0.037) at all except 6 weeks (P=0.14), 12 months (P=0.15) and 24 months (P=0.10). Length and LAZ were significantly lower (P=0.004 to 0.027) in the Abnormal UmA-RI group at 6, 10 and 14 weeks, and length (but not LAZ) at 18 months. The same non-significant differences were observed for length at 6 months (P=0.10), 9 months (P=0.06) and 24 months (P=0.05), and for LAZ at 18 months (P=0.07). Mean WLZ and BMIZ were significantly lower in the Abnormal UmA-RI group at 6 months (P=0.045 and 0.038, respectively) with the same non-significant differences observed for WLZ at 9 months (P=0.07) and for BMIZ at 9 months (P=0.07) and 12 months

(*P*=0.10). MUAC and MUACZ were significantly lower in the Abnormal UmA-RI group at 6 months (*P*=0.004 and 0.003) and 9 months (*P*=0.017 and 0.020), and HC at 6 weeks (*P*=0.00.025), 14 weeks (*P*=0.00.014) and 6 months (*P*=0.033), and HCZ at 6 weeks (*P*=0.022) and 14 weeks (*P*=0.018).

Of the BC parameters, TBW (*P*=0.003 to 0.019), TBW z-score (*P*=0.002 to 0.018) and FFM (*P*=0.002 to 0.025) were significantly lower in the Abnormal UmA-RI group at all visits from 6 weeks to 9 months. At 18 months, the Abnormal UmA-RI group's TBW (*P*=0.011) and FFM (*P*=0.014) were also significantly lower, but TBW z-score did not differ significantly. The Abnormal UmA-RI group's FFM z-score was significantly lower at all visits except 12 months and 24 months (*P*=0.002 to 0.028). FFMI differed significantly only at 6 months (*P*=0.049), with a similar non-significant difference at 10 weeks (*P*=0.10), but FFMI z-score did not differ significantly at any age. FM was significantly lower in the Abnormal UmA-RI group only at 12 months (*P*=0.049), but FMI and FMI z-score did not differ significantly. Non-significant differences were observed in FM at 6 months (*P*=0.10) and 9 months (*P*=0.07), in FM z-score at 9 months (*P*=0.10) and 12 months (*P*=0.06), in FMI at 6 weeks (*P*=0.05), and in FMI z-score at 6 weeks (*P*=0.06) and 6 months (*P*=0.09); these values were higher in the Abnormal UmA-RI group at 6 weeks while the reverse was true at all ages thereafter. A significant difference in %FM (and %FFM) was only seen at 6 weeks (*P*=0.035), and a non-significant difference observed at 12 months (*P*=0.09). No significant differences were seen in the proportions of infants still breastfeeding at any age, although the small numbers of breastfeeding infants at 12-18 months suggest caution in interpreting the calculated p-value.

DISCUSSION

This study presents novel data on BC at various time points in the first two years of life, in infants with and without a history of placental insufficiency. The findings are important in light of the high prevalence of placental insufficiency demonstrated in South African Umbiflow™ studies (13, 14). Like these studies, our study showed that although neonates with abnormal UmA-RI had a lower mean birth weight and birth weight z-score, the majority were not SGA

at birth (13, 14). Although the significantly lower gestational age of infants with abnormal UmA-RI could account in part for the lower birth weight, the difference in gestational-age specific z-score is also statistically significant. No significant differences were seen between mothers of Normal and Abnormal UmA-RI fetuses. The sample HIV prevalence is high, though within typical South African ranges (30), and maternal HIV infection was not found to be associated with abnormal UmA-RI in the study sample. This is consistent with the findings from the Umbiflow™ study by Nkosi *et al*, which found significantly lower rates of abnormal UmA-RI in HIV-infected women (13). Likewise, maternal height, age, gravidity, parity, education level and employment status were not associated with abnormal UmA-RI. Maternal BMI was not assessed due to the unavailability of early-pregnancy weight measurements. The reason for the high prevalence of Abnormal UmA-RI in otherwise healthy, low-risk South African pregnant women remains unknown at this time.

Anthropometrically, the study sample showed a tendency towards lower-than-expected length, with LAZ below zero at most visits. Weight-related indices showed the opposite, with WAZ, WLZ and BMIZ above zero at most ages. Indices relating weight to length (WLZ and BMIZ) were consistently higher than WAZ, suggesting disproportionate weight and length growth. These findings are consistent with national surveys showing a high prevalence of stunting (18.3-42.6%) and overweight (12.6-28.9%) in South African children under two years (31). Mean z-scores for BC compartments related to fat-free mass (TBW, FFM and FFMI z-scores) were higher than those related to fat mass (FM, FMI z-score) throughout, suggesting that children in the study sample had comparatively more FFM and less FM than comparable children in the reference population (29). It should be noted that the Wells *et al* reference data were developed in the United Kingdom; as such, various ethnic, socio-economic and nutritional factors could account for the observed differences. Our results contrast with a study by Wells *et al* comparing BC by isotope dilution in Gambian and UK children up to 18 months of age; in their study, Gambian children had lower mean FM, FFM, FMI and FFMI than UK children (32). However, unlike our study sample, the Gambian

sample also had mean BMIZ well below zero, which may account for some of the observed differences.

When comparing infants with normal and abnormal UmA-RI, none of the anthropometric or BC outcomes evaluated differed significantly across all age groups. The small sample sizes (particularly in the Abnormal Um-RI group, which had only 11-20 samples per age group) limits the statistical power of the analyses: for many indicators, the observed effect sizes would require a sample size in excess of 200 to detect statistical significance with $\alpha=0.05$ and 80% power (i.e. $\beta=0.20$). Nonetheless, some significant differences and non-significant trends were observed. Weight was significantly lower in the Abnormal UmA-RI group at all ages except 6 weeks, with WAZ showing similar patterns except at 12 and 24 months. Length and LAZ were significantly lower in the Abnormal UmA-RI group up to 14 weeks, with inconsistent trends thereafter. WLZ and BMIZ were not significantly different except at 6 months. This suggests, taking into account the limitations imposed by the small sample size, that the infants with abnormal UmA-RI were smaller than the infants with normal UmA-RI, but that the deficits in length and weight were reasonably proportionate. Weight-related differences were evident even at birth, which suggests a prenatal growth deficit that is never fully recovered. This is consistent with published literature from low- and middle-income countries showing that infants who are small at birth (whether preterm, low birth weight or SGA) often remain shorter and more underweight throughout childhood (33-35). In the study sample, the Abnormal UmA-RI group had a mean gestational age at birth approximately 1 week below that of the Normal UmA-RI group; this may have led to slightly lower age-specific z-scores, although the expected impact would be small, particularly at later ages.

The observed differences in BC were less consistent across different, albeit related indices. Absolute FFM and TBW, and their z-scores, were significantly lower in the Abnormal UmA-RI group up to 9 months and at 18 months. However, there was no significant difference in %FFM (except at 6 weeks) or FFMI (except at 6 months), suggesting that the difference in absolute FFM is related to lower overall infant weight and length, rather than altered

proportions of FFM and FM. The BC findings are broadly in agreement with two published studies included in a recent meta-analysis (18). The first study, conducted in preterm-born Dutch infants, investigated BC in relation to FGR assessed by ultrasound biometry rather than Doppler assessment of placental function. It found that %FM at 6 months of age was decreased in infants with FGR, regardless of birth weight, compared to non-SGA infants with no FGR (36). The second study, conducted in term-born Spanish infants, included only infants with ultrasound-identified FGR, and compared infants with normal and abnormal Doppler findings. No significant differences in weight, BMI, FM or FFM were seen at 4 and 12 months of age (37). The meta-analysis reported significantly lower FM and FFM in infants with FGR in the Spanish study, although it is not clear whether this is an artefact of lower overall body weight in FGR infants; a comparison of FM:FFM ratios at each age suggests that this might be the case (18, 37).

Breastfeeding rates in the normal and abnormal UmA-RI group were not significantly different at any age, suggesting that a history of placental dysfunction was not related to breastfeeding cessation. However, this does not account for other feeding practices such as the exclusivity of breastfeeding, the use of infant formula and the introduction of complementary foods. These factors merit further investigation, since breast milk naturally forms a progressively smaller part of the diet as a child ages, and nutrition significantly affects growth and BC (38, 39).

The main limitation of the study is its sample size, and the effect this has on statistical analyses should be borne in mind when interpreting the results. If the observed associations (or lack thereof, particularly at older ages) hold true, it suggests two things: firstly, that prenatal placental dysfunction affects overall growth (length and weight) to a greater degree than BC (FM and FFM are reduced proportionately to the reduction in weight and length), and secondly, that the magnitude of the difference may decline over time, suggesting some catch-up growth. Furthermore, the data as presented here cannot be interpreted longitudinally since the same infants were not consistently assessed at each time point;

more sophisticated analyses that account for missing data and individual trends would be needed. Approaches such as Latent Class Growth Analysis and Growth Mixture Modeling may be useful to identify whether distinct anthropometric and/or BC trajectories are associated with placental function or with later adverse outcomes (40). Nonetheless, the direction of the differences between the two groups, though statistically non-significant, remained consistent throughout, suggesting that the findings should be corroborated in a larger sample with sufficient statistical power before drawing any conclusions, and as such the presented results can therefore be seen as a pilot study pointing towards the need for a larger study.

The main strength of the UmbiBaby study was the large number of time points included. This gives a more comprehensive picture of growth and BC throughout the first two years of life and reveals some nuances that may be missed when measurements are only taken at one time point. This study also contributes data to two understudied research areas: BC of South African infants (and African countries in general), and the association between prenatal placental function and BC in infancy. Use of the Umbiflow™ device makes the research particularly applicable to resource-limited settings. Deuterium dilution can be used throughout infancy, unlike air-displacement plethysmography, which is only suitable for use in infants weighing ≤10 kg or children >2 years of age (41). Moreover, unlike e.g. dual-energy x-ray absorptiometry (DEXA), these two-compartment methods cannot differentiate between different FFM components (i.e. water, protein or soft tissue, and bone) (42). The minimal dose of D_2O given (3mL) would not be expected to disrupt breastfeeding, and the WHO definitions of exclusive breastfeeding allows for the administration of small amounts of medicine or supplements.

Considering the high prevalence of elevated UmA-RI in otherwise healthy South African women (13, 14), it is crucial to understand the long-term impact on children affected by suboptimal placental function *in utero*. However, the UmA-RI cut-off used in this and other Umbiflow™ studies would benefit from rigorous statistical validation and optimization.

Although the cut-off used in the Umbiflow™ studies performs well for prevention of stillbirths, it is possible that a different cut-off may be more appropriate for predicting growth and developmental outcomes in infancy. The role of infant feeding and dietary practices also merits investigation, both as an explanatory variable and a potential target for intervention. Future studies should also incorporate reliable measurements of birth length, to investigate how placental function impacts length at birth and the trajectory of length growth thereafter. This is particularly important in light of evidence suggesting that stunting is most often present from birth, and that poor *in utero* length growth may be resistant to postnatal catch-up (43). Finally, research into the underlying etiology of placental dysfunction in otherwise healthy pregnant women is urgently needed, accompanied by the development of appropriate intervention strategies to optimize placental function and fetal wellbeing.

CONCLUSION

This study found evidence that prenatal placental insufficiency may be associated with anthropometry (and, to a lesser extent, BC) in the first two years of life. Infants with an abnormally elevated UmA-RI often had lower weight, WAZ, length and LAZ compared to their counterparts with normal UmA-RI, particularly at younger ages. Absolute FFM appears to be reduced proportionally to the deficits in length and weight, with minimal differences in FFM% and FFMI. These findings merit further investigation in larger cohorts, incorporating longitudinal analysis of growth and BC trajectories.

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TABLES

Table 1: Sample description: pregnancy and birth data of mother-infant pairs with normal and abnormal umbilical artery resistance index

		Total sample (N=81)	Normal UmA-RI (n=55)	Abnormal UmA-RI (n=26)	P-value: normal vs abnormal UmA-RI
Maternal data					
▪ Age (years)	Mean ± SD	28.9 ± 5.71	29.4 ± 5.92	27.7 ± 5.15	0.21 [1]
▪ Unemployed	n(%)	59 (72.8)	42 (76.4)	17 (65.4)	0.24 [2]
▪ Formal education (years) - Primary (0-7) - Some secondary (8-11) - Completed secondary (12) - Tertiary	n(%)	 7 (8.6) 47 (58.0) 18 (22.2) 9 (11.1)	 3 (5.5) 32 (58.2) 14 (25.5) 6 (10.9)	 4 (15.4) 15 (57.7) 4 (15.3) 3 (11.5)	0.43 [3]
▪ Gravidity	Median (IQR)	2 (2; 3)	2 (2; 3)	2 (2; 3)	0.94 [1]
▪ Parity	Median (IQR)	1 (0; 2)	1 (0; 2)	1 (0; 3)	0.60 [1]
▪ HIV-positive	n(%)	25 (30.9)	20 (36.4)	5 (19.2)	0.13 [3]
▪ Height (cm)	Mean ± SD	158.7 ± 6.22	159.0 ± 5.35	158.1 ± 7.85	0.78 [1]
Doppler results					
▪ UmA-RI	Mean ± SD	0.67 ± 0.08	0.63 ± 0.04	0.75 ± 0.06	<0.001 [1] *
▪ UmA-RI z-score [5]	Mean ± SD	0.53 ± 1.21	-0.11 ± 0.61	1.89 ± 0.91	<0.001 [1] *
Birth data					
▪ Sex (male)	n (%)	41 (50.6)	30 (54.4)	11 (42.3)	0.30 [2]
▪ Gestational age (weeks)	Mean ± SD	39.3 ± 1.18	39.7 ± 1.12	38.7 ± 1.03	<0.001 [2] *
▪ Birth weight (kg)	Mean ± SD	3.06 ± 0.48	3.17 ± 0.49	2.82 ± 0.36	0.002 [1] *
▪ Birth weight z-score [6]	Mean ± SD	-0.45 ± 1.02	-0.30 ± 1.10	-0.77 ± 0.75	0.026 [4] *
▪ SGA [7]	n (%)	18 (22.2)	12 (21.8)	7 (26.9)	0.61 [3]
▪ Breastfeeding initiated	n (%)	79 (97.5)	54 (98.2)	25 (96.2)	>0.99 [3]

** Statistically significant (P<0.05)*
[1] Wilcoxon rank sum (Mann-Whitney) test (data not normally distributed).
[2] Chi-squared test.
[3] Fisher's exact test.
[4] Independent samples t-test.
[5] UmA-RI Z-score calculated using INTERGROWTH-21ST Doppler resistance index reference values (25).
[6] Birth weight z-score calculated using INTERGROWTH-21ST Newborn Size Standards (26).
[7] SGA: sex-normalized birth weight <10th percentile on the INTERGROWTH-21ST Newborn Size Standards (26).
Abbreviations: HIV = human immunodeficiency virus; IQR = interquartile range; SD = standard deviation; SGA = small for gestational age; UmA-RI = Umbilical artery resistance index.

Table 2: Proportion of infants with valid body composition data at each visit

Visit	Attended visit, n	Valid body composition data available, n		
		Whole sample, n(%)	Normal UmA-RI,[2] n	Abnormal UmA-RI,[2] n
6 weeks	58	44 (75.9)	32	12
10 weeks [1]	71	58 (81.7)	44	14
14 weeks [1]	72	47 (65.3)	31	16
6 months [1]	70	56 (80.0)	37	19
9 months [1]	72	67 (93.1)	47	20
12 months	64	51 (79.7)	36	15
18 months	56	47 (83.9)	36	11
24 months	51	42 (82.4)	31	11

[1] During Stage 5 COVID-19 lockdown (27 March – 30 April 2020), collection of saliva samples was not allowed, although study visits continued. Sample collection was permitted to resume from 11 May 2020 with introduction of new appropriate social distancing measures for sample collection. During this period, there were 4x 10 weeks visits, 15x 14 weeks visits, 12x 6 months visits and 4x 9 months visits where no body composition assessment could be done.

[2] UmA-RI – umbilical artery resistance index

Table 3: Infant anthropometry and body composition results for the entire study sample

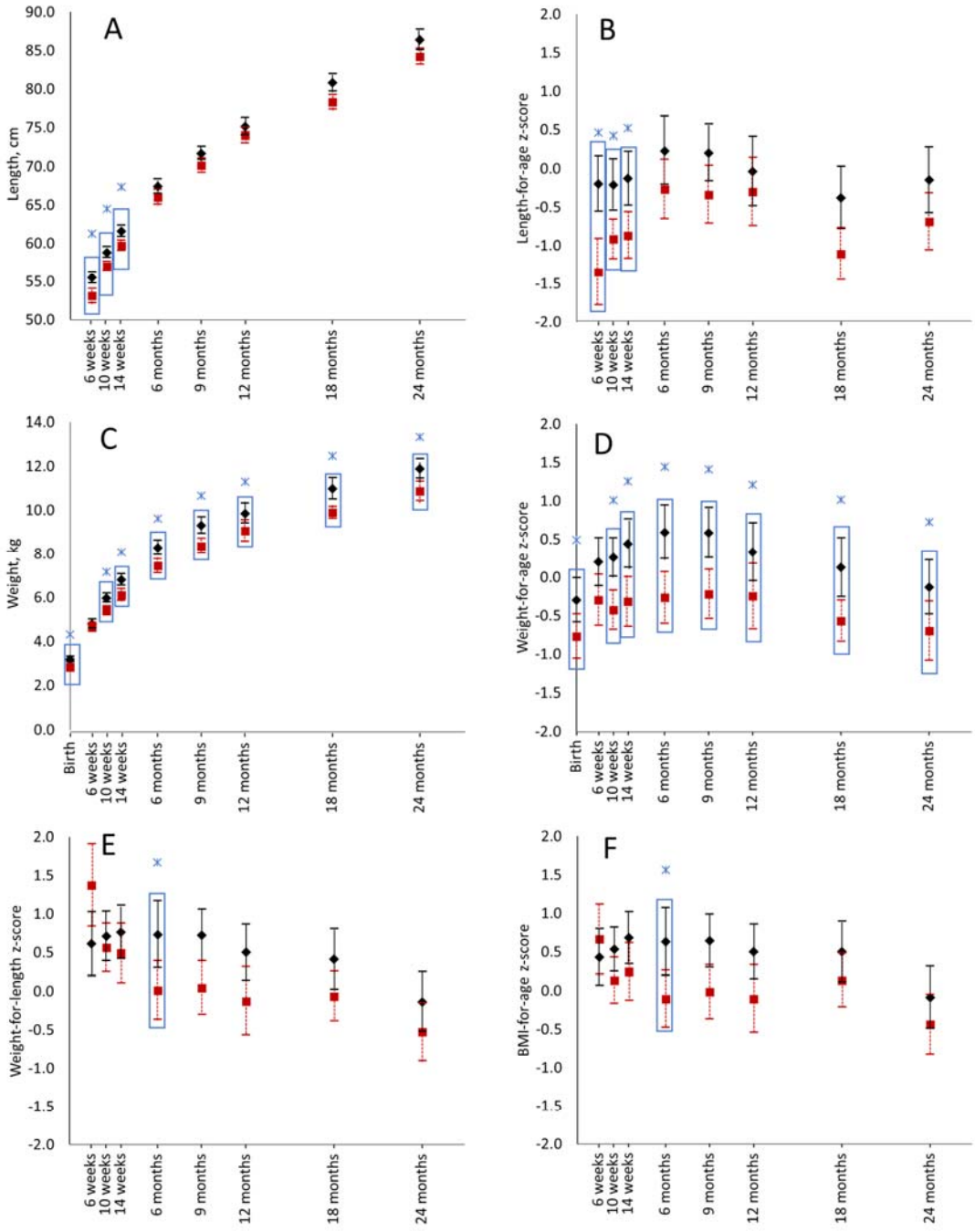
	Visit							
	6 weeks	**10 weeks**	**14 weeks**	**6 months**	**9 months**	**12 months**	**18 months**	**24 months**
n with BC data	44	58	47	56	67	51	47	42
Age (months)	1.5 ± 0.10	2.4 ± 0.14	3.4 ± 0.18	6.1 ± 0.19	9.1 ± 0.15	12.1 ± 0.20	18.3 ± 0.62	24.3 ± 0.30
Sex (male) [n(%)]	19 (43.2)	33 (56.9)	28 (59.6)	27 (48.2)	31 (46.3)	26 (51.0)	25 (53.2)	24 (57.1)
Any breastfeeding [n(%)]	38 (86.4)	50 (86.2)	40 (85.1)	39 (69.6)	39 (58.2)	24 (47.1)	12 (25.5)	0
Anthropometry [1]								
Length (cm)	54.8 ± 2.51	58.4 ± 2.44	60.9 ± 2.24	66.9 ± 3.01	71.2 ± 3.13	74.8 ± 3.36	80.2 ± 3.50	85.8 ± 3.68
▪ LAZ	-0.5 ± 1.21	-0.4 ± 1.11	-0.4 ± 1.01	0.1 ± 1.34	0.0 ± 1.30	-0.1 ± 1.33	-0.6 ± 1.22	-0.3 ± 1.19
Weight (kg)	4.88 ± 0.61	5.83 ± 0.71	6.57 ± 0.83	7.99 ± 1.10	9.00 ± 1.31	9.62 ± 1.43	10.71 ± 1.45	11.60 ± 1.34
▪ WAZ	0.1 ± 0.94	0.1 ± 0.90	0.2 ± 0.97	0.3 ± 1.15	0.3 ± 1.19	0.2 ± 1.22	-0.0 ± 1.14	-0.3 ± 1.05
▪ WLZ	0.8 ± 1.33	0.7 ± 1.08	0.7 ± 1.02	0.5 ± 1.34	0.5 ± 1.21	0.3 ± 1.21	0.3 ± 1.16	-0.2 ± 1.09
▪ BMIZ	0.5 ± 1.11	0.4 ± 0.98	0.5 ± 1.01	0.4 ± 1.34	0.4 ± 1.23	0.3 ± 1.19	0.4 ± 1.17	-0.2 ± 1.12
HC (cm)	38.9 ± 1.30	40.4 ± 1.31	41.7 ± 1.34	44.4 ± 1.05	45.8 ± 1.66	47.1 ± 1.42	48.1 ± 1.74	49.1 ± 1.12
▪ HCZ	0.9 ± 1.05	0.8 ± 0.98	1.0 ± 0.93	1.2 ± 0.88	1.1 ± 1.20	1.2 ± 0.98	0.9 ± 1.17	0.9 ± 0.76
MUAC (cm)	13.1 ± 1.00	13.8 ± 1.09	14.5 ± 1.14	15.3 ± 1.06	15.9 ± 1.22	16.0 ± 1.72	16.0 ± 1.21	16.0 ± 1.17
▪ MUACZ [2]	N/A [2]	N/A [2]	1.0 ± 0.97	1.1 ± 0.84	1.3 ± 0.94	1.2 ± 1.46	1.1 ± 0.98	0.7 ± 0.97
Body composition [3]								
TBW (kg)	3.3 ± 0.42	3.8 ± 0.47	4.2 ± 0.47	4.7 ± 0.53	5.5 ± 0.77	6.0 ± 0.87	6.7 ± 0.81	7.2 ± 0.94
▪ TBW Z-score	0.5 ± 1.02	1.0 ± 0.92	1.1 ± 0.85	0.8 ± 0.93	0.9 ± 1.14	0.7 ± 1.18	-0.0 ± 0.96	-0.6 ± 1.08
FM (kg)	0.7 ± 0.26	1.1 ± 0.33	1.4 ± 0.47	2.1 ± 0.73	2.0 ± 0.72	1.9 ± 0.92	2.2 ± 0.78	2.4 ± 0.74
▪ FM z-score	-0.7 ± 1.10	-0.6 ± 0.93	-0.5 ± 1.04	0.1 ± 1.00	-0.4 ± 1.01	-0.7 ± 1.14	-0.3 ± 0.59	-0.6 ± 0.68
▪ %FM	14.6 ± 4.4	18.1 ± 4.8	20.3 ± 5.4	26.0 ± 6.0	22.5 ± 5.98	19.9 ± 7.4	20.2 ± 5.6	20.7 ± 5.3
▪ FMI	2.4 ± 0.81	3.1 ± 0.95	3.6 ± 1.19	4.7 ± 1.54	4.0 ± 1.30	3.4 ± 1.51	3.4 ± 1.14	3.3 ± 1.04
▪ FMI z-score	-0.8 ± 1.05	-0.5 ± 0.94	-0.4 ± 1.03	0.1 ± 1.02	-0.3 ± 0.99	-0.7 ± 1.15	-0.5 ± 0.89	-0.5 ± 0.75
FFM (kg)	4.1 ± 0.52	4.8 ± 0.59	5.2 ± 0.59	5.9 ± 0.66	6.9 ± 0.95	7.7 ± 1.10	8.5 ± 1.04	9.2 ± 1.20
▪ FFM z-score	0.5 ± 1.01	1.0 ± 0.93	1.1 ± 0.85	0.8 ± 0.93	0.9 ± 1.13	0.7 ± 1.17	0.0 ± 0.97	-0.5 ± 1.08
▪ %FFM	85.4 ± 4.4	81.9 ± 4.8	79.7 ± 5.4	74.0 ± 6.0	77.5 ± 6.0	80.1 ± 7.4	79.8 ± 5.6	79.3 ± 5.3
▪ FFMI	13.8 ± 1.45	14.0 ± 1.26	14.0 ± 1.18	13.1 ± 1.36	13.7 ± 1.52	13.7 ± 1.45	13.2 ± 1.10	12.4 ± 1.18
▪ FFMI z-score	1.5 ± 1.19	1.5 ± 0.92	1.4 ± 0.87	0.6 ± 1.14	1.0 ± 1.20	0.9 ± 1.21	0.5 ± 0.85	-0.2 ± 1.06

[1] Anthropometric z-scores calculated using WHO MGRS Growth Standards (WHO Anthro software) (27, 28).
[2] MUAC z-score only calculated from 3 months of age.
[3] Z-scores for body composition calculated using reference data from Wells et al (2020) (29).
Abbreviations: BC = body composition; BMIZ = body mass index-for-age z-score; FFM = fat-free mass; %FFM = percentage fat-free mass (FFM/weightx100); FFMI = fat-free mass index (FFM/[length in m]^2); FM = fat mass; %FM = percentage fat mass (FM/weightx100); FMI = fat mass

index (FM/[length in m]^2; HC = head circumference; HCZ = HC-for-age z-score; LAZ = length-for-age z-score; MUAC = mid-upper arm circumference; MUACZ = MUAC-for-age z-score; N/A = not applicable; TBW = total body water; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score.

FIGURES

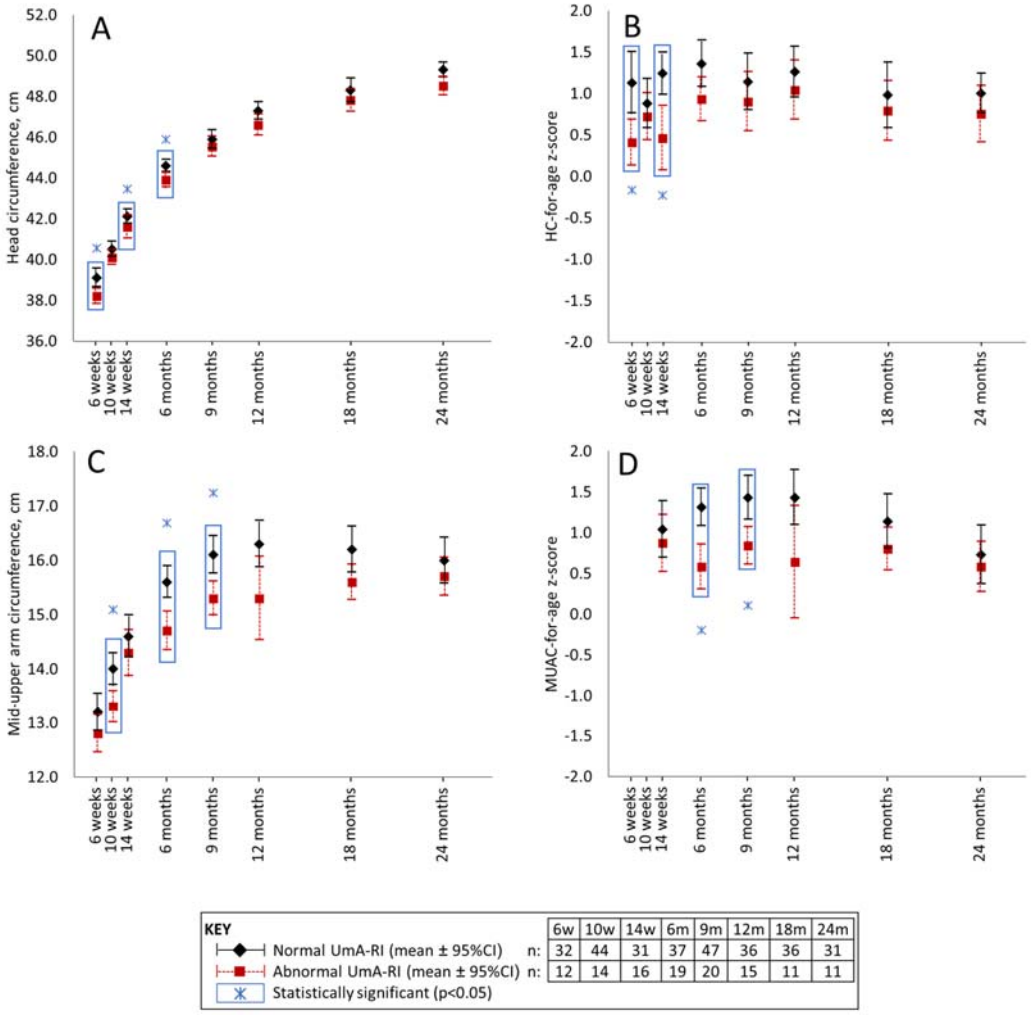
Figure 1: Anthropometry through two years of age of infants with normal and abnormal umbilical artery resistance index: weight and length



	6w	10w	14w	6m	9m	12m	18m	24m
n:	32	44	31	37	47	36	36	31
n:	12	14	16	19	20	15	11	11

A: length in cm; B: length-for-age z-score; C: weight in kg; D: weight-for-age z-score; E: weight-for-length z-score; F: BMI-for-age z-score

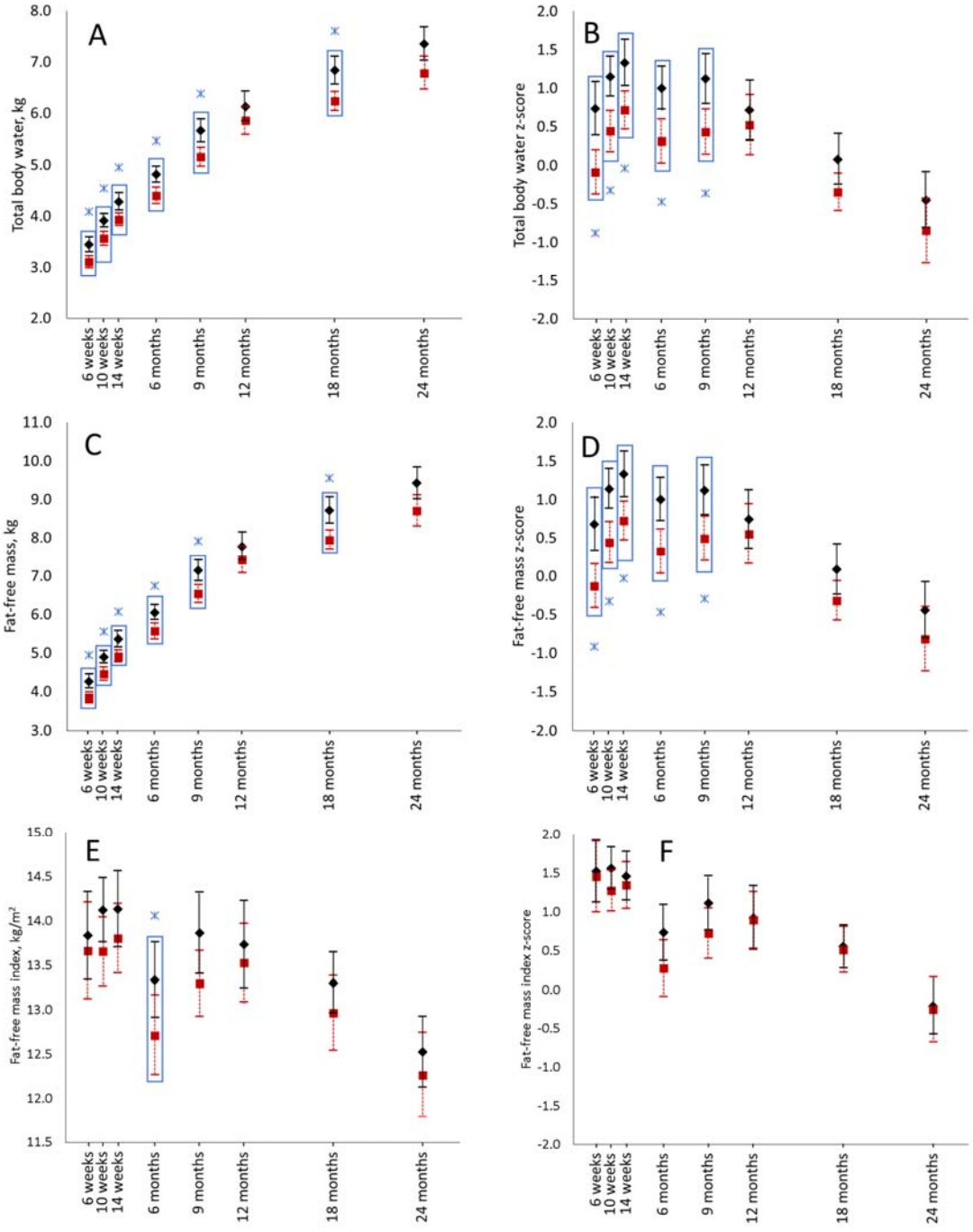
Figure 2: Anthropometry through two years of age of infants with normal and abnormal umbilical artery resistance index: head circumference and mid-upper arm circumference



	6w	10w	14w	6m	9m	12m	18m	24m
n:	32	44	31	37	47	36	36	31
n:	12	14	16	19	20	15	11	11

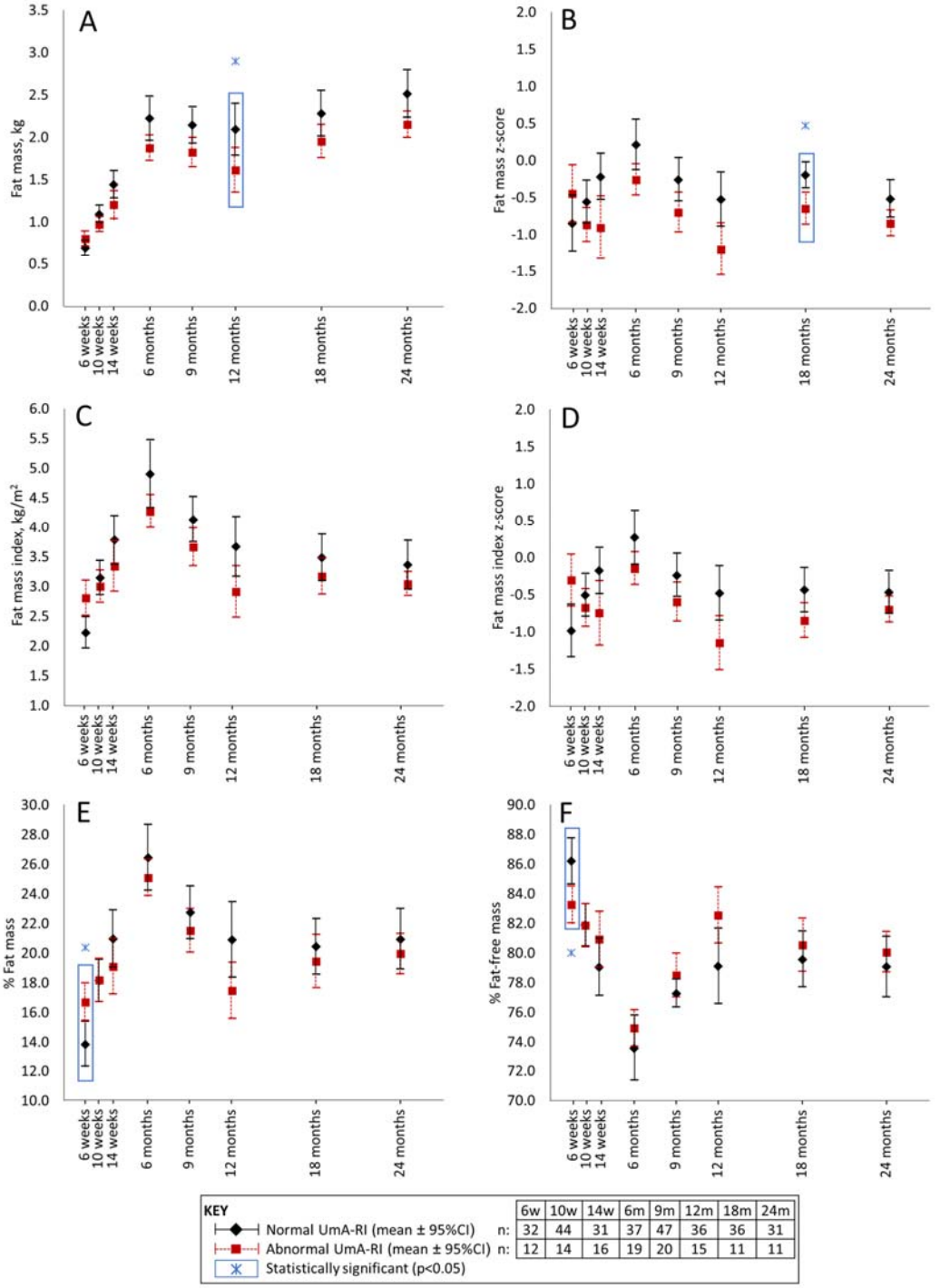
A: head circumference in cm; B: head circumference-for-age z-score; C: mid-upper arm circumference in cm; D: MUAC-for-age z-score;.

Figure 3: Body composition through two years of age of infants with normal and abnormal umbilical artery resistance index: total body water, fat-free mass and fat-free mass index



A: total body water in kg; B: total body water z-score; C: fat-free mass in kg; D: fat-free mass z-score; E: fat-free mass index in kg/m²; F: fat-free mass index z-score

Figure 4: Body composition through two years of age of infants with normal and abnormal umbilical artery resistance index: fat mass, fat free mass index, fat mass percentage and fat-free mass percentage



	6w	10w	14w	6m	9m	12m	18m	24m
n:	32	44	31	37	47	36	36	31
n:	12	14	16	19	20	15	11	11

A: fat mass in kg; B: fat mass z-score; C: fat mass index in kg/m²; D: fat mass index z-score; E: percentage fat mass; F: percentage fat-free mass

SUPPLEMENTARY TABLES

Supplementary Table 1: Anthropometry and body composition at 6, 10 and 14 weeks and 6 months of age of infants with normal and abnormal prenatal umbilical artery resistance index (UmA-RI)

	6 weeks			10 weeks			14 weeks			6 months		
	Normal UmA-RI (n=32)	Abnormal UmA-RI (n=12)	p-value[1]	Normal UmA-RI (n=44)	Abnormal UmA-RI (n=14)	p-value[1]	Normal UmA-RI (n=31)	Abnormal UmA-RI (n=16)	p-value[1]	Normal UmA-RI (n=37)	Abnormal UmA-RI (n=19)	p-value[1]
Age (months)	1.5 ± 0.09	1.5 ± 0.12	0.54 [2]	2.4 ± 0.13	2.4 ± 0.16	0.87 [2]	3.4 ± 0.13	3.4 ± 0.26	0.87 [2]	6.1 ± 0.21	6.1 ± 0.13	0.66
Sex (male) [n(%)]	15 (48.4)	4 (30.8)	0.51 [3]	27 (61.4)	6 (40.0)	0.22 [4]	21 (67.7)	7 (43.8)	0.11 [4]	20 (54.1)	8 (42.1)	0.40 [4]
Any breastfeeding [n (%)]	28 (87.5)	10 (83.3)	1.00 [3]	39 (88.6)	11 (78.6)	0.65 [3]	28 (90.3)	12 (75.0)	0.16 [3]	27 (73.0)	12 (63.2)	0.52 [4]
Length (cm)	55.5 ± 2.16	53.1 ± 2.66	0.014 *	58.8 ± 2.45	57.0 ± 1.93	0.010 *	61.6 ± 2.15	59.7 ± 1.92	0.004 *	67.4 ± 3.01	66.0 ± 2.88	0.10
▪ LAZ [5]	-0.2 ± 1.04	-1.3 ± 1.25	0.011 *	-0.2 ± 1.13	-0.9 ± 0.87	0.021 *	-0.1 ± 1.00	-0.9 ± 0.87	0.014 *	0.2 ± 1.37	-0.3 ± 1.20	0.17
Weight (kg)	4.97 ± 0.60	4.64 ± 0.60	0.12	5.97 ± 0.67	5.39 ± 0.67	0.010 *	6.80 ± 0.75	6.11 ± 0.79	0.008 *	8.28 ± 1.04	7.43 ± 1.00	0.005 [2] *
▪ WAZ [5]	0.2 ± 0.91	-0.3 ± 0.96	0.14	0.3 ± 0.85	-0.4 ± 0.87	0.017 *	0.4 ± 0.90	-0.3 ± 0.92	0.013 *	0.6 ± 1.09	-0.3 ± 1.05	0.007 *
▪ WLZ [5]	0.6 ± 1.20	1.4 ± 1.55	0.15	0.7 ± 1.09	0.6 ± 1.06	0.65	0.7 ± 0.98	0.5 ± 1.09	0.43	0.7 ± 1.35	0.0 ± 1.17	0.045 *
▪ BMIZ [5]	0.4 ± 1.05	0.7 ± 1.31	0.61	0.5 ± 0.96	0.1 ± 1.01	0.21	0.7 ± 0.96	0.2 ± 1.06	0.18	0.6 ± 1.35	-0.1 ± 1.15	0.038 *
HC (cm)	39.1 ± 1.31	38.2 ± 1.07	0.025 *	40.5 ± 1.33	40.1 ± 1.22	0.34	42.1 ± 1.02	41.0 ± 1.58	0.014 *	44.6 ± 0.93	43.9 ± 1.14	0.033 *
▪ HCZ [5]	1.1 ± 1.07	0.4 ± 0.80	0.022 *	0.9 ± 1.00	0.7 ± 0.96	0.59	1.2 ± 0.72	0.5 ± 1.10	0.018 *	1.4 ± 0.87	0.9 ± 0.83	0.09
MUAC (cm)	13.2 ± 1.00	12.8 ± 1.00	0.34	14.0 ± 1.01	13.3 ± 1.17	0.041 *	14.6 ± 1.10	14.3 ± 1.23	0.48	15.6 ± 0.89	14.7 ± 1.10	0.004 *
▪ MUACZ [5]	N/A [6]	N/A [6]	N/A [6]	N/A [6]	N/A [6]	N/A [6]	1.0 ± 0.98	0.8 ± 0.99	0.59	1.3 ± 0.71	0.6 ± 0.86	0.003 *
TBW (kg)	3.4 ± 0.42	3.1 ± 0.33	0.009 *	3.9 ± 0.45	3.6 ± 0.46	0.003 [2] *	4.3 ± 0.49	3.9 ± 0.35	0.019 [2] *	4.8 ± 0.49	4.4 ± 0.50	0.006 *
▪ TBW Z-score [7]	0.7 ± 1.00	-0.1 ± 0.83	0.011 *	1.1 ± 0.87	0.4 ± 0.90	0.002 [2] *	1.3 ± 0.86	0.7 ± 0.70	0.012 *	1.0 ± 0.87	0.3 ± 0.88	0.009 *
FFM (kg)	4.3 ± 0.52	3.8 ± 0.40	0.009 *	4.9 ± 0.56	4.5 ± 0.58	0.002 [2] *	5.4 ± 0.60	4.9 ± 0.44	0.025 [2] *	6.0 ± 0.61	5.6 ± 0.63	0.009 *
▪ FFM z-score [7]	0.7 ± 1.00	-0.1 ± 0.82	0.011 *	1.1 ± 0.88	0.4 ± 0.91	0.002 [2] *	1.3 ± 0.85	0.7 ± 0.71	0.012 *	1.0 ± 0.87	0.3 ± 0.89	0.010 *
▪ %FFM	86.2 ± 4.46	83.3 ± 3.61	0.035 *	81.9 ± 4.81	81.8 ± 4.91	0.98	79.0 ± 5.46	80.9 ± 5.34	0.27	73.6 ± 6.88	74.9 ± 3.83	0.35
▪ FFMI	13.8 ± 1.43	13.7 ± 1.57	0.744	14.1 ± 1.23	13.6 ± 1.31	0.10 [2]	14.1 ± 1.22	13.8 ± 1.11	0.36	13.3 ± 1.32	12.7 ± 1.39	0.049 [2] *
▪ FFMI z-score [7]	1.5 ± 1.16	1.4 ± 1.33	0.874	1.6 ± 0.93	1.3 ± 0.89	0.21 [2]	1.5 ± 0.89	1.3 ± 0.86	0.59	0.7 ± 1.12	0.3 ± 1.15	0.17
FM (kg)	0.7 ± 0.26	0.8 ± 0.26	0.217 [2]	1.1 ± 0.34	1.0 ± 0.29	0.22	1.4 ± 0.46	1.2 ± 0.47	0.11	2.2 ± 0.81	1.9 ± 0.47	0.10 [2]
▪ FM z-score [7]	-0.9 ± 1.09	-0.5 ± 1.11	0.299	-0.6 ± 0.97	-0.9 ± 0.77	0.15 [2]	-0.2 ± 0.88	-0.9 ± 1.21	0.05	0.2 ± 1.06	-0.3 ± 0.65	0.06
▪ %FM	13.8 ± 4.46	16.7 ± 3.61	0.035 *	18.1 ± 4.81	18.2 ± 4.91	0.98	21.0 ± 5.46	19.1 ± 5.34	0.27	26.4 ± 6.88	25.1 ± 3.83	0.35
▪ FMI	2.2 ± 0.75	2.8 ± 0.85	0.051	3.1 ± 0.97	3.0 ± 0.92	0.63	3.8 ± 1.18	3.3 ± 1.21	0.24	4.9 ± 1.76	4.3 ± 0.86	0.21 [2]
▪ FMI z-score [7]	-1.0 ± 1.02	-0.3 ± 1.01	0.062	-0.5 ± 0.97	-0.7 ± 0.86	0.38 [2]	-0.2 ± 0.88	-0.7 ± 1.23	0.11	0.3 ± 1.13	-0.2 ± 0.69	0.09

** Statistically significant (P<0.05)*
[1] p-values calculated using independent t-test unless otherwise specified.
[2] Wilcoxon rank sum (Mann-Whitney) test (data not normally distributed).
[3] Fisher's exact test
[4] Chi-squared test
[5] Anthropometric z-scores calculated using WHO MGRS Growth Standards (WHO Anthro software) (1, 2).
[6] MUAC z-score only calculated from 3 months of age.
[7] Z-scores for body composition calculated using reference data from Wells et al (2020) (3)
Abbreviations: BMIZ = body mass index-for-age z-score; FFM = fat-free mass; %FFM = percentage fat-free mass (FFM/weightx100); FFMI = fat-free mass index (FFM/[length in m]^2); FM = fat mass; %FM = percentage fat mass (FM/weightx100); FMI = fat mass index (FM/[length in m]^2; HC = head circumference; HCZ = HC-for-age z-score; LAZ = length-for-age z-score; MUAC = mid-upper arm circumference; MUACZ = MUAC-for-age z-score; N/A = not applicable; TBW = total body water; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score; UmA-RI = umbilical artery resistance index.

Supplementary Table 2: Anthropometry and body composition at 9, 12, 18 and 24 months of age of infants with normal and abnormal prenatal umbilical artery resistance index (UmA-RI)

	9 months			12 months			18 months			24 months		
	Normal UmA-RI (n=47)	**Abnormal UmA-RI (n=20)**	**p-value[1]**	**Normal UmA-RI (n=36)**	**Abnormal UmA-RI (n=15)**	**p-value1[1]**	**Normal UmA-RI (n=36)**	**Abnormal UmA-RI (n=11)**	**p-value[1]**	**Normal UmA-RI (n=31)**	**Abnormal UmA-RI (n=11)**	**p-value[1]**
Age (months)	9.1 ± 0.16	9.1 ± 0.11	0.38 [2]	12.2 ± 0.21	12.1 ± 0.17	0.35 [2]	18.3 ± 0.70	18.2 ± 0.15	0.94 [2]	24.3 ± 0.33	24.2 ± 0.22	0.76 [2]
Sex (male) [n(%)]	24 (51.1)	7 (35.0)	0.23 [3]	21 (58.3)	5 (33.3)	0.10 [3]	21 (58.3)	4 (36.4)	0.31 [3]	21 (67.7)	3 (27.3)	0.033 [3] *
Any breastfeeding [n(%)]	30 (63.8)	9 (45.0)	0.22 [3]	19 (52.8)	5 (33.3)	0.38 [3]	11 (30.6)	1 (9.1)	0.12 [3]	0	0	N/A
Length (cm)	71.7 ± 2.96	70.1 ± 3.27	0.06	75.1 ± 3.45	74.0 ± 3.09	0.17 [2]	80.8 ± 3.48	78.3 ± 2.91	0.027 *	86.4 ± 3.79	84.2 ± 2.86	0.05
▪ LAZ [4]	0.2 ± 1.28	-0.3 ± 1.31	0.13	0.0 ± 1.36	-0.3 ± 1.27	0.41 [2]	-0.4 ± 1.24	-1.1 ± 1.04	0.07	-0.1 ± 1.22	-0.7 ± 1.06	0.17
Weight (kg)	9.29 ± 1.29	8.35 ± 1.18	0.006 *	9.85 ± 1.36	9.05 ± 1.48	0.032 [2] *	10.97 ± 1.51	9.88 ± 0.82	0.004 *	11.88 ± 1.28	10.85 ± 1.26	0.033 *
▪ WAZ [4]	0.6 ± 1.15	-0.2 ± 1.12	0.013 *	0.3 ± 1.16	-0.2 ± 1.31	0.15	0.1 ± 1.18	-0.6 ± 0.82	0.037 *	-0.1 ± 1.00	-0.7 ± 1.10	0.08 [2]
▪ WLZ [4]	0.7 ± 1.17	0.0 ± 1.21	0.07	0.5 ± 1.11	-0.1 ± 1.35	0.12 [2]	0.4 ± 1.20	-0.1 ± 0.98	0.19	-0.1 ± 1.09	-0.5 ± 1.07	0.13 [2]
▪ BMIZ [4]	0.6 ± 1.20	-0.0 ± 1.22	0.07 [2]	0.5 ± 1.08	-0.1 ± 1.34	0.10 [2]	0.5 ± 1.20	0.1 ± 1.06	0.34	-0.1 ± 1.14	-0.4 ± 1.10	0.38
HC (cm)	45.9 ± 1.64	45.5 ± 1.72	0.31	47.3 ± 1.32	46.6 ± 1.63	0.20	48.3 ± 1.76	47.8 ± 1.68	0.39	49.3 ± 1.00	48.5 ± 1.27	0.10
▪ HCZ [4]	1.1 ± 1.19	0.9 ± 1.25	0.47	1.3 ± 0.94	1.0 ± 1.09	0.51	1.0 ± 1.21	0.8 ± 1.10	0.63	1.0 ± 0.68	0.8 ± 0.97	0.50 [2]
MUAC (cm)	16.1 ± 1.23	15.3 ± 1.06	0.017 [2] *	16.3 ± 1.31	15.3 ± 2.36	0.15	16.2 ± 1.26	15.6 ± 0.97	0.15	16.0 ± 1.24	15.7 ± 0.79	0.41
▪ MUACZ [4]	1.4 ± 0.94	0.8 ± 0.81	0.020 [2] *	1.4 ± 1.03	0.6 ± 2.11	0.08 [2]	1.1 ± 1.02	0.8 ± 0.81	0.26	0.7 ± 1.02	0.6 ± 0.87	0.63
TBW (kg)	5.7 ± 0.76	5.1 ± 0.65	0.008 [2] *	6.1 ± 0.89	5.9 ± 0.83	0.22 [2]	6.8 ± 0.83	6.2 ± 0.57	0.011 *	7.4 ± 0.92	6.8 ± 0.91	0.09
▪ TBW Z-score [5]	1.1 ± 1.13	0.4 ± 1.02	0.018 *	0.7 ± 1.18	0.5 ± 1.19	0.40 [2]	0.1 ± 1.00	-0.3 ± 0.74	0.137	-0.5 ± 1.03	-0.9 ± 1.19	0.34
FFM (kg)	7.1 ± 0.96	6.5 ± 0.80	0.010 *	7.8 ± 1.12	7.4 ± 1.05	0.22 [2]	8.7 ± 1.06	7.9 ± 0.76	0.014 *	9.4 ± 1.18	8.7 ± 1.17	0.10
▪ FFM z-score [5]	1.1 ± 1.13	0.5 ± 1.00	0.028 *	0.7 ± 1.17	0.5 ± 1.19	0.60	0.1 ± 1.00	-0.3 ± 0.78	0.17	-0.4 ± 1.04	-0.8 ± 1.19	0.37
▪ %FFM	77.3 ± 6.23	78.5 ± 5.16	0.41	79.1 ± 7.78	82.5 ± 5.80	0.09	79.6 ± 5.72	80.5 ± 5.51	0.63	79.1 ± 5.78	80.1 ± 3.87	0.84 [2]
▪ FFMI	13.9 ± 1.60	13.3 ± 1.30	0.18 [2]	13.7 ± 1.51	13.5 ± 1.35	0.62	13.3 ± 1.05	13.0 ± 1.29	0.53 [2]	12.5 ± 1.13	12.3 ± 1.36	0.58
▪ FFMI z-score [5]	1.1 ± 1.22	0.7 ± 1.13	0.23	0.9 ± 1.26	0.9 ± 1.12	0.93	0.6 ± 0.85	0.5 ± 0.90	0.87 [2]	-0.2 ± 1.04	-0.3 ± 1.18	0.49 [2]
FM (kg)	2.1 ± 0.75	1.8 ± 0.61	0.07	2.1 ± 0.94	1.6 ± 0.80	0.049 [2] *	2.3 ± 0.82	1.9 ± 0.60	0.15	2.5 ± 0.80	2.2 ± 0.44	0.16 [2]
▪ FM z-score [5]	-0.3 ± 1.02	-0.7 ± 0.94	0.10	-0.5 ± 1.12	-1.2 ± 1.08	0.06	-0.2 ± 0.53	-0.7 ± 0.67	0.022 [2] *	-0.5 ± 0.72	-0.8 ± 0.50	0.11
▪ %FM	22.7 ± 6.23	21.5 ± 5.16	0.40	20.9 ± 7.78	17.5 ± 5.80	0.09	20.4 ± 5.72	19.5 ± 5.51	0.63	20.9 ± 5.78	19.9 ± 3.87	0.84 [2]
▪ FMI	4.1 ± 1.35	3.7 ± 1.11	0.15	3.7 ± 1.54	2.9 ± 1.33	0.09 [2]	3.5 ± 1.20	3.2 ± 0.93	0.37	3.4 ± 1.17	3.0 ± 0.57	0.57 [2]
▪ FMI z-score [5]	-0.2 ± 1.02	-0.6 ± 0.91	0.16	-0.5 ± 1.12	-1.2 ± 1.11	0.06	-0.4 ± 0.92	-0.9 ± 0.71	0.13	-0.5 ± 0.82	-0.7 ± 0.49	0.65 [2]

** Statistically significant (P<0.05)*

[1] p-values calculated using independent t-test unless otherwise specified.

[2] Wilcoxon rank sum (Mann-Whitney) test (data not normally distributed).

[3] Chi squared test

[4] Anthropometric z-scores calculated using WHO MGRS Growth Standards (WHO Anthro software) (1, 2)

[5] Z-scores for body composition calculated using reference data from Wells et al (2020) (3).

Abbreviations: BMIZ = body mass index-for-age z-score; FFM = fat-free mass; %FFM = percentage fat-free mass (FFM/weightx100); FFMI = fat-free mass index (FFM/[length in m]^2); FM = fat mass; %FM = percentage fat mass (FM/weightx100); FMI = fat mass index (FM/[length in m]^2; HC = head circumference; HCZ = HC-for-age z-score; LAZ = length-for-age z-score; MUAC = mid-upper arm circumference; MUACZ = MUAC-for-age z-score; N/A = not applicable; TBW = total body water; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score; UmA-RI = umbilical artery resistance index.

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