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POSTNATAL GROWTH AND BODY COMPOSITION

UP TO TWO YEARS OF AGE

OF TERM AND PRETERM INFANTS

WITH PLACENTAL INSUFFICIENCY AND/OR

SMALL SIZE FOR GESTATIONAL AGE AT BIRTH

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POSTNATAL GROWTH AND BODY COMPOSITION UP TO TWO YEARS OF AGE OF TERM AND PRETERM INFANTS WITH PLACENTAL INSUFFICIENCY AND/OR SMALL SIZE FOR GESTATIONAL AGE AT BIRTH

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DECLARATIONS BY THE AUTHOR

DECLARATION OF ORIGINALITY

I, Sanja Nel, declare that the dissertation, which I hereby submit for the degree PhD Dietetics at the University of Pretoria, is my own work and has not previously been submitted by me for a degree at this or any other tertiary institution.

Signature  Date 29/05/2024

ETHICS STATEMENT

I, Sanja Nel, have obtained, for the research described in this work, the applicable research ethics approval. (Faculty of Health Sciences Research Ethics Committee approval number 468/2017). Written permission to conduct data collection was obtained from all health facilities and their research ethics departments.

The author declares that he/she has observed the ethical standards required in terms of the University of Pretoria's Code of ethics for researchers and the Policy guidelines for responsible research.

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ABSTRACT

Background: Growth in the first thousand days can affect lifelong health, yet joint clinical management between prenatal, perinatal and postnatal healthcare providers is often limited. Preterm birth and/or foetal growth restriction (FGR), often presenting as small-for-gestational age (SGA), affect short- and long-term outcomes. Placental insufficiency affects foetal growth and body composition (BC) even in appropriate-for-gestational age (AGA) newborns. Preterm birth, SGA and placental insufficiency are prevalent in South Africa.

Aims: This thesis aimed to (a) develop an integrated framework for foetal/infant growth assessment, (b) compare the predictive value of two commonly used preterm infant growth charts, (c) describe one-year growth and its early life predictors in preterm infants with/without SGA (d) describe two-year growth and BC, and early-life predictors thereof, in term infants with/without placental insufficiency.

Methods: Framework development (*objective a*): An interdisciplinary (obstetricians, paediatricians and dietitians) iterative think-tank approach, supported by published literature, was used for framework development.

Cohort 1, a *preterm* historical cohort (*objectives b and c*), utilised patient records (N=321, 111 SGA, 310 AGA) from the kangaroo mother care follow-up clinic at a tertiary South African hospital. Using anthropometric data up to 12 months, z-scores were calculated with the Fenton Growth Chart (FGC), INTERGROWTH-21ST Newborn Size Standards (IG-NBSS), and INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants (IG-PPGS). Birth weight z-score (BWZ, FGC *vs*. IG-NBSS) and weight gain up to 50 weeks postmenstrual age (ΔWZ, FGC *vs*. IG-PPGS) were compared (Cohen's Kappa) for association with one-year anthropometry (malnutrition).

Cohort 2, the *UmbiBaby* cohort (*objective d*), included 81 term-born infants with Doppler-derived umbilical artery resistance index (UmA-RI) assessed at 28-34 weeks' gestation (55 normal, 26 abnormal UmA-RI). During eight follow-up visits over two years, anthropometric measurements were taken, and fat-free mass (FFM) and fat mass (FM) assessed using deuterium dilution. Z-scores were calculated for FM (FMZ), FFM (FFMZ), FM index (FMIZ) and FFM index (FFMIZ).

For both cohorts, z-scores were calculated for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), BMI-for-age (BMIZ), MUAC-for-age (MUACZ) and HC-for-age (HCZ) using WHO Anthro (age-corrected for preterm infants). Underweight (WAZ<-2), stunting (LAZ<-2), wasting (WLZ<-2) and overweight (BMIZ>+2) rates were calculated at last

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visit. Outcomes were compared for SGA (birth weight-for-GA <10th percentile) *vs*. AGA (birth weight-for-GA ≥10th - ≤90th percentile) infants (preterm cohort), and normal *vs*. abnormal UmA-RI (*UmbiBaby* cohort). Longitudinal growth was characterised using latent class trajectory modelling (LCTM). Multivariable analysis investigated early-life predictors of growth trajectories (both cohorts) and one-year malnutrition (*preterm* cohort).

Results: *Objective a:* An integrated framework of measurements, indices and indicators used by various health care providers in antenatal, perinatal and postnatal care and research informed all subsequent investigations.

Objective b (preterm cohort): FGC and IG-PPGS produced similar ΔWZ (IG-PPGS=-0.26±1.23, FGC=-0.11±1.14; P=0.153) and performed similarly in multivariable analysis. Using ΔWZ<-1, FGC predicted more underweight (42.0% *vs*. 36.0%), more wasting (43.5% *vs*. 39.1%), and equal stunting (33.3%), while ΔWZ>+1 on FGC predicted more overweight (57.1% *vs*. 38.1%). There was substantial agreement between the charts in terms of number of infants with ΔWZ<-1, -1≤ΔWZ≤+1 and ΔWZ>+1 (K=0.647) and the association between these classes and malnutrition outcomes (K=0.734 to 0.627)

Objective c (preterm cohort): At one year, SGA infants had lower anthropometric z-scores and more stunting (34.2% *vs*. 9.1%; P<0.001), underweight (31.2% *vs*. 7.2%; P<0.001) and wasting (12.6% *vs*. 4.3%, P=0.012), despite larger first-year WAZ gains (+0.70±1.30 *vs*. +0.05±1.30, P<0.001). In multivariable analysis, birth weight z-score (BWZ) predicted one-year undernutrition better than being born SGA. LCTM identified three WAZ and LAZ trajectories (faltering, gradual gain, catch-up), and two WLZ trajectories (faltering, gain). Lower BWZ was associated with WAZ and LAZ catch-up but WLZ faltering. Larger ΔWZ was associated with WAZ catch-up and gradual LAZ gain. WAZ and WLZ faltering were associated with more underweight (49.1%, 22.4%), stunting (45.5%, 23.5%) and wasting (21.8%, 10.3%), while WAZ catch-up and WLZ gain were associated with more overweight (24.4%, 17.6%; all P<0.001). Gradual LAZ gain was associated with the least underweight (2.0%), stunting (2.1%) and wasting (2.1%, all P<0.001).

Objective d (UmbiBaby cohort): Infants with abnormal UmA-RI had lower WAZ up to 18 months (mean±SD [-0.6±0.82 to -0.2±1.12] *vs*. [0.1±1.18 to 0.6±1.09]; P=0.037-0.017 for measurements at different ages), LAZ up to 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 FFMZ up to 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). LCTM identified three WAZ, LAZ, WLZ, BMIZ, HCZ and FFMZ trajectories, and two MUACZ, FMZ, FMIZ and FFMIZ trajectories. While FMZ and FMIZ trajectories converged around 2 years, FFMZ and FFMIZ trajectories

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declined. In multivariable analysis, lower BWZ (or SGA) predicted lower WAZ, WLZ, BMIZ, FMZ and FFMZ trajectories, while higher (or abnormal) UmA-RI predicted lower LAZ and FFMZ trajectories.

Conclusions and recommendations: The complex associations of prenatal and early postnatal growth with growth and BC outcomes at 1-2 years underscore the importance of an integrated approach to growth in the first thousand days. Careful documentation on the Road-to-Health Booklet of pregnancy conditions (including UmA-RI screening results, when available) and accurately measured birth anthropometry can facilitate interdisciplinary communication. For preterm infants, FGC and IG-PPGN perform similarly, as long as the change in z-score (rather than an absolute z-score) is used to assess growth. Abnormal UmA-RI predicts lower LAZ and FFMZ trajectories up to 24 months, while lower BWZ predicts lower WAZ, LAZ and WLZ at 12 months in preterm infants (accompanied by higher rates of underweight, stunting and wasting), and at 24 months in term infants. Though the cause of the high observed rates of abnormal UmA-RI in the South African population is currently unknown, interventions to support healthy pregnancies and foetal growth should be prioritised. Early and ongoing assessment of WAZ, LAZ and WLZ can guide nutrition interventions for optimal longer-term growth; faltering growth in any anthropometric index should prompt further assessment of health conditions and nutrition status, followed by appropriate caregiver counselling, referral or other interventions.

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TABLE OF CONTENTS

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LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

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LIST OF ABBREVIATIONS

%FM	Percentage fat mass
ΔWZ	Change in weight-for-PMA z-score from birth until the last measurement before 50 weeks PMA
AC	Abdominal circumference
AGA	Appropriate-for-gestational age
ART	Antiretroviral therapy
BMI	Body mass index
BMIZ	Body mass index-for-age z-score
BWZ	Birth weight z-score
EFW	Estimated foetal weight
FGC	Fenton growth chart
FGR	Foetal growth restriction
FFM	Fat-free mass
FFMI	Fat-free mass index
FFMIZ	Fat-free mass index z-score
FFMZ	Fat-free mass z-score
FM	Fat mass
FMI	Fat mass index
FMIZ	Fat mass index z-score
FMZ	Fat mass z-score
HC	Head circumference
HCZ	Head circumference-for-age z-score
HIC	High-income countries
HIV	Human immunodeficiency virus
IG-NBSS	INTERGROWTH-21ST Newborn Size Standards
IG-PPGS	INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants
LAZ	Length-for-age z-score
LBW	Low birth weight
LMIC	Low- and middle-income countries
MUAC	Mid-upper arm circumference
MUACZ	Mid-upper arm circumference-for-age z-score
PI	Pulsatility index
PMA	Postmenstrual age
PMA50	The last PMA up to a maximum of 50 weeks at which anthropometric measurements were recorded

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RI	Resistance index
SGA	Small-for-gestational age
UmA	Umbilical artery
UmA-RI	Umbilical artery resistance index
UmA-RIZ	Umbilical artery resistance index z-score
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHO MGRS	World Health Organization Multicentre Growth Reference Study
WLR	Weight-length ratio
WLZ	Weight-for-length z-score

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DEFINITIONS OF CORE TERMINOLOGY

Appropriate-for-gestational age (AGA)	Birth weight between the 10th and 90th percentile (inclusive of both) for gestational age and sex on a suitable birthweight-for-GA growth chart,[1] such as the Fenton Growth Chart or INTERGROWTH-21ST Newborn Size Standards.
Asymmetric foetal growth	Disproportion between birth weight and length/ head circumference: birth weight falls on a markedly lower percentile or z-score than the length and/ or HC.[2-4]
Body composition	The division of the body into different compartments, on an atomic, molecular, cellular, or functional (tissue) level.[5] In this thesis, a simple two-compartment model was used, dividing the body into fat mass and fat-free mass.
Catch-up growth	A temporary increase in growth velocity (i.e. increase in z-scores over time) following a period of faltering growth,[6] culminating in a return to the z score preceding the period of faltering growth.
Chronological age	The age of an infant calculated from the time of birth, irrespective of gestational age at birth.
Constitutionally small	A newborn that is small-for-gestational age (birth weight below the 10th percentile) but is meeting its genetic growth potential.
Corrected age	The age that a preterm infant would have been if birth occurred at exactly 40 weeks' gestation. Calculated by subtracting the number of days/ weeks of prematurity (i.e. 40 weeks minus GA) from the chronological age.
Doppler / Doppler ultrasound	A non-invasive ultrasound technique that utilises the deflection of sound wave to measure the velocity of

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	blood flow (in this thesis, specifically blood flow in the umbilical arteries).[7,8]
Faltering growth (or growth faltering)	A reduction in WFA *z* score of ≥1.0 that occurs over a period of 1 month or more and does not include the first 2 weeks after birth.[6] In this thesis, "faltering" is also used to describe a growth trajectory in any anthropometric index where the z-score declines over time.
Fat-free mass (FFM)	The sum of all body tissues except fat mass; including soft tissue (muscles, organs), bone, blood and extracellular fluid.[5]
Fat-free mass index (FFMI)	The proportion of fat-free mass to body length squared, calculated as FFM/length^2. The sum of the fat-free mass index and fat mass index is the body mass index (BMI).[9]
Fat mass (FM)	Body fat (adipose tissue).[5]
Fat mass index (FMI)	The proportion of fat mass to body length squared, calculated as FM/length^2. The sum of the fat mass index and fat-free mas index is the body mass index (BMI).[9]
Foetal growth restriction (FGR)	Failure of the foetus to reach its genetic growth potential. Foetal growth (in weight, length or other body measurements) falls short of what would be achieved under ideal conditions.[2,10,11] Clinically manifests as declining foetal growth percentiles over time.[11,12]
Gestational age (GA)	A measure of the duration of pregnancy. Calculated from the first day of the last menstrual period before conception.[13]
Growth	The change in the size of a measured parameter (e.g. weight) over time.[14]

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Growth faltering (or faltering growth)	A reduction in WFA *z* score of ≥1.0 that occurs over a period of 1 month or more and does not include the first 2 weeks after birth.[6] In this thesis, "faltering" is also used to describe a growth trajectory in any anthropometric index where the z-score declines over time.
Growth trajectory	An infant or group of infants' growth plotted over time, assessed longitudinally as a measurement index (e.g. weight-for-age) or z-score.
Low birth weight (LBW)	Birth weight <2500 g.[1]
Malnutrition	In this thesis, malnutrition is used as a collective term to include both undernutrition (operationalised as underweight, stunting and wasting) and overnutrition (operationalised as overweight).
Overweight	BMI-for-age z-score >+2 in children under five years of age.[15]
Obesity	BMI-for-age z-score >+3 in children under five years of age.[15]
Percentage fat mass (%FM)	The percentage of body weight consisting of fat mass; calculated as FM/weight*100.
Postmenstrual age (PMA)	The age of an infant calculated from the first date of the last menstrual period before conception; equal to the sum of gestational age and chronological age. PMA is used when monitoring the postnatal growth of preterm infants.[16]
Placental insufficiency	An impairment in the ability of the placenta to transfer adequate nutrients and oxygen to the foetus.[2,1,17] In this thesis, placental insufficiency is diagnosed using an increase in the umbilical artery resistance index on Doppler ultrasound.

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Preterm/ preterm birth	Birth before 37 completed weeks of gestation.[1]
Small-for-gestational age (SGA)	Birth weight below the 10th percentile for gestational age and sex on a suitable birthweight-for-GA growth chart,[1] such as the Fenton Growth Chart or INTERGROWTH-21ST Newborn Size Standards.
Stunting	Length/height-for-age z-score <-2 in children under five years of age.[15]
Underweight	Weight-for-age z-score <-2 in children under five years of age.[15]
Umbilical artery resistance index (UmA-RI)	An index derived from Doppler-measured blood flow velocity in the umbilical artery. RI is calculated from the difference between the systolic (S) and diastolic (D) flow rates, divided by the systolic flow rate (i.e. RI=(S-D)/S). In a healthy pregnancy, UmA-RI decreases over time. Elevated UmA-RI indicates decreased placental transfer.[7]
Wasting	Weight-for-length/height z-score <-2 in children under five years of age.[15]

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CHAPTER 1: GENERAL INTRODUCTION

BACKGROUND AND RATIONALE

The first thousand days of life – from conception to the second birthday – are a time of immense developmental plasticity. Nutritional, environmental, and other exposures during this critical developmental period can influence genetic expression and organ development, thereby affecting the infant's lifelong resilience and susceptibility to ill health.[1-4] Nutrition and growth in the first thousand days can be adversely impacted by numerous events, including impaired placental function (leading to restricted foetal nutrient and oxygen supplies, thus impairing foetal growth),[5,6] infections, including prenatal HIV exposure (which may affect growth even if HIV transmission did not occur)[7] and preterm birth (which interrupts intrauterine growth and complicates adequate early nutrient delivery).[8]

A recent Lancet series introduced the term "small, vulnerable newborn" to describe infants that are born preterm (i.e. before 37 completed weeks of gestation), small-for-gestational age (SGA, i.e. with a birth weight below the 10th sex- and gestational age-specific percentile) and/or low birth weight (LBW, birth weight <2500g).[9] Though the exact burden of preterm and SGA birth in South Africa is unknown, it is likely to be high.[10] One review estimated the 2020 preterm birth rate in South Africa at 13.0 (95%CI 9.2-17.9) per 100 live births, amounting to >150 000 preterm births annually.[11] This figure has remained unchanged since 2010, and exceeds the Sub-Saharan average estimate of 10.1%.[11] Concurrently, the 2019-2020 district health barometer reported an estimated LBW rate of 12.9%.[12] Perinatal conditions – including complications of preterm birth – account for >40% of infant mortality and ~80% of neonatal mortality in South Africa.[10,13-14] Recent research has also revealed unexpectedly high levels of impaired placental functioning (assessed using Doppler ultrasonography of the umbilical artery) in otherwise healthy, low risk pregnancies.[15-17] Placental insufficiency is described in the literature as a leading cause of stillbirth and foetal growth restriction (FGR),[5,6,18-20] an observation that has been borne out in local studies.[16,17] Importantly, FGR due to later-onset placental insufficiency does not always result in SGA, making birth size alone an unreliable indicator of intrauterine malnutrition.[21] Asymmetry at birth – i.e. a birth weight that falls on a markedly lower percentile/ z-score than head circumference (HC) – can indicate later-onset placental insufficiency, as limited foetal nutrient supplies are directed primarily to the brain at the cost of muscle and fat deposition.[22]

Widespread antenatal Doppler screening has become feasible with the development of the Umbiflow^{TM} device, a portable, low-cost continuous-wave Doppler device that can be used by nursing staff providing antenatal care in a primary health care setting.[15,23] Studies have shown that routine Umbiflow screening in low-risk pregnancies, coupled with appropriate

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management, markedly reduced stillbirth without increasing neonatal deaths.[16] Implementation of Umbiflow in the primary health care setting is currently being investigated in Tshwane District, and, if successful, will be expanded to the rest of the country. It is not known whether a history of placental insufficiency has long-term consequences for surviving infants, but it is plausible that FGR, even when it does not result in SGA or asymmetry at birth, could affect postnatal growth and/or body composition.

The data suggest high rates of preterm birth, SGA, FGR and placental insufficiency in South Africa, which could have appreciable effects on population-level nutrition status. Though the population prevalence of childhood underweight and wasting have declined in recent decades,[24-25] infants born preterm and/or SGA remain at higher risk of these conditions throughout childhood, especially in LMICs.[24] Moreover, the prevalence of childhood stunting has remained high at 13.5% (4-6 years) and 26.9% (0-3 years) in the 2013 South African National Health and Nutrition Survey, [24] and 27.2% (0-5 years) in the 2016 Demographic and Health Survey,[24] with little improvement in this period. Research from a variety of settings has shown that early length deficits due to preterm birth or SGA are less likely to catch up to age-appropriate levels than weight or HC.[27-30] It is not clear to what extent this is true for South African infants. Furthermore, little is known about growth outcomes in non-SGA infants with FGR or a history of placental insufficiency, yet it is plausible that these may also contribute to childhood stunting.

In summary, growth in the first thousand days occurs as a continuous, non-linear process from the moment of conception. Events during each stage (prenatal/ intrauterine, perinatal/ birth and postnatal/ infancy) influence subsequent stages, as illustrated in the conceptual framework for this thesis (Figure 1-1). Considering these exposures and outcomes longitudinally is crucial for obtaining a complete and comprehensive understanding of child growth and malnutrition. This research aimed to contribute to such an understanding by investigating the growth-related factors shown in the conceptual framework, relevant to the South African context. The conceptual framework was developed by the student while planning the research; the first publication expands upon the framework, and it served as a foundation for all the subsequent research.

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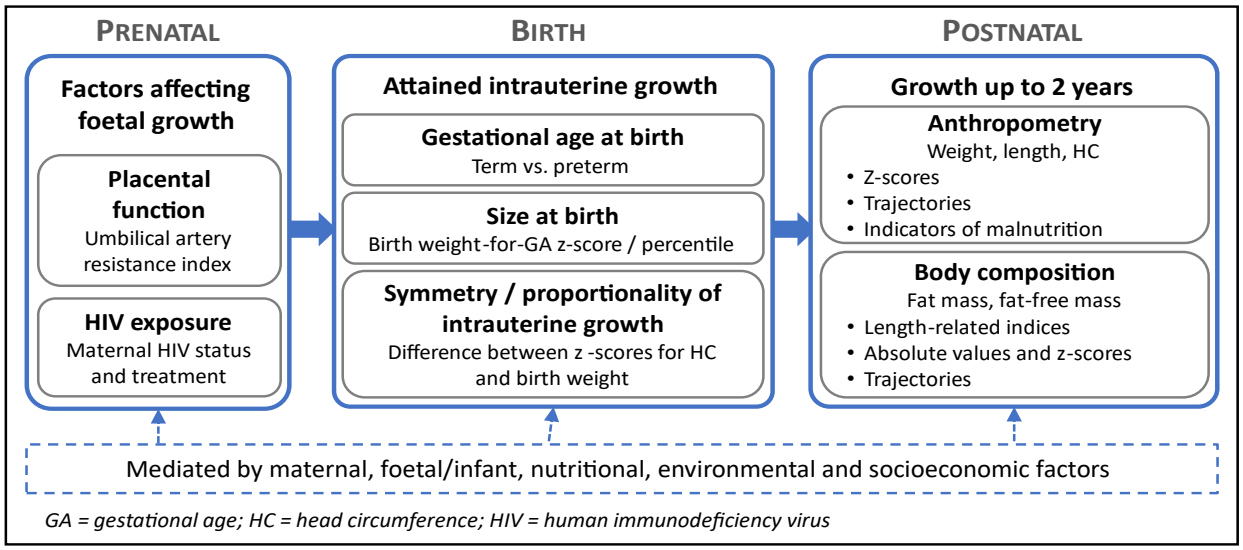

Figure 1-1: Conceptual framework underlying the thesis.

CORE RESEARCH PROBLEM

In a setting where child malnutrition is prevalent, it is important from both a clinical and a public health perspective to characterise at-risk newborns and infants, as this will help to identify appropriate targets for monitoring and intervention. If, for example, certain prenatal or neonatal characteristics increase the likelihood of stunting, growth monitoring in these infants should focus on their length growth (providing appropriate nutrition and other support) while guarding against disproportionate weight gain which, in shorter children, could predispose to overweight. If scaled up to population level, this could reduce the incidence of stunting, while the prevention of childhood overweight could help stem the rising flood of obesity in the next generation.[31,32]

There is a need to clarify the relative contribution of various aspects of foetal and early-life undernutrition to later growth outcomes. These include:

- evaluating to what extent being SGA contributes to poor growth outcomes in preterm infants, in a setting where preterm infants receive high quality follow-up care within the bounds of a typical, resource-constrained South African context;
- evaluating which of two commonly used preterm infant growth charts performs better at predicting adverse growth outcomes in preterm infants; and
- evaluating whether SGA (i.e. birth weight-for-gestational age (GA) alone), asymmetry (i.e. the proportionality of birth weight and HC) or a history of placental insufficiency (i.e. an abnormal antenatal umbilical artery Doppler in the third trimester) is the strongest predictor of growth outcomes.

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Investigating body composition alongside anthropometry is necessary, because children from the ethnically and socioeconomically dissimilar settings in the United Kingdom and the Gambia had different body composition even with similar anthropometric measurements.[33] This suggests that the available research from high income countries cannot be assumed to apply to South African infants, warranting local studies.

PROBLEM STATEMENT

Even though the health outcomes of small vulnerable infants have been extensively researched in high-income countries, there remain several gaps in the body of knowledge, not only in LMIC's but worldwide. The potential contribution of prenatal placental insufficiency, in particular, has received very little research attention, despite being widely recognised as the leading cause of FGR. In the South African setting, research is even more limited. It is well established that childhood stunting is prevalent in South Africa, and childhood overweight/ obesity is on the rise, yet little is known about the association of these problems with prenatal and early-life factors such as preterm birth, FGR and particularly placental insufficiency. An integrated life-course approach to investigating child growth is further hampered by the limited common understanding, clear communication, and inter-disciplinary coordination between prenatal, perinatal, and paediatric clinicians and researchers. Growth in infancy cannot be comprehensively understood without taking into consideration foetal growth and nutrition.

Few studies have reported on the growth outcomes of South African preterm and/or SGA infants, and none has investigated the postnatal growth effects of prenatal placental insufficiency beyond 6 months of life. There is a need for data characterising and comparing the longer-term growth effects of factors affecting early postnatal growth, including preterm birth (including the use of different growth charts to assess early growth), SGA, asymmetric foetal growth, and prenatal placental insufficiency. There is also a paucity of body composition data for South African infants, although recent publications from the Multicentre Infant Body Composition Reference Study have begun to rectify this.[34] Amid growing acknowledgement that preterm birth and FGR impact body composition as well as growth, and that the association between body composition and health outcomes is not fully captured by anthropometric measurements alone, investigating these associations in local populations is important.

This research investigated some of these questions through the analysis of longitudinally collected growth data in two cohorts of infants in Tshwane District, Gauteng Province, South Africa. The first was a historical cohort of preterm infants, whose growth data were used to compare the consequences of using different preterm growth charts, to describe typical

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growth trajectories of preterm infants over the first postnatal year, and to investigate the contribution of being SGA to growth in preterm infants. The second cohort, consisting of term infants recruited from a previous study on prenatal placental insufficiency, was used to investigate the ability of Doppler screening results to predict growth and body composition over the first two years of life, and compare its predictive ability to that of SGA and asymmetry. Both cohorts were recruited in a low socioeconomic status community with a considerable burden of maternal HIV infection. Ultimately, this study hoped to arrive at an understanding of what the "small, vulnerable newborn" might look like in a South African setting, with special focus on identifying risk factors for later growth anomalies and malnutrition.

RESEARCH AIM AND OBJECTIVES

This research aimed to describe the postnatal growth and body composition up to two years of age of two cohorts of small and vulnerable infants in Tshwane District, Gauteng Province, South Africa. "Small and vulnerable" was defined according to GA at birth (preterm birth at <37 weeks gestation), birth weight-for-GA (SGA with birth weight <10th percentile for GA), presence of asymmetric growth restriction (assessed by the difference between birth head circumference (HC) and birth weight (BW) z-scores) and history of placental insufficiency (assessed by third-trimester Doppler screening).

The objectives of the research were:

1. To develop an integrated, interdisciplinary understanding of growth assessment in the first thousand days of life, from conception to the second birthday, including investigating the available measurements, indices, reference charts and classification systems, and understanding the interconnections between different methods of growth assessment at different ages.
2. In cohort one (preterm infants, assessed up to one year of age using existing clinic records):
   a) to investigate the differences between two commonly used growth charts for preterm infants (FGC and IG-PPGS) to determine which best predicts one-year anthropometry,
   b) to describe and compare one-year anthropometric outcomes (including weight-for-age, length-for-age, weight-for-length, and body mass index (BMI)-for-age z-scores and associated rates of underweight, stunting, wasting and overweight) of SGA and appropriate-for-GA (AGA) preterm infants, and
   c) to characterise longitudinal growth trajectories (weight, length, and head circumference) of preterm infants in the first year of life and investigate early life

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factors (including maternal factors, birth size, and early weight growth) as predictors of first-year growth trajectories.

3. In cohort two (term-born infants whose mothers underwent third trimester Umbiflow Doppler screening, assessed longitudinally at regular intervals from 6 weeks to two years of age):
   a) to describe anthropometry and body composition in the first two years of life, comparing infants with and without a history of placental insufficiency (as indicated by third trimester Doppler screening), and
   b) to characterise and compare two-year longitudinal growth and body composition trajectories of infants with/without a history of placental insufficiency (assessed by third trimester Doppler screening), infants born SGA/AGA/large-for-GA, and infants with symmetric/ asymmetric intrauterine growth; and subsequently to investigate whether any of these is a superior predictor of growth and body composition in the first two years of life.

The aim and objectives stated here were reworded and re-arranged from the original protocol, to align to the additional publications/ outputs that presented themselves over time. These changes had no ethical implications.

DELIMITATIONS AND ASSUMPTIONS

Delimitations

- Body composition analysis in this study is delimited to a two-compartment model (differentiating only fat mass and fat-free mass) due to the isotope dilution method used.[33]
- Follow-up for cohort one was delimited to one year of age.
- Cohort two was delimited to term-born infants.
- Assessment of infant feeding was delimited to basic practices (breastfeeding, formula feeding, whether complementary foods had been introduced) but did not include detailed assessment of nutritional adequacy.

Assumptions

- Reasonable accuracy of data in clinic records used for cohort one, including acceptable accuracy and precision of anthropometric measurements.
- The inherent assumptions of the various assessment methods used apply:

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- For umbilical artery Doppler screening: that an increased RI indicates impaired blood flow through the placenta, which in turn indicates reduced nutrient and oxygen transfer to the foetus.[5]
- For body composition analysis by deuterium dilution, that[35]:
  - deuterium oxide is equally distributed in all body water compartments,
  - the rate of equilibration of deuterium oxide is rapid enough that equilibration is achieved within the specified time, and
  - neither deuterium oxide nor water is lost during the equilibration time.
- Normal infant hydration (adjusted for sex and age)[35] is assumed, in the absence of clinical signs of dehydration.

GENERAL METHODOLOGY

A brief overview of the methodology is presented here; full descriptions can be found in each publication.

Cohort one: preterm infants

Study population and sampling

Cohort one consisted of (clinic records of) preterm infants, admitted to the kangaroo mother care (KMC) unit of a peri-urban tertiary hospital in Tshwane, Gauteng Province South Africa, and followed up at the hospital's KMC outpatient clinic for one year. Power-driven, reverse chronological sampling was used to select records meeting predefined inclusion criteria starting from infants born in December 2018, with purposive over-sampling of SGA infants to achieve adequate sample size. Sample size calculations determined that 130 participants per group (SGA and AGA) would be sufficient to detect an effect size of 0.3 with α=0.05 and power of 80% (G*Power v3.1.9.2, Heinrich-Heine-Universität, Düsseldorf).

Data collection and analysis

Data were extracted in duplicate from written clinic records and quality control was applied. Anthropometric data were converted to z-scores and prepared for analysis as indicated in Table 1-1.

Table 1-1: Preparation of anthropometric data for analysis in the preterm infant cohort

Age	Indices	References/ standards	Categorical classifications
Birth	Birth weight (BW)-for-GA percentile and z-score	FGC[36] IG-NBSS[37,38]	• SGA: BW < 10th percentile • AGA: BW ≥10th and ≤90th percentile • LGA: BW >90th percentile
Early growth (up to 50 weeks	Sex- specific z-scores for • Weight-for-PMA (WZ) • Length-for-PMA	FGC[36] IG-PPGS[39]	

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Age	Indices	References/ standards	Categorical classifications
postmenstrual age (PMA50))	• HC-for-PMA		
	Early weight growth (ΔWZ): change in WZ from birth to PMA50		• Growth deceleration: ΔWZ <-1 • Growth maintenance: -1 ≤ ΔWZ ≤+1 • Growth acceleration: ΔWZ >+1
Infant growth (up to 1 year of age)	Z-scores (using corrected age) • Weight-for-age (WAZ) • Length-for-age (LAZ) • Weight-for-length (WLZ) • Body mass index-for-age (BMIZ)	WHO Growth Standards[40,41] (WHO Anthro)	• Underweight: WAZ <-2 • Stunting: LAZ <-2 • Wasting: WLZ <-2 • Overweight: BMIZ >+2
AGA = appropriate-for-gestational age; FGC = Fenton 2013 growth charts[36]; HC = head circumference; IG-NBSS = INTERGROWTH-21ST Newborn Size Standards[37,38]; IG-PPGS = INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants[39]; LGA = large-for-gestational age; PMA = postmenstrual age; SGA = small-for-gestational age; WHO = World Health Organization.			

These anthropometric data were used in various analyses in publications 2-4 (chapters 4-6) to achieve different objectives:

- Early life anthropometric indices derived from FGC and IG-PPGS were compared to each other and to one-year anthropometric outcomes, with the aim of determining which growth chart better predicted anthropometry at one year (publication 2, objective 2a, chapter 4).
- One-year anthropometric outcomes of SGA and AGA infants were compared, to determine the association between SGA (as well as other early life exposures) and anthropometry at one year of age (publication 3, objective 2b, chapter 5).
- Longitudinal first-year growth trajectories were compiled by combining indices derived from the Fenton growth charts (up to 50 weeks PMA) and the WHO Growth Standards (from 50 weeks PMA to one year, with age correction), and latent class trajectory modelling techniques were used to identify typical growth trajectories. Associations between early-life exposures and subsequent growth trajectory, and growth trajectories and ultimate anthropometric outcomes, were investigated (publication 4, objective 2c, chapter 6).

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Cohort two: term infants (UmbiBaby study)

Study population and sampling

Cohort two was part of the longitudinal UmbiBaby Study cohort, recruited from the South African arm of the Umbiflow International study.[15] The UmbiBaby Study recruited singleton infants with no congenital abnormalities at 6 weeks of age. Preterm infants were excluded.

Data collection and analysis

Follow-up visits were conducted at a dedicated research unit situated within the peri-urban tertiary hospital in Tshwane, Gauteng Province, South Africa. Follow-up visits and data collection are detailed in publications 5 an6 6 (Chapters 7 and 8)

Anthropometric and body composition data were converted to z-scores and prepared for analysis as indicated in Table 1-2.

Table 1-2: Preparation of anthropometric data for analysis in the UmbiBaby Study cohort

Age	Indices	References/ standards	Categorical classifications
Birth	• Birth weight (BW)-for-GA percentile and z-score • Length-for-GA z-score • HC-for-GA z-score • Difference between HC and BW z-score (HCZ-BWZ)	IG-NBSS[37]	• SGA: BW < 10th percentile • AGA: BW ≥10th and ≤90th percentile • LGA: BW >90th percentile • Asymmetric: HCZ-BWZ >1
Anthropometry (up to 2 years of age)	Z-scores for • Weight-for-age (WAZ) • Length-for-age (LAZ) • Weight-for-length (WLZ) • Body mass index-for-age (BMIZ)	WHO Growth Standards[40,41] (WHO Anthro)	• Underweight: WAZ <-2 • Stunting: LAZ <-2 • Wasting: WLZ <-2 • Overweight: BMIZ >+2
Body composition (up to 2 years of age)	Fat mass (FM) • FM and FM z-score • FM index (FMI = FM/length^2) and FMI z-score • %FM (= FM / weight *100) Fat free mass (FFM) • FFM and FFM z-score • FFM index (FFMI = FFM/length^2) and FFMI z-score	Reference data from Wells *et al*.[42]	No classification – only analysed as continuous variables
AGA = appropriate-for-gestational age; BW = birth weight; HC = head circumference; IG-NBSS = INTERGROWTH-21ST Newborn Size Standards[37]; LGA = large-for-gestational age; PMA = postmenstrual age; SGA = small-for-gestational age; WHO = World Health Organization.			

These anthropometric data were used in various analyses in publications 5 and 6 (see chapters 7 and 8 for details) to achieve different objectives:

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- Differences in anthropometric and body composition data between infants with a normal and abnormal prenatal UmA-RI were investigated cross-sectionally at each follow-up age (objective 3a)
- Longitudinal first-year growth trajectories were compiled using z-scores derived from the WHO Growth Standards, and latent class trajectory analysis modelling were used to identify typical growth trajectories. Early-life exposures (including birth weight/ SGA, UmA-RI, and HC-BW asymmetry) were compared to subsequent growth and body composition trajectories (objective 3b).

LAYOUT OF THE THESIS FOR PHD BY PUBLICATION

This thesis by publication contains the following nine chapters:

- Chapter 1: General introduction.
    - This chapter introduces the research, including the background, research problem, research aims and objectives, and general methodology.
- Chapter 2: Literature review.
    - This chapter comprehensively reviews the published literature, excluding that which is covered in the first publication (i.e. chapter 3).
- Chapter 3: Publication 1: Integrated growth assessment in the first 1000 d of life: an interdisciplinary conceptual framework.
    - This publication provides contextual background for the rest of the thesis. It collects and integrates methods that are used to assess growth across the first thousand days of life, from conception up to the second birthday, across different life stages and clinical disciplines (Objective 1).
- Chapter 4: Publication 2: Infant growth by INTERGROWTH-21st and Fenton Growth Charts: predicting one-year anthropometry in South African preterm infants.
    - This publication compares the FGC and IG-PPGS for assessing early growth in preterm infants (cohort 1), and compares these early growth indices to one-year anthropometric outcomes, to determine whether either chart is better able to predict malnutrition at one year (Objective 2a).
- Chapter 5: Publication 3: One-year anthropometric follow-up of South African preterm infants in kangaroo mother care: Which early-life factors predict malnutrition?
    - This publication compares one-year anthropometry of SGA and AGA preterm infants, and investigates the ability of other early-life factors (including maternal conditions, birth size and GA, and early growth) to predict malnutrition at one year of age (Objective 2b).

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- Chapter 6: Manuscript 4: first-year growth trajectories of preterm infants receiving kangaroo mother care, and their relationships to early life predictors and anthropometric outcomes.
    - This publication describes the longitudinal growth trajectories of preterm infants (cohort 1), modelled using latent class trajectory modelling techniques. The relationships between early life predictors of growth trajectory, and growth trajectory as predictor of anthropometric outcomes, are also investigated (Objective 2c)
- Chapter 7: Publication 5: Association of prenatal placental function with anthropometry and body composition through 2 years of age in South African infants: The UmbiBaby Study.
    - This publication compares the anthropometric and body composition outcomes of infants with a normal and abnormal UmA-RI (cohort 2) at eight time points in the first year of life (Objective 3a).
- Chapter 8: Manuscript 6: Longitudinal anthropometry and body composition trajectories of South African infants with and without prenatal placental insufficiency.
    - This publication describes the longitudinal growth trajectories of the infants in cohort 2, modelled using latent class trajectory modelling techniques. Three potential indicators of foetal growth restriction – SGA, asymmetry (HCZ-BWZ >1) and abnormal UmA-RI – are investigated as potential predictors of growth trajectory, alongside other important early life exposures (Objective 3b).
- Chapter 9: General discussion and conclusion.
    - This final chapter integrates the findings presented in each of the publications into a coherent understanding of the postnatal growth of the small, vulnerable infant in a South African context, and presents the overall conclusions of the research.

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CHAPTER 2: LITERATURE REVIEW

INTRODUCTION

The first thousand days of life – from conception to the second birthday – are a critical and sensitive developmental period. Nutrition and other exposures during gestation, infancy and early childhood can have lifelong effects on health status and disease risk.[1-4] Weight and length growth up to two years of life have been associated with adult obesity, cardiometabolic disease and even educational attainment.[5] Nutritional exposures throughout the life course cumulatively modulate the expression of genetic tendencies to health or disease.[1,6] Thus, it is important that child health research and practice take a life course approach in order to understand the early-life determinants of disease risk, which can then guide the development of appropriate interventions to optimise health outcomes.[7] This chapter reviews the literature on growth in the first thousand days as a determinant of longer-term health outcomes, particularly in relation to anthropometric growth and body composition. Specifically, foetal growth restriction (including placental insufficiency and small size at birth) and preterm birth are investigated as early risk factors. The evidence for their potential consequences on childhood growth, the neurological and metabolic consequences of poor growth, and potential for alterations in body composition is reviewed.

THE SMALL VULNERABLE NEWBORN

Globally, neonatal mortality is the single biggest contributor to under-five mortality rates.[8] The same holds true for South Africa, where neonatal deaths (i.e. up to 28 days of age) account for over two thirds of in-hospital deaths[9] and more than a quarter of total deaths[10,11] in children under five. Infants who are born “too soon” and/ or “too small” – collectively termed “small vulnerable newborns” – are at increased risk of neonatal death as well as poorer long-term health and developmental outcomes.[8]

Criteria for identifying small vulnerable newborns have evolved with time. The first operationally useful definition, introduced in the 1960s, was *low birth weight* (LBW, i.e. birth weight below 2.5 kg). However, although LBW infants are indeed at higher risk of neonatal morbidity and mortality, the definition does not distinguish between the physiologically distinct phenomena of preterm birth and foetal growth restriction. This led to the creation of additional diagnostic categories of *preterm birth* (i.e. birth before 37 competed weeks of gestation) in the 1970s and *small-for-gestational age* (SGA, birth weight <10th percentile for sex and gestational age) in the 1990s. Each of these groups of infants have increased risk of adverse outcomes, but they overlap only partly, so that using any one criterion exclusively will miss some at-risk infants. Thus, the term “small vulnerable newborns” has been

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proposed as an umbrella classification incorporating LBW, SGA, and preterm birth, as illustrated in Figure 2-1.[8,12]

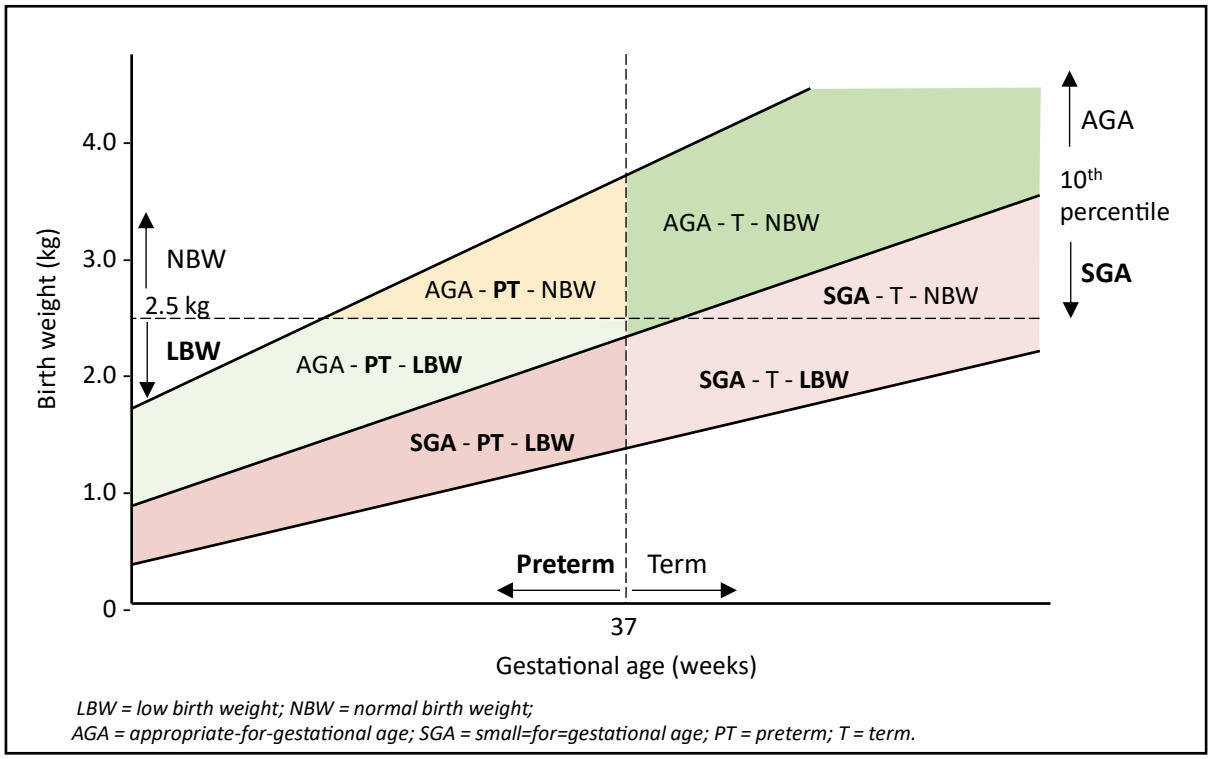

Figure 2-1: Schematic illustration of different small vulnerable newborn phenotypes (adapted from Ashorn, 2020)[12]

Whilst the small vulnerable newborn classification addresses some of the limitations of the isolated use of LBW, preterm birth and SGA, it still fails to identify newborns with a history of foetal growth restriction (FGR) born at term with a birth weight above the 10th percentile.[13] While FGR is known to be an important cause of stillbirth[14] and perinatal complications[15], the long-term effects of FGR in the absence of preterm birth or SGA are less clear.

FOETAL GROWTH RESTRICTION

Theoretical definition, aetiology and consequences

Foetal growth restriction (FGR) can theoretically be defined as the failure of the foetus to reach its genetic growth potential – in other words, foetal growth (in weight, length or other body measurements) falls short of what would be achieved under ideal conditions.[13,15,16] Unfortunately, "genetic growth potential" is impossible to quantify, necessitating more operationally useful definitions and diagnostic criteria. These are discussed in the next section.

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Placental insufficiency underlies the majority of FGR.[13-16] Since the placenta is the sole source of nutrients and oxygen for the foetus, any significant impairment in placental functioning deprives the foetus of these critical substrates, thus impairing growth and development.[14,16] However, the severity of FGR occurs along a spectrum that evolves over time.[14] At the onset of placental insufficiency, foetal blood flow is redistributed to vital organs (most notably, the brain), at the cost of less critical body systems (including skeletal muscle, kidneys and the gastrointestinal tract).[17] Thus, abdominal circumference growth (and consequently estimated foetal weight) is affected long before head circumference (HC).[14]

Serious consequences of FGR include a markedly increased risk of perinatal mortality (including stillbirth) and perinatal complications such as intrapartum asphyxia, hypoglycaemia, hypothermia and pulmonary haemorrhage.[14,15] Additionally, longer-term health, growth and cognitive development may be negatively affected.[15,18] It is therefore important to identify neonates with FGR to ensure timeous initiation of appropriate monitoring and interventions.

Operational definitions and diagnostic criteria

The theoretical definition of FGR is operationally challenging, since “genetic growth potential” is impossible to quantify.[13] Clinically, FGR is characterised by foetal growth that is slower than that of a healthy foetus under ideal conditions. Assessing foetal growth in this way necessitates multiple foetal measurements throughout gestation, as well as a reference for healthy foetal growth to compare these measurements to.[13,19] While numerous foetal growth references are available (see publication 1, chapter 3), there are some practical challenges. Firstly, the resource cost (time, equipment, and operator skill) of repeated ultrasound biometry is significant, making it unfeasible in many settings. In the South African public health sector, for example, ultrasound devices are only available at hospital level for the minority of women with high-risk pregnancies. Secondly, foetal growth shows a certain amount of normal intra-individual variation, and it is unclear what degree of slowing growth indicates problematic FGR. Various methods of quantification have been proposed, including calculating the change in z-scores between two time points, calculating estimated foetal weight (EFW) growth in grams per day, and projecting from the observed EFW trajectory (based on two or more sequential measurements) an estimated expected birth weight at term.[19] Unfortunately, none of these methods have clearly defined and validated limits of normality where clinical intervention would be indicated. An alternative approach, developed by the Perinatal Institute (Birmingham, United Kingdom) uses predictive software to describe an individual foetus’ expected growth trajectory and birth weight (including acceptable limits of deviation) based on factors such as foetal sex, maternal weight and height, parity and

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ethnic origin.[20] While promising, this approach requires validation in ethnically and geographically diverse populations.

The most widely used guidelines for identifying FGR – the Delphi Consensus criteria (Table 2-1) – do not require multiple ultrasound assessments.[13,21]

Table 2-1: Delphi consensus criteria for the identification of foetal growth restriction (FGR)[21]

Early FGR: GA<32 weeks	**Late FGR: GA≥32 weeks**

Any one of:
• AC or EFW <3rd percentile
• Absent end-diastolic flow in the umbilical artery
or
• AC or EFW <10th percentile plus:
  ○ Uterine artery PI >95th percentile
and/or
  ○ Umbilical artery PI >95th percentile
	Any one of:
	• AC or EFW <3rd percentile
	• Absent end-diastolic flow in the umbilical artery
	or at least 2 of the following:
	• AC or EFW <10th percentile
	• AC or EFW decreasing by >2 quartiles
	• Cerebroplacental ratio <5th percentile or Umbilical artery PI >95th percentile

Note: Delphi criteria apply only in the absence of congenital anomalies. *Abbreviations: FGR = foetal growth restriction; GA = gestational age; AC = abdominal circumference; EFW = estimated foetal weight; PI = pulsatility index.*	

Nonetheless, the need for at least one ultrasound assessment limits the usefulness of these criteria in resource-constrained environments where the majority of pregnant women do not have access to ultrasound.[22] In these settings, alternative means must be used to identify FGR. Two such approaches will be discussed here: the use of birth anthropometry (weight, length and HC) to identify neonates with a history of FGR, and the use of Doppler screening (without ultrasound biometry) to identify placental insufficiency antenatally.

The role of birth anthropometry in identifying FGR

Birth weight is the simplest and most ubiquitous neonatal measurement used to retrospectively assess foetal growth, with SGA considered indicative of FGR.[13,23] However, as suggested above, SGA and FGR are not synonymous: a foetus may have significant growth deceleration (i.e. FGR) yet have a birth weight above the 10th percentile. Conversely, a constitutionally small foetus may be achieving its genetic growth potential while growing consistently below the 10th percentile.[13,23-25]

More comprehensive birth size assessment includes measuring and interpreting neonatal length and HC alongside birth weight. Asymmetry or disproportion – i.e. when the birth weight falls on a markedly lower percentile or z-score than the length and/ or HC – may indicate FGR.[15,26,27] As discussed before, asymmetric growth restriction most commonly occurs as a consequence of placental insufficiency, as limited nutrient supplies are directed

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toward brain growth at the cost of muscle and fat tissue deposition.[14,17,27] There are no widely accepted criteria for identifying asymmetric FGR, but some available options are described in Publication 1 (Chapter 4).[28] Neonatal wasting (low weight-for-length) can be assessed using the weight-length ratio (WLR = birth weight/length) or ponderal index (birth weight/(length^3)); however, obtaining reliable birth length measurements in routine care is challenging.[29] Head-sparing growth (i.e. birth weight that is low relative to HC) can be assessed using the birth weight-to-HC ratio (birth weight/HC) or the difference between the z-scores for HC and birth weight. Gonçalves *et al*. proposed a cut-off for BW:HC, but since their study included only term infants, its usefulness across a range of gestational ages is unknown.[30] Converting weight and HC measurements to z-scores accounts for variation in gestational age and sex, increasing the potential usefulness of the indicator, though it requires an accurate estimate of GA and, ideally, access to electronic calculators. A difference of more than one z-score has been proposed as an indicator of asymmetry.[31]

Foetal growth patterns have implications for postnatal growth: infants with true FGR (including term or preterm infants with appropriate birth weight for gestational age) can be expected to display accelerated growth in infancy as they return to their genetic growth potential. This is particularly evident in asymmetrically growth restricted infants: in early infancy, the weight z-score could be expected to increase until it “catches up” to length and HC z-scores.[26] Conversely, constitutionally small infants would not be expected to display any catch-up growth, as they are already achieving their genetic growth potential.[26] Considering the adverse long-term effects of inappropriate catch-up growth on metabolic and cardiovascular outcomes,[32-34] it is important to identify appropriate growth targets for any given infant, and to understand that infants with similar birth weights may have different ideal weight gain patterns. In the absence of prenatal ultrasound biometry, the proportionality between weight, length and head circumference may be a useful guide for postnatal growth monitoring.[26] However, body proportions are still unable to distinguish between symmetrically growth restricted and constitutionally small infants. In these cases, antenatal Doppler assessment of the umbilical artery may be useful for identifying foetal malnutrition.

The role of Doppler in identifying FGR

Doppler ultrasonography is used to determine the velocity (i.e. speed and direction) of blood flow by making use of the Doppler effect: when a sound wave is reflected from a moving object (in this case, red blood cells), the frequency of the reflected sound wave is altered in proportion to the velocity at which the object is moving.[35] In obstetrics, Doppler ultrasonography is used to examine blood flow in various maternal and foetal arteries.[36] Unlike traditional ultrasonography, Doppler examination is feasible in primary health care

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settings, using the low-cost, easy to operate Umbiflow™ continuous-wave Doppler device.[22,37]

Umbiflow™ is used to examine blood flow in the umbilical arteries, which transport blood from the foetus to the placenta.[38] Impairments in placental functioning will increase the resistance to blood flow through the umbilical arteries, causing changes in flow velocity that can be measured using Doppler.[36,38,39] Analysis of the Doppler waveform is based on comparisons between the maximum (systolic) and minimum (diastolic) blood flow velocity, expressed as various ratios. The resistance index (RI), used in this research, is calculated from the difference between the systolic (S) and diastolic (D) flow rates, divided by the systolic flow rate (i.e. RI=(S-D)/S).[36] Other indices that may be calculated include the pulsatility index (PI=(S-D)/[(S+D)/2]) and the S/D ratio.[36]

In a healthy pregnancy, the placental resistance to blood flow decreases over time as the surface area of the placental capillary bed enlarges, causing the umbilical artery RI (UmA-RI) to decrease as gestation progresses.[16,36] In placental insufficiency, blood flow across the placenta is impaired, and the UmA-RI increases.[36] Undetected placental insufficiency can result in foetal distress, hypoxia and foetal demise.[36,40,41] As such, Doppler is a useful tool for preventing perinatal mortality and stillbirth, particularly in high-risk pregnancies.[42] Studies using Umbiflow™ to screen otherwise healthy, low-risk pregnant women in South Africa have demonstrated unexpectedly high prevalence of placental insufficiency (>10%),[43,44] accompanied by increased rates of stillbirth.[43] Crucially, referring women with abnormally high UmA-RI to a higher level of care resulted in a 45% reduction in stillbirth with no concomitant increase in neonatal mortality.[44] This underscores the potential life-saving value of umbilical artery Doppler screening during routine antenatal care in the South African primary health care setting.

Beyond identifying foetuses at risk of stillbirth, Doppler screening may also be useful for detecting potential FGR. Since the placenta is the foetus' sole source of nutrients and oxygen, impaired placental function can hamper foetal growth and development.[14,36] Thus, while Doppler does not directly measure foetal size, it may be useful for identifying foetuses who are malnourished *in utero* and likely to develop FGR. Specifically, the presence of placental insufficiency may help differentiate FGR from constitutional smallness.[40] It has been suggested that a combination of Doppler ultrasonography and EFW may offer the best way to diagnose FGR that is predictive of poor perinatal outcome.[40]

In summary, then, Umbiflow™ Doppler screening of low-risk pregnant women has been proven to reduce stillbirth rates, and may be useful for identifying possible FGR. What

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remains to be determined is whether the surviving infants with a history of placental insufficiency have any long-term negative outcomes or health risk that need to be actively managed; the UmbiBaby study was conceptualised to begin to answer this question.

PRETERM BIRTH

Definition, aetiology and consequences

Preterm birth (birth before 37 completed weeks of gestation) is associated with a range of short- and long-term adverse outcomes.[8] Preterm birth and FGR often co-occur, both due to shared aetiological factors and because FGR may necessitate preterm delivery to prevent stillbirth.[24,36,39-41,45] Preterm birth and SGA are independently associated with adverse outcomes, including perinatal and infant morbidity and mortality as well as long-term deficits in health and human capital.[8] When both SGA and preterm birth are present, these risks are even greater.[8]

Challenges in monitoring preterm infant growth

Assessing the growth of preterm infants is not straightforward, and there is active debate about appropriate growth targets to optimise short- and long-term health outcomes. Traditionally, the approach has been that the postnatal growth of preterm infants should mimic the intrauterine growth of a foetus of the same gestational age as closely as possible, achieving similar size and body composition as a term infant by 40 weeks postmenstrual age (PMA).[46-48] Thus, growth charts based on birth size of infants of different gestational ages were used to monitor the postnatal growth of preterm infants.[47] The majority of preterm infant growth charts are compiled from birth size data, including the popular Fenton 2013 Growth Chart (FGC), which is widely used in South Africa. The validity of this practice has been called into question on the basis that foetal growth and postnatal growth are physiologically distinct processes that cannot simply be conflated.[49,50] Instead, the actual growth of healthy preterm infants under ideal nutritional and environmental conditions has been proposed as a more appropriate target. This approach, which mirrors the approach used in the World Health Organization (WHO) Multicentre Growth Reference Study (MGRS), was used to construct the INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants (IG-PPGS).[51]

A number of key conceptual and methodological differences between the FGC and IG-PPGS are summarised in Table 2-.

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Table 2-2: A comparison of the Fenton 2013 and INTERGROWTH-21st growth charts for preterm infants

	Fenton 2013[52]	INTERGROWTH-21ST [51,53,54]
Available charts	Single chart for size-at-birth and postnatal growth. Weight, length, head circumference. Sex-specific.	Size at birth charts: weight, length, HC, weight-length ratio. Postnatal growth charts: weight, length, head circumference. Sex-specific.
Age range	22 to 50 weeks GA/ PMA	Size at birth charts: 24 to 42 weeks GA (Separate chart for very preterm [24 to 32 weeks] with a smaller sample size). Postnatal growth charts: 27-64 weeks PMA.
Type of data	Cross-sectional (size at birth)	Cross-sectional (size at birth charts) and longitudinal (postnatal growth charts)
Sample source	Germany, United States, Italy, Australia, Scotland, and Canada	Brazil, China, India, Italy, Kenya, Oman, United Kingdom and United States of America → wider range of ethnicities
Inclusion criteria	Less stringent; based on dataset characteristics	Very stringent, based on individual mother/ infant characteristics
Sample size	3,986,456 (22-40 weeks GA) Statistical smoothing of curves from 40-50 weeks PMA, to join with WHO Growth Standards.	Cross-sectional (size at birth): 20 486 Longitudinal (postnatal growth): 4321 data points from 201 infants.
GA = gestational age; HC = head circumference; PMA = postmenstrual age; calculated postnatally as gestational age at birth plus chronologic age.		

The very different underlying paradigms of appropriate postnatal growth targets resulted in different approaches to collecting reference data on which the charts are based. The FGC relies on birth data (i.e. cross-sectional data collected only at birth)[52] while the IG-PPGS was compiled from longitudinally collected data from infants born preterm to healthy mothers with uncomplicated pregnancies.[51] The INTERGROWTH-21ST growth standards also provide growth charts for size at birth (the INTERGROWTH-21ST Newborn Size Standards, IG-NBSS), which were constructed using cross-sectional birth data. These are not intended for use as postnatal growth charts.[53] Each of these charts has methodological strengths and weaknesses: the FGC boasts a large sample size and can be used from an earlier GA (22 weeks); however, the reference data pool has lower ethnic diversity and little to no quality control on the health status of individual included infants. The IG-PPGS, conversely, included only infants with no medical complications from mothers known to be healthy, and the long-term health and appropriate development of the infants was confirmed by a two-year follow-up study[55]; however, the sample size at lower GAs is very small (i.e. 28 infants born ≤33 weeks[51]), calling into question their validity. Moreover, the IG-PPGS is based on data collected longitudinally, and the growth chart was truncated at the point where it naturally converged with the WHO Growth Standards (i.e. 64 weeks PMA[51]), whereas the FGC used cross-sectional birth data up to 36 weeks PMA, and statistically smoothed the

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curves to align with the WHO growth standards at 50 weeks PMA (i.e. 10 weeks corrected age on the WHO Growth Standards)[52]. Cumulatively, these methodological differences result in the FGC and IG-PPGS following very different trajectories, as shown in Figure 2-2.

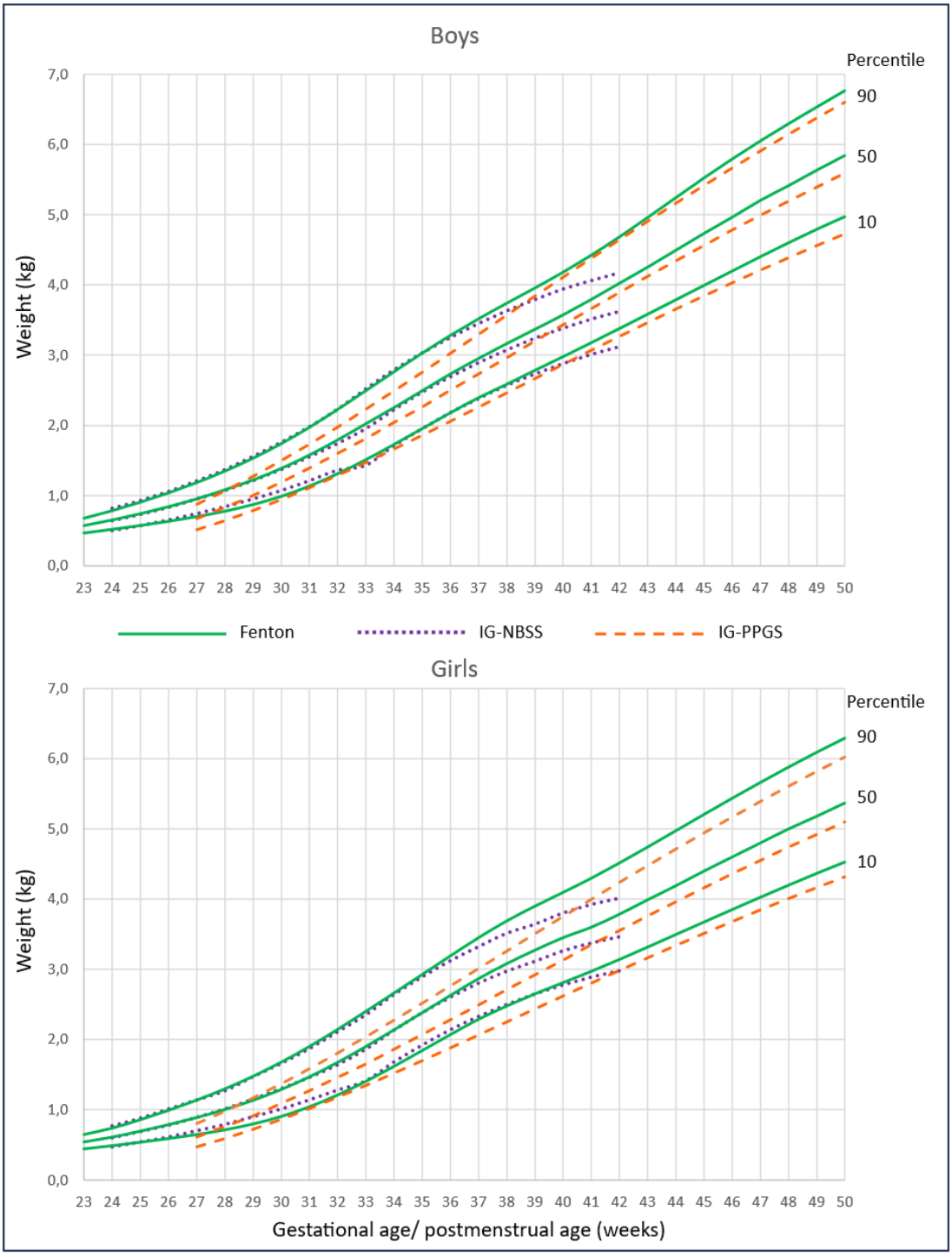

Figure 2-2: Comparison of the Fenton 2013 Growth Chart, INTERGROWTH-21ST Newborn Size Standards (IG-NBSS) and INTERGROWTH-21ST Postnatal Growth Standard for Preterm Infants (IG-PPGS), created by plotting the 10th, 50th and 90th percentiles using Excel.

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The discordance between the FGC and INTERGROWTH-21ST Growth Standards creates problems for researchers and clinicians alike.[56] In research, it complicates inter-study comparisons and meta-analyses. In practice, clinical decision making may be affected as different charts indicate different degrees of growth faltering, maintenance or catch-up, each of which would prompt different approaches to nutrition care.

Numerous studies (summarised in Table 2-) have demonstrated that using FGC and IG-PPGS to assess the same group of infants leads to different outcomes, though the magnitude and direction of the difference is not consistent.

Table 2-3: Summary of studies comparing preterm infant growth according to the Fenton 2013 Growth Chart and INTERGROWTH-21ST Postnatal Growth Standards for preterm infants

Reference and details of study setting and participants	Findings
El Rafei *et al*., 2020.[57] • Europe (11 countries). • Born <32 weeks GA. • Assessed: at discharge (up to 50 weeks PMA) • N=6259. • Feeding: 28% EBF, 41% EFF, 31% MF	Growth restriction (once-off assessment) on FGC > IG-PPGS: • Weight <10th percentile at discharge: FGC 45%, IG-PPGS 30%. • Weight <3rd percentile at discharge: FGC 24%, IG-PPGS 17%.
Cordova *et al*., 2020.[58] • Australia. • Born <33 weeks GA. • Assessed: 40 weeks PMA. • N=657. • Feeding: not reported	Z-scores (once-off assessment) on IG-PPGS > FGC: • Weight: 0.41 z-score higher. • Length: 0.20 z-score higher. Growth faltering (repeated assessment) IG-PPGS > FCG: • Weight: loss of >0.8 z-score: FGC 40%, IG-PPGS 68% (agree: 56%). • Length: loss of >2 z-score: FGC 15%, IG-PPGS 32% (agree: 47%).
González-García, 2021.[59] • Spain. • Born <37 weeks GA, <1500g. • Assessed: at discharge. • N=635 • Feeding: not reported	Growth restriction (once-off assessment) on FGC > IG-PPGS: • Weight <10th percentile at discharge: FGC 73.7%, IG-PPGS 57.6% (κ=0.580) • In AGA only: FGC 60.4%, IG-PPGS 35.7%. Growth faltering (repeated assessment) FGC ≥ IG-PPGS: • Weight: loss of >1 z-score: FGC 44.3%, IG-PPGS 43.8% (κ=0.672). • In AGA only: FGC 52.7%, IG-PPGS 39.6%.
Yitayew *et al*., 2021.[60] • United States of America. • Born 24-<37 weeks GA. • Assessed: at discharge. • N=340. • Feeding: not reported	Growth faltering (repeated assessment) FGC > IG-PPGS: • Weight: loss of >1 z-score: FGC 39.7%, IG-PPGS 27.9% (κ=0.60). • Length: loss of >1 z-score: FGC 67.4%, IG-PPGS 49.2% (κ=0.44).

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Reference and details of study setting and participants	Findings
Reddy *et al*., 2019.[61] • India. • Born <32 weeks GA. • Assessed: at discharge. • N=603 • Feeding: not reported	Growth restriction (once-off assessment) on FGC > IG-PPGS: • Weight <10th percentile at discharge: FGC 55.4%, IG-PPGS 48%, both 45.7% (agree: 88%). • Length <10th percentile at discharge: FGC 35.1%, IG-PPGS 32.1%, both 29.8% (agree: 92.3%).
Kim, 2021.[62] • Korea. • Born <28 weeks GA. • Assessed: at discharge (up to 50 weeks PMA) • N=1356. • Feeding: not reported	Discharge weight z-score (once-off assessment) on IG-PPGS > FGC: • FGC -1.44; IG-PPGS -1.03. Discharge length z-score (once-off assessment) on FGC > IG-PPGS: • FGC -1.94; IG-PPGS -2.10. Change in z-score (repeated assessment) on IG-PPGS > FGC: • Change in weight z-score: FGC -1.67; IG-PPGS -1.21. • Change in length z-score: FGC -1.94; IG-PPGS -1.76.
EBF = exclusive breastfeeding or breast milk feeding; EFF = exclusive formula feeding; FGC = Fenton Growth Chart; GA = gestational age; IG-NBSS = INTERGROWTH-21ST Newborn Size Standards; IG-PPGS = INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants; K = Kappa statistic; MF = mixed feeding (i.e. breast milk and formula); PMA = postmenstrual age.	

In most cases, FGC is a stricter standard than IG-PPGS: using FGC resulted in lower mean z-scores,[58,62] more infants lost >1 z-score between birth and discharge,[59,60] and it classified more infants <10th percentile.[57,59,61] Fewer differences are seen when comparing FGC and IG-NBSS. In most studies, there was no significant difference in the proportion of infants classified as SGA by FGC or IG-PPGS.[59-61,63,64] Only one large study found a significant (but still small) difference, with IG-NBSS identifying slightly more SGA than FGC in extremely preterm Korean infants (born <28 weeks GA).[62]

Though these results describe the differences between FGR and IG-PPGS, they offer little guidance on which growth chart would be best to use in clinical practice. Pragmatically, the ideal growth chart should be able to identify infants who are at risk of adverse outcomes. Few published studies have compared the ability of different growth charts to predict outcomes. Two studies that examined neurodevelopmental outcomes came to opposite conclusions: an American study conducted in 340 preterm infants born at 24-<37 weeks GA found that the association between weight faltering (defined as losing >1 weight-for-PMA z-score from birth to term) and neurodevelopment at 12 and 24 months did not significantly differ between FGC and IG-PPGS, though there was a trend for stronger associations using IG-PPGS.[60] Conversely, an Australian study including 613 infants born before 33 weeks' GA found that only FGC-related changes in anthropometric z-scores were significantly related to neurodevelopmental outcomes at 18 months, though these associations mostly disappeared by seven years of age.[48] Only one study examined the ability of birth size (assessed using FGC and IG-NBSS) to predict later malnutrition; IG-NBSS was found to be a slightly better

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predictor of stunting and overweight at 12 months, though the differences were small.[63] No published research could be found comparing FGC and IG-PPGS as predictors of later growth and malnutrition – outcomes that are of particular importance in preterm infants, as will be described in the next section.

POSTNATAL CONSEQUENCES OF FGR IN TERM AND PRETERM INFANTS

Growth outcomes

Published research shows that being born preterm and/ or SGA can affect growth into childhood, but different studies have described different growth patterns in these infants. Most of the published research has focused on the growth outcomes of preterm infants, rather than term-born SGA infants. Table 2-4 summarises a number of these individual studies.

Table 2-4: Summary of findings from studies investigating growth outcomes in infants and children born preterm, low birth weight and/ or small-for-gestational age.

Reference and details of study setting and participants	Findings
Studies conducted in high-income countries	
Boccca-Tjeertes, 2011,[65] 2013,[66] and 2014.[31] • Netherlands. • GA 32-<36 weeks. • Assessed at several time points up to 4 years (routine health visits). • N=981-1100. • Feeding/ diet: not reported.	From birth to 4 years • Compared to preterm AGA infants, preterm SGA infants had smaller absolute weight gains, slightly larger length gains, and larger gains in WAZ and LAZ.[66] At age 4 years • Preterm infants had higher rates of stunting (HAZ <-2) and underweight (WAZ <-2) compared to population levels.[65] • Children born preterm have lower WAZ and LAZ, and higher rates of stunting and underweight, than term-born children.[66] • Children born SGA have lower WAZ and LAZ, and higher rates of stunting and underweight, than children born AGA (comparing preterm-SGA to preterm-AGA and term-SGA to term-AGA children).[66] • No significant difference in WAZ and LAZ of symmetric *vs*. asymmetrically growth restricted (SGA) infants.[31]
Lindström *et al*., 2019.[67] • Uppsala County, Sweden. • GA 32-40 weeks. • Assessed at 1.5, 3 and 3 years. • N=41 669. • Feeding/ diet: not reported.	• Preterm-AGA children had caught up to term-AGA children in height, weight, and BMI by 3 years. • Preterm-SGA had lower height, weight, and BMI than term-SGA up to 5 years, and a higher proportion of BMI <10th percentile. • Lower gestational age at birth was associated with smaller size up to 5 years.

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Reference and details of study setting and participants	Findings
Figueras-Aloy, 2020.[68] • Barcelona, Spain. • GA <32 weeks. • Assessed: 2-2.5 years months. • N=479. • Feeding/ diet: Analyses adjusted for any BF at 2 months (yes 59.6%, no 3.1%, missing 37.3%).	• SGA infants follow a similar z-score trajectory, but at a lower value, than AGA infants. • SGA infants did not catch up to WAZ>10th percentile at 2-2.5 years. • Singleton SGA infants caught up to LAZ>10th percentile at 2-2.5 years, but SGA infants who were part of a multiple pregnancy did not. • SGA: higher rates of WAZ<-2, LAZ<-2 and HCZ<-2 than AGA at 2-2.5 years, but rates of all these indicators decrease over time (some catch-up).
Gortner *et al*., 2003.[69] • Lübeck, Germany. • GA <36 weeks. • Assessed: 2 years. • N=148 (1:1 SGA:AGA). • Feeding/ diet: not reported.	• SGA had significantly lower weight and height (but similar HC) at 6, 12 and 22 months of corrected age.
Studies conducted in low-and middle-income countries	
Kirk *et al*., 2017.[70] • Kayonza District, Rwanda. • Preterm (GA<37 weeks) or birth weight <2000g. • Assessed: median (IQR) 22.5 (17.5-30.5) months. • N=158. • Feeding/ diet: not reported, but 46.5% reported feeding difficulties (choking, coughing or gagging).	• High rates of stunting (78.3%), wasting (8.8%), underweight (38.1%) compared to population prevalences (41% stunting, 2% wasting and 10% underweight).
Tchamo *et al*., 2017.[71] • Maputo, Mozambique. • Compared LBW to normal birth weight. • Assessed: 7-10 years • N=353. • Feeding/ diet: not reported.	• LBW children had lower weight, height, BMI, calf circumference, and mid-upper arm circumference than children with normal birth weight. • Weight-for-height, skinfold thicknesses, and waist circumference were similar in LBW and normal birth weight children.
Deng *et al*., 2019.[72] • China. • GA <37 weeks. • Assessed: 6 and 12 months • N=834. • Feeding/ diet: not reported.	For Very LBW and LBW (smaller) compared to normal birth weight infants (larger), and SGA (smaller) compared to AGA (larger) infants: • Smaller infants displayed significant catch-up in LAZ, WLZ and BMIZ, but remained lower in all z-scores at 12 months. • The larger infants displayed accelerated WLZ and BMIZ growth. • Higher rates of stunting (LAZ<-2) and wasting (WLZ<-2) among smaller infants, but rates decreased from birth to 12 months.

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Reference and details of study setting and participants	Findings
Arifeen *et al*., 2000.[73] • Dhaka, Bangladesh. • Singleton newborns of any GA. • Assessed: 1, 3, 6, 9, 12 months. • N=1207-1654 per visit. • Feeding/ diet: analyses adjusted for breastfeeding status in first 4 months and complementary foods and drinks.	• Term-AGA infants were the largest throughout all visits and preterm-SGA the smallest, with term-SGA and preterm-AGA following a similar trajectory in-between. • All infants, regardless of birth size, maintained a similar growth velocity and parallel growth trajectories. • Lower birth weight and SGA/ preterm infants followed a lower trajectory for weight and length, remaining smaller throughout.
Namirembe *et al*., 2021.[74] • Uganda. • All GA. • Assessed: 3, 6, 9, 12 months. • N=4528. • Feeding/ diet: 100% EBF at 3 months; 61.8% food insecure (24.8% mildly, 23.2% moderately, 13.8% severely), children meeting minimum dietary diversity: 4.1% at 6 months, 3.1% at 9 months, 9.5% at 12 months. Incorporated in multinomial regression analyses.	Length growth trajectory over 12 months: • Majority of infants maintained a trajectory in line with their birth LAZ, only a small group (359, 10%) displayed length catch-up. • Larger proportion of preterm and LBW infants in the chronically stunted (LAZ remains <-2) and catch-up (i.e. recovery from LAZ <-2 to normal LAZ) trajectory groups.
Krebs *et al*., 2022.[75] • Four LMICs: Democratic Republic of the Congo Guatemala, India, Pakistan. • All GA (enrolled before/ during pregnancy). • Assessed: 6, 12, 18, 24 months. • N=2324. • Feeding/ diet: not reported.	• LBW associated with lower LAZ and higher rates of stunting (LAZ <-2). • Birth LAZ is the strongest predictor of LAZ and stunting at 24 months.
AGA = appropriate for gestational age, BF = breastfeeding; BMI = body mass index; BMIZ = BMI-for-age z-score; HAZ = height-for-age z-score; HC = head circumference; GA = gestational age; LAZ = length-for-age z-score; LMIC = low- and middle-income country; LBW = low birth weight; SGA = small-for-gestational age; VLBW = very low birth weight; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score.	

The studies summarised in Table 2- suggest that, in general, preterm and/ or SGA infants remain smaller than their term-born AGA peers at various ages, often despite a higher growth velocity. Studies from high income countries have focused predominantly on preterm infants. Some studies have found prematurity itself to be associated with poor growth outcomes[65,66], while others found that only SGA (but not AGA) preterm infants had persistent anthropometric deficits.[67] Where SGA and AGA infants were compared, SGA consistently had poorer growth outcomes for length/ height-for-age and weight-for-age, despite similar or greater growth rates in infancy.[65-69] These studies, conducted in populations with a low background incidence of undernutrition, demonstrate that catch-up growth among SGA preterm infants is limited and inconsistent even in well-nourished populations.

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In low- and middle-income countries (LMICs), socioeconomic and nutritional deprivation may further hamper child growth. Two meta-analyses have demonstrated the adverse long-term effects of LBW, SGA and/ or preterm birth on growth outcomes in LMICs. The first meta-analysis included 19 cohort studies from 14 LMICs (six in Sub-Saharan Africa).[76] In the Sub-Saharan African cohorts, the risk of stunting, wasting and underweight at 12-60 months was increased in the presence of any one of LBW, SGA or preterm birth, with co-occurrence of preterm birth and SGA greatly increasing the likelihood of these outcomes.[76] Additionally, SGA was associated with increased risk of later undernutrition even when the infants were not LBW (and, by implication, not preterm).[76] The second meta-analysis reported data from birth cohorts from 5 LMICs (including South Africa).[77] It found that being born preterm or SGA was associated with height deficits persisting into adulthood.[77] These meta-analysis results are supported by more recent individual studies, summarised in Table 2-. In settings of nutritional and socioeconomic deprivation, the persistent growth deficits associated with preterm birth, LBW and SGA are even more stark.[70,71,73]. Other studies have also demonstrated that birth length may be a more important predictor of length growth trajectory than birth weight: a multi-site pregnancy supplementation trial (up to 24 months)[75] and a Ugandan cohort study (up to 12 months)[74] both found that birth length strongly predicts subsequent length growth trajectories in term and preterm infants alike. The Ugandan cohort, however, had an interesting exception: a small group (~10%) of infants that were severely stunted at birth went on to catch up to a similar LAZ as children with a normal birth length at 12 months.[74] It is not clear what distinguishes these infants from the majority who maintained their birth LAZ, but one could speculate that the represent a subgroup of true FGR returning to their genetic growth potential postnatally.

It is worth noting that all the preceding studies relied on the classification of infants at birth to identify SGA (as a proxy for FGR), and different growth charts may have been used to do this. None of these studies included prenatal measures of foetal growth (such as ultrasound biometry) or placental function (such as Doppler ultrasonography). It remains to be determined whether these are better predictors of postnatal growth and malnutrition than size at birth. One local South African study of 271 term infants found that an abnormal third trimester UmA Doppler was significantly associated with lower LAZ at 18 months, and in the presence of antenatal HIV exposure, also lower WAZ and HCZ.[78] Conversely, a Spanish study of 48 SGA infants, comparing those with normal and abnormal Doppler findings, found no difference in length, weight or BMI at 10 days, 4 months or 12 months.[79]

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Associations between growth and other outcomes

Achieving optimal postnatal growth in small vulnerable newborns presents a unique challenge: while slow weight gain has long been associated with poor short-term outcomes and impaired neurodevelopment, excessive weight gain may be associated with poor long-term cardiometabolic health outcomes.[15,24]

Neurodevelopmental outcomes

SGA *per se* has been associated with poorer neurodevelopmental outcomes, although the effects may be subtle.[18,23,80] Taking a more nuanced approach, one study identified FGR using serial ultrasound biometry, and found that this was more strongly associated with reductions in intelligence quotient than SGA assessed at birth.[81] An additional finding of interest was that the infants with the largest deceleration in foetal growth were not necessarily the ones with the lowest birth weight percentiles, suggesting that ultrasound biometry and birth weight cannot be used interchangeably.[81]

In preterm SGA infants, observational studies have found associations between postnatal catch-up growth and improvements in neurodevelopmental outcome and later cognition, though the effect is less clear in intervention studies that aimed to promote catch-up growth.[34] One systematic review (mostly from HICs) suggests that, in term-born AGA infants, rapid weight gain in the first two years of life has little association with improved cognitive outcomes in childhood.[82] Conversely, a meta-analysis of 5 LMIC birth cohorts found that greater postnatal growth velocity was associated with improved educational attainment in adulthood.[76] This suggests that findings may not be interchangeable across different populations; an unsurprising conclusion, since neurodevelopment and cognition at the individual level is influenced by a myriad of complex biological and environmental factors.[80]

Metabolic health

Recently, potential associations between excessive postnatal catch-up growth and later adverse metabolic health outcomes has received more research attention.[32-34] Excessive early weight gain, particularly in the first 3-6 months of life, has been associated with increased fat mass (especially visceral adiposity) and indicators of cardiovascular and metabolic risk in several large birth cohort studies in HICs.[83,84] Conversely, a meta-analysis of five LMIC birth cohorts (n=4518 individuals) found that higher postnatal growth rates were associated with greater stature and educational achievement in adulthood, but not with any increase in blood pressure or blood glucose.[76] However, the overall short stature of the analysed cohorts included in the aforementioned meta-analysis[76] is suggestive of chronic undernutrition, which raises the possibility that even infants with the highest rates of weight gain were still within a healthy range. Additionally, weight gain in later infancy, childhood and

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throughout life further confounds any associations that may be drawn between early catch-up growth and obesity and its metabolic sequelae.

It is conceivable that the differences in outcome can be explained by differences in body composition: weight gain consists of a combination of fat mass (FM) and fat-free mass (FFM, including of bone, soft tissue and water).[85] The amount and distribution of fat mass in relation to lean body mass is known to be associated with cardiometabolic outcomes in adults.[86] The evidence relating to body composition development in preterm and SGA infants will be explored in the next section.

Body composition

Significant changes in foetal body composition occur in the third trimester of pregnancy, with rapid accretion of both FM and FFM, and a gradual increase in percentage FM (%FM, calculated as FM/weight*100).[87,88] If normal foetal growth is disrupted – whether by preterm birth or by intrauterine undernutrition such as occurs with placental insufficiency – it could plausibly affect not only on the birth weight, but also neonatal body composition. It is therefore important to not only consider FM and FFM (which are proportionate to weight and length), but also %FM (to account for differences in weight) and the length-related indices, FM index (FMI, calculated as FM/length^2) and FFM index (FFMI, calculated as FFM/length^2).

Body composition at birth

The INTERGROWTH-21st Newborn Body Composition Study described neonatal body composition in 1019 infants born from healthy, uncomplicated pregnancies. This study found that healthy, AGA, term infants had a wide range of body compositions, with %FM ranging from 3-20%.[87] Nonetheless, SGA infants on average had lower FM, %FM and FM/FFM ratio than AGA infants at all gestational ages, suggesting that FM was reduced to a greater extent than FFM in these SGA infants. Likewise, preterm neonates were found to have significantly lower FM, FFM, FM% and FM/FFM ratio than term neonates.[87] This is consistent with the interruption of fat accumulation in the third trimester.

The majority of neonatal body composition studies have been conducted in preterm infants. A 2012 meta-analysis, summarising eight studies from HICs, found that preterm infants, when they reach term age, consistently have lower FFM than term neonates (460g on average), alongside consistently lower weight and length.[89] The results for FM and %FM were less consistent across studies, but the meta-analysis found a lower FM (50 g) and higher %FM (3%) in preterm infants at term-equivalent age, compared to term neonates.[89] Interestingly, the two studies using air-displacement plethysmography reported a markedly higher %FM than the studies using magnetic resonance imaging or dual-energy x-ray

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absorptiometry, which raises questions about the comparability of these methods. The reason for these differences is unclear. It has been suggested that methodological limitations (e.g. the presence of swaddling blankets, which may be “read” as FM, and infant movement introducing artefacts during x-ray scanning) may contribute. Additionally, even in healthy, term-born infants, FFM hydration changes rapidly throughout the first days and weeks of life, and by implication so do the constants that are used to calculate body composition parameters (e.g. x-ray attenuation factors or density of FFM).[90] It is possible that these parameters may not have been adequately adjusted to account for preterm birth, or preterm birth has a larger distorting effect on the constants used for one of the methods.

A later study from Italy reported that preterm infants born at 34-<37 weeks GA (when compared to term-born infants) have lower FM, %FM, FMI, FFM and FFMI on day 5 of life.[91] However, by the time they reached term-equivalent age, the preterm infants had higher FM, FMI and %FM than term neonates, suggesting that their postnatal body composition development did not match normal intrauterine development in healthy foetuses.[91] Differences were also observed between SGA and AGA preterm infants: SGA infants had lower FFM and FFMI at day 5, but by term only FFM remained lower while FFMI was equal.[90] This suggests some FFM catch-up, proportionate to their reduced length, in the SGA infants.

One study from India described differences between SGA and AGA infants in term-born neonates. Not unexpectedly, SGA infants were found to have lower weight, length, FM, %FM, FMI, FFM and FFMI than AGA infants.[92] However, SGA neonates had a higher %FFM than AGA neonates, suggesting a relatively greater accretion/ retention of FFM over FM.[92] This is in agreement with the INTERGROWTH-21ST cohort mentioned above.[87] It is plausible that nutrient deprivation later in pregnancy (e.g. due to reductions in placental transport capacity) could hamper FM accumulation and even lead to the foetus utilising its own fat stores as an additional energy source.

The wide range of body compositions seen in healthy, term AGA neonates raises the question of how significant the observed differences between preterm *vs*. term and SGA *vs*. AGA infants truly are in terms of clinical outcomes, since many (perhaps even most) of these infants would still fall within the “normal” range for FM%. One important consideration for long-term outcomes would be whether these changes persist into adulthood, or whether they are attenuated over time. This will be investigated in the next section.

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Body composition in infancy and early childhood

A 2012 review by Griffin *et al.* suggests that the differences in body composition between preterm and term infants diminish over the first year of life.[93] A more recent review by Hamatschek *et al*. concurs: though preterm infants' FM and FM% were higher at term equivalent age, it dropped to below those of term infants by 52 wees PMA, with %FM in both groups remaining similar from that time onward.[94] Preterm infants also had lower FFM at term-equivalent age, but gradually caught up to a difference of <100g by 60 weeks' PMA (i.e. 20 weeks or 4.6 months corrected age).[94]

Similar patterns have been noted when comparing SGA and AGA infants. An Italian study showed that although preterm SGA infants had significantly lower %FM than preterm AGA infants at term equivalent age, both groups were similar by 3 months corrected age, and remained similar at the final assessment two months later.[95] On the other hand, a cohort study conducted among term and preterm, singleton infants in Soweto, South Africa found that SGA infants had a lower FFM and FFMI than AGA infants at the age of 24 months, even when these differences were not apparent at younger ages.[96] However, relative weight gain from 0-12 and 12-24 months was a far stronger predictor of all BC outcomes, highlighting the important role of postnatal growth.[96] The Multicentre Infant Body Composition Reference Study likewise found that birth weight strongly predicts FFM and FFMI at 6 and 24 months.[97]

Few studies have examined body composition in relation to intrauterine growth patterns or placental function, though a recent meta-analysis suggests that infants with a history of FGR may have lower FM and FFM up to 6 months of age.[98] This finding was echoed in the preliminary UmbiBaby data, with FFM and FFM-for-age z-score remaining lower at 6 months of age in term infants with abnormal UmA-RI, compared to those with a normal UmA-RI.[99]

Body composition throughout childhood, adolescence and adulthood

The evidence for body composition changes in preterm and SGA infants through childhood and beyond is mixed. The review by Griffin *et al*. notes that some studies have found that preterm infants have lower FM, FM% and FMI in childhood compared to those born at term, while others found no significant difference in FMI, when comparing preterm AGA to term AGA and preterm SGA to term SGA infants.[93] However, when comparing SGA to AGA preterm infants, one study found that by 4 years old the SGA group had a higher FM%, higher gains in FM, and higher abdominal fat mass (accompanied by poorer insulin sensitivity).[93] The most recently published meta-analysis, including outcomes measured at 3-41 years of age, found that SGA preterm had significantly lower FFM than their AGA counterparts, but found no significant difference in FFMI (suggesting that the significant decrease in height reported in the same analysis accounts for the difference in FFM) and no

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differences in FM or any FM-related indices.[100] Locally, one analysis of the South African Birth-to-20+ cohort found that being SGA at birth and stunting (HAZ<-2) at 2 years of age were independently associated with lower soft-tissue-FFM at 22 years of age; whereas FM was more strongly predicted by weight gain throughout infancy, childhood and adolescence.[101] An Ethiopian study likewise found that FFMI at 4 years was predicted by birth weight, birth FFMI and the increase in FFM from 0-6 months.[102]

Associations between body composition and anthropometric outcomes

Anthropometry and body composition are inextricably intertwined: any change in weight involves changes in the FM and FFM, potentially in different proportions.[103] Longitudinal studies from South Africa have found that conditional/ relative weight gain and length growth are both predictive of FM and FFM at 24 months[96] and 22 years.[101] In one of these studies, stunting in the first two years of life was associated with lower FM and FFM, but similar or higher FMI, FFMI, and FM/FFM ratio suggesting that the decrease in FM and FFM are proportionate to the decrease in overall body size.[96] This finding concurs with studies from Cambodia[104] and Kenya.[105] Wasting was also associated with decreases in both FM and FFM.[104] A South African cohort study that followed participants up to 23 years found that the association between early stunting and FFM remained, but disappeared when adjusting for adult height, suggesting that height gain in later childhood and adolescence modulates the relationship.[106] Childhood stunting was not related to FM at 23 years.[106] This is broadly in agreement with Ethiopian[106] and South African[101] cohort studies that found that linear growth was more strongly associated with FFM than FM at 5 and 22 years of age.

Importance of local data

The Multicentre Infant Body Composition Reference Study included a cohort of South African infants among cohorts from India and Australia (0-6 months) as well as Pakistan, Sri Lanka and Brazil (3-24 months).[97] This study found some inter-country differences in body composition, despite all infants following similar feeding recommendations. From 0-3 months, South African infants had significantly higher FM, FMI and %FM than Australian or Indian infants.[108] At 6 months, South African infants had significantly lower FFM, %FFM and FFMI than Australian infants, and higher %FM.[109] Similarly, at ages 3-24 months, South African infants generally had the highest FM, FMI and FM%, and the lowest FFM and FFMI.[108] Using a 3-compartment model, South African infants were found to have a lower FFM hydration and higher FFM density that the widely-used reference infants described by Fomon *et al.* (girls only) and Butte *et al*. (boys and girls).[109] All this evidence indicated that the results from studies in other settings cannot be assumed to apply to South African infants, and local studies are warranted.

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LOCAL CONTEXT

The exact burden of small vulnerable newborns in South Africa is unknown, since data on preterm birth and SGA are not routinely collected in the health system. The 2019-2020 district health barometer reported an estimated LBW rate of 12.9%.[110] South African studies investigating Doppler screening in low-risk pregnant women across all nine provinces further support this:

- Over 25% of infants were born preterm (the majority of these at 34-37 weeks' gestation).[44]
- 19.5-24.3% of infants were SGA, far exceeding the theoretical incidence of 10% in a healthy population.[43,44]
- 10.4-11.3% of infants were LBW, which is consistent with the rate reported in the district health barometer.[43,44]
- Abnormal UmA-RI was found in 11.3-13.0% of pregnant women, with absent end-diastolic flow (indicative of advanced placental insufficiency) present in 1.2-1.3%.[43,44]

> Thus, South Africa indisputably has a large population of these especially vulnerable infants. Poor growth outcomes in these infants could contribute substantially to the population prevalence of childhood malnutrition. Characterising the growth patterns of infants born preterm, SGA and/ or with a history of placental insufficiency will provide valuable insights into how these conditions might be contributing to observed childhood malnutrition.

CONCLUSION

There is ample evidence that, when foetal growth is restricted or prematurely interrupted, it can affect growth and malnutrition rates in childhood. Yet, despite the evidence for a high burden of small vulnerable newborn births in South Africa, the growth of this population of South African infants has not been thoroughly described. Moreover, the emergence of UmA-RI as a potential indicator of FGR merits investigation of the long-term growth outcomes associated with placental insufficiency, particularly considering the high prevalence of abnormal UmA-RI in otherwise healthy pregnant women. The utility of assessing asymmetry between birth weight and head circumference as a predictor of growth outcomes also warrants investigation. Finally, the differences between the FGC and IG-PPGS growth charts for preterm infants have never been described in an African population, and no studies have investigated their ability to predict later growth outcomes. This research will contribute to filling in these gaps in the evidence.

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CHAPTER 3: FIRST PUBLICATION: Integrated growth assessment in the first 1000 d of life: an interdisciplinary conceptual framework

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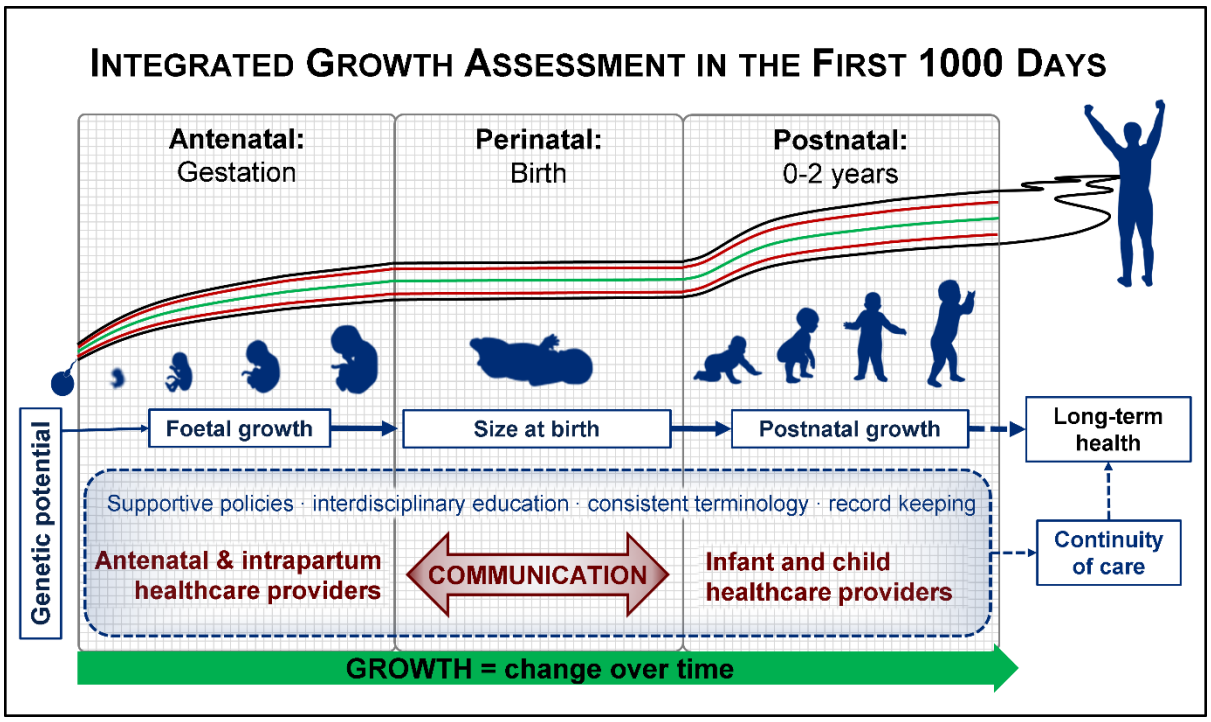
GRAPHICAL ABSTRACT



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Review Article

Integrated growth assessment in the first 1000 d of life: an interdisciplinary conceptual framework

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Abstract

Objectives: Prenatal growth affects short- and long-term morbidity, mortality and growth, yet communication between prenatal and postnatal healthcare teams is often minimal. This paper aims to develop an integrated, interdisciplinary framework for foetal/infant growth assessment, contributing to the continuity of care across the first 1000 d of life.

Design: A multidisciplinary think-tank met regularly over many months to share and debate their practice and research experience related to foetal/infant growth assessment. Participants' personal practice and knowledge were verified against and supplemented by published research.

Setting: Online and in-person brainstorming sessions of growth assessment practices that are feasible and valuable in resource-limited, low- and middle-income country (LMIC) settings.

Participants: A group of obstetricians, paediatricians, dietitians/nutritionists and a statistician.

Results: Numerous measurements, indices and indicators were identified for growth assessment in the first 1000 d. Relationships between foetal, neonatal and infant measurements were elucidated and integrated into an interdisciplinary framework. Practices relevant to LMIC were then highlighted: antenatal Doppler screening, comprehensive and accurate birth anthropometry (including proportionality of weight, length and head circumference), placenta weighing and incorporation of length-for-age, weight-for-length and mid-upper arm circumference in routine growth monitoring. The need for appropriate, standardised clinical records and corresponding policies to guide clinical practice and facilitate interdisciplinary communication over time became apparent.

Conclusions: Clearer communication between prenatal, perinatal and postnatal health care providers, within the framework of a common understanding of growth assessment and a supportive policy environment, is a prerequisite to continuity of care and optimal health and development outcomes.

Keywords
First 1000 d
Growth monitoring
Foetal growth restriction
Doppler
Infant growth
Interdisciplinary care
Continuity of care

Growth assessment in the first 1000 d of life is a shared interest of all health professionals involved in the care of pregnant women, infants and children. Primary care providers, nurses, midwives, obstetricians, paediatricians and dietitians/nutrition professionals all share a common goal to support the foetus/infant to achieve its genetic potential for growth and development[1,2].

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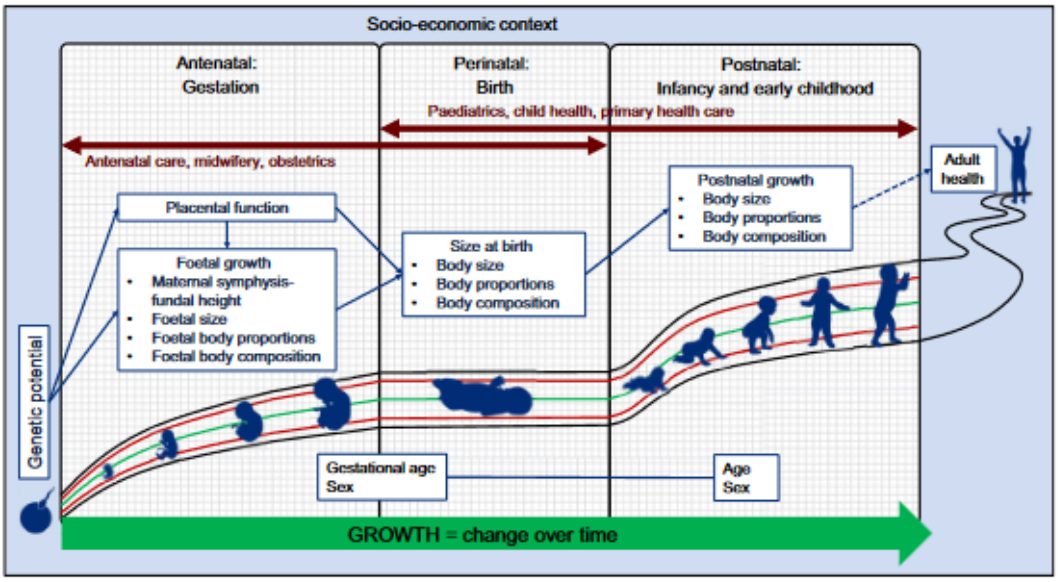

Fig. 1 Growth assessment in the first 1000 d of life: continuity over time and across disciplines

In the context of growth assessment, growth refers to changes (increases/decreases) in measurable physical properties (e.g. weight, lengths and circumferences) over time[3]. The multi-dimensional, non-linear nature of growth necessitates sequential measurements – usually of more than one physical property – to accurately assess changes in body size, proportion and composition[1,3,4]. Once-off anthropometric assessment has only limited value, as any given size may be the result of consistent growth, growth faltering or excessive growth, each of which implies different health and nutritional conditions and requires different clinical management[4].

Within a life-course approach, anthropometric assessment serves a purpose beyond the evaluation of current health and nutritional status; it provides summative information about past growth and predicts likely future health outcomes[5,6]. The first 1000 d of life (from conception to the second birthday) are particularly important as a critical window of opportunity for health promotion and disease prevention, and nutritional insults during this time can have serious short-term and life-long consequences[7,8]. For example, foetal growth restriction (FGR) is an important cause of potentially avoidable stillbirth[9,10], size at birth may predict neonatal mortality[11–13] and future growth[14] and growth in infancy (as a sensitive marker for nutritional status and overall health) may predict mortality, neurodevelopment, lifetime educational achievement and future non-communicable disease risk[7,15–17]. Low- and middle-income countries (LMIC) remain burdened by early childhood malnutrition, and growth monitoring and promotion are a cornerstone of primary health care for children[18–20]. Additionally, many LMIC are experiencing a nutrition transition, with widespread chronic undernutrition complicated by increasing obesity prevalence, the so-called double burden of malnutrition. This emphasises the need for appropriate growth monitoring and timely intervention where needed[7,17].

Birth is a key event in the first 1000 d of life. In physiological terms, birth represents an interruption in the growth continuum, with a temporary cessation of growth (including weight loss) as the neonate adjusts to extra-uterine life. For the health care team, the perinatal period is the point of overlap between the prenatal (obstetrics, midwifery and primary antenatal care) and postnatal (paediatric, child health and primary health care) health care providers (Fig. 1). Clear communication between all these professions is essential for maintaining continuity of care and ensuring optimal outcomes for mothers, infants and young children. This necessitates that we 'speak the same language' across disciplines, while also staying abreast of the latest developments in the field of growth assessment. The same is true in research so that findings may be compared across studies and over time. As studies in life-course nutrition show that the consequences of poor growth may only be evident in the distant future; it is important, therefore, that at least the basic measurements lend themselves to such longitudinal analyses.

Various factors complicate the interdisciplinary harmonisation of growth assessment in the first 1000 d. Primary among these are the fundamental differences in the

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established measurements, indices and indicators used by different clinical disciplines. For instance, foetal growth assessment relies on indirect measurements – maternal symphysis-fundal height, ultrasound biometric measurements and calculated estimated foetal weight – as opposed to direct measurement after birth. Discipline-specific measurements may further exacerbate this disconnect: for example, abdominal circumference is a useful measurement in the foetus but is of limited value postnatally; proportionality between weight and head circumference (HC) is of interest at birth but rarely thereafter; and nutritional assessment in infancy and childhood relies heavily on weight-for-length (WFL) or BMI which is never assessed prenatally and only rarely at birth[21]. This complicates communication between different disciplines. A final challenge is that policy frameworks, while encouraging interdisciplinary cooperation in principle, rarely provide any practical framework for communication across disciplines serving mother–infant dyads during different life stages[22]. Rather, they often perpetuate the division of prenatal, perinatal, maternal and infant healthcare by separating them at both the policy and the practical level[23–25].

Addressing the communication gap between healthcare providers will require, firstly, an awareness of the overlap and discrepancies between clinical disciplines as well as an understanding of the ways in which growth is assessed by these disciplines. Clear, open communication in a common language is needed for the health care team to holistically understand the growth of the individual in their care, both in the past and in the future. Finally, the policy environment and healthcare systems should encourage and facilitate interdisciplinary communication and teamwork.

Aim

This paper aims to contribute to evidence-based, integrated implementation of growth assessment and to contribute to the continuity of care in the first 1000 d, by the development of a unified conceptual framework that integrates measurements, indices and indicators of foetal/infant growth assessment from the time of conception until 2 years of age, with an emphasis on application in LMIC. The intention is to promote continuity of transdisciplinary health care provision, based on current scientific understanding and practice.

Key definitions

For the sake of clarity, a distinction was made between measurements, indices and indicators (Table 1). Measurements refer to the quantification of a physical parameter. Indices combine a measurement with other measurement(s) and/or characteristic(s) such as age, gestational age (GA) and sex, in biologically meaningful ways. Indicators place indices in relation to what is expected in healthy individuals, allowing clinically useful conclusions to be drawn[26].

Table 1 Differentiation between measurement, index and indicator in growth assessment (based on and adapted from Waterlow, 1992:213)[26]

Term	Definition	Examples
Measurement	The quantification of a physical parameter or property; primarily includes biometric and anthropometric data.	- Weight - Length - Abdominal circumference - Body volume (plethysmography)
Index	The combination of measurements/characteristics to allow biologically meaningful interpretation.	- Age-related e.g. weight-for-(gestational) age - Ratios e.g. BMI, foetal head circumference to abdominal circumference ratio - Calculated indices, e.g. estimated foetal weight, fat-free mass
Indicator	Tools for evaluating measurements and/or to allow for clinically meaningful judgements.	- References/standards, e.g. growth charts - Reporting systems, e.g. percentiles, z-scores, percentage of median - Classification systems, e.g. the Waterlow classification for differentiating between stunting and wasting - Cut-offs that classify and label a once-off assessment of a growth index/indices.

This paper is intended to contribute to implementation science, which may be defined as 'an interdisciplinary body of theory, knowledge, frameworks, tools and approaches whose purpose is to strengthen implementation quality and impact'[27]. The topics under discussion are relevant to all professionals who assess foetal and infant growth, whether in clinical practice or for research purposes, as well as to policies governing maternal, neonatal, infant and young child healthcare provision.

Methods

Using a multidisciplinary interactive think-tank approach over many months of regular meetings, a workgroup of researchers and clinicians with specialisation in obstetrics (n 4), paediatrics (n 2) and dietetics/nutrition (n 4) in consultation with a statistician, shared and debated their practice and research experience related to foetal/infant growth assessment. Weekly virtual meetings of academic staff, researchers and postgraduate students affiliated with

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the Research Centre were initiated in February 2021, in order to maintain contact among geographically remote affiliates, support postgraduate students and foster inter-disciplinary thinking and collaboration among researchers from diverse academic backgrounds. This was considered essential in light of the transdisciplinary nature of the Research Centre's activities. It soon became apparent that different clinical specialties within the team were approaching matters relating to foetal and infant growth from widely differing perspectives, which complicated communication among the group. Establishing a common understanding and language for matters related to growth monitoring was included as a fixed agenda item, and from these discussions, the framework presented here emerged and was formalised and refined. The discussions focussed particularly on identifying parameters that contributed meaningfully to continuous growth assessment by different clinical disciplines over the first thousand days of life. The information was grouped according to antenatal, perinatal and postnatal periods, the domains of the three clinical disciplines represented in the think-tank. The measurements, indices and indicators within each period were identified by the subject specialists in the team, based on clinical practice and evidence-based guidelines, and reviewed by all members of the team. Disagreements were resolved by discussion and referral to published research and clinical guidelines.

The information was further organised using the terminology of measurements, indices and indicators introduced by Waterlow, one of the fathers of child growth monitoring (Table 1)[26]. As the process advanced, recurring sub-themes emerged within the three assessment periods, namely body size and proportions, body composition and placenta-related matters (in the antenatal and perinatal periods). These were incorporated into the basic framework. The personal practice and research knowledge of the participants was supplemented and verified by published information, and evaluated for clinical applicability, particularly in resource-limited settings.

Results

Figure 1 shows the basic conceptual framework, incorporating the somatic aspects of growth assessment within each of the three distinct assessment periods in the first 1000 d.

The genetic growth potential of the foetus/infant represents the starting point of the framework: conceptually, healthy growth is growth that achieves the genetic potential without overshooting it. However, 'genetic potential' is operationally difficult, as it is impossible to quantify. Recently, researchers have begun to incorporate proxies for genetic factors (e.g. ethnicity and maternal height) to develop individualised foetal growth curves and birthweight targets[2]. However, in practice, foetal and infant growth assessment relies on comparing the size/growth of the individual foetus/infant to the expected growth pattern described by reference growth charts[1,4].

Although this framework is concerned mainly with the objective anthropometric assessment of growth, the crucial role of socio-economic factors cannot be ignored. Thus, the socio-economic context is represented as a background that encloses and underlies the framework.

Placental growth and function are included in the antenatal and perinatal phases, firstly because the placenta is derived from foetal tissue and grows in tandem with the foetus, and secondly, because of its critical role in foetal nutrition and growth. Throughout the antenatal and postnatal periods, the emphasis is on change over time, dynamically depicted by an arrow. Conversely, birth is shown as an interruption of the growth continuum, with a temporary flattening of growth curves. Anthropometric assessment at birth is commonly used as a proxy for intrauterine growth, but it provides only limited information, as an understanding of foetal growth is needed to appreciate the value and limitations of birth anthropometry.

The following sections detail the available measurements, indices and indicators in each period, followed by an integrated framework illustrating the relationship between selected growth parameters throughout the first 1000 d.

Antenatal period: foetal growth assessment

During the antenatal period, ultrasound can be used for biometric measurements of the foetus and placenta. The measurements and functional tests, along with their associated indices and indicators, are presented in Table 2.

Foetal measurements are assessed independently of foetal sex, but according to GA. The first important requirement to assess foetal growth, then, is an accurate GA estimate. In the absence of a certain date of conception (or last menstrual period), GA is estimated based on ultrasonographic measurements. However, this approach is less reliable after 14 weeks GA, since foetal growth becomes more variable with advancing GA[28]. Where ultrasound is unavailable, symphysis-fundal height measurement may be used for GA estimation, although the accuracy is inferior to ultrasound and may be challenging in women with obesity[29–31].

Foetal abdominal circumference (AC), HC, femur length and biparietal diameter are commonly measured. Each of these can be assessed according to GA-specific reference charts (Table 2)[32–36], with values between the 10th and 90th percentile considered appropriate for gestational age[28]. The same holds true for estimated foetal weight, which is calculated using the aforementioned biometric measurements. Various estimated foetal weight equations (i.e. indices) are available, including the widely used Hadlock equations[37] and the newer equation from the

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International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st)[34]. However, 10–15 % errors in estimated foetal weight *v.* actual weight are not uncommon and may be attributed to high inter- and intra-observer variability in biometric measurements, the choice of equation and the amplification of errors in single parameters when included in a calculation[28,38–42].

The aim of foetal growth assessment is the detection of FGR or excessive foetal growth. Numerous diagnostic criteria (i.e. indicators) for FGR have been proposed, but the Delphi Consensus Statement for Foetal Growth Restriction (Table 2)[43] is the most widely accepted. Other potentially useful indicators include biometric measurements and/or estimated foetal weight < 10th or >90th percentile for GA (indicating small-for-GA and large-for-GA, respectively)[28], as well as foetal proportions and ratios (most commonly the HC/abdominal circumference ratio) as indicators of asymmetric FGR[44].

Comprehensive growth assessment implies multiple measurements over time[1,3], but the appropriate interpretation of serial foetal biometry remains unclear[44]. Various approaches have been proposed, including calculation of growth velocity, conditional percentiles, projection of expected birth weight and individualised growth charts[2,44]; however, none of these have been sufficiently validated for widespread incorporation into clinical practice. A minimum interval of three weeks between ultrasound assessments is recommended to minimise over-detection of foetal growth problems[28].

In LMIC, ultrasound assessment is mostly limited to high-risk pregnancies. In these settings, maternal symphysis-fundal height measurement is commonly used to monitor foetal growth[29]. However, the sensitivity of a single symphysis-fundal height measurement for detecting small-for-GA/large-for-GA is poor except at the extremes of foetal size[45,46]. Nonetheless, repeated symphysis-fundal height measurements (at least 2 weeks apart), plotted on an appropriate growth chart (e.g. the INTERGROWTH-21st standard[47]) may be used as a first-level screening tool to identify women who require referral for ultrasound[45,47].

Measures of placental function by Doppler screening may be useful to detect foetuses at risk of FGR. Doppler devices measure blood flow velocity in maternal or feto-placental blood vessels, including the umbilical, uterine and foetal mid-cerebral arteries. Various indices can be calculated (including the resistance index, pulsatility index, systolic/diastolic ratio and cerebro-placental ratio) and compared to GA-specific reference data (see Table 2), with increasing indices indicating placental dysfunction. Crucially, the low-cost, portable, easy-to-use Umbiflow™ Doppler device makes Doppler screening feasible in resource-limited settings and has value as a once-off assessment of placental function[48]. Optimal indicators and cut-offs for Doppler-derived indices (particularly in the absence of biometric measurements) require further investigation, although some Doppler-derived indicators are included in the Delphi Consensus Statement for FGR[43].

Foetal body composition is not routinely assessed. Numerous publications describe visceral and subcutaneous fat thickness in various locations and its association with maternal diabetes mellitus, but no standards are available[49–51]. Likewise, measurements of foetal organ size may be used for disease detection, but do not form part of routine foetal growth monitoring[38].

Perinatal period: newborn size and body composition

For the majority of infants, birth marks the first growth assessment, as direct measurements of body size become possible. The infant and placental measurements that can be taken at birth, as well as their associated indices and indicators, are presented in Table 3.

Meaningful interpretation of newborn size relies on sex- and GA-specific reference data (e.g the INTERGROWTH-21st Newborn Size Standards[52] and the Fenton 2013 growth chart[53]). The 10th and 90th percentiles of birth weight-for-GA are commonly used to distinguish small, appropriate and large for GA infants[1]. However, birth anthropometry only gives a summative snapshot of foetal growth, without any indication of the preceding foetal growth trajectory. Thus, true FGR or excessive foetal growth may be missed. For example, a neonate with birth weight < 10th percentile may simply be constitutionally small, yet growing consistently (i.e. achieving its genetic growth potential), whereas a foetus with faltering growth may remain above the 10th percentile at birth[1,54]. This highlights the crucial importance of communication between pre- and postnatal healthcare providers: measurements taken during pregnancy (e.g. serial ultrasound biometry or umbilical artery Doppler) can help to identify truly growth-restricted neonates who are at risk of adverse outcomes and guide paediatric healthcare providers' expectation for appropriate postnatal growth.

In the absence of antenatal measurements, the proportionality (or symmetry) of the neonate can provide clues about foetal growth. An infant is considered proportional/symmetrical if the GA-related z-scores for weight, length and HC are similar; conversely, if the z-score for weight is markedly lower than that of length and/or HC, the neonate is considered asymmetrically growth restricted. Asymmetrical growth restriction is believed to result from cranial redistribution of foetal circulation due to placental insufficiency, maintaining brain growth at the cost of somatic growth[13,55]. Various attempts have been made to mathematically quantify the relationship between weight and length (including weight-length ratio[56], BMI-for-GA[57] and ponderal index[13,56]) or weight and HC (including BW/HC ratio[58] and the difference between HC and BW z-scores[59]), but none of the related cut-off values have been sufficiently validated for adoption into

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Table 3 Measurements, indices and indicators that can be assessed at birth

Measurements	Indices	Indicators
Placenta		
Placental weight	Feto-placental ratio: ratio of birth weight to placental weight (BW:PW). Increases with advancing gestation (doubles from 24 weeks GA to term)[61]	References/standards: none, but lower BW:PW suggests impaired nutrient transfer across placenta[61] Cut-offs: no universal cut-off – normal BW:PW at term = 5–7[61]
Body size and proportions		
Birth anthropometry: - Weight - Length - Head circumference	Gestational age-related - Weight-for-GA - Length-for-GA - HC-for-GA (Sex-specific)	References/standards: - INTERGROWTH-21st[52,102] - Fenton 2013 (includes Olsen data)[53] Cut-offs: Weight-for-GA[1]: - < 10th percentile = SGA –10th–90th percentile = AGA - > 90th percentile = LGA
	Proportionality - BW/HC ratio - Difference between BW and HC z-score - W/L ratio (GA- and sex-specific) - Ponderal index (GA-specific) - BMI (BMI; GA- and sex-specific)	References/standards: - INTERGROWTH-21st: W/L ratio-for-GA[103] - Olsen 2015: BMI-for-GA[57] - Landmann 2006: ponderal index-for-GA[56] Cut-offs: - BW/HC ratio < 90 (proposed, unvalidated)[58] - HCZ-BWZ > 1 (proposed, unvalidated)[59] - PI < 2 or < 10th percentile for GA[13,55]
Body composition		
Body volume (by air-displacement plethysmography)	Body density à FM, FFM à related to weight: %FM, %FFM à related to length: FMI, FFMI (Sex- and GA-specific)	References/standards: - INTERGROWTH-21st: (36–42 weeks GA) – FM, %FM, FFM[103] - Norris 2019 (30–41 + 6 weeks GA) – FM, %FM, FFM[104] Cut-offs: None established

Abbreviations: BW, birth weight; PW, placental weight; GA, gestational age; HC, head circumference; INTERGROWTH-21st, International Fetal and Newborn Growth Consortium for the 21st Century; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; W, weight; L, length; HCZ, head circumference-for-GA z-score; BWZ, birth weight-for-GA z-score; PI, ponderal index FM, fat mass; FFM, fat-free mass; FMI, fat mass index; FFMI, fat-free mass index.

routine clinical practice. Likewise, it is not yet clear which, if any, of these indices and indicators have superior predictive value for short- and long-term adverse outcomes.

The placenta is routinely weighed at birth, but standardised procedures and consensus on indicators of abnormality are lacking. The birth weight to placental weight ratio (BW:PW; also called the foeto-placental ratio) has been shown to correlate with foetal abdominal circumference growth velocity and Doppler indices of placental function; as such, a low BW:PW ratio may suggest a history of placental insufficiency and FGR[60]. The BW:PW ratio increases with advancing gestation, doubling from 24 to 38–40 weeks to reach a ratio of 5–7:1 at term, but a definite cut-off for abnormality remains elusive[61].

Body composition at birth can be assessed using air-displacement plethysmography (ADP, e.g. using the PEAPOD™ device), which measures body volume and calculates body density, fat mass (FM) and fat-free mass (FFM). Further indices can be calculated relative to total body weight (%FM and %FFM) or length (fat mass index and fat-free mass index – that is, FM or FFM (in kg) divided by length (in m) squared). The interpretation of these indices is linked to infant sex and GA. Various reference charts are available (see Table 3), but as yet no cut-offs have been established for body composition indicators.

Postnatal period: growth in infancy and early childhood

Routine growth monitoring has long been one of the cornerstones of primary health care provision for infants and children[18]. The various measurements, indices and indicators for assessing growth in the first 2 years after birth are shown in Table 4.

Anthropometric and body composition parameters are interpreted according to the infant/child's sex and age (with age correction for preterm infants born at < 37 weeks GA). Weight, length, HC and mid-upper arm circumference (MUAC) are commonly measured, while triceps skinfold and subscapular skinfold are technically much more challenging and much less commonly used. Any of these measurements can be interpreted as a sex-specific index-for-age (i.e. weight-for-age, length-for-age, HC-for-age, MUAC-for-age, triceps skinfold-for-age and subscapular skinfold-for-age), while weight can also be interpreted in relation to length, e.g. WFL or BMI (weight (in kg) divided by length (in m) squared), interpreted as BMI-for-age. This is particularly important in LMIC, where the high prevalence of stunting complicates the interpretation of simple weight-for-age.

Growth charts remain the cornerstone of interpreting growth indices in childhood[62]. WHO Multicentre Growth Reference Study (MGRS) Growth Standards are intended as a single, global growth standard by which children of all

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Table 4 Measurements, indices and indicators for assessment of growth in infancy and early childhood

Measurements	Indices	Indicators
Body size and proportions		
Weight Length	Once-off assessment - Weight-for-age - Length-for-age - Weight-for-length - BMI-for-age (Sex-specific) (GA-specific and/or age-corrected for preterm infants)	References/standards: - Preterm infants: Fenton 2013[53], INTERGROWTH-21st Preterm Postnatal Growth Standards[90] - WHO MGRS Growth Standards[66] - Population- and disease/condition-specific growth charts Cut-offs: WHO MGRS Growth Standards[82,105] - WFA z-score <–2 = underweight (<–3 = severe) - WFL z-score <–2 = wasting (<–3 = severe) - LFA z-score <–2 = stunting (<–3 = severe) - BMI-for-age z-score >+2: = overweight WHO/UNICEF diagnostic criteria for moderate/severe acute malnutrition (MAM/SAM) (6–59 months) include WFL (with MUAC and clinical assessment)[65] - WFL z-score <–2 = MAM, <–3 = SAM
	Serial assessments - Weight velocity (e.g. g/interval) - Length velocity (e.g. cm/interval) (Sex-specific)	References/standards: WHO MGRS Growth Standards[71] Cut-offs: None established
Head circumference	Once-off assessment HC-for-age (Sex-specific)	References/standards: WHO MGRS Growth Standards[67] Cut-offs: HC z-score <–2 or >+2 warrants investigation
	Serial assessments: HC velocity (cm/interval) (Sex-specific)	References/standards: WHO MGRS Growth Standards[71] Cut-offs: None established
MUAC	MUAC-for-age (Sex-specific)	References/standards: WHO MGRS Growth Standards[67] Cut-offs: WHO/UNICEF diagnostic criteria for moderate/severe acute malnutrition (MAM/SAM) (6–59 months) include MUAC (with WFL and clinical assessment)[65]: - MUAC < 115 mm = SAM –115mm ≤MUAC < 125 mm = MAM
Skinfolds: triceps, subscapular	- TSF-for-age - SSF-for-age (Sex-specific)	References/standards: WHO MGRS Growth Standards[67] Cut-offs: None established
Body composition		
Body volume (plethysmography)	Body density à FM, FFM à in relation to weight: %FM, %FFM à in relation to length: FMI, FFMI (Sex- and GA-specific)	References/standards: - Norris 2019 (1–27 weeks) - FM, %FM, FFM[104] - De Fluiter 2020 (0–6 months) - FM, %FM, FMI, FFM, FFMI[85] Cut-offs: None established
Stable isotope concentration (dilution)	Total body water à FM, FFM à related to weight: %FM, %FFM à related to length: FMI, FFMI (Sex- and age-specific)	References/standards: - Wells 2020 (6 weeks to 5 years) - TBW, FM, FMI, FFM, FFMI[106] Cut-offs: None established
X-ray attenuation (DEXA)	FFM (differentiated into bone mineral content, cell mass (water, protein)), FM. à FM, FFM à related to weight: %FM, %FFM à related to length: FMI, FFMI (Sex- and age-specific)	References/standards: - De Fluiter 2020 (6–24 months) - FM, %FM, FMI, FFM, FFMI[85] Cut-offs: None established

Abbreviations: GA = gestational age; INTERGROWTH-21st, International Fetal and Newborn Growth Consortium for the 21st Century; WHO, World Health Organization; MGRS, Multicentre Growth Reference Study; WFA, weight-for-age; LFA, length-for-age; WFL, weight-for-length; MUAC, mid-upper arm circumference; UNICEF, United Nations Children's Fund; MAM, moderate acute malnutrition; SAM, severe acute malnutrition; HC, head circumference; TSF, triceps skinfold; SSF, subscapular skinfold; FM, fat mass; FFM, fat-free mass; FMI, fat mass index; FFMI, fat-free mass index; DEXA, dual-energy X-ray absorptiometry.

nationalities and ethnicities can be assessed[63,64], although some countries continue to use population-specific growth charts[20]. Growth standards can be used to determine percentile positions and/or calculate z-scores or to identify the median of a given growth index. Z-score values between –2 and +2 are considered normal, although a small proportion (< 5%) of a normally distributed population could be expected to fall outside these limits.

Different indicators and classification systems exist for the diagnosis of malnutrition, based on weight-for-age, WFL and length-for-age, and using either z-scores or the measured value as a percentage of the median (see Table 4). Additionally, MUAC is used as such to identify moderate and severe acute malnutrition in children aged 6 months to < 5 years[65]. MUAC-for-age charts are available[66], but the appropriate interpretation of z-scores is not

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clear. The interpretation of BMI-for-age to identify overweight in young children is controversial, but the rise of obesity among children even in LMIC cannot be ignored[7,17]. Skinfold measurements may be used as a rough indicator of adiposity, and reference data for triceps skinfold and subscapular skinfold are available (WHO-MGRS Growth Standards[67]), but the appropriate interpretation remains unclear. Additionally, skinfolds are technically challenging to measure, and intra-observer measurement reliability tends to be poor[68].

Anthropometric status (WFL z-score, MUAC) at a single time point may be used to classify moderate and severe acute malnutrition in children aged 6–59 months. Additionally, the presence of bilateral nutritional oedema and/or severe wasting is diagnostic of severe acute malnutrition regardless of anthropometric status[65]. Indicators of malnutrition based on the percentage of the median of older reference data have become obsolete in light of the WHO MGRS growth standard, and their routine use is no longer recommended. These include the Waterlow classification[69] (used to distinguish between wasting (low WFL) and stunting (low length-for-age)) and the Wellcome classification[26] (used to distinguish between underweight, wasting, kwashiorkor and marasmic kwashiorkor, on the basis of weight-for-age and the presence of oedema).

Growth, as stated earlier, refers to change over time; thus, serial interpretation of anthropometric indices is imperative[62]. Healthy growth is characterised by growth indices maintaining approximately constant z-scores over time, with some intra-individual variation[62]. It is unclear what degree of deviation from an individual's expected z-score trajectory should be considered problematic[62,70]. Nonetheless, accurately plotting of consecutive measurements on a suitable growth chart, with consideration of multiple indices, remains the best available method to identify growth faltering or excessive growth[4,62,70]. The WHO-MGRS Growth Standards include growth velocity standards for weight, length and HC[71] but these indices are challenging to use and interpret.

Growth assessment in preterm-born infants is less straightforward. There are several controversies, including the type of growth charts to use (charts based on longitudinally collected data, such as the INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants, *v.* charts based on cross-sectional birth data, such as the Fenton 2013 Growth Charts), the most desirable growth trajectory (regaining the birth weight z-score, maintaining the z-score achieved after the initial weight loss, or various methods for calculating growth velocity), and the desirability of catch-up growth and speed thereof[4,72–77]. Similarly, growth assessment in infants and children with certain chronic conditions can be challenging. Length measurement may be impossible in infants/children with neurological impairment, necessitating the use of proxy measurements such as limb segments and circumferences[78]. Furthermore, standard growth charts may not be applicable in conditions where 'normal' growth cannot reasonably be expected. Specialised growth charts are available for several clinical conditions, including (but not limited to) cerebral palsy[79], Down Syndrome[80], Turner Syndrome[81], Prader–Willi syndrome[82] and Noonan Syndrome[83], but their use is not universally accepted, particularly in infancy and early childhood[78]. Body composition assessment may be of value in these populations, although the appropriate indicators of malnutrition remain unclear[78].

Body composition can be assessed by various methods in the first two postnatal years. Although uncommon in clinical practice, research settings may use ADP, stable isotope dilution and dual-energy X-ray absorptiometry[68]. Body volume is measured by ADP and combined with weight to calculate body density, from which FM and FFM can be calculated[68,84]. The PEAPOD™ ADP device is only suitable for infants up to 10 kg[84,85], which some infants may reach already at 6–8 months, although smaller infants may remain under 10 kg up to 2 years of age or beyond[66]. The BODPOD™ with paediatric attachment can be used for infants from 12 kg, but is only validated from 2 years of age[86]. Stable isotope dilution may be used to assess body composition in infants and children of any age but may be impractical in neonates[68,87]. The method involves administering a known dose of a stable isotope (e.g. deuterium-containing water), allowing it to equilibrate in the body and measuring its concentration in saliva or urine. This allows for the calculation of total body water mass and, by extension, FFM and FM[87]. The final method, dual-energy X-ray absorptiometry, estimates body composition from the measured attenuation of X-rays through the body[68]. Unlike the previous two methods, dual-energy X-ray absorptiometry can further distinguish between bone and soft tissue (water and protein). The high cost limits the availability of dual-energy X-ray absorptiometry, and repeated X-ray exposure may not be desirable[68]. Reference data have been published for each of these methods (Table 4). Bioelectrical impedance analysis has been proposed as potentially useful in infants, but at this time none of the available predictive equations for the calculation of body composition parameters have been sufficiently validated to be recommended for clinical or research use, as found in a recent (2021) systematic review[88]. It should be emphasised that body composition data obtained using different methods are not interchangeable[68,89], so it is important to use reference data compiled using the same methodology. No cut-off values for indicators of body composition abnormality have been established.

Integrated framework

The preceding discussion identifies numerous measurements, indices and indicators for assessing growth in the

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first 1000 d of life. Integrating these disparate parameters into a single, unified framework implies identifying those parameters that can meaningfully be compared across the antenatal, perinatal and postnatal periods. The relationship between selected measurements and indices is illustrated in Fig. 2, with solid arrows indicating directly comparable parameters and dashed arrows indicating parameters that are related but not identical. The transition between prenatal and postnatal growth assessment is necessarily somewhat disjointed due to the indirect nature of foetal biometry.

Discussion and recommendations

Growth assessment in the first 1000 d of life involves numerous clinical disciplines, measurements, indices and indicators. Growth assessment is inextricably linked to a life-course approach: current growth status results from earlier growth patterns and guides future clinical management. Unfortunately, limited contact between pre- and postnatal healthcare providers undermines interdisciplinary communication and continuity of care. This paper proposes an integrated, interdisciplinary framework for growth assessment in the first 1000 d of life, with the aim of promoting a common understanding among all clinical disciplines involved in this critical period.

Developing a common language among professions as diverse as obstetrics, midwifery, paediatrics, nursing and dietetics/nutrition is no small feat. A shared understanding of measurements and indices and the relationship between them (as shown in Fig. 2) is an important first step. Of course, not all possible measurements, indices and indicators can (or need to) be included in a unified framework, but those parameters that may meaningfully predict future outcomes should be understood by and communicated to all. To this end, differences in terminology, measurement methods, reference data, reporting systems and indices and indicators of interest need to be identified and, where possible, harmonised. For example, in paediatrics, the use of z-scores has become ubiquitous due to their mathematical and statistical utility, whilst percentiles are still preferred in many obstetric settings. Indeed, until recently, no z-score reference data were available for foetal growth indices, but presently the INTERGROWTH-21st Fetal Growth Standards[33,34] and Fetal Medicine Foundation's Fetal Growth calculator[32] both include z-scores. Furthermore, the INTERGROWTH-21st Growth Standards and the Fenton 2013 Growth Chart all demonstrate good continuity with the WHO MGRS Growth Standards, further facilitating the integration of pre- and postnatal growth assessment[53,90–92]. Thus, the tools for integration of growth assessment from conception through childhood are there; it is up to us – the clinical and research communities – to embrace these opportunities and optimise patient care and research reporting. Selecting the best set of tools to facilitate such integration will require careful consideration of the scientific merits and drawbacks of each reference. The debate surrounding the optimal growth chart for preterm infants is a good example: despite the conceptual coherence and strict individual-level inclusion criteria of the INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants, the limited sample size at postmenstrual ages < 36 weeks is a serious concern[72]. For this reason, the American Academy of Paediatrics recommend the use of intrauterine (i.e. birth-weight-derived) charts for monitoring the postnatal growth of preterm infants[93]. Evidence of the superiority of one growth chart over the other, particularly in ethnically diverse LMIC populations, is still lacking.

Three additional practical considerations underlie the successful integration of growth assessment across the first 1000 d. Firstly, measurements must be taken accurately, which requires functional equipment and adequately skilled and motivated measurers. This also implies standardised measurement techniques, e.g. of length measurements at birth and during infancy. Secondly, accurate assessment and documentation of GA is crucial, owing to the non-linearity of growth in the first 1000 d. And finally, measured values must be documented and made available to all members of the health care team. In industrialised countries, universally accessible electronic health records can facilitate this. Where such infrastructure may not be available, a patient-held document (such as the child's vaccination record) may fulfil the same role.

The measurements, indices and indicators outlined in this paper represent an ideal. However, some of the mentioned equipment and skills may not be available in LMIC and other resource-limited settings. Nonetheless, there are feasible, accessible practices that can be incorporated to improve growth assessment and contribute meaningfully to patient care outcomes. In the prenatal period, routine screening with a low-cost Doppler device (e.g. the Umbiflow™ device) has proven valuable for detecting foetuses at risk of FGR and stillbirth[48,94]. At birth, accurate assessment of length and HC, and standardised weighing of the placenta (with calculation of BW:PW ratio), may provide important information about foetal growth. During infancy and childhood, routine assessment of length-for-age, WFL and MUAC can provide valuable information about health and nutrition status that will be missed if only weight-for-age is assessed.

Figure 3 places this theoretical discussion into a practical context, showing how clear communication and information sharing between the antenatal and postnatal care teams can help identify neonates with FGR, who may be at increased risk of growth anomalies, and guide appropriate growth monitoring and promotion in infancy and childhood. Crucially, this information allows postnatal care providers to set appropriate growth targets for postnatal growth and tailor nutrition interventions accordingly. Nutrition, acute/chronic illness and socio-economic

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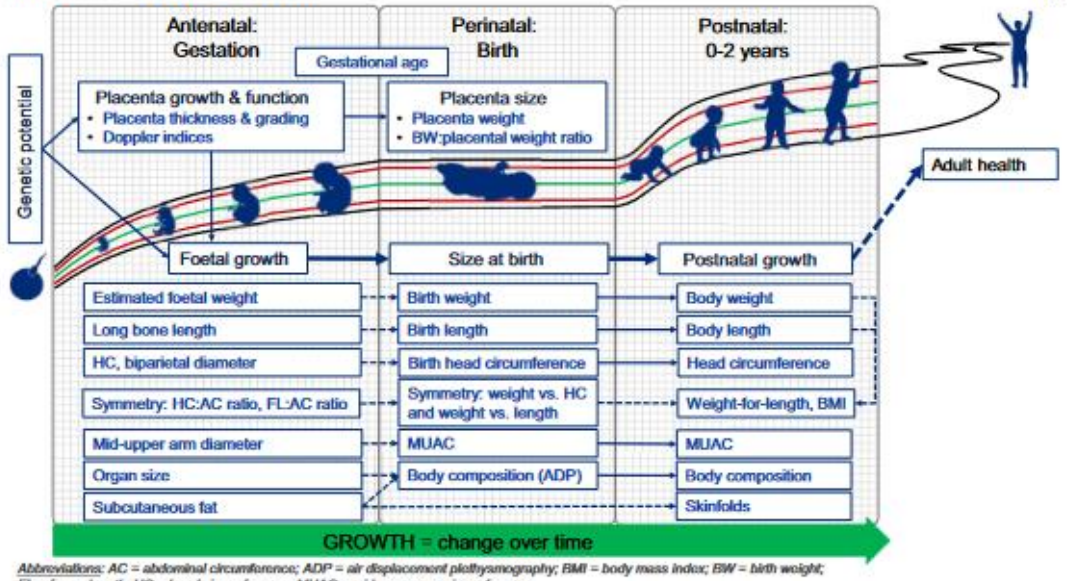
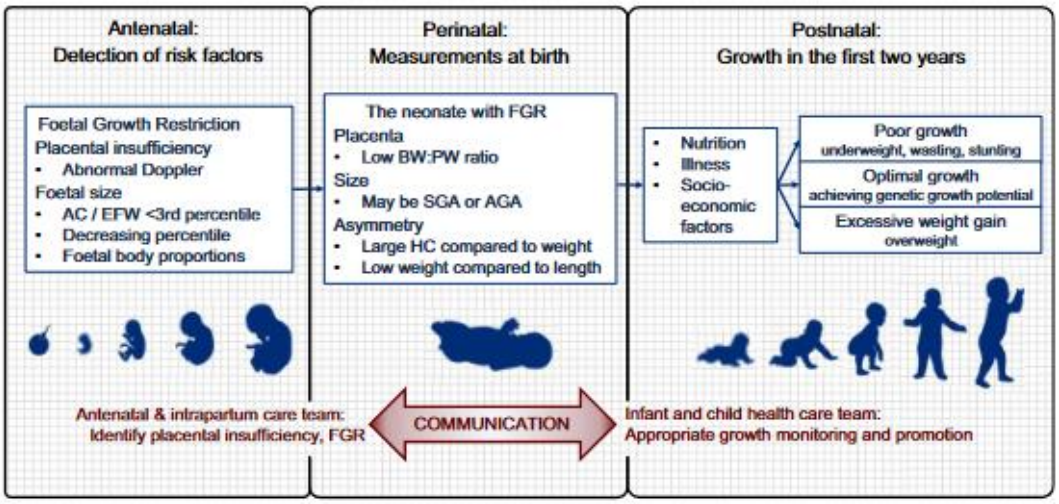


Abbreviations: AC = abdominal circumference; ADP = air displacement plethysmography; BMI = body mass index; BW = birth weight; FL = femur length; HC = head circumference; MUAC = mid-upper arm circumference;

Fig. 2 Integration of growth parameters throughout the first 1000 d of life



Abbreviations: AC = abdominal circumference; AGA = appropriate-for-gestational age; BMI = body mass index; BW = birth weight; BWZ = birth weight z-score; FGR = foetal growth restriction; HC = head circumference; PW = placental weight; WfL = weight/length.

Fig. 3 Birth as link between antenatal and postnatal health care teams, in the context of identifying and managing the neonate with foetal growth restriction (FGR)

factors are highlighted as important determinants of growth; these represent potential areas for intervention to optimise growth and, by extension, long-term health. It also underscores the fact that some factors contributing to poor/excessive growth are systemic and not under the control of the individual. The purpose of clinical labelling is to achieve a concise common language among those involved in health promotion, malnutrition prevention and clinical care. Stigmatisation and blaming of the child and caregiver should be avoided at all cost. Using non-judgemental 'people-first' language – for example, using the term 'child with obesity' or 'child with a BMI in the obese category' rather than 'obese child' – can further help to mitigate possible negative effects of clinical labelling.

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Policy and programmatic implications

Any change in the *status quo* requires a supportive policy environment. In a public healthcare system that uses standardised clinical documents and practice guidelines, the following is recommended:

- Incorporating Doppler screening as a test for placental function in basic antenatal care services and recording these results in the child's health record and vaccination card at birth;
- Standardising measurement techniques of birth anthropometry, particularly length measurement;
- Standardising methods for weighing the placenta, and including calculation of BW:PW ratio;
- Incorporating newborn growth charts for birth weight, HC and length in maternity and child health care records;
- Including the measurement of length and the assessment of WFL and/or BMI-for-age in routine growth monitoring; and
- Ensuring that all policies and practices relating to health care worker education, clinical practice and clinical record keeping foster and support the integration of health care across disciplines and over time.

Each of these recommendations requires investment in equipment and training, but the benefit to the lives of infants and young children is likely to be substantial. The political will of policy makers, integrated record-keeping systems, the willingness of health care practitioners to put child well-being above disciplinary advancement, fostering teamwork in professional education and ongoing validation of growth assessment are at the foundation of achieving each child's genetic potential in the first 1000 d.

Recommendations for research and practice

This framework is not presented as a conclusive standard, but rather as a proposal to prompt discussion, collaboration and research. The long-term usefulness of some indices and indicators (e.g. the various proposed indicators of asymmetry at birth) in predicting short- and long-term adverse outcomes presents an important research opportunity. For this reason, we also recommend that basic measurements (e.g. accurate birth weight, length and HC) always be carefully done and recorded, as the emergence of new indices/indicators can then potentially allow for re-analysis of existing datasets. Research into novel measurements and indices is ongoing, yet even well-established indices still lack agreement in terms of indicators and cut-offs. Research in these fields should focus on identifying indicators that can usefully predict important outcomes, including mortality, morbidity, growth and neurodevelopment. The validity, predictive value and optimal cut-offs of proxy indicators to replace ultrasonography (such as Doppler screening and measurement of the placenta at birth) particularly require investigation. Finally, interdisciplinary approaches should be integrated into pre-service education and continuing professional development initiatives.

Conclusion

Growth occurs on a continuum from conception throughout infancy and childhood, with events in the first 1000 d of life known to have life-long effects. It is crucial, therefore, that clinicians providing care to mothers, infants and young children in different life stages should be able to clearly communicate about common goals and concerns. This paper presents a framework to act as a starting point for such an integrated approach and also highlights areas where further research and policy initiatives are required. Clear communication, a collaborative approach and strong policy-level support will be needed to ensure continuity of care throughout the first 1000 d of life and ultimately promote optimal health and developmental outcomes.

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BRIDGING TEXT

The framework presented in the preceding publication integrates the assessment of growth in the first thousand days, from conception to the second birthday. Comprehensive assessment of infant growth requires an understanding of what happened during the intrauterine phase: intrauterine growth restriction (or excess) not only affects birth size but may have implications for growth in infancy and beyond. This principle lies at the heart of a life-course approach to health and nutrition. The research that follows applies this way of thinking to assessing the growth of two high-risk neonatal/ infant populations: preterm-born infants and infants with a history of placental insufficiency as detected by early third-trimester Doppler.

The next three papers focus on cohort one, preterm infants. The integrated framework introduced two sets of growth references/ standards that are commonly used to assess preterm infants' postnatal growth, namely the INTERGROWTH-21ST Growth Standards and the Fenton Growth Chart. There is no consensus in the literature on which of these growth charts (if any) should be preferred. Therefore, the first paper compares the performance of the INTERGROWTH-21ST and Fenton growth charts when used to assess the growth of the same sample of infants, focusing on the ability of early growth to predict indicators of malnutrition at one year of age.

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CHAPTER 4: SECOND PUBLICATION: Infant growth by INTERGROWTH-21st and Fenton Growth Charts: predicting one-year anthropometry in South African preterm infants

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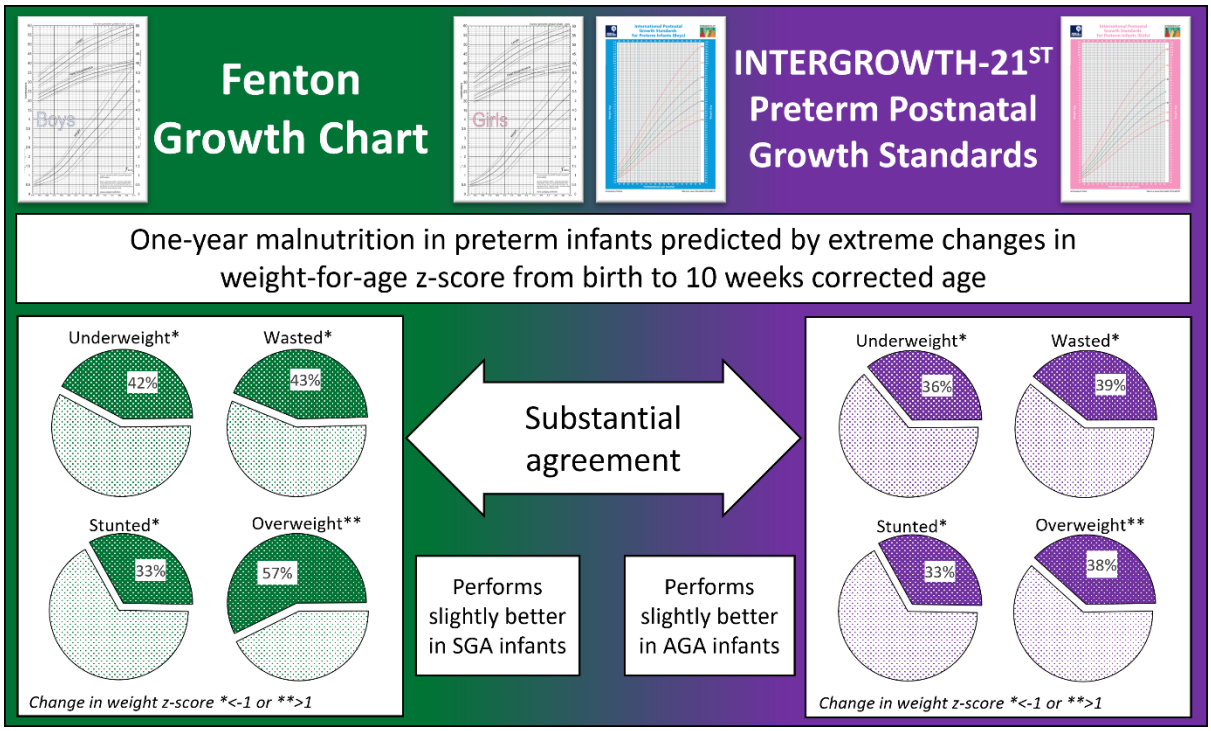
GRAPHICAL ABSTRACT



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Infant growth by INTERGROWTH-21st and Fenton Growth Charts: Predicting 1-year anthropometry in South African preterm infants

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Abstract

Post-natal growth influences short- and long-term preterm infant outcomes. Different growth charts, such as the Fenton Growth Chart (FGC) and INTERGROWTH-21st Preterm Post-natal Growth Standards (IG-PPGS), describe different growth curves and targets. This study compares FGC- and IG-PPGS-derived weight-for-postmenstrual age *z*-score (WZ) up to 50 weeks postmenstrual age (PMA50) for predicting 1-year anthropometry in 321 South African preterm infants. The change in WZ from birth to PMA50 (ΔWZ, calculated using FGC and IG-PPGS) was correlated to age-corrected 1-year anthropometric *z*-scores for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ) and BMI-for-age (BMIZ), and categorically compared with rates of underweight (WAZ < −2), stunting (LAZ < −2), wasting (WLZ < −2) and overweight (BMIZ > + 2). Multivariable analyses explored the effects of other early-life exposures on malnutrition risk. At PMA50, mean WZ was significantly higher on IG-PPGS (−0.56 ± 1.52) than FGC (−0.90 ± 1.52; $p < 0.001$), but ΔWZ was similar (IG-PPGS −0.26 ± 1.23, FGC −0.11 ± 1.14; $p = 0.153$). Statistically significant ΔWZ differences emerged among small-for-gestational age infants (FGC −0.38 ± 1.22 vs. IG-PPGS −0.01 ± 1.30; $p < 0.001$) and appropriate-for-gestational age infants (FGC + 0.02 ± 1.08, IG-PPGS −0.39 ± 1.18; $p < 0.001$). Correlation coefficients of ΔWZ with WAZ, LAZ, WLZ and BMIZ were low ($r < 0.45$), though higher for FGC than IG-PPGS. Compared with IG-PPGS, ΔWZ < −1 on FGC predicted larger percentages of underweight (42% vs. 36%) and wasting (43% vs. 39%) and equal percentages of stunting (33%), while ΔWZ > + 1 predicted larger percentages overweight (57% vs. 38%). Both charts performed similarly in multivariable analysis. Differences between FGC and IG-PPGS are less apparent when considering ΔWZ, highlighting the importance of assessing growth as change over time, irrespective of growth chart.

KEYWORDS
birthweight, growth, growth charts, malnutrition, (MeSH terms) Infant, premature, weight gain

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1 | INTRODUCTION

Small, vulnerable newborns—born preterm and/or small-for-gestational age (SGA)—are at risk of adverse outcomes, including neonatal morbidity and mortality, childhood growth restriction, poor neurodevelopmental outcomes and later cardiometabolic disease (Ashorn et al., 2023; De Bie et al., 2010). Post-natal growth may modulate these outcomes. Inadequate weight gain is associated with poorer neurodevelopmental outcomes (Ong et al., 2016; Stein et al., 2013) and persistent growth deficits (Christian et al., 2013; Kirk et al., 2017; Stein et al., 2013), while excessive early weight gain may be associated with later metabolic and cardiovascular disorders (Ong et al., 2016), though this is less evident resource-limited populations (Stein et al., 2013). Determining appropriate growth targets for preterm infants is necessary for achieving optimal short- and long-term outcomes.

Infant growth is assessed as a change in anthropometric measurements (commonly weight, length and head circumference) over time (Lampl et al., 2015). Calculation of age- and sex-specific anthropometric z-scores enables meaningful comparisons between groups and over time (Cordova & Belfort, 2020; World Health Organization Expert Committee on Physical Status, 1995). However, preterm infants present unique growth monitoring challenges, due to the missed period of intrauterine growth and its effect on post-natal growth patterns. Traditionally, post-natal growth that mimics intrauterine growth has been considered desirable, leading to the widespread use of growth charts based on cross-sectional birth data (Cordova & Belfort, 2020). This includes the Fenton 2013 Growth Chart (FGC) (Fenton & Kim, 2013) which is widely used in South Africa. More recently, some researchers challenged this assumption on the basis that intrauterine and extrauterine growth are distinct physiologic processes occurring in very different environments. They proposed the actual growth of healthy preterm infants under ideal conditions as a more appropriate yardstick (Villar et al., 2018). This approach was used to compile the INTERGROWTH-21st Post-natal Growth Standards for Preterm Infants (IG-PPGS) (Villar et al., 2015). These differences in the underlying premises (and, consequently, different study designs) resulted in FGC and IG-PPGS following different trajectories.

Numerous studies have shown that FGC and IG-PPGS differently identify early post-natal growth faltering (up to term-equivalent age) in preterm infants: FGC generally classifies more infants in a given group as exhibiting post-natal growth restriction than the IG-PPGS, whether infant size is assessed a single time point or as a change in z-score from birth to discharge or term-equivalent age (Barreto et al., 2021; Ceratto et al., 2020; Cordova et al., 2020; El Rafei et al., 2020; González-Garcia et al., 2021; Kim et al., 2021; Lebrão et al., 2020; Reddy et al., 2019; Yitayew et al., 2021). Each growth chart has strengths and weaknesses: the IG-PPGS can claim greater global representativeness and strict individual-level control, but is handicapped by very small sample sizes at lower gestational ages (GAs); whereas the FGC boasts a very large sample but with less ethnic diversity and no control over the individual characteristics of included infants (Cormack et al., 2016). While the relative importance of these characteristics remains open to debate, the pragmatic clinician will choose the growth chart that best identifies infants at risk of adverse outcomes, a question that remains under-researched, especially for longer term growth outcomes. This research aimed to compare the FGC and INTERGROWTH-21st Growth Standards (including the INTERGROWTH-21st Newborn Size Standards [IG-NBSS] and IG-PPGS) for assessing weight-for-GA z-scores in a historical cohort of South African preterm infants at birth and up to 50 weeks postmenstrual age (PMA) and to investigate their ability to predict 1-year anthropometric outcomes (weight-for-age, weight-for-length, length-for-age and body mass index [BMI]-for-age), with additional emphasis on differences between SGA and appropriate-for-GA (AGA) infants.

Key messages

- Differences between the Fenton 2013 Growth Chart (FGC) and INTERGROWTH-21st (IG-PPGS) growth charts complicate growth assessment.
- The choice of growth chart should rest on its ability to predict adverse outcomes such as malnutrition.
- Though a given body weight produces different z-scores (WZ) on FGC and IG-PPGS, there is moderate-to-substantial agreement between the charts when considering the change in WZ from birth to 50 weeks postmenstrual age, and neither chart is clearly superior at predicting 1-year malnutrition.
- Assessing WZ as change over time mitigates the differences between FCG and IG-PPGS.

2 | METHODS

2.1 | Sample selection

This study analysed existing clinic records from the postdischarge follow-up clinic at the kangaroo mother care (KMC) unit of a tertiary academic hospital in Tshwane District, Gauteng Province, South Africa. Records of preterm infants (GA < 37 weeks) born before 1 January 2019 were eligible for inclusion if they had a recorded birthweight, GA and follow-up data up to at least 1 year of age. Exclusion criteria included major anatomic abnormalities or medical treatments that hamper measurement (e.g., hydrocephalus, plaster casts) and conditions requiring specialised growth monitoring (e.g., trisomies). Sampling was purposefully planned to include a proportion of SGA (BW <10th percentile) infants above population prevalence to ensure sufficient numbers for meaningful subgroup analysis. Very few LGA infants were available in the sampling population, and they were thus excluded a posteriori.

Sample size calculations indicated that 130 each of SGA and AGA infants were needed to detect an effect size of 0.3 (difference

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between SGA and AGA infants) with $\alpha = 0.05$ and power of 80% (G*Power v3.1.9.2; Heinrich-Heine-Universität, Düsseldorf). Records from 2018 to 2016 provided enough AGA infants, while records dating back to the clinic inception in 2012 were used to meet sample size requirements for the SGA infants. No major changes in infant feeding policies or clinical management protocols were implemented in this time period.

2.2 | Data collection

2.2.1 | Creation of clinic records

Birth information was copied from the maternity ward file to the KMC clinic record by the treating physicians in the KMC ward. Birthweight was measured with electronic scales. If pregnancy dating was uncertain, GA was confirmed by the paediatric doctors at birth using the Ballard score.

All follow-up anthropometric measurements were taken by a single experienced hospital dietitian, limiting inter-rater variation. Following KMC clinic protocols, infants were weighed naked using electronic infant weighing scales, and weight was recorded to the nearest 0.01 kg. Length was measured according to standard procedures using a portable measuring mat (with fixed, rigid headpiece and moveable footpiece) placed on a hard tabletop, and recorded to 0.1 cm. Paediatric doctors conducted and recorded medical examinations, and the dietitian collected and recorded infant feeding information.

2.2.2 | Data extraction

Data were extracted from hand-written clinic records twice, to two separate Excel spreadsheets, and checked for discrepancies using EpiInfo v3.5.1 (2008, CDC). Extracted data included birthweight, GA and relevant maternal and infant medical information, as well as infant anthropometry and feeding practices at each follow-up visit. All infant ages were calculated in days: chronologic age was calculated electronically using the birth date and dates of visits, PMA (i.e., days since conception) was calculated as the sum of GA at birth and chronological age, and corrected age was calculated by subtracting the number of days of prematurity (280 minus GA) from the infant's age.

2.2.3 | Data management

All anthropometric measurements were converted to age- and sex-specific z-scores using electronic calculators available online (IG-NBSS: https://intergrowth21.tghn.org/newborn-size-birth/ [version 1.0.6257.25111, downloaded February 2021], IG-PPGS: https://intergrowth21.tghn.org/postnatal-growth-preterm-infants/ [version 1.0.6257.25165, downloaded July 2021], FGC: https://ucalgary.ca/resource/preterm-growth-chart/calculators [downloaded July 2019] and WHO Anthro: http://www.who.int/childgrowth/software/en/ [version 3.2.2, downloaded May 2017]). The timeline of the study, including the three key time points at which data were collected and the growth charts used at each time point, is illustrated in Figure 1.

Birthweight-for-GA z-scores and percentiles were calculated using the FGC and IG-NBSS and infants classified as SGA or AGA (BW between 10th and 90th percentiles, inclusive) using each growth chart.

Early post-natal growth (ΔWZ) was quantified as the difference between weight-for-PMA z-scores (WZ) at birth and at the last post-natal visit that fell within the range of FGC (i.e., ≤50 weeks PMA, abbreviated as PMA50), using both FGC and IG-PPGS.

$$\Delta WZ = (WZ \text{ at PMA50}) - (\text{birth WZ}).$$

Measurements between 50 and 64 weeks PMA were disregarded despite falling within the range of the IG-PPGS, to ensure comparison of the same measurements on both growth charts. Group mean ΔWZ was calculated from individual ΔWZ values. Three patterns of early WZ growth were described: $\Delta WZ < -1$ (growth deceleration), $-1 \le \Delta WZ \le +1$ (growth maintenance) and $\Delta WZ > +1$ (growth acceleration). This was further dichotomised to $\Delta WZ < -1$

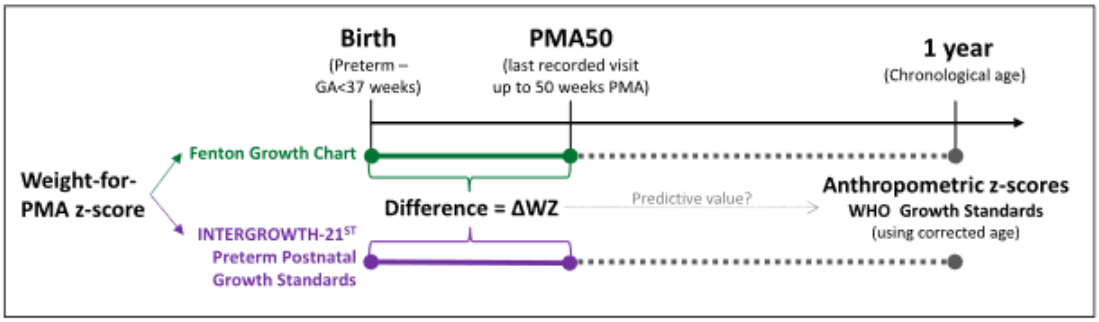

FIGURE 1 Timeline of study data collection, including growth charts used for analysis of anthropometric data at each time point.

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(growth deceleration) versus ΔWZ ≥ −1 (no growth deceleration) when investigating outcomes related to undernutrition, and to ΔWZ > +1 (growth acceleration) versus ΔWZ ≤ +1 (no growth acceleration) when investigating overweight as an outcome.

One year anthropometric z-scores were calculated for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), and BMI-for-age (BMIZ) using WHO Anthro software with corrected age. Proportions of underweight (WAZ < −2), stunted (LAZ < −2), wasted (WLZ < −2), and overweight (BMIZ > + 2) infants were calculated (World Health Organization, 2008).

2.3 | Data analysis

Data were analysed using R Statistical Software (version 4.1.2, 2021; R Foundation for Statistical Computing). All analyses were done for the whole sample and for SGA and AGA infants separately. Statistical significance was set at $p < 0.05$ for all analyses.

Continuous data were assessed for normality with the Shapiro–Wilk test. To compare results derived from FGC and IG-PPGS, only those infants that were classified identically as SGA/AGA by both charts were included, to ensure that the comparator groups were consistently the same. Continuous variables (including WZ and ΔWZ on FGC vs. IG-PPGS) were compared using the paired *t* test (normally distributed data) or Wilcoxon rank sign test (nonnormally distributed data), as the samples cannot be considered independent. Categorical agreement between the two charts was assessed using the Cohen's Kappa (*K*), calculated unweighted for nonordinal variables (SGA vs. AGA classification) and weighted for ordered variables (ΔWZ categories), and interpreted according to Altman's guidelines (Altman, 1990).

Pearson (normally distributed data)/Spearman (nonnormally distributed data) correlation coefficients (*r*) were used to investigate relationships between ΔWZ (using FGC and IG-PPGS) and 1-year anthropometric z-scores (WAZ, LAZ, WLZ and BMIZ). Additionally, ΔWZ was dichotomised and compared with the presence or absence of malnutrition: ΔWZ categories of growth deceleration (ΔWZ < −1) versus no growth deceleration (ΔWZ ≥ −1) were compared with the presence or absence of underweight, stunting and wasting, while ΔWZ categories of growth acceleration (ΔWZ > + 1) versus no growth acceleration (ΔWZ ≤ +1) was compared with the presence or absence of overweight.

Finally, multiple regression analysis investigated associations between early life factors and anthropometric indicators of malnutrition at 1 year. First, univariate analyses related each exposure variable (i.e., maternal age, parity, gravidity, human immunodeficiency virus (HIV) status, antiretroviral drug use in pregnancy, maternal conditions, infant sex, GA at birth, birthweight-for-GA z-score and SGA status [by FGC and IG-NBS], multiple pregnancy, congenital heart conditions, breast-feeding status during KMC stay and ΔWZ [calculated using FGC and IG-PPGS]) to each outcome indicator of malnutrition (i.e., underweight, stunting, wasting and overweight, as defined above). Variables with significant associations (i.e., $p < 0.05$) were included in multivariable models to determine the relative strength of their relationships to the outcomes of interest, expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs), and McFadden's R^2 was calculated as a measure of the model's predictive ability. Since initial multivariable analyses indicated strong collinearity between anthropometric indices using the FGC and the INTERGROWTH-21st Growth Standards, separate models were developed for each, and the two models were compared by investigating the ORs of comparable variables (with mutually exclusive 95% CIs indicating a true difference).

2.4 | Ethical and legal considerations

Approval to conduct the study was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (Protocol 227-2021) and the hospital (KPTH 23/2021). All data were processed anonymously.

3 | RESULTS

3.1 | Sample description

The sample included 321 infants born to 301 mothers, as described in Table 1. The sample included 18 (6.4%) mothers aged ≤19 years and 74 (26.1%) aged ≥35 years. Sixty-six mothers (23.3%) were primigravidae, gravidity exceeded parity in and 85 (30.0%), implying previous pregnancy loss or termination. Ethnicity was not recorded, but can reasonably be presumed to be majority Black African. Despite a 21.3% maternal HIV infection rate, none of the infants contracted HIV. Of note among the infants was the high rate of maternal breast milk feeding in the KMC unit, and the substantial number of infants with congenital heart conditions (100 [31.2%] infants, some with multiple abnormalities, including 65 [17.4%] patent ductus arteriosus, 47 [14.6%] patent foramen ovale, and eight [2.5%] ventricular/atrial septum defects. Only one infant required cardiac surgery.)

3.2 | Birthweight

Table 2 shows birth anthropometry. Birthweight z-score according to FGC and IG-NBSS did not differ significantly ($p = 0.237$). Both charts classified 305 infants (95.0%) the same way (99 SGA and 206 AGA); of the remaining 16 infants, four (1.3%) were classified as SGA by FGC but AGA by IG-NBSS, and 12 (3.7%) were classified as AGA by FGC but SGA by IG-NBSS. There was almost perfect agreement between the charts ($K = 0.887$).

3.3 | Early post-natal growth

Table 2 and Figure 2 show infant anthropometry at PMA50 (mean PMA 45.6 ± 2.3 weeks, range 35.0–49.9 weeks). Mean WZ at PMA50

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TABLE 1 Characteristics of sample (301 mothers[a]; 321 preterm infants) at birth and 1 year.

Characteristic	N	Value
Maternal age [Median (IQR)]	283	29 (25; 35)
Maternal parity [Median (IQR)]	283	2 (1; 3)
Maternal gravidity [Median (IQR)]	283	2 (2; 3)
Mother is a self-reported foreign national [*n* (%)]	301	76 (25.2)
Maternal HIV infection [*n* (%)]	301	64 (21.3)
Timing of antiretroviral therapy (ART) initiation	64	
ART initiated before or during pregnancy		44 (68.8)
ART initiated after delivery		10 (15.6)
Timing of ART initiation not recorded		10 (15.6)
Maternal conditions[b] [*n* (%)]	301	
Conditions of the placenta, cord and membranes		13 (4.3)
Conditions of pregnancy		60 (19.9)
Conditions of labour and delivery		64 (21.3)
Maternal medical and surgical conditions		115 (38.2)
Infant sex (male)	321	159 (49.5)
Gestational age (weeks) [Mean ± SD]	321	32.8 ± 2.4
Birthweight (kg) [Mean ± SD]	321	1.64 ± 0.48
Infant feeding in KMC unit [*n* (%)]	321	
Maternal breast milk		314 (97.8)
Infant morbidities [*n* (%)]	321	
Neonatal jaundice		191 (59.5)
Respiratory distress syndrome		180 (56.1)
Congenital heart conditions[c]		100 (31.2)
Twins [*n* (%)]	321	53 (16.5)
1 year: Anthropometric z-scores[d] [mean ± SD]		
Weight-for-age (WAZ)	321	−0.59 ± 1.36
Length-for-age (LAZ)	320	−0.91 ± 1.16
Weight-for-length (WLZ)	320	−0.16 ± 1.31
BMI-for-age (BMIZ)	320	−0.09 ± 1.30
Indicators of malnutrition[d] [*n*(%)]		
Underweight: WAZ < −2	321	50 (15.6)
Stunting: LAZ < −2	320	57 (17.8)
Wasting: WLZ < −2	320	23 (7.2)
Overweight: BMIZ > + 2	320	21 (6.6)
Infant feeding: any breastfeeding at 1 year [*n*(%)]		181 (56.4)

Abbreviations: ART, antiretroviral therapy; BMIZ, BMI-for-age z-score; HIV, human immunodeficiency virus; IQR, interquartile range; KMC, kangaroo mother care; LAZ, length-for-age z-score; SD, standard deviation; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score.

[a]Twenty duplicates records of mothers of twins were removed (thus mothers *N* = 301).

[b]Maternal conditions are classified according to WHO ICD10-PM categories (Word Health Organization, 2016). Conditions of labour and delivery only include conditions other than preterm delivery.

[c]Includes patent ductus arteriosus (*n* = 65), patent foramen ovale (*n* = 47) and ventricular/atrial septum defects (*n* = 8); some infants had multiple abnormalities.

[d]All age-specific z-scores were calculated using the WHO Growth Standards with corrected age. Length was only available for *N* = 320 infants.

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TABLE 2 Birthweight characteristics and early growth (up to 50 weeks postmenstrual age) of the sample according to the Fenton Growth Chart and INTERGROWTH-21st Growth Standards.

Birthweight characteristic	Fenton	IG-NBSS	Test statistic
Classification [*n*(%)] (Entire sample, *N* = 321)			
SGA	103 (32.1)	111 (34.6)	*K* = 0.887[a]
AGA	218 (67.9)	210 (65.4)	
Birthweight-for-GA z-score in infants with identical SGA/AGA class on Fenton and IG-NBSS (*N* = 303)	−0.78 ± 0.93	−0.84 ± 1.06	*p* = 0.237[b]
Weight characteristics at PMA50[c] in infants with identical SGA/AGA class on Fenton and IG-NBSS	**FentonMean ± SD**	**IG-PPGSMean ± SD**	**Test statistic**
Weight-for-PMA z-score at PMA50			
All (N = 303)	−0.90 ± 1.52	−0.56 ± 1.52	*p* < 0.001[b]
AGA (*N* = 204)	−0.25 ± 1.11	0.09 ± 1.09	*p* < 0.001[d]
SGA (*N* = 99)	−2.22 ± 1.40	−1.90 ± 1.42	*p* < 0.001[d]
ΔWZ: Change in weight z-score from birth to PMA50			
All (*N* = 303)	−0.11 ± 1.14	−0.26 ± 1.23	*p* = 0.153[b]
AGA (*N* = 204)	+0.02 ± 1.08	−0.39 ± 1.18	*p* < 0.001[d]
SGA (*N* = 99)	−0.38 ± 1.22	−0.01 ± 1.30	*p* < 0.001[d]
ΔWZ growth class	**Fentonn (%)**	**IG-PPGSn (%)**	**Test statistic**
All (*N* = 303)			
Acceleration: ΔWZ > +1	43 (14.2)	41 (13.5)	*K* = 0.647[e]
Maintenance: −1 ≤ ΔWZ ≤ +1	195 (64.4)	192 (63.4)	
Deceleration: ΔWZ < − 1	65 (21.5)	70 (23.1)	
AGA (*N* = 204)			
Acceleration: ΔWZ > +1	35 (17.2)	22 (10.8)	*K* = 0.693[e]
Maintenance: −1 ≤ ΔWZ ≤ +1	131 (64.2)	130 (63.7)	
Deceleration: ΔWZ < − 1	38 (18.6)	52 (25.5)	
SGA (*N* = 99)			
Acceleration: ΔWZ > +1	8 (8.1)	19 (19.2)	*K* = 0.556[e]
Maintenance: −1 ≤ ΔWZ ≤ +1	64 (64.6)	62 (62.6)	
Deceleration: ΔWZ < − 1	27 (27.3)	18 (18.2)	

Abbreviations: AGA, appropriate-for-gestational age (birthweight ≥10th and ≤90th percentile); GA, gestational age; IG-NBSS, INTERGROWTH-21ST Newborn Size Standards; IG-PPGS, INTERGROWTH-21st Post-natal Growth Standards for Preterm Infants; PMA, postmenstrual age; SGA, small-for-gestational age (birthweight <10th percentile).

[a]Cohen's Kappa, unweighted.

[b]Wilcoxon Signed Rank test.

[c]PMA50: the latest recorded visit up to 50 weeks postmenstrual age.

[d]Paired *t* test.

[e]Cohen's Kappa, weighted.

was significantly higher on IG-PPGS than FGC, but ΔWZ did not differ significantly, with wide interindividual variation in ΔWZ on both charts. Some significant differences between FGC and IG-PPGS emerged when ΔWZ of SGA and AGA infants were analysed separately. For AGA infants, weight z-score remained nearly constant on FGC while decreasing substantially on IG-PPGS. The reverse was true for SGA infants, with ΔWZ decreasing substantially on FGC but remaining stable on IG-PPGS. Similar patterns were seen when ΔWZ was considered categorically: more AGA infants displayed growth deceleration (ΔWZ < −1) on IG-PPGS than FGC (*K* = 0.693, substantial agreement), while more SGA infants exhibited growth deceleration on FGC than IG-PPGS (*K* = 0.556, moderate agreement).

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FIGURE 2 Early growth (up to 50 weeks postmenstrual age) of South African preterm infants ($N = 303$) according to the Fenton Growth Chart and INTERGROWTH-21st Growth Standards. ΔWZ = the change in weight-for-age z-score from birth to the last recorded visit up to 50 weeks postmenstrual age.

3.4 | One-year anthropometry

Table 1 shows infant characteristics at the 1-year visit (mean chronological age 382 ± 19 days [12.6 ± 0.6 months], mean corrected age 332 ± 23 days [10.9 ± 0.8 months]). The SGA infants had consistently lower anthropometric z-scores and higher rates of underweight, stunting and wasting than AGA infants (data not shown).

Figure 3 shows correlations between ΔWZ (using FGC and IG-PPGS) and 1-year anthropometric z-scores (WAZ, LAZ, WLZ and BMIZ). One-year z-scores were more strongly correlated to ΔWZ on FGC than IG-PPGS, although correlation coefficients were low ($r < 0.45$). The same was true for AGA and SGA infants analysed separately (Supporting Information S1: Table 1). Figure 3 also shows that, in most cases, <50% of malnutrition was correctly predicted by ΔWZ category. Few of these relationships remained statistically significant in AGA or SGA infants separately (Supporting Information S1: Table 2). In AGA infants, IG-PPGS identified a larger proportion of infants with underweight (IG-PPGS 64.2% vs. FGC 43.8%) and stunting (IG-PPGS 47.3% vs. FGC 29.2%), while the reverse was true for overweight (FGC 66.7% vs. IG-PPGS 41.2%). For SGA infants, FGC performed better in predicting underweight (FGC 41.1% vs. IG-PPGS 25.0%), stunting (FGC 36.4% vs. IG-PPGS 26.3%) and wasting (FGC 53.8% vs. IG-PPGS 21.4%). Numbers of overweight SGA infants and wasted AGA infants were insufficient for robust statistical analysis.

Univariate analyses found significant associations ($p < 0.05$) between indicators of malnutrition and birthweight z-score (underweight, stunting and wasting), being SGA (underweight, stunting and wasting), ΔWZ (all outcomes), infant congenital heart conditions (underweight, wasting and overweight) and maternal conditions of pregnancy and labour/delivery (underweight only), shown in Table 3. The 95% CI of the ORs for FGC- and IG-PPGS-derived indicators overlapped, suggesting that they did not differ significantly.

Multivariable predictive models all had low R^2 values (<0.3), indicating poor predictive abilities. Models using FGC had higher R^2 values for predicting underweight, wasting and overweight, whereas the INTERGROWTH-21st model performed better for stunting. Underweight increased with maternal conditions of pregnancy and decreased with higher birthweight z-score and larger ΔWZ. Stunting increased with being SGA on IG-NBSS (but not FGC) and decreased with higher birthweight z-score and larger ΔWZ. Wasting increased with congenital heart conditions (INTERGROWTH-21st model only) and decreased with higher birthweight z-score and larger ΔWZ (FGC only). Overweight increased with greater ΔWZ. The overlap between the 95% CI of the ORs for FGC- and IG-PPGS-derived indicators precludes definitive statements about the superiority of one chart over the other.

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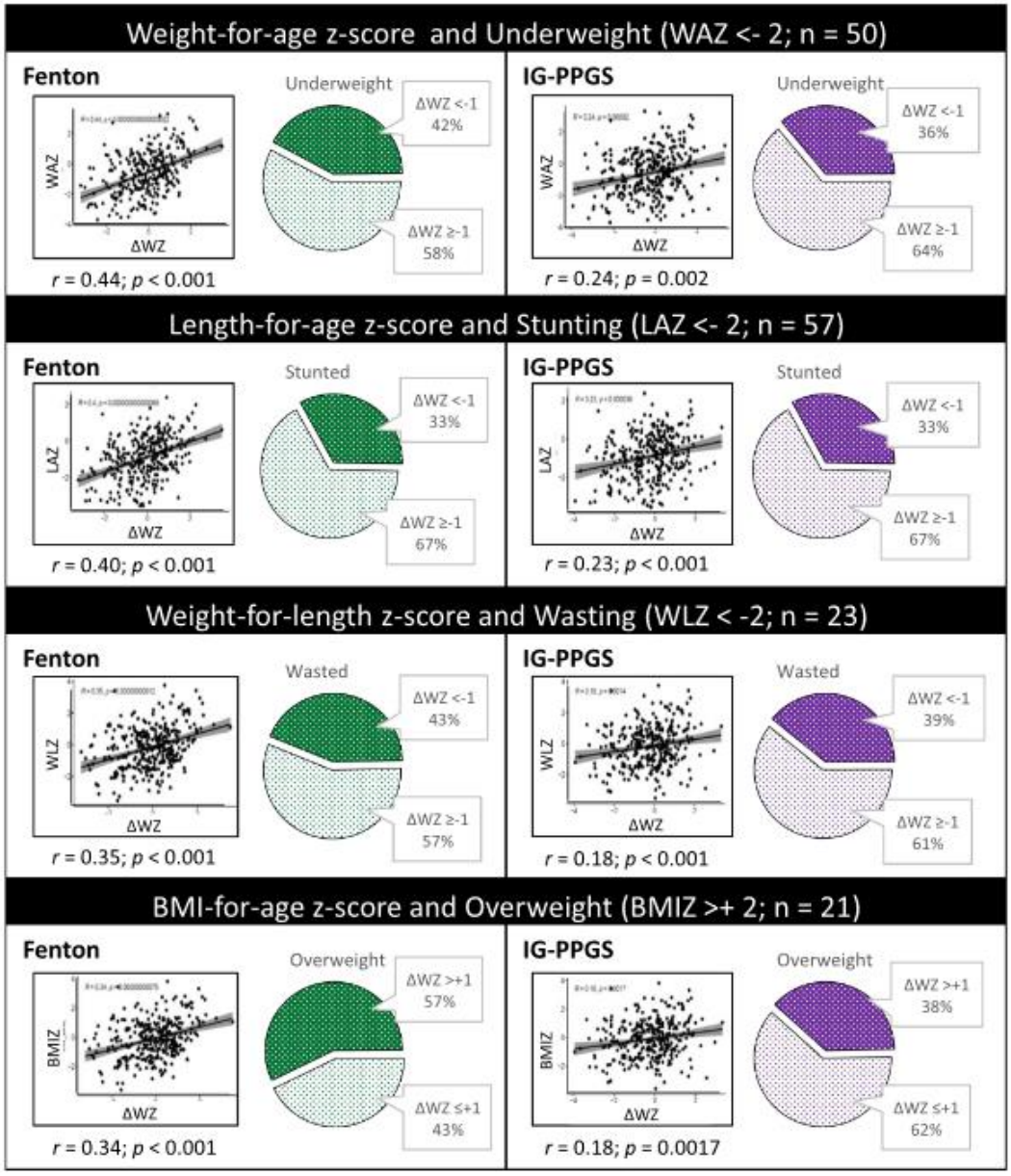

FIGURE 3 Relationships between 1-year anthropometry and change in weight-for-age z-score (ΔWZ) according to the Fenton Growth Chart and INTERGROWTH-21st Growth Standards, in terms of correlations and dichotomous categories.

4 | DISCUSSION

This study highlighted key similarities and differences between the FGC and the IG-PPGS for monitoring early growth in a South African cohort of preterm-born infants, with particular reference to relationships between early growth and anthropometric outcomes at 1 year of age. Apart from the high proportion of SGA infants (due to deliberate over-sampling), the study sample is comparable to preterm infant study populations described in other South African KMC units (Pike et al., 2017; Ramdin et al., 2021).

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TABLE 3 Multiple regression analysis: odds ratios (with 95% confidence intervals) for selected exposure variables significantly associated with underweight, stunting, wasting and overweight at 1 year of age in preterm-born infants.

Exposure	Outcome[a] Underweight OR (95% CI)	Stunting OR (95% CI)	Wasting OR (95% CI)	Overweight OR (95% CI)
Univariate analysis[b]				
Maternal conditions of pregnancy[c]	2.43 (1.21, 4.73)	–	–	–
Maternal conditions of labour & delivery[d]	0.31 (0.09, 0.79)	–	–	–
Infant congenital heart conditions	2.15 (1.15, 3.97)	–	4.68 (1.96, 12.0)	0.22 (0.03, 0.76)
Birthweight z-score on IG-NBSS	0.40 (0.28, 0.55)	0.48 (0.35, 0.64)	0.47 (0.32, 0.69)	–
Birthweight z-score on Fenton	0.30 (0.19, 0.43)	0.42 (0.29, 0.59)	0.40 (0.25, 0.62)	–
SGA[e] on IG-NBSS	6.72 (3.50, 13.55)	5.31 (2.91, 9.98)	3.25 (1.38, 8.07)	–
SGA[e] on Fenton	6.22 (3.28, 12.24)	3.87 (2.15, 7.06)	3.04 (1.29, 7.37)	–
ΔWZ on IG-PPGS	0.77 (0.60, 0.98)	0.71 (0.56, 0.89)	0.79 (0.56, 1.11)	1.79 (1.21, 2.75)
ΔWZ on Fenton	0.51 (0.38, 0.67)	0.54 (0.41, 0.70)	0.52 (0.35, 0.75)	2.62 (1.66, 4.37)
Multivariable analysis—Model 1—Fenton				
Maternal conditions of pregnancy[c]	0.39 (0.17, 0.89)*	–	–	–
Birthweight z-score—Fenton	0.30 (0.15, 0.57)***	0.43 (0.24, 0.73)**	0.31 (0.14, 0.64)**	–
ΔWZ on Fenton	0.49 (0.34, 0.69)***	0.55 (0.40, 0.72)***	0.55 (0.35, 0.86)**	2.43 (1.52, 4.10)***
Model R^2[f]	0.261	0.155	0.192	0.133
Multivariable analysis—Model 2—IG-PPGS				
Maternal conditions of pregnancy[c]	0.33 (0.15, 0.75)**	–	–	–
Infant congenital heart conditions	–	–	0.37 (0.14, 0.99)*	–
Birthweight z-score—IG-NBSS	0.45 (0.25, 0.78)**	0.61 (0.37, 0.99)*	0.42 (0.21, 0.81)**	–
SGA[e] on IG-NBSS	–	2.99 (1.07, 8.65)*	–	–
ΔWZ on IG-PPGS	0.60 (0.44, 0.80)***	0.58 (0.44, 0.75)***	–	1.73 (1.15, 2.70)*
Model R^2[f]	0.223	0.166	0.150	0.037

Note: –, no significant association.

Abbreviations: ΔWZ, Change in weight z-score between birth and 50 weeks; Fenton, Fenton 2013 growth chart; IG-NBSS, INTERGROWTH-21st Newborn Size Standards; IG-PPGS, INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants.

[a]Underweight: weight-for-age z-score <−2; stunting: length-for-age z-score <−2; wasting: weight-for-length z-score <−2; overweight: BMI-for-age z-score >+2 (Z-scores calculated using the WHO Growth Standards, with age corrected for preterm birth).

[b]On univariate analysis: no significant relationships for maternal age, parity, gravidity, HIV, timing of ART initiation, maternal conditions of the placenta, cord or membranes, maternal medical and surgical conditions, infant sex, breastfeeding at last visit.

[c]Maternal conditions of pregnancy include incompetent cervix, preterm rupture of membranes, oligohydramnios/polyhydramnios, ectopic pregnancy, multiple pregnancy, malpresentation and other complications of pregnancy (excluding pregnancy-related medical conditions like hypertensive disorders, pre-eclampsia and gestational diabetes mellitus) (World Health Organization, 2016).

[d]Maternal conditions of labour and delivery include breech delivery, malposition and disproportion during labour and delivery, forceps delivery/vacuum extraction, Caesarean delivery, spontaneous preterm labour, and other complications of labour and delivery (World Health Organization, 2016).

[e]SGA, small for gestational age (birthweight-for-GA <10th percentile).

[f]McFadden's R^2. Values > 0.4 indicate good predictive ability.

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

The FGC and IG-NBSS evaluated birthweight similarly, suggesting that the choice of growth chart at birth has little effect on clinical decision-making. Similar results were found in studies from Spain (González-García et al., 2021), the United States of America (Yitayew et al., 2021), and Brazil (Lebrão et al., 2020). Other studies have found statistically significant (though quantitatively small) differences in SGA classification, particularly in term infants (Barreto et al., 2021) or when considering length (Kim et al., 2021) or head circumference (Reddy et al., 2019).

More substantial differences between FGC and IG-PPGS were seen with post-natal growth assessment. The higher mean WZ at PMA50 on IG-PPGS than FGC echoes previous studies (Cordova

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et al., 2020; El Rafei et al., 2020; González-García et al., 2021; Kim et al., 2021). This is consistent with the charts' trajectories: at most ages, FCG reference curves have a higher absolute weight than the IG-PPGS (though there are some exceptions at low z-scores); thus, a given weight at the same GA will generally have a lower z-score on FCG than IG-PPGS (Villar et al., 2018).

When considering WZ change over time (i.e., ΔWZ), the difference between FGC and IG-PPGS was small and not statistically significant, except when SGA and AGA infants were considered separately, with the direction of the difference depending on the chart used. On average, FGC showed normal growth in AGA infants and growth faltering in SGA infants, while IG-PPGS showed normal growth in SGA infants and growth faltering in AGA infants. This pattern persisted when ΔWZ was categorised as growth acceleration, growth maintenance or growth deceleration. SGA infants followed the pattern described in previous studies, with FGC identifying higher rates of growth deceleration than IG-PPGS when applied in the same sample (Ceratto et al., 2020; El Rafei et al., 2020; González-García et al., 2021; Kim et al., 2021; Reddy et al., 2019; Yitayew et al., 2021). However, in this study, the opposite was true for AGA infants with IG-PPGS identifying higher rates of growth deceleration than FGC. Only one Australian study of very preterm infants (GA < 33 weeks) had a similar finding, with IG-PPGS identifying more growth faltering up to 40 weeks PMA than FGC (Cordova et al., 2020). The differences between this study and previous research may be due to the timing of the final growth assessment: while we used the last measurement up to PMA50, other studies assessed growth at 36–40 weeks PMA or hospital discharge. It is conceivable that the home environment and post-term physiologic maturation may differently affect the growth of SGA and AGA infants.

In clinical practice, early growth monitoring is useful if it can timeously identify infants who are at risk of adverse outcomes, such as later malnutrition. In this study, ΔWZ on FGC was more strongly correlated to 1-year anthropometry than IG-PPGS, although correlation coefficients were poor throughout. When ΔWZ was dichotomised, FGC predicted a greater proportion of later underweight, stunting, wasting and overweight than IG-PPGS, in the whole group and in SGA infants, while in AGA infants, IG-PPGS better predicted underweight and stunting. Numerous studies have reported associations between poor early growth and low childhood weight and length (reviewed by Martínez-Jiménez et al., 2020), but no published studies were found that compared the performance of two early growth charts in this way.

In multivariable analyses, ΔWZ was inversely associated with 1-year underweight (both charts), stunting (both charts), wasting (only FGC) and positively associated with overweight (both charts). These effects have been described in the literature (Martínez-Jiménez et al., 2020). This study adds new information about the relative ability of FGC and IG-PPGS to predict anthropometric outcomes. All models were poor predictors of the outcomes in question, and while models using FGC had higher R^2 values than those using IG-NBS and IG-PPGS, the considerable overlap between 95% CIs of the ORs for individual exposure variables suggests that they do not differ significantly. Thus, while birthweight z-score and ΔWZ do predict anthropometry at 1 year, the choice of growth chart appears to be a relatively minor matter.

Regardless of the growth chart used, birthweight z-score and ΔWZ were imperfect predictors of 1-year anthropometry. This is not unexpected: while early growth (including fetal growth) plays an important role in setting the growth trajectory, growth in infancy and childhood is affected by a myriad of factors, including dietary intake, illness, caregiving practices and socioeconomics. The multivariable analysis included some maternal factors and exposures that were present at birth and during pregnancy, but few of these contributed significantly to the outcomes. However, the limitations of using routinely collected clinical data must be acknowledged here, particularly the potential incompleteness of data on maternal factors and conditions during pregnancy. Infant feeding data, including breastfeeding information, was limited to simple yes/no answers, with no information on the frequency or adequacy of feeds. The only infant feeding characteristic included was breastfeeding at PMA50 (i.e., whether the infant was still receiving any breast milk at the same visit that was used to calculate ΔWZ), and no significant associations were found. Other feeding practices, particularly during the complementary feeding phase, should be investigated in more detail in future studies.

Although the follow-up anthropometric data can be considered complete and reliable, due to the careful and consistent measurement procedures employed by the clinic dietitian, the analyses are limited by the lack of reliable birth length measurements. Birth length is an important predictor of stunting (Krebs et al., 2022; Namirembe et al., 2022), and stunting is the most prevalent form of child malnutrition in South Africa (National Department of Health, Statistics South Africa, & South African Medical Research Council, 2017). Thus, it is strongly recommended that future studies include accurate, reliable measurements of birth length, and investigate changes in the birth length z-score over time as a predictor of length-for-age and stunting at later ages. This would also allow for the inclusion of weight-length ratio (Villar et al., 2017) and BMI at birth (Olsen et al., 2015) as predictive variables, factors that may be of interest when investigating overweight as an outcome. Additionally, though the WHO Growth Standards are the best available tool for infant and young child growth assessment, the reference sample included only infants born at term. However, we compensated for this by correcting infant age for prematurity, a method supported by the fact that the age-corrected weight, height and length of infants in the INTERGROWTH-21st sample naturally reached the same levels and distribution as the WHO Growth Standards by 64 weeks PMA (Villar et al., 2015).

Finally, future research could also investigate the differences between FGC and IG-PPGS in predicting other outcomes of interest, including infant mortality and neurodevelopmental outcomes. The little available research relating to neurodevelopmental outcomes has all come from high-income countries, and results have been conflicting (Cordova et al., 2020; Yitayew et al., 2021).

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5 | CONCLUSION

In this sample, FGC and IG-PPGS differed in their assessment of weight-for-PMA z-score up to 50 weeks of PMA, but the differences between the charts were less apparent when the change in weight-for-PMA z-score over time was considered. On average, SGA infants followed the growth trajectory described by IG-PPGS more closely (seen as a minimal change in the z-score over time), while AGA infants followed the FGC more closely. Neither chart was consistently superior at predicting malnutrition at 1 year, though FGC performed slightly better in SGA infants and the group as a whole (possibly due to the high proportion of SGA infants included in the sample), while IG-PPGS performed slightly better in AGA infants. Regardless of the chart used, evaluating infant growth as trends over time, rather than as an absolute z-score at one timepoint, may go some way towards harmonising the differences between different preterm infant growth charts.

AUTHOR CONTRIBUTIONS

Sanja Nel, Friedeburg Anna Maria Wenhold, Ute Dagmar Feucht, and Tanita Botha planned the study. Sanja Nel collected the data. Friedeburg Anna Maria Wenhold and Ute Dagmar Feucht provided supervision. Tanita Botha performed all statistical analyses. Sanja Nel wrote the first draft and all authors contributed substantially to subsequent drafts.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict 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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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Correlations between early growth (change in weight z-score up to 50 weeks postmenstrual age) and anthropometric z-scores at one year, using Fenton growth chart and the INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants

	N§	Change in weight z-score: birth to PMA50† (ΔWZ)									
		Whole sample		AGA‡ only				SGA‡ only			
		Fenton	IG-PPGS	Fenton		IG-PPGS		Fenton		IG-PPGS	
		r††	r‡‡	n	r††	n	r‡‡	n	r††	n	r††
WAZ¶	319	0.44 ***	0.24 ***	216	0.41 ***	208	0.34 ***	103	0.43 ***	111	0.28 **
LAZ¶	318	0.40 ***	0.23 ***	216	0.35 ***	208	0.28 ***	102	0.43 ***	110	0.35 ***
WLZ	318	0.35 ***	0.18 **	216	0.34 ***	208	0.28 ***	102	0.29 **	110	0.14
BMIZ¶	318	0.34 ***	0.18 **	216	0.32 ***	208	0.28 ***	102	0.27 **	110	0.13

** p < 0.05; ** p < 0.01; *** p < 0.001.*

† PMA50: the latest recorded visit up to 50 weeks postmenstrual age.

‡ infants classified as AGA/SGA using the INTERGROWTH-21st Newborn Size Standards for correlations with IG-PPGS, and the Fenton growth chart for correlations with Fenton.

§ 3 infants excluded: gestational age at birth fell outside the range of IG-PPGS. Length was only available for 318 infants.

¶ All age-specific z-scores calculated using corrected age.

†† Pearson correlation coefficient – all variables normally distributed.

‡‡ Spearman correlation coefficient – one or both variables not normally distributed.

Abbreviations: Fenton = Fenton 2013 Growth Chart; IG-PPGS = INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants; WAZ = weight-for-age z-score; LAZ = length-for-age z-score; WLZ = weight-for-length z-score; BMIZ = body mass index (BMI)-for-age z-score.

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Supplementary Table 2: Occurrence of malnutrition at one year among infants gaining or losing more or less than one weight z-score unit from birth up to 50 weeks PMA, using the Fenton Growth Chart and INTERGROWTH-21ST Growth Standards.

			ΔWZ[†]: Fenton		p-value[‡]	ΔWZ[†]: IG-PPGS		p-value[‡]
			ΔWZ < -1	**ΔWZ ≥ -1**		**ΔWZ < -1**	**ΔWZ ≥ -1**	
Underweight (WAZ < -2)	**All**	**Yes**	21	29	< 0.001	18	32	0.026
		No	47	222		55	214	
	AGA [§]	**Yes**	7	9	0.018	9	5	0.002
		No	33	167		44	150	
	SGA [§]	**Yes**	14	20	0.045	9	27	0.288
		No	14	55		11	64	
			ΔWZ < -1	**ΔWZ ≥ -1**		**ΔWZ < -1**	**ΔWZ ≥ -1**	
Stunted (LAZ < -2)	**All**	**Yes**	19	38	0.024	19	38	0.060
		No	49	212		54	207	
	AGA [§]	**Yes**	7	17	0.252	9	10	0.043
		No	33	159		44	145	
	SGA [§]	**Yes**	12	21	0.247	10	28	0.178
		No	16	53		10	62	
			ΔWZ < -1	**ΔWZ ≥ -1**		**ΔWZ < -1**	**ΔWZ ≥ -1**	
Wasted (WLZ < -2)	**All**	**Yes**	10	13	0.016	9	14	0.097
		No	58	237		64	231	
	AGA [§]	**Yes**	3	7	(0.398) [d]	6	3	(0.009) [d]
		No	37	169		47	152	
	SGA [§]	**Yes**	7	6	0.051	3	11	(0.717) [d]
		No	21	68		17	79	
			ΔWZ > +1	**ΔWZ ≤ +1**		**ΔWZ > +1**	**ΔWZ ≤ +1**	
Overweight (BMIZ > +2)	**All**	**Yes**	12	9	< 0.001	8	13	0.003
		No	36	261		37	260	
	AGA [§]	**Yes**	12	6	< 0.001	7	10	< 0.001
		No	28	170		16	175	
	SGA [§]	**Yes**	0	3	(> 0.999) [¶]	1	3	(> 0.999) [¶]
		No	8	91		21	85	

N=319: 3 infants excluded: gestational age at birth fell outside the range of IG-PPGS. Length measurement was only available for 318 infants.

[†] ΔWZ: change in weight-for-PMA z-score from birth to the last recorded measurement up to 50 weeks PMA.

[‡] All p-values calculated using Chi squared test unless otherwise indicated.

[§] Infants classified as AGA/SGA using the INTERGROWTH-21st Newborn Size Standards for comparisons with ΔWZ from IG-PPGS, and the Fenton growth chart for comparisons with ΔWZ from Fenton.

[¶] Fisher's exact test (small sample size in one/more sub-groups – cautious interpretation necessary).

Abbreviations: ΔWZ = Change in weight z-score between birth and ≤ 50 weeks; WAZ = weight-for-age z-score; LAZ = length-for-age z-score; WLZ = weight-for-length z-score; BMIZ = BMI-for-age z-score; Fenton = Fenton 2013 growth chart; IG-PPGS = INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants.

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BRIDGING TEXT

The preceding paper highlighted several important points. Firstly, that there are only minimal differences between the Fenton Growth Chart and the INTERGROWTH-21ST Newborn Size Standards when using them for the assessment of size at birth. Thus, either chart could be used for the assessment and classification of birth size and very similar results would be obtained.

Secondly, it became clear that there are more substantial differences between the Fenton Growth Chart and the INTERGROWTH-21ST Preterm Postnatal Growth Standards. This is particularly evident when absolute z-scores are considered: in all cases (whole group, AGA, and SGA infants), weight-for-PMA z-scores were significantly lower on the Fenton Growth Chart and the INTERGROWTH-21ST Preterm Postnatal Growth Standards. Thus, if a weight-for-PMA falling below a specified z-score (or percentile) is used as an indicator of malnutrition, more infants would be considered malnourished when using the Fenton Growth Chart. However, this approach gives an incomplete picture of nutrition status since it does not take the preceding growth pattern into account. An assessment of growth – operationalised as the change in z-score over time – is thus a more appropriate indicator of nutrition status and health than simply body size.

This introduces the third important finding: the magnitude of the difference between the Fenton Growth Chart and the INTERGROWTH-21ST Preterm Postnatal Growth Standards is diminished when the change in weight-for-PMA z-score over a fixed period is compared rather than the weight-for-PMA z-score at a single point in time. Some differences were, however, apparent when SGA and AGA infants were considered separately: SGA infants more closely followed the Fenton Growth Charts (with AGA infants displaying more growth deceleration), while AGA infants more closely followed the INTERGROWTH-21ST Standard (with SGA infants displaying more faltering growth). Nonetheless, the agreement between the charts was substantial, both for the classification of ΔWZ as ΔWZ<-1, -1≤ΔWZ≤+1 and ΔWZ>+1 (Cohen's Kappa = 0.647 for the whole sample, 0.693 for AGA infants only, and 0.556 for SGA infants only) and the association between these classes and malnutrition outcomes (Cohen's Kappa = 0.854 for underweight, 0.863 for stunting, 0.830 for wasting and 0.734 for overweight). The overarching conclusion from this analysis is that the choice of chart may be less important than the manner in which it is used, and that growth (as an indicator of nutrition status) is best assessed in terms of change over time rather than from a single measurement.

With the above in mind, the next question to be addressed concerned the growth outcomes in preterm infants. In preterm infants, the interruption of the foetal-infant growth continuum

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due to birth occurs at a much earlier stage. Thus, these infants miss out on a period of intrauterine growth and start their lives at smaller size – even more so in the case of SGA infants. It is important to know whether, and to what extent, this growth deficit is recovered during infancy. The next paper explores the one-year growth outcomes in the sample of preterm infants. The differences between SGA and AGA infants were explored, as well as the contribution of other early-life factors to growth outcomes, in an attempt to identify risk factors for malnutrition at one year of age.

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CHAPTER 5: THIRD PUBLICATION: One-year anthropometric follow-up of South African preterm infants in kangaroo mother care: Which early-life factors predict malnutrition?

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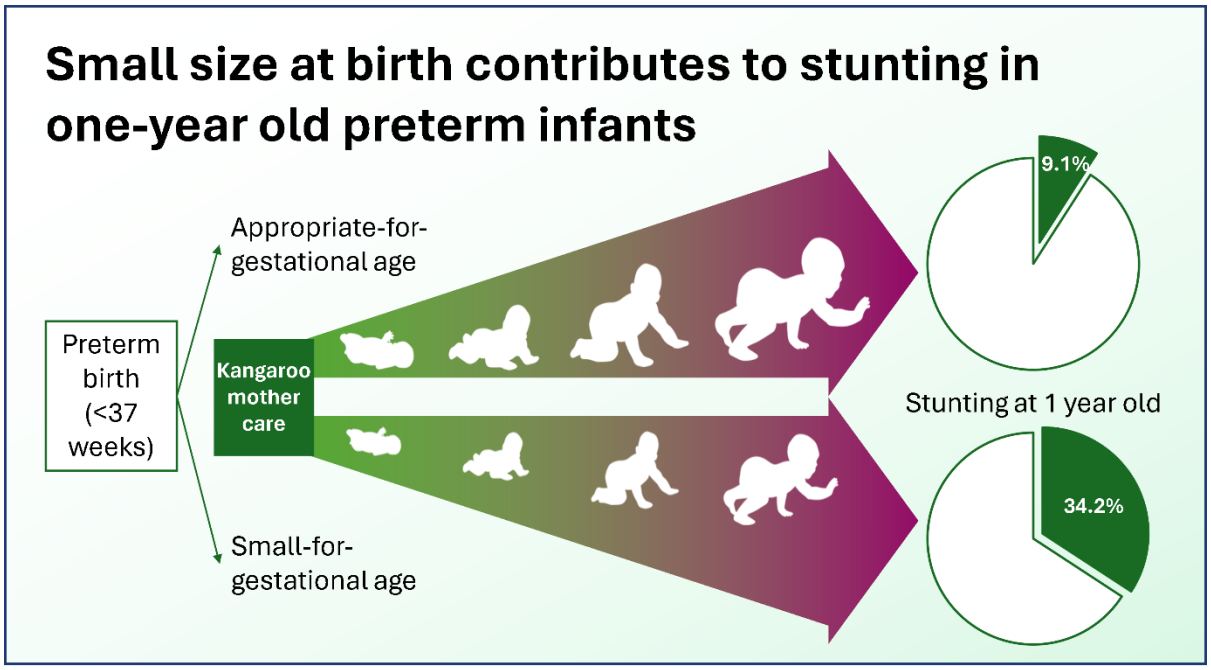
GRAPHICAL ABSTRACT



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RESEARCH ARTICLE

One-year anthropometric follow-up of South African preterm infants in kangaroo mother care: Which early-life factors predict malnutrition?

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Abstract

Background: Preterm infants often have poor short- and long-term growth. Kangaroo mother care supports short-term growth, but longer-term outcomes are unclear.

Methods: This study analysed longitudinally collected routine clinical data from a South African cohort of preterm infants (born <37 weeks gestation) attending the outpatient follow-up clinic of a tertiary-level hospital (Tshwane District, South Africa) for 1 year between 2012 and 2019. At 1 year, small-for-gestational age (SGA) and appropriate-for-gestational age (AGA) infants were compared with regard to age-corrected anthropometric z-scores (weight-for-age [WAZ], length-for-age [LAZ], weight-for-length [WLZ] and BMI-for-age [BMIZ]) and rates of underweight (WAZ < −2), stunting (LAZ < −2), wasting (WLZ < −2) and overweight (BMIZ > + 2). Multiple regression analysis was used to investigate associations between maternal/infant characteristics and rates of underweight, stunting, wasting and overweight.

Results: At 1 year, compared with AGA infants ($n = 210$), SGA infants ($n = 111$) had lower WAZ (−1.26 ± 1.32 vs. −0.22 ± 1.24, $p < 0.001$), LAZ (−1.50 ± 1.11 vs. −0.60 ± 1.06, $p < 0.001$), WLZ (−0.66 ± 1.31 vs. 0.11 ± 1.24, $p < 0.001$) and BMIZ (−0.55 ± 1.31 vs. 1.06 ± 1.23, $p < 0.001$), despite larger WAZ gains from birth (+0.70 ± 1.30 vs. +0.05 ± 1.30, $p < 0.001$). SGA infants had significantly more stunting (34.2% vs. 9.1%; $p < 0.001$), underweight (31.2% vs. 7.2%; $p < 0.001$) and wasting (12.6% vs. 4.3%, $p = 0.012$), with no difference in overweight (4.5% vs. 7.7%, $p = 0.397$). In multiple regression analysis, birth weight-for-GA z-score more consistently predicted 1-year malnutrition than SGA.

Conclusion: Preterm-born SGA infants remain more underweight, stunted and wasted than their preterm-born AGA peers at 1 year, despite greater WAZ gains. Interventions for appropriate catch-up growth especially for SGA preterm infants are needed.

KEYWORDS
child growth, malnutrition, preterm infants, small-for-gestational age (SGA), stunting

INTRODUCTION

Infants born preterm and/or small-for-gestational age (SGA)—so-called 'small vulnerable newborns [1]'—are at risk of short-and long-term adverse outcomes, including poor growth throughout childhood [1–5]. While most appropriate-for-gestational age (AGA) preterm infants catch up to their term-born peers in weight and height, SGA infants more often remain small throughout childhood [2, 3, 5]. In low- and middle-income countries (LMICs), socio-economic and nutritional deprivation further exacerbate underweight, wasting and stunting in these infants [6–9]. Poor postnatal growth is detrimental to neurodevelopment in preterm infants, particularly in resource-constrained environments [9]. The deleterious effects of growth faltering, but also the neurodevelopmental benefits

Sustainable Development Goal: Zero Hunger

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of catch-up growth, are particularly evident in SGA infants [9–12]. On the other hand, excessive early growth makes these infants particularly prone to obesity, metabolic syndrome and cardiovascular disease [11, 13–16]. Appropriate growth, therefore, must be adequate to support optimal neurodevelopment without compromising metabolic health through excessive weight gain.

The World Health Organisation (WHO) recommends kangaroo mother care (KMC) for all preterm and low birth weight infants [17]. Key components of KMC include constant mother-infant skin-to-skin contact, promotion of exclusive human milk feeding and continued skin-to-skin care after discharge [18]. Systematic reviews confirm that KMC supports better short-term growth in weight, length and head circumference (proportionately to daily KMC duration), while also improving morbidity, mortality and breastfeeding outcomes [18, 19]. Less is known about longer-term growth, although limited research from India and Colombia suggests that infants receiving KMC attain similar weight, height and head circumference at 6–12 months as infants receiving traditional incubator-based care [20, 21]. The South African Department of Health recommends KMC for all small and sick infants [22, 23] and it has been implemented in numerous settings [24, 25] However, local research on long-term infant outcomes after KMC discharge is lacking. While national preterm birth rates are unknown, a local study suggests up to 25% of infants may be born preterm (particularly at 34 to <37 weeks), and one in five infants are SGA [26], indicating a significant potential public health burden.

This research investigated first-year anthropometric outcomes (as weight-for-age, length-for-age [LAZ], weight-for-length and body mass index (BMI)-for-age z-scores and associated indicators of malnutrition) in a South African cohort of preterm infants who received early-life KMC. The outcomes of infants born SGA and AGA were compared, and various infant and maternal characteristics were investigated as possible predictors of 1-year anthropometric outcomes.

METHODS

Sampling

This study examined clinic records of preterm-born infants attending the post-discharge KMC follow-up clinic at a Baby-Friendly accredited tertiary-level academic hospital in Tshwane District (Gauteng Province, South Africa). The 1100-bed hospital primarily serves a low-income peri-urban African population. The KMC unit admits approximately 70 preterm infants per month, mostly from the hospital's own maternity unit and neonatal intensive care and high care units, with a small percentage from clinics and lower level hospitals in the catchment area. Preterm infants are discharged home soon as they are clinically stable and feeding orally; usually at <40 weeks post-menstrual age (PMA) and weighing <2 kg. Home KMC is encouraged, and infants visit the hospital's KMC outpatient clinic for regular follow-up (initially weekly to bi-weekly, increasing to 1- to 3-monthly) until the age of 9–12 months.

Power-driven reverse chronologic sampling was performed of infants born before 1 January 2019 (to exclude the effects of the COVID-19 pandemic). All infants born preterm (<37 weeks gestation), with a known birth weight and 1 year of follow-up data were eligible. Those with major anatomic abnormalities (e.g., hydrocephalus) and genetic conditions complicating growth (e.g., trisomies) were excluded. For statistical reasons, four large-for-gestational age infants were excluded.

A priori power calculations (G*Power v3.1.9.2; Heinrich-Heine-Universität, Düsseldorf) indicated 130 infants per group (SGA and AGA) to detect an effect size of 0.3 with $\alpha = 0.05$ and power = 80%. Each included infant was immediately classified as SGA or AGA to ensure adequate sample sizes per group. Initial sampling of 1788 records from 2018 to 2016 yielded 270 infants who met the inclusion and exclusion criteria (211 AGA and 59 SGA), all of whom were included. Additionally, records dating back to the clinic's inception in 2012 were screened to identify additional SGA infants; all 53 SGA infants who met the inclusion criteria were included in the study. Treatment and infant feeding policies had remained consistent during 2012–2019.

Data collection

Birth weight was measured in the maternity ward using electronic infant weighing scales, where pregnancy dating was uncertain, paediatric doctors estimated GA using the Ballard score. Birth information was copied to the paper KMC clinic record by medical doctors prior to KMC discharge. Clinic records were stored in a dedicated, restricted-access filing cabinet in the KMC ward.

Follow-up anthropometric measurements were taken by a single experienced hospital dietitian following KMC clinic protocols. Weight was measured naked, to 0.01 kg, using electronic infant weighing scales. Length was measured using a portable measuring mat, placed on a hard tabletop, with a rigid headboard and moveable footboard, and recorded to 0.1 cm. Head circumference was measured to 0.1 cm using a non-elastic measuring tape. Feeding information was collected and recorded by the dietitian, and medical examinations were conducted and recorded by the paediatric doctors.

Socio-demographic information, birth data, maternal medical conditions (classified according to WHO ICD10-PM categories [27]), infant medical information, infant feeding practices and anthropometric measurements were extracted from clinic records to Excel. Data were captured in duplicate, and discrepancies identified using EpiInfo v3.5.1 (2008, CDC, Washington DC). Anthropometry at birth, 50 weeks PMA, and the final clinic visit (≥1 year old) were used for this analysis.

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Data preparation and analysis

Infant chronologic age (in days) was calculated electronically using birth- and visit dates. Corrected age was calculated as chronologic age minus the number of days of prematurity (=280 days minus GA at birth). Birth weight-for-GA *z*-score (BWZ) was determined using the INTERGROWTH-21st Newborn Size Standards [28] computer application (https://intergrowth21.tghn.org/newborn-size-birth/), and infants classified as SGA (birth weight < 10th percentile) or AGA (birth weight ≥ 10th but ≤90th percentile). Early weight growth was quantified as the change in weight-for-GA *z*-score from birth to 50 weeks PMA, using the INTERGROWTH-21st Postnatal Growth Standards for Preterm Infants [29] (https://intergrowth21.tghn.org/postnatal-growth-preterm-infants/). Anthropometry at 1 year was assessed using WHO Anthro software (http://www.who.int/childgrowth/software/en/). *Z*-scores for weight-for-age (WAZ), LAZ, weight-for-length (WLZ) and BMI-for-age (BMIZ) were calculated using corrected age, along with rates of underweight (WAZ < −2), stunting (LAZ < −2), wasting (WLZ < −2) and overweight (BMIZ> + 2) [30]. First-year weight growth (ΔWZ) was quantified by subtracting BWZ from the WAZ at 1 year. The proportion of infants with ΔWZ < −1, ΔWZ ± 1 and ΔWZ > +1 was calculated and compared.

Analyses were performed using R Statistical Software (version 4.1.2, 2020; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were assessed for normality using the Shapiro–Wilk test. Birth characteristics and 1-year anthropometry (*z*-scores, ΔWZ and rates of malnutrition) of SGA and AGA infants were compared using the independent *t*-test (normally distributed continuous variables), Mann–Whitney U test (non-normally distributed continuous variables) and Chi-square or Fisher's exact test (categorical variables).

Associations between birth and early life factors (i.e., exposure variables) and anthropometric indicators of nutrition at 1 year (i.e., outcome variables) were investigated using multiple regression analysis. Preliminary univariate analyses compared each exposure variable (maternal age, parity, gravidity, HIV status, antiretroviral drug use in pregnancy, maternal conditions, infant sex, GA at birth, BWZ, SGA status, twins, congenital heart conditions, breastfeeding status during KMC stay and change in weight-for-GA *z*-score up to 50 weeks GA) to each malnutrition outcome (underweight, stunting, wasting and overweight, as defined above). Exposure variables with significant associations to the outcome were included in multivariate models. Associations were expressed as odds ratios (ORs) with 95% confidence intervals. McFadden's R^2 was calculated as overall indicator of each model's predictive ability.

To investigate selection bias arising from including only infants who attended a full year of follow-up visits, the sampled infants were compared to 489 randomly selected excluded infants with <1 year's follow-up data. Maternal and infant birth characteristics, anthropometry at 50 weeks PMA and anthropometry at the last recorded visit were compared. Among non-included infants, those discharged from follow-up before 1 year (i.e., early discharge) and those that were not discharged (i.e., lost to follow-up) were also considered separately.

Ethical and legal considerations

Approval to conduct the study was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (Protocol 227-2021) and the hospital (KPTH 23/2021). Data were processed anonymously.

RESULTS

Description of sample

Maternal ($N = 301$) and infant ($N = 321$) characteristics are described in Table 1, including comparisons between SGA ($n = 111$) and AGA ($n = 210$) infants and their mothers.

Noteworthy maternal characteristics include 21.3% HIV infection rate, 26.1% mothers ≥35 years old, and 30.0% mothers whose gravidity exceeded parity, suggesting previous pregnancy loss. Ethnicity was not recorded, but maternal surnames, recorded home languages and local demographics suggest the majority were Black African. The most prevalent infant conditions were neonatal jaundice (59.9%), respiratory distress syndrome (56.1%) and congenital heart conditions (31.2%, including 65 patent ducti arteriosus, 47 patent foramen ovale and 8 ventricular/atrial septum defects).

Comparisons showed that SGA infants had significantly lower birth weight and BWZ, and higher mean gestational age, rates of anaemia requiring transfusion and rates of congenital heart conditions, particularly patent ductus arteriosus (SGA 31.5%, AGA 14.3%, $p < 0.001$). Significantly more mothers of SGA infants were self-reported foreign nationals.

Anthropometric outcomes AT 1 year of age

The mean chronologic age of infants at the ≥1-year follow-up visit was 381 ± 19 days (12.6 ± 0.6 months), with a mean corrected age of 332 ± 23 days (10.9 ± 0.8 months). Infant anthropometry is detailed in Table 2, and the comparison between SGA and AGA infants is illustrated in Figure 1. At 1 year, SGA infants had significantly lower mean values for all anthropometric measurements (weight, length and head circumference) and *z*-scores (WAZ, LAZ, WLZ, BMIZ and HCZ), along with significantly higher rates of underweight, stunting and wasting. Rates of overweight and combined stunting and wasting did not differ significantly. Additionally, SGA infants had a larger mean gain in WAZ over the first year, (Figure 2) and a larger proportion of SGA infants gained >1 WAZ unit while a smaller proportion lost more than 1 WAZ unit.

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TABLE 1 Maternal and infant characteristics at birth.

Characteristic	Total sample ($N = 321$)		AGA ($N = 210$)		SGA[d] ($N = 111$)		*p*-value: SGA vs. AGA
	N	Value	*N*	Value	*N*	Value	
Maternal age (years)[a] (Mean ± SD)	283	29.5 ± 6.6	193	29.6 ± 6.6	90	29.1 ± 6.6	0.476[g]
Maternal age ≤ 19 (*n* [%])		18 (6.4)		13 (6.7)		5 (5.6)	0.907[h]
Maternal age ≥ 35 (*n* [%])		74 (26.1)		51 (26.4)		23 (25.6)	0.992[h]
Maternal parity[a] (Median [IQR])	283	2 (1–3)	193	2 (1–3)	90	2 (1–3)	0.124[g]
Maternal gravidity[a] (Median [IQR])		2 (2–3)		2 (2–3)		2 (1–3)	0.102[g]
Gravidity > parity (*n* [%])		85 (30.0)		60 (31.1)		25 (27.8)	0.670[h]
Mother is a foreign national (self-report)[a] (*n* [%])	301	76 (25.2)	210	42 (20.0)	111	34 (30.6)	<0.001[h] ***
Maternal HIV infection[a] (*n* [%])	301	64 (21.3)	196	36 (18.4)	105	28 (26.7)	0.194[h]
Antiretroviral treatment[a] (*n* [%])	64		36		28		
Initiated before pregnancy		27 (42.2)		18 (50.0)		9 (32.1)	0.201[i]
Initiated during pregnancy		17 (26.6)		7 (19.4)		10 (35.7)	
Initiated after delivery		10 (15.6)		4 (11.1)		6 (21.9)	
Not recorded		10 (15.6)		7 (19.4)		3 (10.7)	
Maternal conditions[a] (*n* [%])	301		210		111		
Placenta, cord, membranes		13 (4.3)		9 (1.3)		4 (3.6)	>0.999[i]
Pregnancy conditions[b]		60 (19.9)		38 (18.1)		22 (21.0)	0.863[h]
Labour and delivery conditions		64 (21.3)		51 (24.3)		13 (11.7)	0.009[h] **
Medical and surgical conditions		115 (38.2)		72 (34.3)		43 (38.7)	0.553[h]
Infant sex (male) (*n* [%])	321	159 (49.5)	210	105 (50.0)	111	54 (48.6)	0.910[h]
Gestational age (weeks) (Mean ± SD)	321	32.8 ± 2.4	210	32.5 ± 2.4	111	33.3 ± 2.3	0.001[g] **
Birth weight (kg) (Mean ± SD)	321	1.64 ± 0.48	210	1.77 ± 0.46	111	1.39 ± 0.43	<0.001[g] ***
Birth weight *z*-score[c] (Mean ± SD)		−0.86 ± 1.04		−0.26 ± 0.61		−2.00 ± 0.69	<0.001[g] ***
Infant feeding in KMC ward (*n* [%])	321		210		111		
Mother's own breast milk		314 (97.8)		205 (97.6)		109 (98.2)	1.000[i]
Donor breast milk		6 (1.9)		3 (1.4)		3 (2.7)	0.420[i]
Commercial infant formula		9 (2.8)		8 (3.8)		1 (0.9)	0.171[i]
Infant haemoglobin at 0–5 days (Mean ± SD)	108	16.7 ± 2.5	83	16.7 ± 2.6	25	16.9 ± 2.3	0.757[k]
Twins	321	53 (16.5)	210	33 (15.7)	111	20 (18.0)	0.711[h]
Infant morbidities[e] (*n* [%])	321		210		111		
Neonatal jaundice		191 (59.5)		129 (61.4)		62 (55.9)	0.397[h]
Respiratory distress syndrome		180 (56.1)		116 (55.2)		64 (57.7)	0.766[h]
Congenital heart conditions[f]		100 (31.2)		54 (25.7)		46 (41.4)	0.006[h] **
Infant sepsis		61 (19.0)		35 (16.7)		26 (23.4)	0.187[h]
Other infant infections		35 (10.9)		23 (11.0)		12 (10.8)	1.000[h]
Anaemia requiring transfusion		29 (9.0)		12 (5.7)		17 (15.3)	0.008[h] **
Chronic lung disease		19 (5.9)		9 (4.3)		10 (9.0)	0.145[h]

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; KMC, kangaroo mother care.
[a]For maternal characteristics, $n = 20$ duplicates of mothers of twins were removed (thus $N = 301$; 196 AGA, 105 SGA).
[b]Maternal conditions classified according to WHO ICD10-PM categories [27]. Conditions of labour and delivery only include conditions other than preterm delivery, as preterm birth was an inclusion criterion for the study.
[c]Calculated using the INTERGROWTH-21ST Newborn Size Standards [28].
[d]Small-for-gestational age: birth weight < 10th percentile.
[e]Some infants had more than one concurrent morbidity.
[f]Includes patent ductus arteriosus ($n = 65$; 30 AGA, 35 SGA; $p < 0.001$), patent foramen ovale ($n = 47$; 30 AGA, 17 SGA; $p = 0.934$) and ventricular/atrial septum defects ($n = 8$; 3 AGA, 5 SGA; $p = 0.131$).
[g]Mann–Whitney U test.
[h]Chi-squared test.
[i]Fisher's exact test (one or more subgroup $n \leq 5$).
**$p < 0.01$; ***$p < 0.001$.

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TABLE 2 Infant anthropometric characteristics at 1 year of age.

Characteristic	Value/z-score (mean ± SD)			p-value: SGA vs. AGA
	Whole sample ($N = 321$)	AGA ($N = 210$)	SGA ($N = 111$)	
Chronologic age (days)	381 ± 19	383 ± 19	381 ± 19	0.272[c]
Corrected age (days)	332 ± 23	331 ± 23	333 ± 22	0.133[c]
Any breastfeeding at last visit (n [%])	181 (56.4%)	116 (55.2%)	65 (58.6%)	0.663
Early weight growth: WAZ gain from birth to ≤50 weeks PMA[e]	−0.23 ± 1.23	−0.37 ± 1.18	+0.02 ± 1.29	0.010[c] **
Weight (kg)	8.56 ± 1.42	8.91 ± 1.34	7.91 ± 1.35	<0.001[c] ***
Weight-for-age z-score[a]	−0.59 ± 1.36	−0.22 ± 1.24	−1.26 ± 1.32	<0.001[d] ***
Weight-for-length[b] z-score	−0.16 ± 1.31	+0.11 ± 1.24	−0.66 ± 1.31	<0.001[d] ***
BMI-for-age[a, b] z-score	−0.09 ± 1.30	+0.16 ± 1.23	−0.55 ± 1.31	<0.001[d] ***
WAZ change: birth to 1 year (ΔWZ)	+0.28 ± 1.33	+0.05 ± 1.30	+0.70 ± 1.30	<0.001[d] ***
ΔWZ > +1	94 (29.3%)	52 (24.9%)	42 (37.5%)	0.005 **
−1 ≤ ΔWZ ≤ +1	176 (54.8%)	115 (55.0%)	61 (54.5%)	
ΔWZ < −1	51 (15.9%)	42 (20.1%)	9 (8.0%)	
Length[b] (cm)	71.3 + 3.0	72.1 + 2.7	69.9 + 3.0	<0.001[d] ***
Length-for-age[a] z-score	−0.91 ± 1.16	−0.60 ± 1.06	−1.50 ± 1.11	<0.001[d] ***
Head circumference (cm)	45.4 + 1.8	45.7 + 1.62	44.9 + 1.9	<0.001[c] ***
HC-for-age[a] z-score	+0.21 ± 1.28	0.43 ± 1.15	−0.21 ± 1.41	<0.001[c] ***
Indicators of malnutrition (n [%])				
Underweight[a]: WAZ < −2	50 (15.6%)	15 (7.2%)	35 (31.2%)	<0.001[f] ***
Stunting[a, b]: LAZ < −2	57 (17.8%)	19 (9.1%)	38 (34.2%)	<0.001[f] ***
Wasting[b]: WLZ < −2	23 (7.2%)	9 (4.3%)	14 (12.6%)	0.012[g] *
Overweight[a, b]: BMIZ > + 2	21 (6.6%)	16 (7.7%)	5 (4.5%)	0.397[f]
Stunting + Wasting	10 (3.1%)	4 (1.9%)	6 (5.4%)	0.103[g]

Abbreviations: BMIZ, body mass index-for-age z-score; HC, head circumference; LAZ, length-for-age z-score; WAZ, weight-for-age z-score; WLZ, weight-for-length z-score.
[a]All age-related z-scores calculated using corrected age.
[b]Length was only available for $N = 320$ infants ($n = 209$ AGA and $n = 111$ SGA).
[c]Mann–Whitney U test.
[d]Independent t-test.
[e]Calculated using the INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants [29].
[f]Chi-square test.
[g]Fisher's exact test (one or more subgroup $n \leq 5$).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Multiple regression analysis

Univariate analysis identified several significant associations between exposure and outcome variables, some of which became non-significant when included alongside other variables in multivariate analysis. The OR for univariate and multivariate analyses is shown in Table 3.

In multivariate analysis, odds of underweight were significantly increased by maternal conditions of pregnancy, and decreased by higher BWZ and greater early WAZ gains. The odds of stunting were significantly increased by being SGA, and decreased by higher BWZ and greater early WAZ gains. Odds of wasting were significantly increased by infant congenital heart conditions and decreased by higher BWZ. Odds of overweight were only significantly increased by greater early WAZ gains. The multiple regression models for all the variables had low R^2 values ($R^2 = 0.084$–0.223) indicating poor ability to predict underweight, stunting, wasting and overweight at 1 year.

Assessment for selection bias

Comparison of included and non-included infants revealed some significant differences (Supplementary Table S1). Non-included infants had significantly higher gestational age (33.3 ± 2.4 vs. 32.8 ± 2.4 weeks, $p < 0.001$) and BWZ (−0.62 ± 0.94 vs. −0.86 ± 1.04, $p = 0.013$). The study sample had a higher proportion of SGA infants due to deliberate over-sampling; BWZ did not differ significantly when AGA and SGA infants were separated, though the difference in GA remained significant. Non-included infants additionally had higher rates of maternal HIV infection (29.7% vs. 21.8%, $p = 0.013$) and fewer congenital heart defects (24.7% vs. 31.2%, $p = 0.045$).

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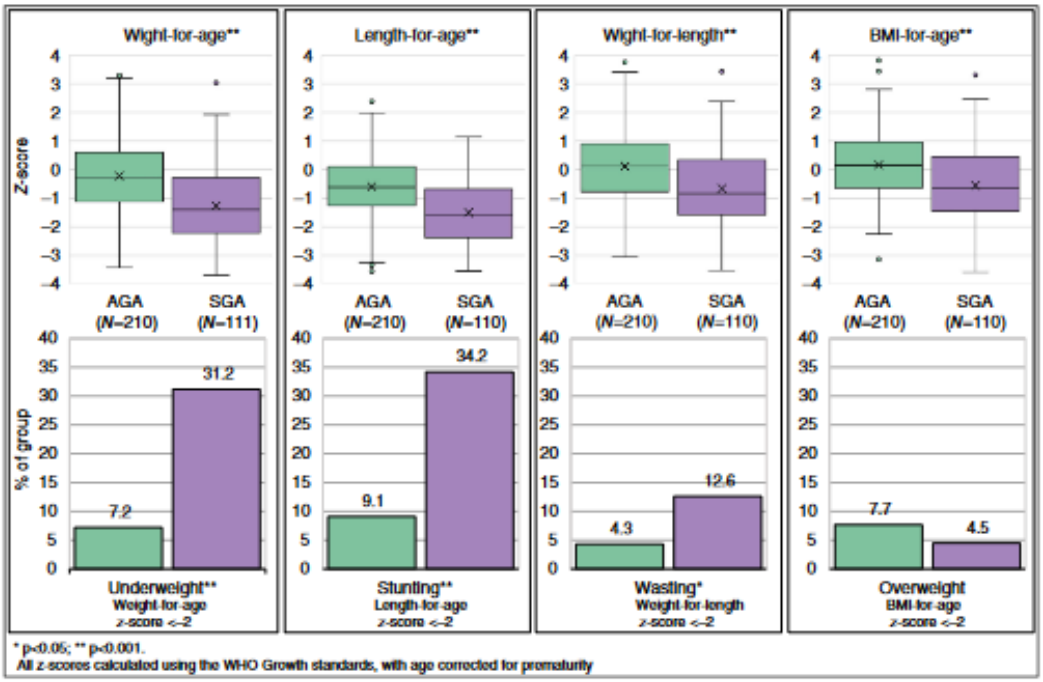

FIGURE 1 One-year anthropometric z-scores and rates of malnutrition in $N = 321$ small- and appropriate-for-gestational age infants.

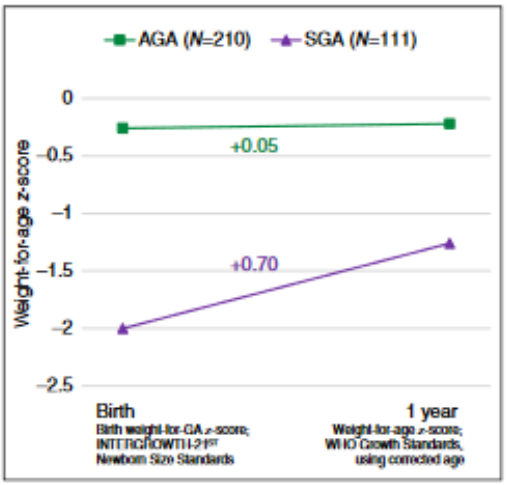

FIGURE 2 Change in weight-for-age z-score from birth to 1 year in $N = 321$ small- and appropriate-for-gestational age infants.

At the last recorded visit, non-included infants had significantly higher mean WLZ than included infants (+0.19 ± 1.24 vs. −0.16 ± 1.31, $p < 0.001$, with no significant difference between infants lost to follow-up and infants discharged early). Mean WAZ, LAZ, BMIZ or HCZ did not differ significantly between included and non-included infants, though infants discharged at <1 year had significantly higher WAZ (−0.21 ± 1.10 vs. −0.68 ± 1.36, $p = 0.011$) and LAZ −0.64 ± 1.24 vs. −1.13 ± 1.39, $p = 0.003$) than those lost to follow-up, with the study infants falling in-between (WAZ −0.59 ± 1.36, LAZ (−0.91 ± 1.16) (Table S2). Similar patterns were seen in SGA and AGA infants separately.

DISCUSSION

Birth weight and early weight growth were important predictors of 1-year anthropometric outcomes in this cohort of South African preterm infants with mixed health status, who received early KMC and close post-discharge follow-up with optimal support for nutrition and growth within the constraints of their socio-economic circumstances. The study infants and mothers had relatively high rates of co-morbidities (including maternal HIV, infant congenital heart conditions, respiratory distress syndrome, sepsis and other infectious illness), yet this is similar to recently published research in a comparable South African setting [24]. High rates of breastfeeding at KMC discharge (97.8%) and 1 year (56.4%, compared with national rates of 51.4% at 12–15 months [31]) attest to effective in- and outpatient breastfeeding support.

At 1 year old, SGA infants remained significantly smaller than AGA infants on all anthropometric measurements

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TABLE 3 Multiple regression analysis: odds ratios (with 95% confidence intervals) for selected exposure variables in relation to underweight, stunting, wasting and overweight at 1 year in $N = 321$ preterm-born infants.

	Outcome							
	Underweight		Stunting		Wasting		Overweight	
Exposure	Univariate[a]	Multivariate	Univariate[a]	Multivariate	Univariate[a]	Multivariate	Univariate[a]	Multivariate
Maternal conditions of pregnancy[b]	2.43 (1.21, 4.73) ($p = 0.010$)	3.01 (1.34; 6.70) ($p = 0.007$)	-	-	-	-	-	-
Maternal conditions of labour/delivery[c]	0.31 (0.09, 0.79) ($p = 0.029$)	-	-	-	-	-	-	-
Infant congenital heart conditions	2.15 (1.15, 3.97) ($p = 0.015$)	-	-	-	4.68 (1.96, 12.0) ($p < 0.001$)	2.67 (1.02; 7.35) ($p = 0.049$)	0.22 (0.03, 0.76) ($p = 0.042$)	-
Birth weight z-score[d] (per 1 unit increase)	0.40 (0.28, 0.55) ($p < 0.001$)	0.45 (0.25; 0.78) ($p = 0.005$)	0.48 (0.35, 0.64) ($p < 0.001$)	0.61 (0.37; 0.99) ($p = 0.047$)	0.47 (0.32, 0.69) ($p < 0.001$)	0.42 (0.21; 0.81) ($p = 0.010$)	-	-
Being SGA[e]	6.72 (3.50, 13.55) ($p < 0.001$)	-	5.31 (2.91, 9.98) ($p < 0.001$)	2.99 (1.07; 8.65) ($p = 0.039$)	3.25 (1.36, 8.07) ($p = 0.008$)	-	-	-
Early weight-for-GA z-score change[f] (per 1 unit increase)	0.77 (0.60, 0.98) ($p = 0.035$)	0.60 (0.44; 0.80) ($p < 0.001$)	0.71 (0.56, 0.89) ($p = 0.004$)	0.58 (0.44; 0.75) ($p < 0.001$)	-	-	1.79 (1.21, 2.75) ($p = 0.005$)	1.73 (1.15; 2.70) ($p = 0.012$)
Model R^2[g]	-	0.223	-	0.166	-	0.150	-	0.037

Note: '-' denotes no significant association.
[a]Univariate analysis found no significant relationships for maternal age, parity, gravidity, HIV, timing of ART initiation, maternal conditions of the placenta, cord or membranes, maternal medical and surgical conditions, infant sex, breastfeeding at last visit.
[b]Maternal conditions of pregnancy include incompetent cervix, preterm rupture of membranes, oligohydramnios/polyhydramnios, ectopic pregnancy, multiple pregnancy, malpresentation and other complications of pregnancy (excluding pregnancy-related medical conditions like hypertensive disorders, pre-eclampsia and gestational diabetes mellitus) [27].
[c]Maternal conditions of labour and delivery include breech delivery, malposition and disproportion during labour and delivery, forceps delivery/vacuum extraction, Caesarean delivery, spontaneous preterm labour, and other complications of labour and delivery [27].
[d]Birth weight z-score calculated using the INTERGROWTH-21ST Newborn Size Standards [26], used as continuous variable.
[e]SGA = small-for-gestational age (birthweight-for-GA < 10th percentile on the INTERGROWTH-21ST Newborn Size Standards [24]).
[f]Early change in weight-for-GA z-score: difference between weight-for-GA z-score at ≤30 weeks PMA and birth; calculated using the INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants [28]; used as continuous variable.
[g]McFadden's R^2 values >0.4 indicate good predictive ability.

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(weight, length and head circumference) and *z*-scores (WAZ, LAZ, WLZ, BMIZ and HCZ), with higher rates of underweight, wasting and stunting. The rates of underweight (15.6%) and wasting (7.2%) in the study sample far exceed the average South African prevalence (underweight 3.1% and wasting 2.8% in children 12–17 months [31]). This is not uncommon in preterm infants in LMICs [8]. SGA infants had much higher rates of underweight (31.2% vs. 7.2%) and wasting (12.6% vs. 4.3%) than AGA infants, despite significantly greater WAZ gains over the first year of life. Thus, catch-up growth in SGA infants is still incomplete at 1 year, and may never be completed if trends seen in other LMICs hold true [8].

Although this study lacked reliable birth length measurements to investigate catch-up length growth, the low mean LAZ in SGA and AGA infants alike is concerning, particularly as length growth in the first 2 years predicts adult height and lifelong educational achievement [32]. Though the overall stunting rate in the sample (17.1%) is lower than the South African population prevalence (31.4%) in children 12–17 months [31], the SGA group had a very high stunting rate (34.2%). This suggest a prenatal length growth deficit that is not recovered in infancy. Recent research from various LMICs have similarly found that birth LAZ strongly predicts LAZ and stunting in the first 1–2 years of life. [33, 34] Thus, optimising foetal growth and preventing preterm birth are key. A recent systematic review identified numerous interventions for reducing preterm birth and/or SGA, including routine multiple micronutrient supplementation and targeted low-dose aspirin to prevent pre-eclampsia [35]. Furthermore, pre-pregnancy and/or prenatal maternal nutrition supplementation were found to increase birth length [34]. Incorporating these interventions in standard antenatal care services could potentially impact rates of preterm and SGA birth and, by extension, reduce childhood malnutrition and its sequelae.

Though this sample contained few overweight children, childhood overweight is an increasing problem in South Africa, occurring in 12.6% of children 12–17 months old [31]. High rates of obesity in adults, existing alongside chronic malnutrition, reflect the nutrition transition taking place in the country [31]. This so-called double burden of malnutrition has been associated with intergenerational cycles of maternal-foetal malnutrition: short maternal stature strongly predicts low birth weight and SGA, which in turn leads to childhood stunting. This, combined with later overnutrition (often against a backdrop of lifelong micronutrient undernutrition) leads to co-existing stunting and overweight in the new generation, which perpetuates the cycle [36].

Multiple regression analysis revealed that smaller size at birth and lower early weight growth were the most important predictors of poor anthropometric outcomes at 1 year. While BWZ and SGA were both independently associated with undernutrition (underweight, stunting and wasting), SGA became non-significant when included in multivariate analyses to predict underweight and wasting. This underscores the importance of accurate birth weight-for-GA assessment even in AGA infants: undernutrition occurred at 4.3%–9.1% in the AGA infants, but none in infants with BWZ > +0.7, suggesting that the association may be less important at higher BWZ.

Greater early weight growth (operationalised as change in weight-for-GA *z*-score up to 50 weeks GA) was associated with significantly lower odds of underweight and stunting, but increased odds of overweight. There is no clear guideline for the range of weight gain associated with either under- or over-nutrition, since the range of changes in weight-for-GA *z*-score in infants with stunting (−3.9 to +1.8) and overweight (−2.1 to +1.8) overlapped almost entirely. This highlights the importance of monitoring length alongside weight in routine growth monitoring and assessing weight in relation to length.

Two other conditions significantly predicted undernutrition: maternal conditions of pregnancy (for underweight) and infant congenital heart conditions (for wasting). Though congenital heart conditions were also significantly associated with underweight and overweight in univariate analysis, these associations became non-significant in multiple regression models. This is likely due to the association between BWZ and congenital heart conditions (evidenced by the high occurrence of these conditions in SGA infants). Additionally, cardiac lesions only affect infant growth if there is significant hemodynamic impairment [37, 38]. Such lesions were not evident in this sample, as none of the infants had evidence of cardiorespiratory failure and only one required surgical intervention.

Surprisingly, breastfeeding status did not predict malnutrition at 1 year. Other studies have found higher rates of breastfeeding difficulties in preterm and/or SGA infants, associated with higher rates of underweight at 6 months [39]. In this sample, intensive in-hospital and post-discharge breastfeeding support may have mitigated these risks. Additionally, study infants transitioned to complementary foods several months before the final visit, which further confounds the association. Future studies would benefit from more detailed dietary assessment.

An important limitation of the sampling design is the possibility of selection bias, as infants with specific characteristics may be discharged earlier, fail to attend clinic visits or be lost to follow-up for other reasons (e.g., hospital admission or death). Indeed, there were some differences between the study sample and non-included infants. The study infants had lower mean gestational age, which could conceivably affect early neonatal morbidity and growth. However, the mean differences were fairly small (0.39–1.03 weeks), and their relevance at 1 year of age is questionable. The non-included infants had a higher mean WLZ (but not BMIZ) at the last visit, particularly in SGA infants, suggesting the study may have included thinner infants. Differences in WAZ, LAZ and WLZ at last visit further suggest that the non-included infants who were discharged before 1 year exhibited better growth than the study sample, while infants who were lost to follow-up either exhibited poorer

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growth than the study sample or were lost to follow-up before substantial catch-up growth was achieved.

The limitations of using routine clinical data must be acknowledged. Quality control during data collection may have been less stringent than in a research setting, although the use of a single experienced dietitian would improve the reliability of anthropometric measurements. Similarly, clinical records may have been incomplete, particularly with regards to maternal comorbidities, leading to underestimation of some conditions.

Future studies should pursue longer follow-up (to 2 years and beyond) to investigate the full extent of catch-up growth, and particularly the evolution of stunting and overweight rates over time. The role of complementary feeding practices in growth also warrants further study. Assessment of alternative outcomes such as body composition, neurodevelopment and cardiometabolic risk factors would further elucidate the impact of early-life growth patterns on long-term health. Context-specific feasibility and cost-effectiveness studies for evidence-based interventions to prevent preterm and SGA births should also be prioritised.

In clinical practice, early identification of infants at risk of poor growth is key, including preterm and/or SGA infants and those with poor early weight growth. Assessment of size at birth requires reliable estimates of gestational age as well as accurate measurement and plotting of weight and length. In infancy, length should be routinely measured (and weight-for-length assessed) to identify faltering linear growth and avoid overfeeding shorter children who then become overweight. Though LAZ and WLZ growth charts are incorporated in the South African patient-held Road-to-Health booklet, the skills, equipment and human resources to use them are often lacking [40–42]; this needs to be urgently addressed. Finally, in the South African context, replacing routine antenatal iron and folate supplementation with multiple micronutrients should be considered. Early attendance of antenatal care is also important, not only for early identification of complications but also for accurate pregnancy dating, and to ensure each infant has the best possible start in life.

CONCLUSION

Size at birth, particularly birth weight-for-GA, remains an important predictor of anthropometric outcomes in the first year of life. Even with early KMC and close post-discharge follow-up, preterm-born SGA infants have significant anthropometric deficits and high rates of undernutrition at 1 year, which may impact long-term well-being. Although SGA infants showed evidence of partial weight catch-up, LAZ remained low in both SGA and AGA infants, increasing their long-term risk of stunting and overweight. Mitigating these adverse outcomes will require a three-pronged approach: prevention of preterm birth and SGA, appropriate growth monitoring (including assessment of length and weight-for-length) and effective interventions to support appropriate postnatal catch-up growth in SGA preterm infants.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Comparison of selected characteristic of infants included in and excluded from the study.

	ENTIRE SAMPLE			ONLY AGA INFANTS			ONLY SGA INFANTS		
Characteristic	**Non-included N=489**	**Included N=321**	**P-value**	**Non-included N=360**	**Included N=210**	**P-value**	**Non-included N=117**	**Included N=111**	**P-value**
BASELINE									
Maternal HIV infection	145 (29.7%)	70 (21.8%)	0.013 [a]	102 (28.3%)	40 (19.0%)	<0.001 [a]	42 (35.9%)	30 (27.0%)	0.150 [a]
Timing of ART initiation [n (%) of HIV-infected mothers]			0.286 [a]			0.048 [b]			0.886 [b]
- ART initiated before pregnancy	59 (40.7%)	31 (44.3%)		42 (11.7%)	21 (10.0%)		16 (13.7%)	10 (9.0%)	
- ART initiated during pregnancy	57 (39.3%)	19 (27.1%)		44 (12.2%)	8 (3.8%)		13 (11.1%)	11 (9.9%)	
- ART initiated after delivery	16 (11.0%)	10 (14.3%)		6 (1.7%)	4 (1.9%)		10 (8.5%)	6 (5.4%)	
- ART initiated not recorded	13 (9.0%)	10 (14.3%)		10 (2.8%)	7 (3.3%)		3 (2.6%)	3 (2.7%)	
Maternal parity	2 (1; 3)	2 (1; 3)	0.882 [c]	2 (2; 3)	2 (2; 3)	0.321 [c]	2 (1; 3)	2 (1; 3)	0.138 [c]
Maternal gravidity	2 (2; 3)	2 (2; 3)	0.215 [c]	2 (1; 3)	2 (1; 3)	0.780 [c]	2 (2; 3)	2 (1; 3)	0.300 [c]
Maternal age	28.7 ± 6.4	29.6 ± 7	0.059 [c]	28.5 ± 6.5	29.7 ± 6.7	0.039 [c]	28.8 ± 5.6	29.4 ± 6.6	0.678 [c]
Mother is a foreign national	139 (28.4%)	79 (24.6%)	0.260 [a]	100 (27.8%)	42 (20.0%)	0.049 [a]	34 (29.1%)	37 (33.3%)	0.580 [a]
Maternal conditions									
- … of placenta, cord, membranes	16 (3.3%)	15 (4.7%)	0.407 [a]	12 (3.3%)	11 (5.2%)	0.371 [a]	4 (3.4%)	4 (3.6%)	>0.999 [b]
- … of pregnancy **	118 (24.1%)	80 (24.9%)	0.863 [a]	88 (24.4%)	52 (24.8%)	>0.999 [a]	27 (23.1%)	28 (25.2%)	0.823 [a]
- … of labor and delivery	104 (21.3%)	69 (21.5%)	>0.999 [a]	82 (22.8%)	54 (25.7%)	0.489 [a]	19 (16.2%)	15 (13.5%)	0.695 [a]
- Medical and surgical conditions	219 (44.8%)	121 (37.7%)	0.054 [a]	156 (43.3%)	76 (36.2%)	0.113 [a]	59 (50.4%)	45 (40.5%)	0.172 [a]
Sex (male)	260 (53.2%)	159 (49.5%)	0.347 [a]	186 (51.7%)	105 (50.0%)	0.766 [a]	66 (56.4%)	54 (48.6%)	0.298 [a]
GA (weeks)	33.3 ± 2.4	32.8 ± 2.4	0.001 [c]	32.9 ± 2.4	32.5 ± 2.4	0.022 [c]	34.4 ± 2.0	33.3 ± 2.3	<0.001 [c]
Birth weight (kg)	1.81 ± 0.51	1.64 ± 0.48	<0.001 [c]	1.84 ± 0.47	1.77 ± 0.46	0.154 [c]	1.62 ± 0.37	1.39 ± 0.43	<0.001 [c]
Birth weight z-score (IG-NBS)	-0.62 ± 0.94 [c]	-0.86 ± 1.04	0.013 [a]	-0.31 ± 0.58	-0.26 ± 0.61	0.333 [c]	-1.85 ± 0.38	-2.00 ± 0.69	0.554 [c]
Infant feeding in KMC unit									
- Mother's own breast milk	473 (96.7%)	314 (97.8%)	0.495 [a]	352 (97.8%)	205 (97.6%)	>0.999 [a]	110 (94.0%)	109 (98.2%)	0.172 [b]
- Donor breast milk	3 (0.6%)	6 (1.9%)	0.167 [b]	0 (0.0%)	3 (1.4%)	0.050 [c]	3 (2.6%)	3 (2.7%)	>0.999 [b]
- Breast milk substitute	12 (2.5%)	9 (2.8%)	0.936 [a]	9 (2.5%)	8 (3.8%)	0.528 [a]	3 (2.6%)	1 (0.9%)	0.622 [b]
Infant morbidities *									
- Congenital heart defects	121 (24.7%)	100 (31.2%)	0.045 [a]	89 (24.7%)	54 (25.7%)	0.870 [a]	32 (27.4%)	46 (41.4%)	0.036 [a]
- Twins	89 (18.2%)	53 (16.5%)	0.600 [a]	65 (18.1%)	33 (15.7%)	0.549 [a]	22 (18.8%)	20 (18.0%)	>0.999 [a]
- Neonatal jaundice	254 (51.9%)	191 (59.5%)	0.041 [a]	191 (53.1%)	129 (61.4%)	0.064 [a]	59 (50.4%)	62 (55.9%)	0.491 [a]
- Respiratory distress syndrome	279 (57.1%)	180 (56.1%)	0.832 [a]	216 (60.0%)	116 (55.2%)	0.306 [a]	55 (47.0%)	64 (57.7%)	0.140 [a]
- Chronic lung disease	15 (3.1%)	19 (5.9%)	0.072 [a]	10 (2.8%)	9 (4.3%)	0.468 [a]	5 (4.3%)	10 (9.0%)	0.240 [a]
- Infant sepsis	98 (20.0%)	61 (19.0%)	0.785 [a]	71 (19.7%)	35 (16.7%)	0.428 [a]	23 (19.7%)	26 (23.4%)	0.596 [a]
- Other infant infections	40 (8.2%)	35 (10.9%)	0.236 [a]	29 (8.1%)	23 (11.0%)	0.304 [a]	10 (8.5%)	12 (10.8%)	0.723 [a]
- Anemia requiring transfusion	28 (5.7%)	29 (9.0%)	0.097 [a]	22 (6.1%)	12 (5.7%)	0.992 [a]	6 (5.1%)	17 (15.3%)	0.020
EARLY GROWTH									
LAZ (IG-PPGS)	-1.16 ± 1.49	-1.22 ± 1.72	0.926	-0.92 ± 1.38	-0.52 ± 1.30	0.003 [c]	-2.15 ± 1.28	-2.55 ± 1.63	0.182 [c]
WAZ (IG-PPGS)	-0.64 ± 1.30	-0.56 ± 1.50	0.197	-0.42 ± 1.22	0.07 ± 1.09	< 0.001 [c]	-1.58 ± 1.03	-1.74 ± 1.46	0.391 [d]
WAZ change on IG-PPGS	-0.09 ± 1.19	-0.23 ± 1.23	0.124	-0.15 ± 1.20	-0.37 ± 1.18	0.038 [c]	0.23 ± 1.04	0.02 ± 1.29	0.213 [d]
HCZ on IG-PPGS	0.17 ± 1.40	0.34 ± 1.58	0.073	0.34 ± 1.39	0.94 ± 1.22	<0.001 [c]	-0.59 ± 1.11	-0.82 ± 1.55	0.253 [d]
LAST RECORDED VISIT									
Actual age (days)	144.1 ± 102.6	381.8 ± 19.1	<0.001	140.6 ± 100.8	382.5 ± 19.0	<0.001 [c]	158.3 ± 108.5	380.5 ± 19.3	<0.001 [c]
Corrected age (days)	96.8 ± 103.2	331.5 ± 22.9	<0.001	90.7 ± 101.2	330.5 ± 23.3	<0.001 [c]	118.9 ± 108.6	333.4 ± 22.1	<0.001 [c]
WLZ (WHO)	0.19 ± 1.24	-0.16 ± 1.31	<0.001	0.25 ± 1.25	0.11 ± 1.24	0.226 [d]	-0.06 ± 1.17	-0.66 ± 1.31	<0.001 [d]
LAZ (WHO, using CA)	-1.02 ± 1.37	-0.91 ± 1.16	0.258	-0.79 ± 1.29 -	0.60 ± 1.06	0.072 [d]	-1.77 ± 1.21	-1.50 ± 1.11	0.097 [d]
WAZ (WHO, using CA)	-0.56 ± 1.32	-0.59 ± 1.36	0.835	-0.34 ± 1.26 -	0.22 ± 1.24	0.603 [c]	-1.33 ± 1.08	-1.26 ± 1.32	0.687 [d]
BMIZ (WHO, using CA)	0.01 ± 1.23	-0.09 ± 1.30	0.319	0.14 ± 1.22	0.16 ± 1.23	0.873 [d]	-0.49 ± 1.12	-0.55 ± 1.31	0.710 [c]
HCZ (WHO, using CA)	0.23 ± 1.13	0.21 ± 1.28	0.467	0.37 ± 1.14	0.43 ± 1.15	0.792 [c]	-0.23 ± 0.97	-0.21 ± 1.41	0.595 [c]

[a] *Chi-squared test*
[b] *Fisher's exact test (one or more subgroup n≤5 – interpret with caution)*
[c] *Mann-Whitney U test*
[d] *Independent samples t-test*
AGA = appropriate for gestational age; SGA = small for gestational age; HIV = human immunodeficiency virus; ART = antiretroviral therapy; IG-NBS = INTERGROWTH-21ST Newborn Size Standards; IG-PPGS = INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants; LAZ = length-for-age z-score; WAZ = weight-for-age z-score; HCZ = head circumference for age z-score; WLZ = weight-for-length z-score; BMIZ = body mass index-for-age z-score; WHO = World Health Organization Growth Standards; CA = corrected age.

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Supplementary Table 2: Comparison of selected characteristic of infants included in the study, infants excluded due to early loss to follow-up, and infants excluded due to being discharged from the clinic before 1 year of age

	WHOLE SAMPLE					AGA INFANTS ONLY					SGA INFANTS ONLY				
Characteristic	**0=Lost (N=390)**	**1=D/C <1yr (N=99)**	**2=Included (N=321)**	**P-value**	**Post-hoc**	**0= Lost (N=292)**	**1=D/C <1yr (N=68)**	**2=Included (N=210)**	**P-value**	**Post-hoc**	**0= Lost (N=87)**	**1=D/C <1yr (N=30)**	**2=Included (N=111)**	**P-value**	**Post-hoc**
Sex (m)	208 (53.3%)	52 (52.5%)	158 (49.4%)	0.567 [a]		151 (51.7%)	35 (51.5%)	104 (49.8%)	0.908 [a]		50 (57.5%)	16 (53.3%)	54 (48.6%)	0.465 [a]	
GA (weeks)	33.1 ± 2.5	33.9 ± 1.8	32.8 ± 2.4	<0.001 [b]	2<0, 2<1, 0<1	32.7 ± 2.5	33.7 ± 1.7	32.5 ± 2.4	0.004 [b]	1>0; 1>2	34.4 ± 2.0	34.2 ± 2.0	33.3 ± 2.3	<0.001 [b]	2<0; 2<1
BW (kg)	1.81 ± 0.53	1.85 ± 0.42	1.64 ± 0.49	<0.001 [b]	2<0, 2<1	1.81 ± 0.49	1.94 ± 0.34	1.77 ± 0.46	0.036 [b]	1>0; 1>2	1.63 ± 0.37	1.58 ± 0.40	1.39 ± 0.43	<0.001 [b]	2<0; 2<1
BWZ (IG-NBS)	-0.56 ± 0.95	-0.87 ± 0.87	-0.87 ± 1.04	<0.001 [b]	0<1; 0<2	-0.28 ± 0.59	-0.47 ± 0.54	-0.27 ± 0.60	0.031 [b]	1<0; 1<2	-1.83 ± 0.39	-1.88 ± 0.36	-2.00 ± 0.69	0.703 [b]	
Maternal HIV	117 (30.0%)	28 (28.3%)	69 (21.6%)	0.036 [a]		84 (28.8%)	18 (26.5%)	39 (18.7%)	0.033 [a]		32 (36.8%)	10 (33.3%)	30 (27.0%)	0.333 [a]	
ART initiated				0.425 [c]					0.146 [c]					0.773 [c]	
- Pre-pregnancy	47 (40.2%)	12 (42.9%)	31 (44.9%)			34 (11.6%)	8 (11.8%)	21 (10.0%)			12 (13.8%)	4 (13.3%)	10 (9.0%)		
- During pregnancy	44 (37.6%)	13 (46.4%)	18 (26.1%)			36 (12.3%)	8 (11.8%)	7 (3.3%)			8 (9.2%)	5 (16.7%)	11 (9.9%)		
- After delivery	14 (12.0%)	2 (7.1%)	10 (14.5%)			5 (1.7%)	1 (1.5%)	4 (1.9%)			9 (10.3%)	1 (3.3%)	6 (5.4%)		
- Not recorded	12 (10.3%)	1 (3.6%)	10 (14.5%)			9 (3.1%)	1 (1.5%)	7 (3.3%)			3 (3.4%)	0 (0.0%)	3 (2.7%)		
Infant feeding in KMC															
- Mother's breast milk	377 (96.7%)	96 (97.0%)	313 (97.8%)	0.803 [c]		285 (97.6%)	67 (98.5%)	204 (97.6%)	0.930 [c]		82 (94.3%)	28 (93.3%)	109 (98.2%)	0.235 [c]	
- Donor breast milk	2 (0.5%)	1 (1.0%)	6 (1.9%)	0.222 [c]		(0.0%)	0 (0.0%)	3 (1.4%)	0.137 [c]		2 (2.3%)	1 (3.3%)	3 (2.7%)	>0.999 [c]	
- Breast milk substitute	10 (2.6%)	2 (2.0%)	9 (2.8%)	>0.999 [c]		8 (2.7%)	1 (1.5%)	8 (3.8%)	0.729 [c]		2 (2.3%)	1 (3.3%)	1 (0.9%)	0.470 [c]	
Gravidity	2 (2; 3)	2 (1; 3.75)	2 (2; 3)	0.986 [b]		2 (2; 3)	2 (1; 4)	2 (2; 3)	0.588 [b]		2 (2; 3)	2 (1.25; 3)	2 (1; 3)	0.548 [b]	
Parity	2 (1; 3)	2 (1; 3)	2 (1; 3)	0.430 [b]		2 (1; 3)	2 (1; 3)	2 (1; 3)	0.931 [b]		2 (1; 3)	2 (1; 3)	2 (1; 3)	0.321 [b]	
Maternal age	28.7 ± 6.3	28.5 ± 6.6	29.6 ± 6.7	0.157 [b]		28.5 ± 6.4	28.7 ± 7.0	29.7 ± 6.7	0.112 [b]		29.2 ± 5.6	27.8 ± 5.6	29.4 ± 6.6	0.599 [b]	
Foreign national	121 (31.0%)	18 (18.2%)	79 (24.7%)	0.018 [a]		86 (29.5%)	14 (20.6%)	42 (20.1%)	0.039 [a]	0>1; 0>2	31 (35.6%)	3 (10.0%)	37 (33.3%)	0.018 [c]	
Maternal conditions															
- of placenta, cord, membranes	15 (3.8%)	1 (1.0%)	15 (4.7%)	0.274 [c]		11 (3.8%)	1 (1.5%)	11 (5.3%)	0.424 [c]		4 (4.6%)	0 (0.0%)	4 (3.6%)	0.613 [c]	
- of pregnancy **	94 (24.1%)	24 (24.2%)	79 (24.7%)	0.984 [a]		71 (24.3%)	17 (25.0%)	51 (24.4%)	0.993 [a]		20 (23.0%)	7 (23.3%)	28 (25.2%)	0.930 [a]	
- of labor and delivery	6 (22.1%)	18 (18.2%)	69 (21.6%)	0.700 [a]		69 (23.6%)	13 (19.1%)	54 (25.8%)	0.523 [a]		4 (16.1%)	5 (16.7%)	15 (13.5%)	0.844 [a]	
- medical and surgical	174 (44.6%)	45 (45.5%)	120 (37.5%)	0.120 [a]		128 (43.8%)	28 (41.2%)	75 (35.9%)	0.202 [a]		42 (48.3%)	17 (56.7%)	45 (40.5%)	0.237 [a]	
Infant morbidities *															
- Congenital heart defects	99 (25.4%)	22 (22.2%)	100 (31.2%)	0.110 [a]		74 (25.3%)	15 (22.1%)	54 (25.8%)	0.807 [a]		25 (28.7%)	7 (23.3%)	46 (41.4%)	0.070 [a]	
- Twins	73 (18.7%)	16 (16.2%)	52 (16.2%)	0.647 [a]		54 (18.5%)	11 (16.2%)	32 (15.3%)	0.633 [a]		17 (19.5%)	5 (16.7%)	20 (18.0%)	0.930 [a]	
- Neonatal jaundice	200 (51.3%)	54 (54.5%)	191 (59.7%)	0.081 [a]		150 (51.4%)	41 (60.3%)	129 (61.7%)	0.055 [a]		47 (54.0%)	12 (40.0%)	62 (55.9%)	0.296 [a]	
- Respiratory distress syndrome	235 (60.3%)	44 (44.4%)	179 (55.9%)	0.017 [a]		185 (63.4%)	31 (45.6%)	115 (55.0%)	0.014 [a]	0>1	42 (48.3%)	13 (43.3%)	64 (57.7%)	0.246 [a]	
- Chronic lung disease	13 (3.3%)	2 (2.0%)	19 (5.9%)	0.149 [c]		10 (3.4%)	0 (0.0%)	9 (4.3%)	0.234 [c]		3 (3.4%)	2 (6.7%)	10 (9.0%)	0.319 [c]	
- Infant sepsis	81 (20.8%)	17 (17.2%)	61 (19.1%)	0.682 [a]		60 (20.5%)	11 (16.2%)	35 (16.7%)	0.480 [a]		17 (19.5%)	6 (20.0%)	26 (23.4%)	0.786 [a]	
- Other infant infections	31 (7.9%)	9 (9.1%)	35 (10.9%)	0.392 [a]		22 (7.5%)	7 (10.3%)	23 (11.0%)	0.389 [a]		8 (9.2%)	2 (6.7%)	12 (10.8%)	0.861 [c]	
- Anemia requiring transfusion	25 (6.4%)	3 (3.0%)	29 (9.1%)	0.100 [c]		22 (7.5%)	0 (0.0%)	12 (5.7%)	0.034 [c]		3 (3.4%)	3 (10.0%)	17 (15.3%)	0.017 [c]	
EARLY GROWTH															
LAZ (IG-PPGS)	-1.15 ± 1.49	-1.18 ± 1.64	-1.22 ± 1.72	0.975		-0.92 ± 1.39	-0.89 ± 0.76	-0.52 ± 1.30	0.011	2>0	-2.12 ± 1.29	-2.70 ± 1.16	-2.55 ± 1.63	0.299	
WAZ (IG-PPGS)	-0.65 ± 1.31	-0.42 ± 1.13	-0.56 ± 1.50	0.373		-0.43 ± 1.24	-0.18 ± 0.51	0.07 ± 1.09	<0.001	2>0	-1.58 ± 1.04	-1.57 ± 0.98	-1.74 ± 1.46	0.722	
WAZ change on IG-PPGS	-0.10 ± 1.20	0.23 ± 0.81	-0.23 ± 1.23	0.194		-0.16 ± 1.21	0.17 ± 0.79	-0.37 ± 1.18	0.084		0.22 ± 1.04 4	0.46 ± 1.00	0.02 ± 1.29	0.452	
HCZ on IG-PPGS	0.19 ± 1.40	-0.24 ± 1.34	0.34 ± 1.58	0.093		0.36 ± 1.39	-0.27 ± 1.18	0.94 ± 1.22	<0.001	2>0	-0.58 ± 1.12	-0.86 ± 1.01	-0.82 ± 1.55	0.514	
LAST RECORDED VISIT															
Actual age (days)	111 ± 80	273 ± 77	382 ± 19	<0.001	2>1, 2>0, 1>0	110 ± 79	274 ± 71	383 ± 19	<0.001	0<1; 0<2; 1<2	1185 ± 84	277 ± 83	381 ± 19	<0.001	0<1; 0<2; 1<2
Corrected age (days)	63 ± 78	230 ± 78	332 ± 23	<0.001	2>1, 2>0, 1>0	58 ± 77	230 ± 71	331 ± 23	<0.001	0<1; 0<2; 1<2	78 ± 83	236 ± 86	333 ± 22	<0.001	0<1; 0<2; 1<2
WLZ (WHO)	0.16 ± 1.28	0.30 ± 1.08	-0.16 ± 1.31	<0.001	2<0, 2<1	0.20 ± 1.28	0.45 ± 1.10	0.11 ± 1.24	0.159		-0.07 ± 1.23	-0.03 ± 0.99	-0.66 ± 1.31	0.002	2<0; 2<1
LAZ (WHO, CA)	-1.13 ± 1.39	-0.64 ± 1.24	-0.91 ± 1.16	0.003	1>0	-0.90 ± 1.32	-0.40 ± 1.10	-0.60 ± 1.06	0.003	1-0; 2-0	-1.93 ± 1.19	-1.34 ± 1.17	-1.50 ± 1.11	0.018	2>0
WAZ (WHO, CA)	-0.68 ± 1.36	-0.21 ± 1.10	-0.59 ± 1.36	0.011	1>0, 1>2	-0.46 ± 1.30	0.05 ± 1.06 -	0.22 ± 1.24	0.023	1>0	-1.49 ± 1.13	-0.91 ± 0.84	-1.26 ± 1.32	0.082	
BMIZ (WHO, CA)	-0.06 ± 1.28	0.22 ± 1.05	-0.09 ± 1.30	0.105		0.08 ± 1.24	0.36 ± 1.11	0.16 ± 1.23	0.459		-0.62 ± 1.19	-0.15 ± 0.83	-0.55 ± 1.31	0.091	
HCZ (WHO, CA)	0.20 ± 1.16	0.34 ± 1.05	0.21 ± 1.28	0.512		0.34 ± 1.16	0.48 ± 1.08	0.43 ± 1.15	0.693		-0.31 ± 1.01	-0.03 ± 0.86	-0.21 ± 1.41	0.516	

[a] *Chi-Squared test*
[b] *Kruskall-wallis test*
[c] *Fisher's exact test (one or more subgroup n≤5 – interpret with caution)*

AGA = appropriate for gestational age; SGA = small for gestational age; HIV = human immunodeficiency virus; ART = antiretroviral therapy; IG-NBS = INTERGROWTH-21ST Newborn Size Standards; IG-PPGS = INTERGROWTH-21ST Postnatal Growth Standards for Preterm Infants; LAZ = length-for-age z-score; WAZ = weight-for-age z-score; HCZ = head circumference for age z-score; WLZ = weight-for-length z-score; BMIZ = body mass index-for-age z-score; WHO = World Health Organization Growth Standards; CA = corrected age.

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BRIDGING TEXT

The preceding paper clearly demonstrates that SGA preterm infants are, on average, more likely to remain undernourished (underweight, stunted, wasted) at one year of age than their AGA counterparts. This occurred even though SGA infants, on average, had greater gains in weight-for-GA z-scores over the first year of life, suggesting that catch-up growth was occurring, but may be incomplete. It is unsurprising that infants with a low BWZ (many of whom would have a similarly low birth length z-score) remain smaller throughout infancy; however, the lower mean WLZ and higher rate of wasting among SGA infants suggest that weight and length growth may not be proportionate.

The observed predictive relationship between SGA and undernutrition was not perfect: a significant proportion of SGA infants did catch up to normal size, while others remained small. Likewise, whilst most AGA infants maintained normal anthropometric status, a portion of AGA infants had faltering growth to the point that they were underweight, stunted and/ or wasted at one year. This was supported by the multivariable analysis, where birth weight z-scores were a stronger predictor of undernutrition than SGA, suggesting that a decrease in birth weight z-score predisposed even AGA infants to poor growth.

Of course, numerous factors influence an infant's growth in the first year of life, including nutrition and episodes of illness. While the available data was not granular enough to examine these effects in any detail, early growth (which can be considered the nett effect of all these influences over the preceding weeks/ months of an infant's life) was investigated. Early weight growth – operationalised as the change in weight-for-PMA z-score up to 50 weeks PMA – was found to be significantly associated with underweight, stunting, and overweight. This underscores the important mediating effect of intervening growth patterns. The use of a single interval, while it is an improvement over only a single measurement, still only gives limited detail on the overall growth pattern. This dataset contained a median of 9 (IQR 8-10) measurements per infant. Including all these measurements would allow for a more nuanced and complete assessment of these infants' growth.

Latent Class Trajectory Modelling techniques provide a meaningful way to analyses large groups of trajectory data. These methods rely on automated pattern recognition to group individual trajectories into a limited number of typical representative trajectories. For example, among a large group of children there may be sub-groups that display consistent growth, faltering growth and catch-up growth. Latent class trajectory modelling techniques can identify these typical trajectories and assign each individual trajectory to the group it most closely resembles. These representative trajectories can then be analysed as outcome or exposure variables, to determine which factors predict certain trajectories, as well as

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which trajectories are more likely to result in outcomes of interest. The next paper describes such an analysis of cohort 1, the premature infants.

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CHAPTER 6: FOURTH MANUSCRIPT: First-year growth trajectories of preterm infants receiving kangaroo mother care, and their relationships to early life predictors and anthropometric outcomes

MANUSCRIPT FOR SUBMISSION

First-year growth trajectories of preterm infants receiving kangaroo mother care, and their relationships to early life predictors and anthropometric outcomes

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RESEARCH SNAPSHOT

Research question: What are characteristic first-year growth trajectories in preterm infants, and which early-life factors predict growth trajectories that are associated with malnutrition at one year?

Key findings: Preterm infants in this historical cohort displayed various first-year growth trajectories, identified using latent class trajectory modelling, including catch-up (increasing z-score) and faltering (decreasing z-score). Lower birth weight z-scores were associated with weight-for-age catch-up, length-for-age catch-up, and weight-for-length faltering. Smaller weight-for-age z-score gains up to 50 weeks postmenstrual age were associated with weight-for-age and length-for-age faltering. Weight-for-age, weight-for-length and length-for-age faltering trajectories were associated with higher rates of underweight, stunting and wasting at one year.

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ABSTRACT

Background: Longitudinal growth of South African preterm infants is inadequately described.

Objective: To characterize first-year growth trajectories in preterm infants, and investigate associations with early-life predictors and one-year anthropometry.

Design: Historical cohort.

Participants/setting: Clinic records of 322 preterm infants followed up for one year after kangaroo mother care discharge at a South African tertiary hospital (Tshwane District, Gauteng Province).

Outcome measures: Characteristic first-year trajectories of weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), and head circumference-for-age (HCZ) z-scores, calculated using Fenton Growth Chart (up to 50 weeks postmenstrual age (PMA50)) and WHO Growth standards (age-corrected). Underweight (WAZ<-2), stunting (LAZ<-2), wasting (WLZ<-2) and overweight (BMI-for-age z-score>+2) at one year.

Statistical analyses: Latent class trajectory modelling characterized WAZ, LAZ, WLZ and HCZ trajectories. Multivariable analysis determined odds ratios (ORs) for early life predictors (maternal/infant factors, birth weight, WAZ gain up to PMA50) of growth trajectories. Per-trajectory rates of underweight, stunting, wasting and overweight were compared (Chi-squared/Fisher's Exact tests).

Results: Best-fit models identified three WAZ and LAZ trajectories (faltering, gradual gain, catch-up), two WLZ trajectories (faltering, gain) and two HCZ trajectories (maintenance, gain).

Lower birth weight z-score (BWZ) increased odds of LAZ catch-up (OR:8.33(3.13-20.00)), WLZ faltering (OR:1.69(1.11-2.70)) and HCZ gain (OR:1.92(1.23-3.13)), but lowered odds of gradual WAZ gain (OR:0.36(0.19-0.68)) and WAZ faltering (OR:0.56(0.34-0.92)). Smaller WAZ gain up to PMA50 was associated with gradual WAZ gain (OR:2.27(1.56-3.33)), WAZ faltering (OR: 1.47(1.11-1.96)), LAZ catch-up (OR:1.85(1.25,2.70)), LAZ faltering (OR:1.39(1.09-1.75)). WAZ and WLZ faltering were associated with higher underweight (49.1%,22.4%), stunting (45.5%,23.5%) and wasting (21.8%,10.3%) rates, while WAZ catch-up and WLZ gain were associated with overweight (24.4%,17.6%). Gradual LAZ gain was

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associated with the least underweight (2.0%), stunting (2.1%) and wasting (2.1%, all P<0.001).

Conclusions: Preterm infants display various first-year growth trajectories. Lower BWZ was associated with catch-up growth, while smaller early WAZ gains were associated with growth faltering.

INTRODUCTION

Preterm infants (born before 37 completed weeks of gestation) and infants born small for gestational age (SGA) typically exhibit different growth patterns in childhood compared to their term-born, appropriate for gestational age (AGA) counterparts. Various growth outcomes have been described at different ages, depending on socioeconomic context and neonatal size. Preterm infants from low-and-middle income countries (LMICs)[1-3], where nutritional and socioeconomic deprivation is common, generally have less catch-up growth and higher rates of stunting, wasting and underweight throughout childhood than their high-income country (HIC) peers[4-7]. Preterm infants born SGA are likewise more likely to have persistent anthropometric deficits than those born AGA, in LMICs and HICs alike[2,5-8].

Growth is best described as a change in an anthropometric parameter over time[9]. Most simply, growth can be quantified as the difference in a measured value (or an associated z-score) between two time points. This can be further refined by expressing growth in terms of the baseline parameter (e.g. g/kg), time (e.g. g/day) or both (e.g. g/kg/day), though the calculations can be complex and there is little agreement on the best method to use[10]. In clinical practice, consecutive measurements are usually plotted on a sex-specific growth chart and the individual's growth curve compared to the shape of the reference curves, which run at consistent percentiles or z-score values. A healthy child's growth curve is expected to run parallel to the reference curves – or, in statistical terms, to maintain an approximately constant z-score over time – though there are situations where the z-score may vary more widely[9]. Assessing growth by considering only the first and last measurement disregards the growth patterns in the interim period, a loss of potentially important data.

Latent class trajectory modelling techniques allow researchers to visualize longitudinal data within a heterogenous population by grouping together trajectories that share similar traits[11-13]. In this way, the growth trajectories of a group of infants can be simplified to a few (usually 2-4) representative trajectories, with each individual infant assigned to the trajectory that best matches their growth data[12-14]. Latent class trajectory modelling has been used to investigate several growth outcomes in the published literature, including linear growth

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patterns and their relationship to stunting[15], relationships between linear and ponderal growth[16], childhood body mass index (BMI) trajectories and their associated determinants and outcomes[17], and fetal growth trajectories in relation to various outcomes[18,19]. Group-based trajectory analysis of the postnatal growth of preterm infants, however, remains an under-researched area.

This research primarily aimed to characterize the latent growth trajectories of weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ) and head circumference-for age (HCZ) z-scores during the first year of life in a cohort of South African preterm infants who received kangaroo mother care (KMC) during early life. Additionally, the relationships of these growth trajectories to selected early-life predictors (including maternal, pregnancy and neonatal conditions, size at birth and early growth according to the change in weight z-score up to 50 weeks postmenstrual age (PMA)) and anthropometric outcomes at one year were investigated.

METHODS

Sample selection

In this historical cohort study, we analyzed existing infant records from the KMC post-discharge clinic at a tertiary academic hospital situated in a low-income peri-urban area in in Tshwane District (Gauteng Province, South Africa). Records were selected systematically and reverse chronologically, starting from December 2018 and working backward until sufficient sample size was reached. Eligible infants were born preterm (<37 weeks gestational age (GA)) with a known birth weight and GA and had at least one year of follow-up anthropometric measurements; infants with major anatomic or genetic abnormalities were excluded. Sampling was deliberately weighted to include SGA infants above the rate of population prevalence: *a priori* power calculations indicated that 130 each of SGA and AGA infants would be sufficient. This necessitated including records of all SGA infants dating back to the clinic's inception in 2012, whilst records from 2018-2016 provided ample AGA infants. Hospital and clinic policies relating to infant feeding (including feeding advice given to mothers) and clinical care remained essentially unchanged during this time, and all infants received comparable care. The same anthropometric equipment was used throughout, professionally calibrated biannually.

Data collection

Paper-based clinic records were created by the physician and dietitian in charge of the clinic. Birth data were transcribed from the maternity records. Birth weight was measured in the

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maternity unit using electronic infant scales, and the GA was confirmed using the Ballard score if pregnancy dates were uncertain.

Follow-up anthropometry was done by a single hospital dietitian following clinic protocols. Weight was measured naked, to 0.01 kg, using electronic infant scales (Seca 354; Seca GmbH & Co. KG, Hamburg, Germany; serviced and calibrated biannually). Length was measured to the nearest 0.1 cm using a rigid wooden measuring board (with fixed headboard and moveable right-angled footpiece) placed on a hard, level tabletop. Head circumference was measured to 0.1 cm using a flexible, non-elastic measuring tape. Information on infant feeding was collected by the dietitian, and medical examinations were performed and recorded by the pediatrician.

Data were captured in Excel spreadsheets in duplicate and checked for discrepancies using EpiInfo v3.5.1 (2008, CDC, Washington DC, USA). Maternal and infant sociodemographic and health status information, birth data and follow-up anthropometric measurements were recorded.

Chronological, postmenstrual and corrected ages at each visit were calculated in days. Chronologic age was calculated automatically by subtraction of dates, and PMA was calculated as the sum of GA at birth and chronologic age. For corrected age number of days of prematurity (i.e. 280 days minus GA at birth) was subtracted from chronologic age.

Birth weight z-score (BWZ) and percentile were calculated using the Fenton 2013 Growth Chart online calculator (https://ucalgary.ca/resource/preterm-growth-chart/calculators) and classified as SGA (<10th percentile), AGA (10th-90th percentile, inclusive) or LGA (>90th percentile). Postnatal z-scores for weight, length, and head circumference were calculated using the Fenton Growth Chart up to 50 weeks PMA. The change in weight-for-PMA z-score from birth to the final measurement recorded on the Fenton Growth Chart (i.e. up to 50 weeks PMA) was used as an estimate of early growth. Birth weight z-score, birth weight class and early growth were included in multivariable analysis as early-life predictors of growth trajectories. The WHO Growth standards (using WHO Anthro: http://www.who.int/childgrowth/software/en/) were used to calculate WAZ, LAZ, WLZ and HCZ from 50 weeks PMA to one year, using corrected age. At the final visit, infants were classified as underweight (WAZ<-2), stunted (LAZ<-2), wasted (WLZ<-2), and overweight (BMIZ>+2).

Data analysis

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All analyses were performed with R (version 4.1.2, 2020; R Foundation for Statistical Computing, Vienna, Austria). All trajectories were plotted as anthropometric z-scores (y-axis) against PMA (x-axis). The analysis was delimited to measurements at PMA 200-650 days, and to infants with three or more data points.

Initially trajectories were plotted per infant for obvious outliers or extreme observation identification. For WAZ, LAZ and HCZ, z-scores from the Fenton Growth Chart (up to 50 weeks PMA) were combined with age-corrected z-scores according to the WHO Growth Standards (from 50 weeks PMA to one year)[20]. For WLZ, only the WHO Growth Standards were used, starting from 40 weeks PMA.

Latent trajectories were identified using both Latent Class Growth Analysis (LCGA) and Growth Mixture Modelling (GMM) approaches, as described by Herle *et al*[12]. For each analysis, models identifying two to four classes were considered. The LCGA models were built with a fixed intercept and slope per class, while the GMM models were built incorporating a random intercept per class, and incorporating both a random intercept and random slope per class. Link functions were also included in the GMM models to investigate non-linear effects of trajectories. Residual plots were visually inspected for bias in the model, and the relative entropy calculated (with a value >0.5 considered acceptable). The fit of each modelled trajectory was assessed individually as described by Lennon et al[11]; models were excluded if any trajectory had an Average of maximum Posterior Probabilities of Assignment (APPA) <0.7, an Odds of Correct Classification (OCC) <5.0, or included <10% of the total sample. After excluding models that did not meet the aforementioned criteria, the lowest Bayesian Information Criterion (BIC) was used to identify the best fitting model for each anthropometric index, and those models were used for further investigations. After assigning individual infants to modelled trajectory groups, the mean trajectories (with 95% CIs) of the actual z-scores were plotted.

Maternal and infant early-life exposures (maternal age, gravidity, parity, HIV infection, timing of ART initiation, maternal health conditions during pregnancy, infant sex, GA at birth, BWZ, SGA/ AGA status, infant congenital heart conditions, multiple gestation and early change in weight z-score) were investigated as predictors of trajectory group membership. Variables with significant associations with trajectory group membership were incorporated in multiple regression models. The associations between trajectory group membership and malnutrition outcomes at one year (underweight, stunting, wasting and overweight) were investigated using frequency distributions and the Chi Squared (Fisher's Exact for smaller groups) test.

Ethical and legal considerations

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Approval to conduct the study was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (Protocol 227-2021) and the hospital (KPTH 23/2021). All data were processed anonymously.

RESULTS

Sample description

The study sample included 322 infants with 4-16 visits (median 9, IQR 8-10) each, providing 2925 data points for weight, 1929 each for length and HC, and 1583 measurements at ≥40 weeks PMA that could be included in the WLZ analysis. Table 1 describes the sample infants and their mothers (N=302, excluding 20 duplicate records of mothers of 40 twin infants). Mothers had an average age of 29.5 ± 6.6 years, with 26.0% aged ≥35 years. Maternal HIV infection was present in 20.9% of mothers, of whom 15.9% did not receive antiretroviral treatment during pregnancy; none of the infants in the sample contracted HIV. Infants had a mean GA of 32.8 ± 2.4 weeks and mean BWZ of -0.77 ± 0.96, with 32.0% of infants being SGA due to deliberate over-sampling. Non-critical congenital heart conditions were present in 100 infants (including 65 patent ducti arteriosus, 47 patent foramen ovale and 8 ventricular/ atrial septum defects), of whom only one required surgical intervention. At one year, mean WAZ and LAZ remained well below zero, while WLZ and BMIZ were close to zero. Rates of underweight (15.2%) and stunting (17.8%) were higher than those of wasting (6.9%) and overweight (6.5%).

Table 1: Maternal and infant characteristics at birth and one year

Characteristic	N	Value
Maternal characteristics [a]		
Maternal age (years) [Mean ± SD]	285	29.5 ± 6.6
Adolescent: age ≤19 years [n (%)]		18 (6.3)
Advanced maternal age: ≥35 years [n (%)]		74 (26.0)
Gravidity (number of pregnancies) [median (IQR)]	285	2 (2; 3)
Primigravida, Gravidity=1 [n (%)]		97 (34.0)
Parity (number of pregnancies carried to viable gestational age) [median (IQR)]	285	2 (1; 3)
Primipara, Parity=1 [n (%)]		66 (23.2)
Maternal HIV infection [n (%)]	302	63 (20.9)
Received ART during pregnancy	63	44 (69.8)
No ART during pregnancy		10 (15.9)
ART not recorded		9 (14.3)
Maternal conditions during pregnancy [b] [n (%)]	302	
Conditions of the placenta, cord, membranes		13 (4.3)
Pregnancy conditions		60 (19.9)
Labor and delivery conditions		64 (21.2)
Medical and surgical conditions		114 (37.7)
Infant characteristics at birth		
Infant sex (male) [n (%)]	322	160 (49.7)

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Characteristic	N	Value
Gestational age (weeks) [Mean ± SD]	322	32.8 ± 2.4
Birth weight (kg) [Mean ± SD]	322	1.65 ± 0.50
Birth weight z-score [c] [Mean ± SD]		-0.77 ± 0.96
SGA [d] [n (%)]		103 (32.0)
Infant is one of a set of twins [n (%)]	322	53 (16.5)
Infant congenital heart conditions [e] [n (%)]	322	100 (31.1)
Infant characteristics at one year		
Chronological age (months) [Mean ± SD]	322	12.55 ± 0.63
Corrected age (months) [Mean ± SD]	322	10.90 ± 0.75
Still breastfeeding at last visit [n (%)]	322	184 (57.1)
Change in WAZ from birth to ≤ 50 weeks PMA[c] [Mean ± SD]	320	-0.10 ± 1.14
Weight (kg) [Mean ± SD]	322	8.58 ± 1.43
Weight-for-age z-score [f] [Mean ± SD]	322	-0.56 ± 1.36
Weight-for-length z-score [f] [Mean ± SD]	321	-0.13 ± 1.31
BMI-for-age z-score [f] [Mean ± SD]	321	-0.07 ± 1.29
Length (cm) [Mean ± SD]	321	71.35 ± 3.01
Length-for-age z-score [f] [Mean ± SD]	321	-0.89 ± 1.17
Head circumference (cm) [Mean ± SD]	322	45.40 ± 1.77
HC-for-age z-score [f] [Mean ± SD]	322	0.22 ± 1.28
Indicators of malnutrition [n (%)]		
Underweight: Weight-for-age z-score [f] <-2	322	49 (15.2)
Stunted: Length-for-age z-score [f] <-2	321	57 (17.8)
Wasted: Weight-for-length z-score [f] <-2	321	22 (6.9)
Overweight: BMI-for-age z-score [f] >+2	321	21 (6.5)

[a] 20 duplicate records of mothers of twins removed: thus N=302 mothers.
[b] Maternal conditions classified according to WHO ICD10-PM categories[38]. Conditions of labor and delivery only includes conditions other than preterm delivery, as preterm birth was an inclusion criterion for the study.
[c] Calculated using the Fenton 2013 Growth Chart[20]
[d] SGA = small-for-gestational age: birth weight <10th percentile.
[e] Includes patent ductus arteriosus (n=65), patent foramen ovale (n=47) and ventricular/ atrial septum defects (n=8).
[f] Z-scores calculated according to the WHO Growth Standards, using corrected age.
Abbreviations: ART = antiretroviral therapy; BMI = body mass index, HC = head circumference; HIV = human immunodeficiency virus; SGA = small-for-gestational age; WAZ = weight-for-age z-score.

Growth Trajectories, early-life predictors and associated outcomes

In all cases, the best trajectory models were achieved using GMM incorporating a random intercept per class, incorporating a link function for HCZ but not for WAZ, LAZ or WHZ. The models and plots of actual data are shown in Figure 1. Characteristics of the infants in each trajectory group can be found in Table 2.

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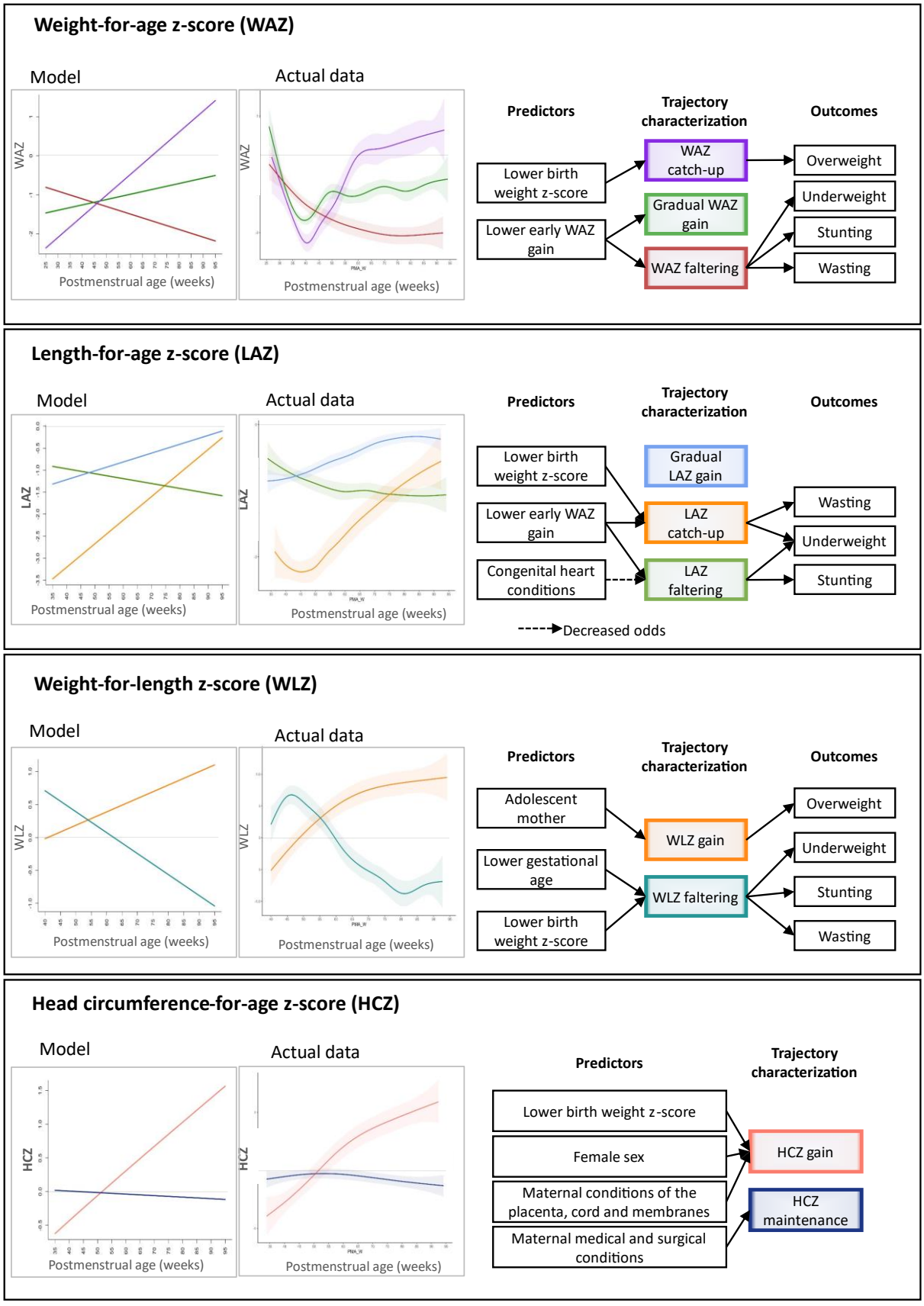

Figure: Anthropometric z-score trajectories (modelled using Growth Mixture Models and plotted using actual sample data) and their associations with early-life predictors and one-year outcomes

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Table 2: Characteristics of infants displaying different growth trajectories

	Trajectory characterizations per growth index z-score									
	Weight-for-age (WAZ)			Length-for-age (LAZ)			Weight-for-length (WLZ)		HC-for age (HCZ)	
	Faltering (N=55)	Gradual gain (N=184)	Catch-up (N=83)	Faltering (N=124)	Gradual gain (N=147)	Catch-up (N=51)	Faltering (N=214)	Gain (N=108)	Maintenance (N=235)	Catch-up (N=87)
Maternal characteristics										
Maternal age (years) [mean ± SD] (N=285)	30.8 ± 7.2	29.4 ± 6.4	28.8 ± 6.5	29.1 ± 6.6	30.2 ± 6.6	28.3 ± 6.6	29.8 ± 6.5	28.9 ± 6.8	29.8 ± 6.6	28.6 ± 6.5
▪ Adolescent (≤19 years) [n (%)]	3/52 (5.8)	8/159 (5.0)	7/74 (9.5)	9/113 (7.9)	6/131 (4.6)	3/41 (7.3)	7/190 (3.7)	11/95 (11.6)	13/214 (6.1)	5/71 (6.9)
▪ Normal/ low risk (20-34 years) [n (%)]	32/52 (61.5)	110/159 (69.2)	51/74 (68.9)	79/113 (69.3)	84/131 (64.6)	30/41 (73.2)	130/190 (68.4)	63/95 (66.3)	141/214 ((66.2)	52/71 (72.2)
▪ Advanced (≥35 years) [n (%)]	17/52 (32.7)	411/59 (25.8)	16/74 (21.6)	26/113 (22.8)	40/131 (30.8)	8/41 (19.5)	53/190 (27.9)	21/95 (22.1)	59/214 ((27.7)	15/71 (20.8)
Parity [median (IQR)] (N=285)	2 (1.75; 3)	2 (1; 3)	2 (1; 3)	2 (1; 3)	2 (1;3)	2 (1; 2)	2 (1;3)	2 (1;3)	2 (1; 3)	2 (1; 3)
▪ Primipara, P=1 [n (%)]	13/52 (25.0)	58/159 (36.5)	26/74 (35.1)	38/113 (33.6)	43/131 (32.8)	16/41 (39.0)	63/190 (33.2)	34/95 (35.8)	40/214 (32.7)	27/71 (38.0)
Gravidity [median (IQR)] (N=285)	2 (2; 4)	2 (2; 3)	2 (1; 3)	2 (2; 3)	3 (2; 3)	2 (1; 3)	2 (2;3)	2 (1;3)	2 (2; 3)	2 (1; 3)
▪ Primigravida, G=1 [n (%)]	9/52 (17.3)	37/159 (23.3)	20/74 (27.0)	25/113 (22.1)	29/131 (22.1)	12/41(29.3)	37/190 (19.5)	29/95 (30.5)	44/214 (20.6)	22/71 (31.0)
Maternal HIV infection [n (%)]	10 (18.2)	42 (22.8)	11 (13.2)	24 (19.4)	30 (20.4)	9 (17.6)	46 (21.5)	17 (15.9)	49 (20.9%)	14 (16.1%)
▪ ART in pregnancy	8 (80.0)	29 (69.0)	7 (63.6)	16 (66.7)	20 (66.7)	8 (88.9)	35 (76.1)	9 (52.9)	35 (71.4)	9 (64.3)
▪ no ART in pregnancy	2 (20.0)	7 (16.7)	1 (9.1)	7 (29.2)	2 (6.7)	1 (11.1)	8 (17.4)	2 (11.8)	8 (16.3)	2 (14.3)
▪ ART timing not recorded	0	6 (14.3)	3 (27.3)	1 (4.2)	8 (26.7)	0	3 (6.5)	6 (32.3)	6 (12.2)	3 (21.4)
Maternal conditions [a] [n (%)]										
▪ ... of placenta, cord, membranes	0	9 (4.9)	4 (4.8)	6 (4.8)	5 (3.4)	2 (3.9)	6 (2.8)	7 (6.5)	5 (2.1)	8 (9.2)
▪ ... of pregnancy	8 (14.5)	37 (20.1)	15 (18.1)	18 (14.5)	32 (21.8)	10 (19.6)	40 (18.7)	20 (18.5)	43 (18.3)	17 (19.5)
▪ ... of labor and delivery	11 (20.0)	37 (20.1)	16 (19.3)	26 (21.0)	31 (21.1)	7 (13.7)	45 (21.0)	19 (17.6)	46 (19.6)	18 (20.7)
▪ Medical and surgical conditions	22 (40.0)	69 (37.5)	23 (27.7)	46 (37.1)	56 (38.1)	12 (23.5)	81 (37.9)	33 (30.6)	92 (39.1)	22 (25.3)
Infant characteristics										
Sex (male) [n (%)]	34 (61.8)	87 (47.3)	39 (47.0)	69 (55.6)	69 (46.9)	22 (43.1)	110 (51.4)	50 (46.3)	126 (53.6)	34 (39.1)
Gestational age (weeks) [mean ± SD]	32.3 ± 2.8	32.7 ± 2.4	33.2 ± 2.1	33.1 ± 2.4	32.7 ± 2.3	32.2 ± 2.5	32.6 ± 2.4	33.2 ± 2.3	32.7 ± 2.5	33.1 ± 2.1
Birth weight z-score [b] [mean ± SD]	-0.45 ± 1.01	-0.70 ± 0.90	-1.14 ± 0.94	-0.52 ± 0.90	-0.62 ± 0.77	-1.82 ± 0.92	-0.98 ± 1.12	-0.57 ± 0.96	-0.65 ± 0.92	-1.11 ± 0.97
SGA [c] [n (%)]	14 (25.5)	52 (28.3)	37 (44.6)	26 (21.0)	38 (25.9)	39 (76.5)	85 (39.7)	26 (24.1)	65 (27.7)	38 (43.7)
Infant is one of a set of twins [n (%)]	6 (10.9)	33 (17.9)	14 (16.9)	13 (10.5)	30 (20.4)	10 (19.6)	34 (15.9)	19 (17.6)	38 (16.2)	15 (17.2)
Any congenital heart condition [d] [n (%)]	15 (27.3)	58 (31.5)	27 (32.5)	19 (15.3)	52 (35.4)	29 (56.9)	74 (34.6)	26 (24.1)	66 (28.1)	34 (39.1)
Early WAZ gain on FGC [mean ± SD]	-0.63 ± 1.01	-0.09 ± 1.04	0.25 ± 1.30	-0.10 ± 0.99	0.12 ± 1.15	-0.72 ± 1.25	-0.17 ± 1.21	-0.37 ± 1.26	-0.08 ± 1.16	-0.14 ± 1.11

[a] Maternal conditions classified according to WHO ICD10-PM categories[38]. Conditions of labor and delivery only includes conditions other than preterm delivery, as preterm birth was an inclusion criterion for the study.

[b] Calculated using the Fenton 2013 Growth Chart[20].

[c] SGA = small-for-gestational age: birth weight <10th percentile on the Fenton Growth Chart.

[d] Includes patent ductus arteriosus (n=65), patent foramen ovale (n=47) and ventricular/ atrial septum defects (n=8).

[e] Anthropometric z-scores calculated according to the WHO Growth Standards, using corrected age

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	Trajectory characterizations per growth index z-score									
	Weight-for-age (WAZ)			Length-for-age (LAZ)			Weight-for-length (WLZ)		HC-for age (HCZ)	
	Faltering (N=55)	Gradual gain (N=184)	Catch-up (N=83)	Faltering (N=124)	Gradual gain (N=147)	Catch-up (N=51)	Faltering (N=214)	Gain (N=108)	Maintenance (N=235)	Catch-up (N=87)
Abbreviations: FGC = Fenton growth chart; HIV = human immunodeficiency virus; ART = antiretroviral therapy; SGA = small-for-gestational age; WAZ = weight-for-age z-score; LAZ – length-for-age z-score; WLZ = weight-for-length z-score; BMIZ = body mass index-for-age z-score.										

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Table 3: Association of prenatal, perinatal and early-life factors with growth trajectories: odds ratios calculated by univariate and multivariate analysis

WEIGHT-FOR-AGE Z-SCORE (WAZ)				
Baseline comparator: WAZ catch-up	**Odds (95%CI) of WAZ faltering**		**Odds (95%CI) of gradual WAZ gain**	
	Univariate analysis	Multivariate model	Univariate analysis	Multivariate model
Lower gestational age at birth (per 1 week decrease)	1.19 (1.03. 1.37) *	NS	NS	NS
Lower birth weight z-score [a] (per 1 z-score decrease)	0.45 (0.43. 0.40) ***	0.36 (0.19. 0.68) **	0.61 (0.83. 0.81) ***	0.56 (0.53. 0.92) *
SGA [b]	0.42 (0.20, 0.89) *	NS	0.49 (0.29, 0.84) **	NS
Lower early WZ gain [c] (per 1 z-score decrease)	2.04 (1.47. 2.86) ***	2.27 (1.56. 3.33) ***	1.33 (1.05. 1.72) *	1.47 (1.11. 1.96) **
	Model R^2: 0.072			
LENGTH-FOR-AGE Z-SCORE (LAZ)				
Baseline comparator: Gradual LAZ gain	**Odds (95%CI) of LAZ faltering**		**Odds (95%CI) of LAZ catch-up**	
	Univariate analysis	Multivariate model	Univariate analysis	Multivariate model
Lower birth weight z-score [a] (per 1 z-score decrease)	NS	NS	6.25 (3.45. 11.11) ***	8.33 (3.13. 20.00) ***
SGA [b]	NS	NS	9.32 (4.42, 19.63) ***	NS
Infant is one of a set of twins	0.46 (0.23, 0.92) *	NS	NS	NS
Any congenital heart condition	0.33 (0.18, 0.60) ***	0.28 (0.14, 0.53) ***	2.41 (1.26, 4.61) **	NS
Lower early WZ gain [c] (per 1 z-score decrease)	NS	1.39 (1.09. 1.75) ***	1.96 (1.45. 2.63) ***	1.85 (1.25. 2.70) **
	Model R^2: 0.193			
WEIGHT-FOR-LENGTH Z-SCORE (WLZ)				
Baseline comparator: WLZ gain	**Odds (95%CI) of WLZ faltering**			
	Univariate analysis		Multivariate model	
Maternal age group: adolescent	0.31 (0.11, 0.82) *		0.27 (0.09, 0.76) *	
Maternal gravidity >1	1.82 (1.03, 3.20) *		NS	
Lower gestational age at birth (per 1 week decrease)	1.12 (1.01. 1.25) *		1.19 (1.05. 1.33) **	
Lower birth weight z-score [a] (per 1 z-score decrease)	1.54 (1.19. 2.00) *		1.69 (1.11. 2.70) *	
SGA [b]	2.05 (1.22, 3.54) **		NS	
	Model R^2: 0.070			
HEAD CIRCUMFERENCE-FOR-AGE Z-SCORE (HCZ)				
Baseline comparator: HCZ maintenance	**Odds (95%CI) of HCZ catch-up**			
	Univariate analysis		Multivariate model	
Maternal conditions of placenta, cord, membranes [d]	4.66 (1.51, 15.81) **		5.70 (1.80, 19.87) ***	
Maternal medical and surgical conditions [d]	0.53 (0.30, 0.90) *		0.49 (0.27, 0.86) *	
Female sex	1.79 (1.10. 3.03) *		1.85 (1.09. 3.13) *	
Lower birth weight z-score [a] (per 1 z-score decrease)	1.69 (1.30. 2.27) ***		1.92 (1.23. 3.13) **	
SGA [b]	1.99 (1.19, 3.32) **		NS	

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	Model R^2: 0.095

** p<0.05; ** p<0.01; *** p<0.001.*

[a] Calculated using the Fenton 2013 Growth Chart[20].

[b] SGA = small-for-gestational age: birth weight <10th percentile on the Fenton Growth Chart.

[c] Change in weight z-score from birth to ≤ 50 weeks PMA, using the Fenton growth chart.

[d] Maternal conditions classified according to WHO ICD10-PM categories[38]. Conditions of labor and delivery only includes conditions other than preterm delivery, as preterm birth was an inclusion criterion for the study.

NS: not significant. Odds ratios are only shown for variables with significant associations.

Variables included in all the analyses: Maternal age; maternal age category (adolescent ≤19 yrs, low risk 20-34 years, advanced ≥35 years); parity; gravidity; maternal HIV infection; timing of ART initiation for mothers with HIV (ART during pregnancy vs. no ART during pregnancy); maternal conditions of the placenta, cord and membranes; maternal conditions of pregnancy; maternal conditions of labor and delivery (other than preterm delivery); maternal medical and surgical conditions, infant sex; gestational age at birth; birth weight z-score; SGA, birth weight <10th percentile; vs. not SGA, birth weight ≥10th percentile); infant is one of a set of twins; infant has a congenital heart condition; early WZ gain (change in weight-for-GA z-score from birth to the last measurement before 50 weeks PMA, calculated using the Fenton 2013 growth chart).

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For WAZ, a three-class model fit the data best, with three distinct trajectories showing gradual WAZ gain (n=184, 57.1%), WAZ catch-up (n=83, 25.8%) and WAZ faltering (n=55, 17.1%). Although the model describes linear trajectories, the actual data consistently showed initial WAZ loss followed by varying degrees of WAZ regain. The WAZ catch-up trajectory fell steeply up to approximately term (40 weeks PMA), followed by a rapid increase up to the BWZ at approximately 60 weeks PMA (equivalent to 4.5 months CA), with gradual WAZ increase thereafter. The gradual WAZ gain trajectory reached a nadir at approximately term, followed by WAZ increasing up to approximately 50 weeks PMA (10 weeks CA) and plateauing thereafter. The WAZ faltering trajectory showed a WAZ decrease up to approximately 70 weeks PMA (7 months CA), plateauing at a low WAZ thereafter. In multivariable analysis (Table 3), compared to WAZ catch-up, the odds of gradual WAZ gain and WAZ faltering were significantly increased by smaller early WAZ gains (OR 2.27 (1.56. 3.33) and 1.47 (1.11. 1.96) per 1 z-score decrease), but their odds were reduced with lower BWZ (OR 0.36 (0.46. 0.40) and 0.56 (0.53. 0.92) per 1 z-score increase), implying that higher BWZ predicts slow WAZ gain. The WAZ faltering trajectory was associated with the highest rates of underweight (49.1%), stunting (45.5%) and wasting (21.8%) at 1 year, while all but one of the overweight infants belonged to the WAZ catch-up trajectory (24.4%, all p<0.001) (Table 4).

Table 4: Association between different growth trajectories and indicators of malnutrition at one year (N=322)

Growth trajectories		**Indicators of malnutrition**			
	N	**Underweight (WAZ <-2) n (%)**	**Stunted (LAZ <-2) n (%)**	**Wasted (WLZ <-2) n (%)**	**Overweight (BMIZ >+2) n (%)**
WEIGHT-FOR-AGE (WAZ)					
WAZ catch-up	83	4 (4.8)	4 (4.9)	3 (3.7)	20 (24.4)
Gradual WAZ gain	184	18 (9.8)	28 (15.2)	7 (3.8)	1 (0.5)
WAZ faltering	55	27 (49.1)	25 (45.5)	12 (21.8)	0
p-value		**<0.001** [a]	**<0.001** [a]	**<0.001** [a]	**<0.001** [a]
LENGTH-FOR-AGE (LAZ)					
LAZ catch-up	51	15 (29.4)	12 (23.5)	9 (17.6)	2 (3.9)
Gradual LAZ gain	147	3 (2.0)	3 (2.1)	3 (2.1)	14 (9.6)
LAZ faltering	124	31 (25.0)	42 (33.9)	10 (8.1)	5 (4.0)
p-value		**<0.001** [a]	**<0.001** [a]	**<0.001** [a]	**0.1616** [a]
WEIGHT-FOR-LENGTH (WLZ)					
WLZ gain	108	1 (0.9)	6 (5.6)	0 (0.0)	19 (17.6)
WLZ faltering	214	48 (22.4)	51 (23.9)	22 (10.3)	2 (0.9)
p-value		**<0.001** [a]	**<0.001** [b]	**<0.001** [a]	**<0.001** [a]
HC-FOR-AGE (HCZ)					
HCZ maintenance	235	40 (17.0)	45 (19.2)	19 (8.1)	8 (3.4)
HCZ catch-up	87	9 (10.3)	12 (13.8)	3 (3.4)	13 (14.9)
p-value		**0.139** [b]	**0.257** [b]	**0.2135** [a]	**0.237** [b]
[a] *Fisher's Exact Test*					

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[b] *Chi Squared Test*
BMIZ = body mass index (BMI)-for-age z-score; HC = head circumference; HCZ = HC-for-age z-score; LAZ = length-for-age z-score; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score.

The best fitting LAZ model also described three classes: LAZ catch-up (n=51, 15.8%), gradual LAZ gain (n=147, 45.6%) and LAZ faltering (n=124, 38.5%). The LAZ catch-up trajectory decreased slightly up to approximately 46 weeks PMA (6 weeks CA) before increasing rapidly, not plateauing by 1 year of age. The gradual LAZ gain and LAZ faltering trajectories both maintained a constant initial slope, plateauing towards the end of the first year. None of the LAZ trajectories exceeded zero at any time. In multivariable analysis (Table 3), compared to gradual LAZ gain, LAZ catch-up was significantly associated with lower BWZ (OR 8.33 (3.13. 20.00) per 1 z-score decrease) and lower early WAZ gain (OR 1.85 (1.25. 2.70) per 1 z-score decrease), while LAZ faltering was associated with lower early WAZ gain (OR 1.39 (1.09. 1.75) per 1 z-score decrease) but inversely associated with the presence of congenital heart conditions (OR 0.28 (0.14, 0.53))] Table 4 shows that the gradual LAZ gain trajectory produced significantly lower rates of underweight (2.0%), stunting (2.1%) and wasting (2.1%) at 1 year (all p<0.001), but non-significantly higher rates of overweight (9.6%). The LAZ catch-up trajectory was associated with the highest rates of underweight (29.4%) and wasting (17.6%), while the LAZ faltering trajectory was associated with the most stunting (33.9%).

The best fitting WLZ model described two trajectories: WLZ gain (n=108, 33.5%) and WLZ faltering (n=214; 66.5%). The WLZ gain trajectory increased gradually from below zero to an end point well above zero, while the WLZ faltering group that exhibited some initial WLZ gain followed by WLZ decrease which plateaued below zero at approximately 80 weeks PMA (9 months CA). Compared to WLZ gain, WLZ faltering trajectory was significantly associated with lower GA at birth (OR 1.19 (1.05. 1.33) per 1 week decrease) and lower BWZ (OR 1.69 (1.11. 2.70) per 1 z-score decrease), but inversely associated with maternal age ≤19 years (OR 0.27 (0.09, 0.76)) (Table 3). The WLZ faltering trajectory was associated with significantly higher rates of underweight (22.4%), stunting (23.9%) and wasting (10.3%), while the WLZ gain trajectory was associated with significantly more overweight (17.6%, all p<0.001) (Table 4).

The best fitting HCZ model described two trajectories: HCZ maintenance near zero (n=87, 27.0%), and HCZ catch-up (n=235, 73.0%) from birth HCZ<0 to HCZ>1 at one year. The HCZ catch-up trajectory was associated with lower BWZ (OR 1.92 (1.23. 3.13) per 1 z-score decrease), female sex (OR 1.85 (1.09. 3.13)) and maternal conditions of the placenta, cord, and membranes (OR 5.70 (1.80, 19.87)), and inversely associated with maternal medical

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and surgical conditions (OR 0.49 (0.27, 0.86)) (Table 3). Neither HCZ trajectory was significantly associated with any indicator of malnutrition at one year (Table 4).

DISCUSSION

This study illustrates that preterm infants can follow different postnatal growth trajectories, that these trajectories are predicted by certain birth and early life factors, and that a growth trajectory can in turn predict malnutrition at one year of age. This longitudinal characterization of growth trajectories helps the clinician to identify infants whose growth patterns are likely to result in adverse growth outcomes and intervene appropriately.

Most of the infants showed acceptable WAZ growth, belonging to either the gradual WAZ gain or WAZ catch-up trajectories. Although the gradual WAZ gain trajectory did not return to the birth WAZ, the mean trajectory was maintained at a level above the lowest WAZ, which may reflect normal postnatal weight loss and regain. Both the gradual WAZ gain and WAZ catch-up trajectories reached their lowest level at around term age, with WAZ only increasing thereafter. Previous research has shown that few preterm infants regain a WAZ equal to the BWZ by 40 weeks PMA; thus, it is recommended for preterm infants to aim for at least maintaining the WAZ at which weight gain starts, even if it is below the BWZ[21-24]. The infants with WAZ, LAZ and WLZ faltering represent the groups of highest concern, considering their strong associations with indicators of undernutrition at 1 year. Given the high prevalence of childhood stunting in South Africa[25], LAZ faltering is particularly concerning.

Of the early-life predictors, BWZ and early WAZ gain were most consistently associated with growth trajectories. Higher BWZ was associated with WAZ faltering and slow WAZ gain, and inversely associated with LAZ catch-up and WLZ faltering. Thus, a lower BWZ was associated with WAZ catch-up and LAZ catch-up, which is consistent with literature describing higher postnatal growth velocity in SGA infants compared to AGA infants[7,26]. Lower BWZ may result from intrauterine growth faltering due to inadequate nutrient and/or oxygen supply, commonly caused by placental insufficiency[27-30]. Once these neonates receive adequate nutrition postnatally, they display accelerated postnatal catch-up growth as they return to their genetic growth potential[21].

Conversely, lower BWZ was associated with WLZ faltering. This suggests that WLZ faltering may co-exist with adequate WAZ and LAZ growth, a finding supported by the considerable proportion of infants in the WLZ faltering trajectory that belonged to the gradual WAZ or LAZ gain trajectories. The link between SGA and poor long-term growth outcomes has been well

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described in the literature[1-3,5,31-33]. Our research suggests that, while smaller infants may have higher postnatal weight and length growth rates, these two parameters may not increase proportionally (resulting in WLZ faltering), and the rate of catch-up growth is still not enough to allow them to catch up to their AGA peers by one year of age. In univariate analyses, SGA predicted growth trajectory similarly to BWZ, but the association disappeared when BWZ was included in multivariable analysis as a continuous variable. This implies that BWZ predicts growth trajectory even in non-SGA infants, particularly since WAZ and LAZ faltering were associated with higher rather than lower BWZ. This further emphasizes the importance of longitudinal growth monitoring and not relying only on SGA at birth to identify infants at risk of poor growth outcomes.

Early WAZ gain was inversely associated with WAZ faltering, slow WAZ growth, LAZ faltering and LAZ catch-up. The highest early WAZ growth was associated with WAZ catch-up and gradual LAZ gain. The associations between early WAZ growth and WAZ trajectory are not surprising since the one is a subset of the other. The relationship between WAZ and LAZ growth trajectory is less well established, though an association between stunting at 12 and 24 months and earlier episodes of insufficient weight gain has been described in a Bangladeshi cohort[34] The WAZ catch-up and LAZ catch-up trajectories were associated with the lowest rates of underweight, wasting and stunting, but the highest rates of overweight. This has been observed in previous studies, where early growth was protective against undernutrition, but excessive early weight gain was associated with later overweight[35]. Other research in LMICs has likewise identified failure to regain birth weight at two weeks of age (an alternative marker of poor early growth) as a risk factor for stunting and underweight at 6 months old in both term and preterm low birth weight infants[31].

Higher GA at birth was inversely associated with WLZ faltering, suggesting that infants born more preterm are more prone to ongoing WLZ faltering, which was in turn associated with higher rates of underweight, stunting and wasting. Preterm birth is well-established as a risk factor for long-term growth deficits, particularly when complicated by SGA[1-4,6]. The reason for the inverse association between adolescent mothers and WLZ faltering (i.e. infants of adolescent mothers being more likely to display WLZ catch-up) is unclear and requires further investigation.

Unlike weight- and length-related indices, our sample did not display any significant HC faltering. This is reassuring, as HC growth is predictive of neurodevelopmental outcomes in preterm infants[36,37]. Our research did not include any neurodevelopmental assessment, but HC trajectory was not associated with any indicator of malnutrition at one year.

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To the best of our knowledge, this study is the first to describe longitudinal WAZ, LAZ, WLZ and HCZ growth in South African preterm infants using latent class trajectory modelling. The identification of high-risk growth trajectories and their associated early-life risk factors can be useful in clinical practice for identifying preterm neonates and infants that may be at even higher risk for long-term growth anomalies. However, the study sample cannot be considered representative of all South African preterm infants, as it was limited to a small geographic area, and included a larger proportion of SGA infants than is typically found in clinical populations. Moreover, there are some limitations to using routine clinical data, particularly in the completeness of data regarding maternal health conditions. The long period of data collection The quality of the follow-up anthropometric data is more reliable, due to the use of consistent, regularly serviced equipment by a single trained dietitian. The lack of reliable birth length measurements is another important gap that should be addressed in future work. Finally, the one-year timeframe of the study may not have been sufficient to capture the full extent of catch-up growth, which may be expected to continue up to two years of age. This may be particularly true of length growth, since in our data the LAZ catch-up trajectory still had a steep upward slope by the end of the study period, suggesting that this group's growth rate had not stabilized. Likewise, more time may be needed to capture the development of overweight/obesity in this population.

Many questions remain for future research to address. The role of infant feeding practices and dietary intake deserve special attention, not only as predictors of growth but also as potential targets for intervention to shift infants onto a more favorable growth trajectory. The inclusion of body composition assessment would also be valuable, since it is known that preterm infants rarely attain body composition similar to that of term infants by term-equivalent age, typically having lower fat-free mass and a higher fat mass percentage[23]. Knowing how body composition evolves throughout childhood and beyond would offer important insights into the metabolic risks associated with different growth patterns.

CONCLUSION

Preterm infants in our study displayed a variety of growth trajectories, including catch-up growth, gradual growth and growth faltering. Lower BWZ was associated with greater likelihood of WAZ and LAZ catch-up, but also WLZ faltering, highlighting the importance of monitoring all three growth indices. While WAZ catch-up was associated with overweight at one year, LAZ catch-up and WLZ faltering were more strongly associated with indicators of undernutrition, especially underweight and wasting. Lower early WAZ gain was associated with WAZ and LAZ faltering, which were, in turn, associated with underweight, stunting and wasting. Conversely, gradual LAZ gain was associated with low rates of malnutrition at one

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year, suggesting that it is an appropriate growth target in preterm infants. Gradual WAZ gain and WAZ catch-up were associated with low rates of malnutrition, though WAZ catch-up was also associated with overweight, indicating the importance of monitoring WLZ alongside WAZ. The growth of an individual preterm infant remains complex, and is influenced by multiple predictors, but longitudinal monitoring of infant growth trajectories can aid the clinician in identifying infants in this vulnerable group that are at increased risk of under- or overnutrition. This allows an opportunity for timeous intervention to support appropriate growth.

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BRIDGING TEXT

The trajectory analysis revealed some nuances to the growth patterns of preterm infants that had not been apparent in the earlier papers, particularly in relation to the predictive value of birth weight z-score and early growth. In concordance with the cross-sectional analysis, lower early weight growth was associated with faltering LAZ and WAZ trajectories, which in turn were associated with higher rates of underweight, stunting and wasting. A few of the results seem to contradict the cross-sectional findings, though: lower birth weight z-score was associated with WAZ and LAZ catch-up, even though lower birth weight z-scores predicted underweight (WAZ <-2) and stunting (LAZ <-2) at one year. One explanation for this finding is that very SGA infants may display substantial catch-up growth, but in many cases that is still not enough to normalise their WAZ and LAZ by one year. This is in concordance with the finding from publication 3 (Chapter 5) that SGA preterm infants had greater WAZ gains in the first year of life, but remained significantly smaller in all anthropometric parameters.

Up to this point, analyses have used birth weight z-scores or percentiles as a proxy measure of intrauterine growth. This potentially misses some of the nuances of foetal growth restriction. It is likely that some of the SGA infants were achieving their full genetic growth potential, while some of the AGA infants did, in fact, have FGR. The papers that follow take a different approach to assessing foetal growth: rather than relying solely on measurements of neonatal size, placental function is used to indicate potential FGR. In these studies, placental function was assessed by early third trimester Doppler screening of the umbilical artery. Impaired placental function – indicated by an abnormal Doppler screening result – is considered indicative of reduced nutrient and oxygen supply to the foetus, thus increasing the likelihood of FGR even when neonatal size remains normal. Whether Doppler screening results are better able to predict growth outcomes is an important question for clinical practice, where early identification of at-risk infants enables earlier intervention and, consequently, potentially better outcomes.

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CHAPTER 7: FIFTH PUBLICATION: 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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Association of Prenatal Placental Function with Anthropometry and Body Composition through 2 years of Age in South African Infants: The UmbiBaby Study

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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.

Objectives: This study aimed to describe and compare anthropometry and BC during the first 2 y 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 8-time points until age 2 y. Anthropometric measurements were taken, and FFM and FM were 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 an 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 with infants with normal UmA-RI, infants with abnormal UmA-RI had significantly lower weight-for-age *z*-scores at birth (−0.77 ± 0.75 compared with −0.30 ± 1.10, $P = 0.026$), ages 10 wk to 9 mo (−0.4 ± 0.87 to −0.2 ± 1.12 compared with 0.3 ± 0.85 to 0.6 ± 1.09; $P = 0.007$–0.017) and 18 mo (−0.6 ± 0.82 compared with 0.1 ± 1.18; $P = 0.037$); length-for-age *z*-scores at ages ≤14 wk (−1.3 ± 1.25 to −0.9 ± 0.87 compared with −0.2 ± 1.04 to −0.1 ± 1.00; $P = 0.004$–0.021); and FFM-for-age *z*-scores at ages ≤9 mo (−0.1 ± 0.82 to 0.7 ± 0.71 compared with 0.7 ± 1.00 to 1.3 ± 0.85; $P = 0.002$–0.028). FFMI, percentage FFM, FM, percentage 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 percentage 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, is widely regarded as a critical developmental period. Nutritional, environmental, and other health-related conditions during this period can have lifelong 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

Abbreviations: BC, body composition; BMIZ, body mass index-for-age *z*-score; FFMI, FFM index; FGR, fetal growth restriction; %FM, percentage FM; FMI, FM index; HC, head circumference; HCZ, HC-for-age *z*-score; LAZ, length-for-age *z*-score; 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.

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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 the 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 the 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 UmA resistance index (RI), as a marker of placental insufficiency. One study conducted in the Tshwane District detected abnormal UmA-RI in 11.3% of the study sample, including end-stage placental insufficiency (absent end-diastolic flow, absent end-diastolic flow) in 1.3% [13]. Likewise, a multisite nationwide study found abnormal UmA-RI in 13.0% of the study sample, with absent end-diastolic flow in 1.2% [14]. The reason for the high prevalence of impaired placental functioning remains unknown because 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 ≤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 subsample of infants recruited from the South African arm of the Umbiflow International Study.

It is plausible that impaired placental functioning may affect fetal BC because fetal fat deposition occurs mainly in the third trimester of pregnancy [15]. Late-onset placental insufficiency could therefore limit fat accumulation, resulting in lower FM at birth. Likewise, muscle wasting because of fetal starvation could deplete 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 percentage FFM and higher percentage FM (%FM) at 6 wk 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 the 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 because 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 SGA, like the 10th percentile, at birth [7]. Studies using Umbiflow confirm that, although fetuses with abnormal UmA-RI are smaller and more likely to be born SGA or with low birth weight (<2500 g), 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 ≤6 mo of age in infants with FGR [18]. No published research of this type could be found for African infants beyond 6 mo of age. It should be noted that results from high income, predominantly Caucasian populations cannot necessarily be extrapolated to the South African setting, as 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 2 y 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 ≤8 time points during in the first 2 y 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

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Umbiflow device was performed at 28–34 weeks of gestation. Study participants were invited to participate in the UmbiBaby study after delivery. Women aged <18 y, 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 wk and 6, 9, 12, 18, and 24 mo of age to coincide with routine well child or 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). Head circumference (HC) was measured above the eyebrows, around the widest part of the occiput, using a nonelastic measuring tape, and recorded to the nearest 0.1 cm. MUAC was measured on the left arm, midway between the acromion of the scapula and the olecranon of the ulna, using a nonelastic 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. Predose samples were collected ≥15 minutes after the infant's last food or beverage intake. A premeasured dose of deuterium-labeled 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 infant-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 preweighed tissue, and the difference in tissue weight was subtracted from the administered dose. Postdose saliva samples were collected 2.5 h 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 with 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 nonaqueous hydrogen exchange), and FFM estimated using age- and sex-specific hydration constants described by Fomon et al. [22], as recommended by the International Atomic Energy Agency [21]. FM 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 or 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 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 multiethnic, multicountry 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 mo 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 were expressed as absolute values of FM and FFM (in kg), as well as in terms of %FM, percentage 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 FFM index (FFMI) were calculated using the lambda-mu-sigma (LMS) method and reference data published by Wells et al. [29] because this is the only available reference for the study sample age group based on isotope dilution. 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 analyzed using R (v 4.1.2, 2020; R Foundation for Statistical Computing). 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 2-sided probabilities and $\alpha = 0.05$.

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

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and health services involved. Informed consent was obtained from all parents or 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 nonsignificantly lower rates in the abnormal UmA-RI group (19.2% compared with 36.4%; $P = 0.13$). Infants in the abnormal UmA-RI group had significantly lower mean gestational age (38.7 ± 1.1 compared with 39.7 ± 1.0 wk; $P < 0.001$), although all infants included were born at ≥37 wk. Abnormal UmA-RI infants also had significantly lower birth weight (2.82 ± 0.36 compared with 3.17 ± 0.49 kg; $P = 0.002$) and birth weight z-score (−0.7 ± 0.75 compared with −0.30 ± 1.10; $P = 0.026$), although similar numbers of infants in both groups were classified as SGA (26.9% compared with 21.8%; $P = 0.61$). In each group, all but one mother initiated breastfeeding ($P > 0.99$).

Infant anthropometry and BC 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 because of 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 $n = 11$–20; Normal UmA-RI $n = 31$–47). The largest percentage of participants had 5 ($n = 20$; 24.7%) or 6 ($n = 22$; 27.2%) BC measurements; with 8 (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 (Supplemental Tables 1 and 2). The data presented at each age includes only those infants for whom both anthropometry and BC were available at that study visit.

TABLE 1
Sample description: pregnancy and birth data of mother-infant pairs with normal and abnormal UmA-RI

		Total sample ($n = 81$)	Normal UmA-RI ($n = 55$)	Abnormal UmA-RI ($n = 26$)	*P* value: normal vs. abnormal UmA-RI
Maternal data					
Age (y)	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 (y)	*n* (%)				
Primary (0–7)		7 (8.6)	3 (5.5)	4 (15.4)	
Some secondary (8–11)		47 (58.0)	32 (58.2)	15 (57.7)	0.43[3]
Completed secondary (12)		18 (22.2)	14 (25.5)	4 (15.3)	
Tertiary		9 (11.1)	6 (10.9)	3 (11.5)	
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[1,4]
UmA-RI z-score[5]	Mean ± SD	0.53 ± 1.21	−0.11 ± 0.61	1.89 ± 0.91	<0.001[1,4]
Birth data					
Sex (male)	*n* (%)	41 (50.6)	30 (54.4)	11 (42.3)	0.30[2]
Gestational age (wk)	Mean ± SD	39.3 ± 1.18	39.7 ± 1.12	38.7 ± 1.03	<0.001[2,4]
Birth weight (kg)	Mean ± SD	3.06 ± 0.48	3.17 ± 0.49	2.82 ± 0.36	0.002[1,4]
Birth weight z-score[6]	Mean ± SD	−0.45 ± 1.02	−0.30 ± 1.10	−0.77 ± 0.75	0.026[4,7]
SGA[8]	*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]

SGA, small for gestational age; UmA-RI, umbilical artery resistance index.
[1] Wilcoxon rank-sum (Mann–Whitney) test (data not normally distributed).
[2] Chi-squared test.
[3] Fisher's exact test.
[4] Statistically significant ($P < 0.05$).
[5] Independent samples t-test.
[6] UmA-RI *z-score* calculated using INTERGROWTH-21st Doppler resistance index reference values [25].
[7] Birth weight *z-score* calculated using INTERGROWTH-21st Newborn Size Standards [26].
[8] SGA: sex-normalized birth weight <10th percentile on the INTERGROWTH-21st Newborn Size Standards [26].

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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, *n*	Abnormal UmA-RI, *n*
6 wk	58	44 (75.9)	32	12
10 wk[1]	71	58 (81.7)	44	14
14 wk[1]	72	47 (65.3)	31	16
6 mo[1]	70	56 (80.0)	37	19
9 mo[1]	72	67 (93.1)	47	20
12 mo	64	51 (79.7)	36	15
18 mo	56	47 (83.9)	36	11
24 mo	51	42 (82.4)	31	11

UmA-RI, umbilical artery resistance index.
[1] During stage 5 COVID-19 lockdown (27 March to 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 4 × 10 wk visits, 15 × 14 wk visits, 12 × 6 mo visits, and 4 × 9 mo visits where no body composition assessment could be done.

TABLE 3
Infant anthropometry and BC results for the entire study sample

A	Visit							
	6 wk	10 wk	14 wk	6 mo	9 mo	12 mo	18 mo	24 mo
n with BC data	44	58	47	56	67	51	47	42
Age (mo)	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
BC[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

BC, body composition; BMIZ, body mass index-for-age z-score; %FFM, percentage FFM (FFM/weight × 100); FFMI, FFM index (FFM/[length in m]^2); %FM, percentage FM (FM/weight × 100); FMI, FM index (FM/[length in m])^2; HC, head circumference; HCZ, HC-for-age z-score; LAZ, length-for-age z-score; 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.
[1] Anthropometric z-scores calculated using WHO Multticentre Growth Reference Study Growth Standards (WHO Anthro software) [27,28].
[2] MUAC z-score only calculated from 3 mo of age.
[3] z-scores for BC calculated using reference data from Wells et al. [29].

For most visits, the mean study sample LAZ was <0 (except at 6 and 9 mo, where the mean LAZ was 0.07 and 0.04, respectively) and the mean WAZ >0 (except at 18–24 mo, where mean WAZ was <0). Similarly, mean WLZ and BMIZ were >0 for all visits except 24 mo. Mean MUACZ (only calculated from 3 mo 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 mo, whereas FFMI z-score was only <0 at the 24 mo visit. Conversely, mean FM and FMI z-scores were <0 for

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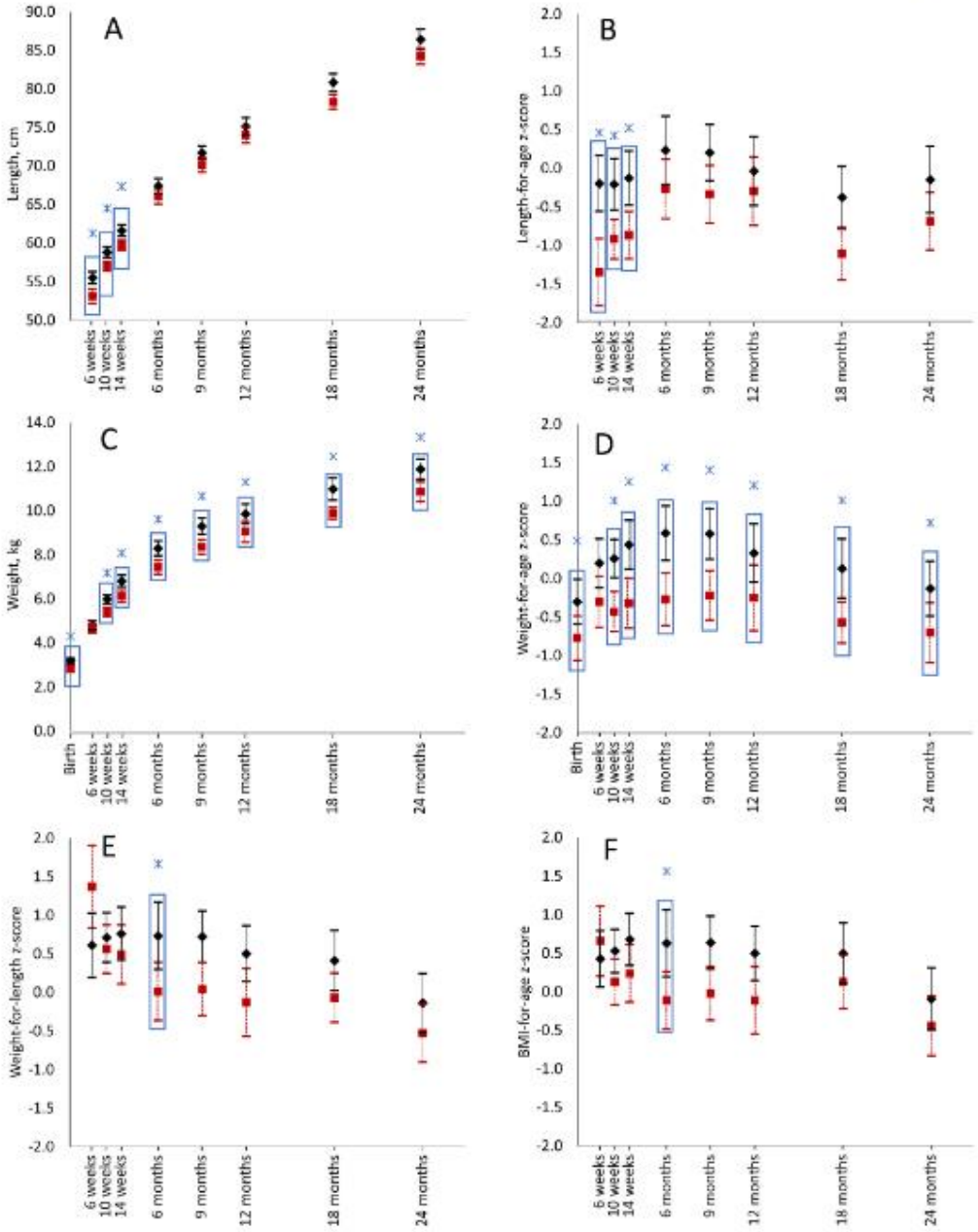

	6w	10w	14w	6m	9m	12m	18m	24m
n:	32	44	31	37	47	36	36	31
n:	12	14	16	19	20	15	11	11

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 1. Anthropometry through 2 y of age of infants with normal and abnormal UmA-RI: weight and length. UmA-RI, umbilical artery resistance index.

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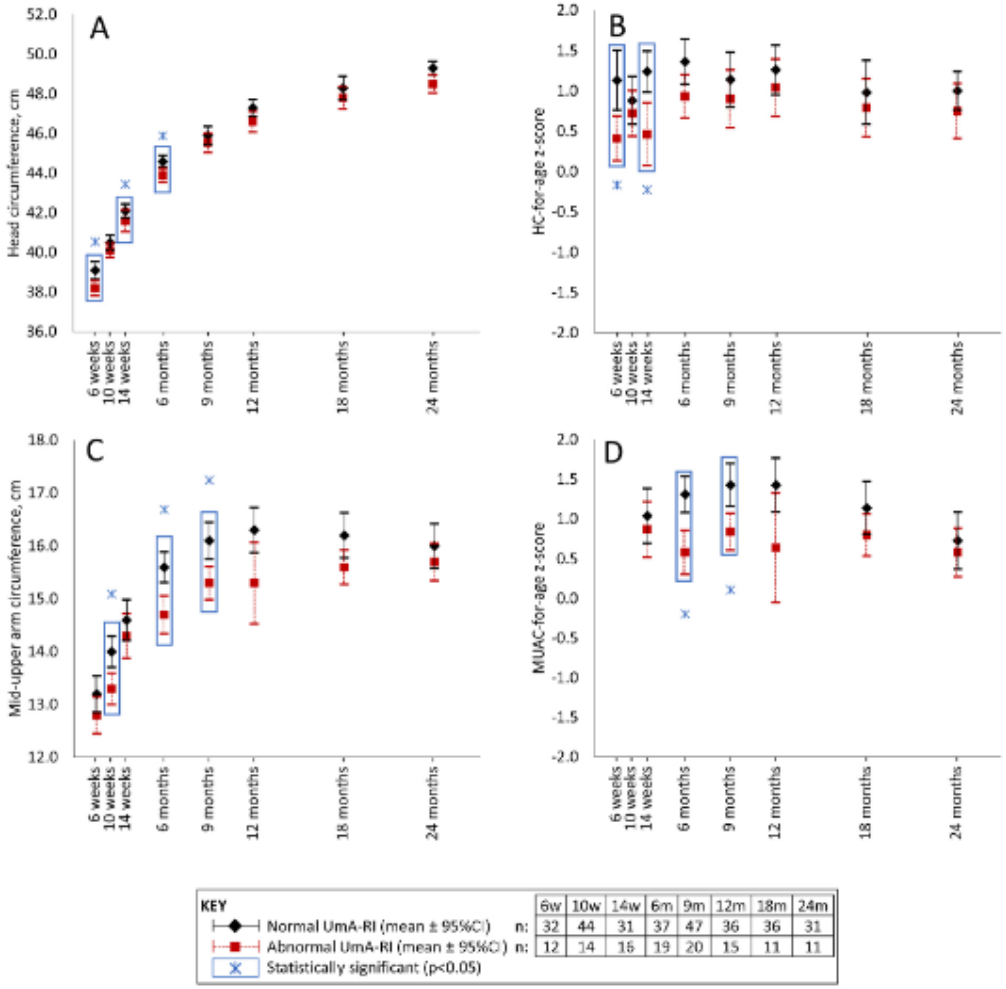

A: head circumference in cm; B: head circumference-for-age z-score; C: mid-upper arm circumference in cm; D: MUAC-for-age z-score;.

FIGURE 2. Anthropometry through 2 y of age of infants with normal and abnormal UmA-RI: HC and MUAC. HC, head circumference; UmA-RI, umbilical artery resistance index.

all visits except 6 mo. Breastfeeding rates were high (>85%) ≤14 wk, declining thereafter; no infants were still breastfeeding at 24 mo.

Comparing the normal and abnormal UmA-RI groups, weight was significantly lower ($P = 0.004$–0.033) in the abnormal UmA-RI group at all visits except 6 wk ($P = 0.12$), whereas WAZ was significantly lower ($P = 0.007$–0.037) at all except 6 wk ($P = 0.14$), 12 mo ($P = 0.15$), and 24 mo ($P = 0.10$). Length and LAZ were significantly lower ($P = 0.004$–0.027) in the abnormal UmA-RI group at 6, 10, and 14 wk, and length (but not LAZ) at 18 mo. The same nonsignificant differences were observed for length at 6 mo ($P = 0.10$), 9 mo ($P = 0.06$), and 24 mo ($P = 0.05$), and for LAZ at 18 mo ($P = 0.07$). Mean WLZ and BMIZ were significantly lower in the abnormal UmA-RI group at 6 mo ($P = 0.045$ and 0.038, respectively) with the same nonsignificant differences observed for WLZ at 9 mo ($P = 0.07$) and for BMIZ at 9 mo ($P = 0.07$) and 12 mo ($P = 0.10$). MUAC and MUACZ were significantly lower in the abnormal UmA-RI group at 6 mo ($P = 0.004$ and 0.003) and 9 mo ($P = 0.017$ and 0.020), and HC at 6 wk ($P = 0.00.025$), 14 wk ($P = 0.00.014$), and 6 mo ($P = 0.033$), and HCZ at 6 wk ($P = 0.022$) and 14 wk ($P = 0.018$).

Of the BC parameters, TBW ($P = 0.003$–0.019), TBW z-score ($P = 0.002$–0.018), and FFM ($P = 0.002$–0.025) were significantly lower in the abnormal UmA-RI group at all visits from 6 wk to 9 mo. At 18 mo, 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 and 24 mo ($P = 0.002$–0.028). FFMI differed significantly only at 6 mo ($P = 0.049$), with a similar nonsignificant

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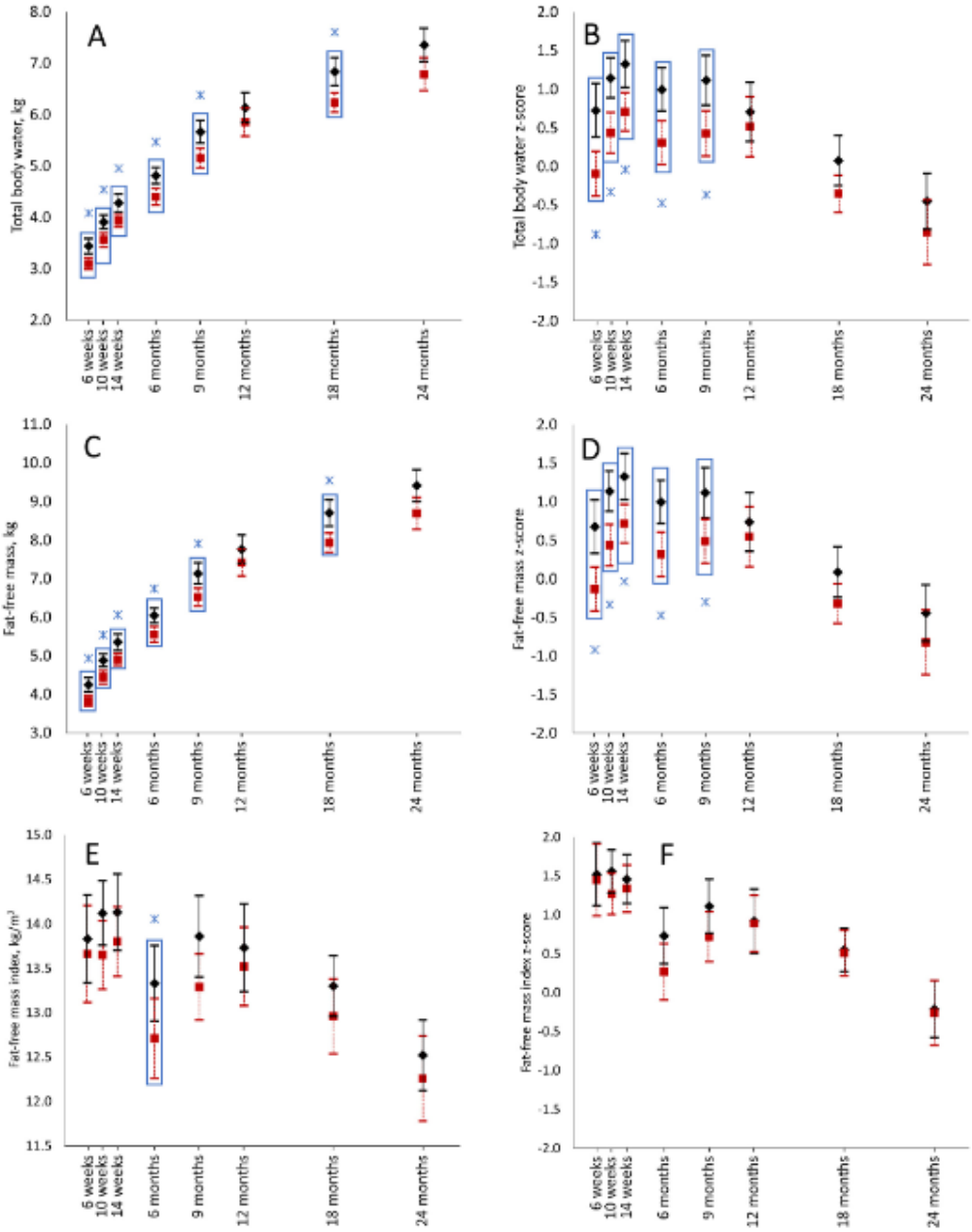

	6w	10w	14w	6m	9m	12m	18m	24m
n:	32	44	31	37	47	36	36	31
n:	12	14	16	19	20	15	11	11

A: 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 3. Body composition through 2 y of age of infants with normal and abnormal UmA-RI: total body water, FFM, and FFM index. UmA-RI, umbilical artery resistance index.

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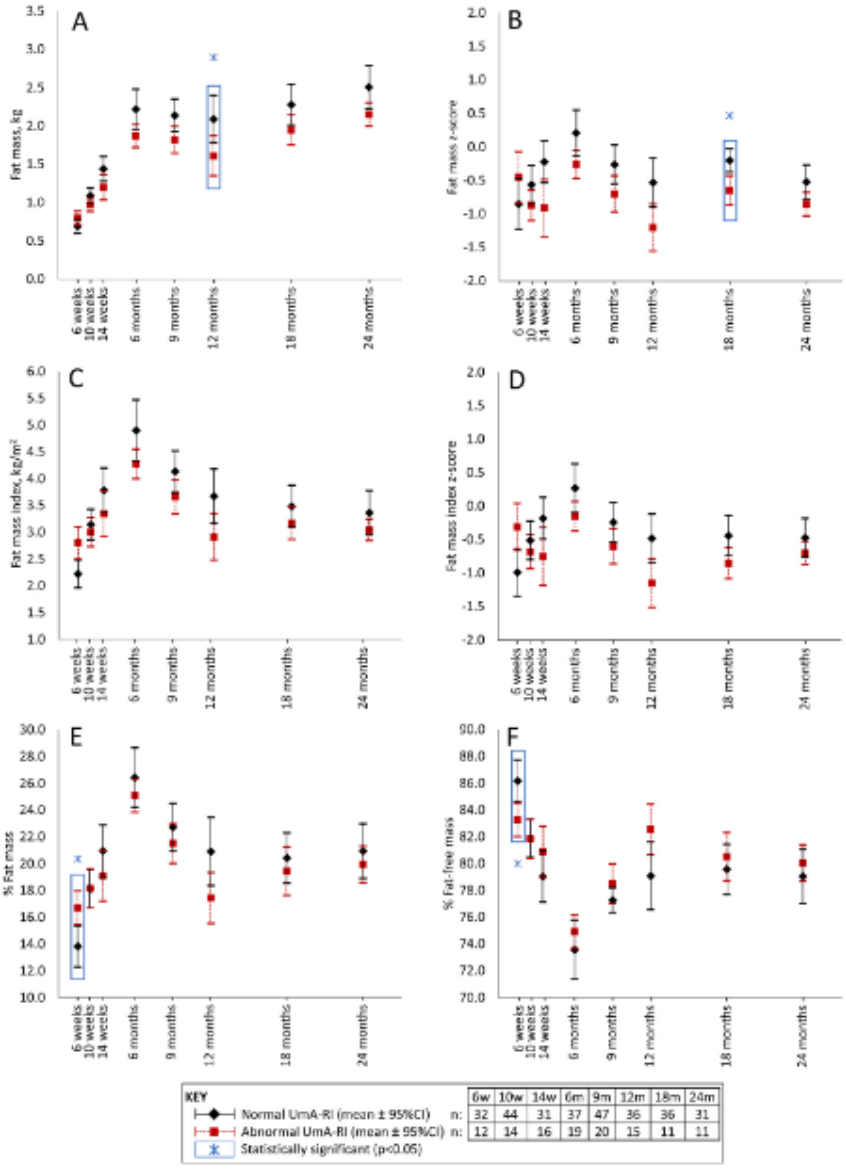

A: fat mass in kg; B: fat mass z-score; C: fat mass index in kg/m²; D: fat mass index z-score; E: percentage fat mass; F: percentage fat-free mass

FIGURE 4. Body composition through 2 y of age of infants with normal and abnormal UmA-RI: FM, FFM index, FM percentage, and FFM percentage. UmA-RI, umbilical artery resistance index.

difference at 10 wk ($P = 0.10$), but FFMI *z*-score did not differ significantly at any age. FM was significantly lower in the abnormal UmA-RI group only at 12 mo ($P = 0.049$), but FMI and FMI *z*-score did not differ significantly. Nonsignificant differences were observed in FM at 6 mo ($P = 0.10$) and 9 mo ($P = 0.07$), in FM *z*-score at 9 mo ($P = 0.10$) and 12 mo ($P = 0.06$), in FMI at 6 wk ($P = 0.05$), and in FMI *z*-score at 6 wk ($P = 0.06$) and 6 mo ($P = 0.09$); these values were higher in the abnormal UmA-RI group at 6 wk whereas the reverse was true at all ages thereafter. A significant difference in %FM (and percentage FFM) was only seen at 6 wk ($P = 0.035$), and a nonsignificant difference was observed at 12 mo ($P = 0.09$). 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 mo suggest caution in interpreting the calculated *P* value.

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Discussion

This study presents novel data on BC at various time points in the first 2 y 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. [13], which found significantly lower rates of abnormal UmA-RI in HIV-infected women. Likewise, maternal height, age, gravidity, parity, education level, and employment status were not associated with abnormal UmA-RI. Maternal BMI was not assessed because of 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 toward 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 2 y [31]. Mean *z*-scores for BC compartments related to FFM (TBW, FFM, and FFMI *z*-scores) were higher than those related to FM (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. [32] reference data were developed in the United Kingdom; as such, various ethnic, socioeconomic, and nutritional factors could account for the observed differences. Our results contrast with a study by Wells et al. [32] comparing BC by isotope dilution in Gambian and UK children ≤18 mo of age; in their study, Gambian children had lower mean FM, FFM, FMI, and FFMI than UK children. 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 (that is, $\beta = 0.20$). Nonetheless, some significant differences and nonsignificant trends were observed. Weight was significantly lower in the abnormal UmA-RI group at all ages except 6 wk, with WAZ showing similar patterns except at 12 and 24 mo. Length and LAZ were significantly lower in the abnormal UmA-RI group ≤14 wk, with inconsistent trends thereafter. WLZ and BMIZ were not significantly different except at 6 mo. 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 −1 wk 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 ≤9 mo and at 18 mo. However, there was no significant difference in percentage FFM (except at 6 wk) or FFMI (except at 6 mo), 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 mo of age was decreased in infants with FGR, regardless of birth weight, compared with 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 mo 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 artifact 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 because 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

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presented here cannot be interpreted longitudinally because 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 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 nonsignificant, 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 toward 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 2 y of life and reveals some nuances that may be missed when measurements are only taken at 1-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 y of age [41]. Moreover, unlike for example, DXA, these 2-compartment methods cannot differentiate between different FFM components (that is, water, protein or soft tissue, and bone) [42]. The minimal dose of D_2O given (3 mL) would not be expected to disrupt breastfeeding, and the WHO definitions of exclusive breastfeeding allow 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 as 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.

In conclusion, this study found evidence that prenatal placental insufficiency may be associated with anthropometry (and, to a lesser extent, BC) in the first 2 y of life. Infants with an abnormally elevated UmA-RI often had lower weight, WAZ, length, and LAZ compared with 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.

Author disclosures

The authors report no conflicts of interest.

Acknowledgments

The authors' responsibilities were as follows–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 article; FW, HM, and UF edited the article; and SN had primary responsibility for the final content.

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Data availability: Data will be made available by the authors upon reasonable request

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2023.02.007.

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SUPPLEMENTARY MATERIAL

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.

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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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BRIDGING TEXT

The repeated cross-sectional analyses presented here show that prenatal placental insufficiency does impact intrauterine growth, evidenced not only by lower BWZ, but also by early-life differences in all the age-related anthropometric z-scores (LAZ, WAZ, MUCZ, HCZ) and BC parameters related to FFM (TBW, FFM and their z-scores). Indices related to FM were, for the most part, not significantly different, suggesting that FFM accretion may be disproportionately affected by placental insufficiency. Additionally, indices that include infant length (i.e. WLZ, BMIZ, FMI and FFMI) tended to not show significant differences, suggesting that reductions in infant length – and thus overall size – may account for some of the observed differences.

Of all the parameters compared, only weight and WAZ remained significantly different up to two years of age. The other differences (including those related to length FFM) were more pronounced at younger ages but diminished over time, though the pattern of the data (i.e. lower mean values in the group with abnormal UmA-RI) remained consistent. There are two possible explanations for this. One possibility is that the smaller sample sizes at older ages compromised the statistical power to detect differences that were, in fact, present. Another possibility is that there truly is no significant difference, and that the growth trajectories of infants with and without placental insufficiency converge over time. This would by a classic example of postnatal catch-up growth. Such a conclusion cannot be drawn from repeated cross-sectional analyses, since not all infants attended all study visits (particularly at later ages). Thus, the groups being compared at different ages did not include all the identical infants, making direct longitudinal comparisons inappropriate.

Longitudinal trajectory analysis offers a way to compensate for this problem, to some extent, by plotting each individual infant's growth trajectory and statistically smoothing missing data to produce an unbroken trajectory curve. Each individual trajectory then becomes a unit of analysis, and Latent Class Trajectory Modelling techniques can be used to identify 2-4 trajectories that represent the typical growth patterns seen in the sample. This then allows us to investigate whether certain early-life factors (including birth size and placental insufficiency) are more strongly associated with certain growth trajectories. The next publication reports on such an analysis.

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CHAPTER 8: SIXTH MANUSCRIPT: Longitudinal anthropometry and body composition trajectories of South African infants with and without prenatal placental insufficiency

MANUSCRIPT FOR SUBMISSION

Longitudinal anthropometry and body composition trajectories of South African infants with and without prenatal placental insufficiency

Intended for submission to World Journal of Pediatrics.

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ABSTRACT

Background: Umbilical artery Doppler screening identifies placental insufficiency, which affects fetal growth and body composition (BC). We describe anthropometric and BC trajectories up to two years in a cohort of term-born infants with and without prenatal placental insufficiency, and investigate their early-life predictors.

Methods: The term-born *UmbiBaby* cohort included 81 infants with umbilical artery resistance index (UmA-RI) assessed at 28-34 weeks' gestation. At eight time points over two

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years, weight, length, HC and mid-upper arm circumference (MUAC) were measured, and z-scores were calculated for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), BMI-for-age (BMIZ), MUAC-for-age (MUACZ) and HC-for-age (HCZ) using WHO Anthro. Fat-free mass (FFM) and fat mass (FM) were assessed using deuterium dilution, and z-scores were calculated for FM (FMZ), FFM (FFMZ), FM index (FMIZ) and FFM index (FFMIZ). Latent class trajectory modelling (LCTM) identified characteristic growth trajectories, and multivariable analysis investigated predictors of growth trajectories.

Results: Three trajectories were identified for WAZ, LAZ, WLZ, BMIZ and FFMZ, and two trajectories for MUACZ, FMZ, FMIZ and FFMIZ. Trajectories for FMZ and FMIZ converged at two years, while FFMZ and FFMIZ declined sharply. In multivariable analysis, lower BWZ predicted lower trajectories for WAZ (OR:9.32(2.32-37.50)), WLZ (OR:2.95(1.33-6.55)), BMIZ (OR:3.70(1.56-9.09)), FMZ (OR:2.78(1.37-5.55)) and FFMZ (OR:2.63(1.45-4.76)). Higher (more abnormal) UmA-RI predicted lower trajectories for LAZ (OR:1.95(1.15-3.30) and FFMZ (OR:1.78(1.13-2.80)) trajectories.

Conclusion: While BWZ predicts WAZ, WLZ, BMIZ, FMZ and FFMZ trajectories, UmA-RI predicts LAZ and FFMZ. Routine UmA-RI screening could help identify infants at increased risk of later stunting.

KEYWORDS

Body composition, fetal growth restriction, growth trajectories, placental insufficiency, stunting.

INTRODUCTION

Nutritional, health, and environmental experiences during the first thousand days of life – from conception to the second birthday – can have lifelong effects on health and development (1). Fetal growth may predict postnatal growth and long-term health (2), but monitoring fetal growth is challenging in resource-constrained environments with limited access to ultrasonography, and often relies on postnatal assessment of neonatal size and clinical features (3). Small for gestational age (SGA, birth weight <10th percentile for gestational age) and asymmetric growth (birth head circumference (HC) percentile/z-score markedly exceeding that of birth weight) are among the commonly used anthropometric indicators of fetal growth restriction (3,4).

Placental insufficiency is the leading cause of fetal growth restriction (FGR), since the placenta is the sole source of fetal nutrition (2, 5-7). Placental function can be assessed by

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Doppler ultrasonography of the umbilical artery, a technology that has recently become more accessible following the development of the low-cost point-of-care Umbiflow™ Doppler device (8). The Doppler device measures systolic and diastolic blood flow velocity in the umbilical artery, from which various indices can be calculated, including the resistance index (RI; [peak systolic velocity – end diastolic velocity]/ peak systolic velocity) (9,10). In a healthy pregnancy, the umbilical artery RI (UmA-RI) decreases gradually throughout the third trimester, with an increased UmA-RI indicating impaired placental transfer (9,10).

South African studies using Umbiflow™ have found high prevalence of abnormally elevated UmA-RI (11.7-13.0%) in otherwise healthy pregnant women (11,12). Pregnancies with elevated UmA-RI resulted in higher rates of low birth weight and SGA neonates (12) and an overall decrease in birth weight-for-gestational age (GA) percentiles even at normal birth weights (11), indicating some degree of FGR. Placenta-mediated nutrient restriction may also affect fetal fat deposition and muscle growth differently, resulting in altered neonatal body composition (BC). In a South African cohort, infants with abnormal UmA-RI were found to have lower length-for-age z-scores (LAZ), higher percentage fat mass (%FM) and lower fat-free mass (FFM) at 6 weeks of age (13). Repeated cross-sectional analysis at various time points in the first two years of life found that differences in weight-for-age z-score persisted, while differences in length and BC parameters diminished over time (14). However, such analyses do not account for the longitudinal nature of the data, or the fact that every infant did not attend every visit. Declining sample sizes at later ages further contribute to statistical volatility. Longitudinal modelling of growth trajectories aims to overcome some of these limitations.

Latent class trajectory modelling techniques, such as Latent Class Growth Analysis (LCGA) and Growth Mixture Modelling (GMM), allow for the grouping of individual growth trajectories into a smaller number of representative trajectories (15-18). The relationship of growth trajectories to other variables of interest can also be explored (16,18). Published research has used latent class trajectory modelling to study linear growth and stunting (19), relationships between linear and ponderal growth (20), the determinants and outcomes associated with childhood body mass index (BMI) trajectories (21), and fetal growth trajectories in relation to various outcomes (22,23). No published research has investigated the postnatal effects of placental insufficiency on anthropometric or BC growth trajectories.

This research aims to describe anthropometric and BC trajectories during the first two years of life in a cohort of term-born South African infants with and without prenatal placental insufficiency, born to otherwise healthy pregnant women recruited at primary health care centers. Additionally, the characteristics of infants who follow different trajectories were

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investigated to identify whether early-life factors can predict anthropometric and BC trajectories.

METHODS

Study design and Sampling

This study analysed data from the UmbiBaby Study, a longitudinal cohort study successive to the South African arm of the Umbiflow International study (described elsewhere (8)). The study was conducted in a low-income peri-urban area in Tshwane District (Gauteng Province, South Africa), and recruited pregnant women at primary health care facilities whose pregnancies were classified as low risk according to local antenatal care guidelines (24). Women with HIV were eligible for inclusion, but women with other pre-existing or pregnancy-related medical conditions were excluded. Maternal age <18 years, multiple pregnancy, and infants with severe chromosomal or structural abnormalities were excluded. Only infants born at term were included in this analysis.

Data collection and preparation

Prenatal data (including UmA-RI) and birth information (date of birth, sex, GA, birth anthropometry) were obtained from the UmbiFlow International Study records. Umbilical artery Doppler examination was performed at 28-34 weeks' gestation. The UmA-RI was classified by the Umbiflow software, using South African reference curves from Pattinson et al. (25), compiled using data from a high-risk South African obstetric population. An UmA-RI >75th percentile was considered abnormal, as validation studies found that this predicted perinatal mortality in otherwise healthy pregnancies (26). Additionally, UmA-RI z-scores (UmA-RIZ) were calculated using INTERGROWTH-21ST UmA Doppler reference values, which was analysed as a continuous variable (27). For birth anthropometry, sex- and GA-specific z-scores and percentiles were calculated using the INTERGROWTH-21ST Newborn Size Standards (28). Birth weight was classified as SGA (<10th percentile), appropriate-for-gestational age (AGA, ≥10th but ≤90th percentile) or large-for-gestational age (LGA, >90th percentile). The difference between birth HC z-score (HCZ) and birth weight z-score (BWZ) was calculated, with a difference of >1 z-score considered indicating asymmetric fetal growth (4).

Follow-up study visits took place at a dedicated research unit (Tshwane District, Gauteng Province) at 6, 10 and 14 weeks and 6, 9, 12, 18 and 24 months, alongside routine well-child services and immunizations. Age (in days) was calculated automatically by subtraction of dates. Anthropometric measurements were taken by two trained research nurses. Infants

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were weighed naked using electronic infant weighing scales (Seca 354; Seca GmbH & Co. KG, Hamburg, Germany), to the nearest 0.01 kg. Recumbent infant length was measured using a rigid infantometer (Seca 416), to the nearest 0.1 cm. Head circumference was measured above the eyebrows and around the widest part of the occiput using a nonelastic measuring tape, to the nearest 0.1 cm. Mid-upper arm circumference (MUAC) was measured midway between the acromion of the scapula and the olecranon of the ulna on the left arm, using a nonelastic measuring tape, to 0.1 cm. The WHO Growth Standards (29,30) (WHO Anthro software (31)) were used to calculate sex-specific z-scores 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). Since all infants were born at term, no age correction was performed.

Infant BC was assessed using deuterium dilution (32). Infants received an oral dose of deuterium-labelled water (D_2O; Sercon, 99.8%) (3g for infants <10kg, 6g for infants ≥10kg). Precise dose consumption was calculated by pre-and post-weighing syringes and tissues used to collect spills. Saliva samples (≥2mL) were collected before and 2.5 hours after dosing using a dental cotton swab. Breastfeeding was not restricted during the equilibration phase, but sampling was delayed if the infant consumed any food or liquid. Pre- and post-dose saliva deuterium concentrations were measured using Fourier Transform Infrared Spectrophotometry (IR-Prestige-21 FTIR Spectrophotometer; Shimadzu, Japan) and deuterium enrichment was calculated using isotope.exe software (UK Medical Research Council; Cambridge, UK). Deuterium enrichment was used to calculate total body water (TBW) and FFM, using age-and sex-specific hydration constants (32,33). Fat mass (FM) was calculated by subtracting FFM from total body weight, and FM index (FMI = FM/[length in m]^2) and FFM index (FFMI = FFM/[length in m]^2) were calculated. Sex- and age-specific z-scores were calculated for FM, FFM, FMI, and FFMI using reference data from Wells et al (34), which is the only available isotope dilution-based reference data for our sample age range. In line with international guidelines, instances where %FM <7.0% were excluded as biologically implausible (35).

Data analysis

Analyses were performed using SAS v9.4 (SAS Institute, Cary, NC, USA) and R v4.3.3 (R Foundation for Statistical Computing, Vienna, Austria). Trajectories were plotted as z-score (y-axis) against infant age (x-axis). LCGA and GMM were used to identify 2-4 latent trajectories (16). Residual plots were inspected for obvious bias. The framework described by Lennon et al was used to investigate the fit of each individual trajectory (15). Models were discarded if any trajectory had an Average of maximum Posterior Probabilities of

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Assignment (APPA) <0.7, an Odds of Correct Classification (OCC) <5.0, or included <10% of the total sample, whereafter, the lowest Bayesian Information Criterion (BIC) indicated the best model fit. Each trajectory was labelled as “upper,” “middle” or “lower,” based on their position relative to other trajectories in the same model. After matching participants to trajectories, the mean of the actual data for each trajectory was plotted.

For each model, the infants displaying different growth trajectories were compared with regards to maternal and neonatal characteristics, placental function, and infant feeding practices (Tables 2 and 3) using independent t-test or ANOVA (normally distributed data), Wilcoxon-Mann-Whitney or Kruskal-Wallis test (non-normally distributed data) and Chi-squared or Fisher’s exact test (categorical data). Multivariable analysis was used to determine which characteristics predict trajectory membership. Two sets of analyses were performed: one including UmA-RI, BWZ and the difference between HCZ and BWZ as continuous variables, and one dichotomizing those variables (normal vs. abnormal UmA-RI, SGA vs not SGA and asymmetric vs. symmetric intrauterine growth). Maternal HIV and any significantly differing characteristics were included in all multivariable analyses.

Ethical considerations

Approval to conduct the study was obtained from the University of Pretoria Faculty of Health Sciences Research Ethics Committee (Protocol 283/2019). Written informed consent was obtained from infants’ mothers/ guardians, and data were processed anonymously.

RESULTS

Sample description

The sample included 81 term infants and their mothers, described in Table 1. Infant anthropometry and BC per visit have been published previously (14), and are included in Supplementary Table 1.

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Table 1: Sample description

Maternal data	**N**	
Age (years) [Median (IQR)]	81	29 (24; 33)
Gravidity [Median (IQR)]	81	2 (2; 3)
Parity [Median (IQR)]	81	2 (1; 3)
Height (cm) [Mean ± SD]	81	158.9 ± 5.1
HIV-positive [n (%)]	81	25 (30.9)
Doppler results		
UmA-RI z-score [a]	81	0.53 ± 1.18
▪ Abnormal UmA-RI [b] [n (%)]	81	26 (32.1)
Birth data		
Sex (male) [n (%)]	81	41 (50.6)
Gestational age (weeks) [Mean ± SD]	81	39.3 ± 1.2
Birth weight (kg) [Mean ± SD]	81	3.06 ± 0.48
▪ Birth weight z-score [b] [Mean ± SD]		-0.45 ± 1.02
▪ Small-for-gestational age (SGA) [c,d] [n (%)]		18 (22.2)
▪ Large-for-gestational age (LGA) [c,d] [n (%)]		3 (3.7)
Birth length (cm) [Mean ± SD]	76	50.0 ± 2.6
▪ Birth length z-score [c] [Mean ± SD]		0.49 ± 1.43
Birth head circumference (cm) [Mean ± SD]	78	34.4 ± 1.6
▪ Birth head circumference z-score [c] [Mean ± SD]		0.55 ± 1.22
Difference between birth HCZ and BWZ (HCZ-BWZ) [Mean ± SD]	78	0.98 ± 1.25
▪ Asymmetric fetal growth (HCZ-BWZ>1) [n (%)]		44 (54.3)
Feeding practices		
Breastfeeding initiated [n (%)]	81	79 (97.5)
Duration of exclusive breastfeeding (months) [Median (IQR)]	73	4.0 (1.0; 6.0)
Duration of any breastfeeding (months) [Median (IQR)]	62	10.5 (4.3; 17.2)
Exclusive breastfeeding for 6 months [n (%)]	74	27 (33.3)
Still breastfeeding at last visit [n (%)]	81	16 (20.3)
Solids introduced (age, months) [Median (IQR)]	71	6.0 (5.0; 6.0)
Solids introduced at <6 months [n (%)]	71	20 (24.7)

[a] Calculated using INTERGROWTH-21ST UmA Doppler reference values (27).
[b] Abnormal UmA-RI: UmA-RI exceeds the 75th percentile for gestational age on the Pattinson et al reference curves (25), classified using the Umbiflow™ device.
[c] Calculated using the INTERGROWTH-21ST Newborn Size Standards (28).
[d] SGA: birth weight <10th percentile; LGA: birth weight >90th percentile.
BWZ = birth weight z-score; HCZ = head circumference z-score; HIV = human immunodeficiency virus; LGA = large-for-gestational age; SGA = small-for-gestational age; UmA-RI = umbilical artery resistance index.

Description and predictors of growth trajectories

In most cases, the best-fit models were obtained using Latent Class Growth Analysis with three classes (WAZ, LAZ, WLZ, BMIZ, HCZ and FFMZ) or two classes (FMZ, FMIZ and FFMIZ), with one index (MUACZ) resolving best with Growth Mixture Modelling (two classes) incorporating a random intercept and slope per class. Figure 1 shows the models and plots of actual data.

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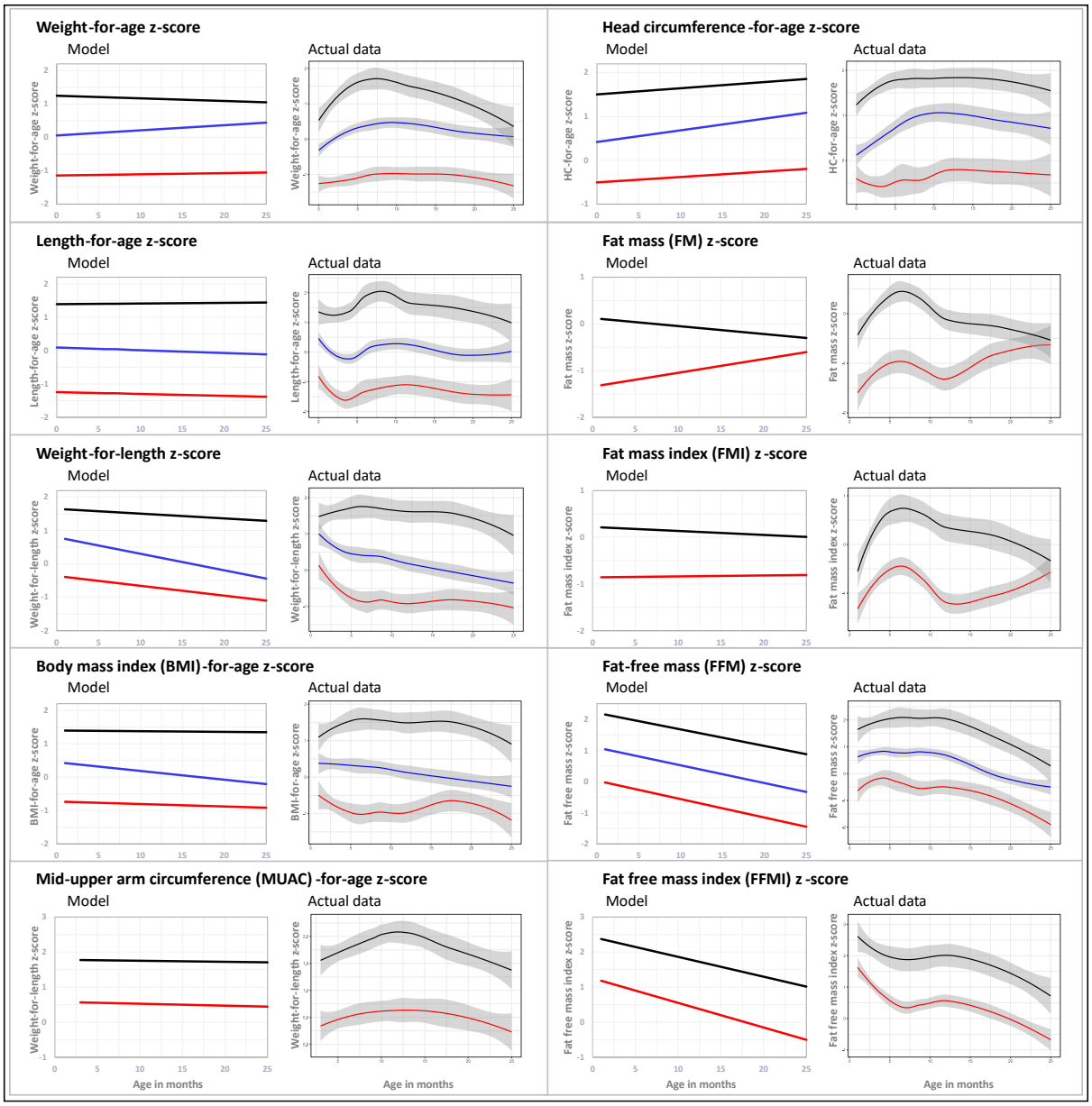

Figure 1: Trajectories of anthropometric and body composition z-scores, as predicted by Latent Class Trajectory Modelling and plotted using actual sample data

Anthropometry

All three WAZ trajectories showed an initial increase followed by a gradual decline. Infants with different WAZ trajectories differed significantly (P<0.5) with respect to UmA-RIZ and UmA-RI category (higher UmA-RIZ and more abnormal UmA-RI in the low trajectory), birth GA (higher in the high trajectory), birth WZ and HCZ (both increasing with higher trajectories). (Table 2). In multivariable analysis, the lower WAZ trajectory was predicted by lower GA and lower BWZ or SGA and GA, while the upper WAZ trajectory was associated with higher BWZ, GA and maternal gravidity (Table 4).

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The LAZ model described three near-parallel trajectories, with the trajectories of the actual data showing some variability in the first 6-9 months. After one year of age, the upper trajectory declined gradually, while the middle and lower trajectories remained more constant. Infants in the lower trajectory group had significantly ($P<0.5$) higher UmA-RIZ, larger proportion of abnormal UmA-RI, more maternal HIV, lower GA, lower BWZ and birth length z-score, and higher rates of SGA (Table 2). In multivariable analysis, the lower trajectory was predicted by higher UmA-RIZ, or abnormal RIZ combined with lower birth length z-score (Table 4).

The WLZ model described three trajectories that all declined over time, with the steepest initial decline in the lower trajectory. Significant differences ($P<0.5$) were seen in BWZ (lowest in the lower trajectory, highest in the middle trajectory) and the introduction of solid foods before 6 months of age (more common in the lower trajectory) (Table 2). In multivariable analysis, the lower trajectory was predicted by lower BWZ, but not SGA (Table 4). No significant predictors were found for the upper trajectory.

The BMIZ model described three trajectories that differed significantly with respect to GA at birth (lowest in the middle trajectory), BWZ and birth HCZ (lowest in the lower trajectory) and birth weight class (highest proportion of SGA in the lower trajectory, but lowest proportion in the middle trajectory) (Table 2). Multivariable analysis found that, compared to the middle trajectory, a higher GA increased the odds of being in the upper trajectory, while a lower BWZ increased the odds of being in the lower trajectory (Table 4).

The two MUACZ trajectories showed an initial increase followed by a decline back to 3-months values over time. Infant in the lower MUAC trajectory had significantly lower GA, BWZ and birth HCZ (Table 2). In multivariable analysis, only BWZ predicted MUACZ trajectory (Table 4).

The three HCZ trajectories increased only slightly over 2 years. Significant differences between the HCZ trajectory groups were seen for infant sex (greater proportion of males in the middle trajectory), BWZ and birth HCZ (increasing with higher trajectories), and birth weight class (higher SGA rate in the lower trajectory) (Table 2), with no significant predictors in multivariable analysis.

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Table 2: Characteristics of infants displaying various anthropometric trajectories

Anthropometric index and trajectory		n	Gravidity	Parity	HIV+	UmA-RI z-score [a]	Abnormal UmA-RI [b]	Sex male	Gestational age	Birth weight z-score [c]	SGA [c,d]	Birth length z-score [c]	Birth HC z-score [c]	Asymmetric [e]	EBF 6 months	Solids <6 months
			med (IQR) N=81	*med (IQR)* N=81	*n (%)* N=81	*mean ± SD* N=81	*n (%)* N=81	*n (%)* N=81	*mean ± SD* N=81	*mean ± SD* N=81	*n (%)* N=81	*mean ± SD* N=78	*mean ± SD* N=78	*n (%)* N=78	*n (%)* N=74	*n (%)* N=71
Weight-for-age (WAZ) [f]	**Upper**	17	3 (2; 4)	3 (2; 3)	5 (29.4)	0.12 ± 0.71	1 (5.9)	9 (52.9)	40.2 ± 1.1	0.47 ± 1.16	1 (5.9)	0.96 ± 1.45	1.24 ± 1.30	7 /16(43.8)	4/17 (23.5)	12/16 (75.0)
	Middle	38	2 (2; 3)	2 (1; 3)	9 (23.7)	0.35 ± 1.07	11 (28.9)	18 (47.4)	38.2 ± 1.1	-0.32 ± 0.80	5 (13.2)	0.62 ± 1.50	0.53 ± 1.12	20/37 (54.1)	13/24 (54.2)	23/32 (71.9)
	Lower	26	2 (2; 3)	2 (1; 3)	11 (42.3)	1.07 ± 1.41	14 (53.8)	14 (53.8)	38.6 ± 0.6	-1.25 ± 0.51	12 (46.2)	-0.02 ± 1.17	0.13 ± 1.17	8/25 (32.0)	22/25 (88.0)	16/23 (69.6)
	p		**0.064[g]**	**0.254[g]**	**0.297[h]**	**0.026[g] ***	**0.003[h] ***	**0.858[i]**	**<0.001[j] ***	**<0.001[g] ***	**0.003[h] ***	**0.074[j]**	**0.015[j] ***	**0.230[h]**	**0.430[h]**	**>0.999[h]**
Length-for-age (LAZ) [f]	**Upper**	10	2 (2; 3)	2 (1; 3)	0	0.09 ± 0.77	1(10.0)	4 (40.0)	39.6 ± 1.2	0.56 ± 1.14	0 (0.0)	1.50 ± 0.96	1.22 ± 1.26	5/9 (55.6)	1/10 (10.0)	4/10 (40.0)
	Middle	46	2 (2; 3)	2 (1; 3)	15 (32.6)	0.34 ± 1.07	12 (26.1)	22 (47.8)	39.6 ± 1.1	-0.34 ± 0.94	9 (19.6)	0.73 ± 1.35	0.58 ± 1.14	21/46 (45.7)	19/41 (46.3)	9/39 (23.1)
	Lower	25	2 (2; 3)	2 (1; 3)	10 (40.0)	1.07 ± 1.36	13 (53.0)	15 (60.0)	38.7 ± 1.0	-1.07 ± 0.70	9 (36.0)	-0.41 ± 1.29	0.23 ± 1.31	17/23 (73.9)	7/23 (30.4)	7/22 (31.8)
	p		**0.981[g]**	**0.737[g]**	**0.048[h] ***	**0.037[g] ***	**0.028[h] ***	**0.534[h]**	**0.004[j] ***	**<0.001[g] ***	**0.021[h] ***	**<0.001[j] ***	**0.115[j]**	**0.080[h]**	**0.087[h]**	**0.501[h]**
Weight-for-length (WLZ) [f]	**Upper**	20	3 (2; 4)	3 (2; 3)	7 (35.0)	0.40 ± 0.90	5 (25.0)	10 (50.0)	39.8 ± 1.1	-0.39 ± 1.09	4 (20.0)	0.18 ± 1.07	0.74 ± 1.09	13/19 (68.4)	5/18 (27.8)	5/17 (29.4)
	Middle	40	2 (2; 3)	2 (1; 3)	14 (35.0)	0.35 ± 1.00	11 (27.5)	23 (57.5)	39.2 ± 1.1	-0.24 ± 1.03	6 (15.0)	0.54 ± 1.72	0.73 ± 1.23	20/38 (52.6)	14/37 (37.8)	6/36 (16.7)
	Lower	21	2 (1; 3)	2 (1; 3)	4 (19.0)	1.02 ± 1.59	10 (47.6)	8 (38.1)	39.2 ± 1.3	-0.92 ± 0.79	8 (38.1)	0.68 ± 1.15	0.05 ± 1.24	10/21 (47.6)	8/19 (42.1)	9/18 (50.0)
	p		**0.084[g]**	**0.091[g]**	**0.424[h]**	**0.344[g]**	**0.233[h]**	**0.354[i]**	**0.102[j]**	**0.032[g] ***	**0.137[h]**	**0.524[j]**	**0.094[j]**	**0.381[i]**	**0.632[i]**	**0.040[h] ***
BMI-for-age (BMIZ) [f]	**Upper**	22	3 (2, 4)	3 (2, 3)	7 (31.8)	0.33 ± 0.93	5 (22.7)	10 (45.5)	40.0 ± 1.1	-0.31 ± 1.27	5 (22.3)	0.43 ± 1.36	0.90 ± 1.17	14/21 (66.7)	6/20 (30.0)	5/19 (26.3)
	Middle	38	2 (2, 3)	2 (1, 3)	14 (36.8)	0.37 ± 0.94	10 (26.3)	22 (57.9)	39.2 ± 1.2	-0.18 ± 0.82	3 (7.9)	0.57 ± 1.60	0.65 ± 1.20	17/36 (47.2)	13/36 (36.1)	7/34 (20.6)
	Lower	21	2 (2, 3)	2 (1, 3)	4 (19.0)	1.04 ± 1.64	11 (52.4)	9 (42.9)	40.0 ± 1.0	-1.09 ± 0.77	10 (47.6)	0.41 ± 1.24	0.02 ± 1.20	12/21 (57.1)	8/18 (44.4)	8/18 (44.4)
	p		0.059[g]	0.082[g]	0.392	0.243[g]	0.078[h]	0.462[i]	0.010[j] *	<0.001[g] *	0.002[h] *	0.908[j]	0.048[j] *	0.355[i]	0.651[i]	0.195[h]
MUAC-for-age (MUACZ) [f] (N=76)	**Upper**	32	3 (2; 3)	3 (1.8; 3)	10 (31.3)	0.26 ± 0.94	6 (18.8)	19 (59.4)	39.8 ± 1.1	-0.03 ± 1.18	5 (15.6)	0.73 ± 1.34	0.91 ± 1.15	17/31 (54.8)	9/32 (28.1)	7/31 (22.6)
	Lower	44	2 (1.8; 3)	2 (1; 3)	15 (34.1)	0.72 ± 1.30	17 (38.6)	19 (43.2)	39.1 ± 1.2	-0.77 ± 0.79	12 (27.3)	0.32 ± 1.50	0.18 ± 1.23	21/42 (50.0)	7/43 (20.6)	13/40 (32.5)
	p		0.075[k]	0.181[k]	0.063[i]	0.218[k]	0.063[i]	0.163[i]	0.004[l] *	0.003[k] *	0.275[h]	0.228[l]	0.012[l] *	0.683[i]	0.792[i]	0.357[i]
HC-for-age (HCZ) [f]	**Upper**	35	2 (2; 3)	2 (2; 3)	8 (22.9)	0.33 ± 0.98	10 (28.6)	14 (40.0)	39.6 ± 1.2	0.14 ± 0.97	2 (5.7)	0.87 ± 1.33	1.18 ± 1.18	20/34 (58.8)	11/31 (35.5)	10/31 (32.3)
	Middle	33	2 (1; 3)	2 (1; 3)	13 (39.4)	0.53 ± 1.13	10 (30.3)	24 (72.7)	39.2 ± 1.0	-0.74 ± 0.83	9 (27.3)	0.07 ± 1.56	0.16 ± 1.04	16/32 (50.0)	9/30 (30.0)	8/28 (28.6)
	Lower	13	2 (2; 3)	2 (1; 3)	4 (30.8)	1.09 ± 1.66	6 (46.2)	3 (23.1)	38.8 ± 0.9	-1.34 ± 0.57	7 (53.8)	0.48 ± 1.12	-0.21 ± 0.95	7/12 (58.3)	7/12 (58.3)	2/12 (16.7)
	p		**0.687[g]**	**0.460[g]**	**0.326[h]**	**0.311[g]**	**0.490[i]**	**0.003[h] ***	**0.116[j]**	**<0.001[g] ***	**<0.001[h] ***	**0.081[j]**	**<0.001[j] ***	**0.785[h]**	**0.221[h]**	**0.687 [h]**

[a] Calculated using INTERGROWTH-21ST UmA Doppler reference values (27).

[b] Abnormal UmA-RI: UmA-RI exceeds the 75th percentile for gestational age on the Pattinson et al reference curves (25), classified using the Umbiflow™ device.

[c] Calculated using the INTERGROWTH-21ST Newborn Size Standards (28).

[d] SGA: small-for-gestational age, birth weight <10th percentile.

[e] Asymmetric fetal growth: birth HC z-score exceeds birth weight z-score by more than 1 (HCZ-BWZ>1).

[f] Anthropometric z-scores calculated according to the WHO Growth Standards, using WHO Anthro software.

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[g] *Kruskal-Wallis test.*
[h] *Fisher's exact test.*
[i] *Chi-squared test.*
[j] *ANOVA.*
[k] *Wilcoxon Mann-Whitney test*
[l] *Independent t-test*
** P <0.5*
No significant (p<0.05) or near-significant (p<0.10) differences for any anthropometric index for maternal age, maternal height, difference between birth HC and birth weight z-scores, breastfeeding initiated, total months of exclusive breastfeeding, total months of breastfeeding, or age at first introduction of solid foods.
Abbreviations: BMI = body mass index; EBF = exclusive breastfeeding; HC = head circumference; HIV = human immunodeficiency virus; MUAC = mid-upper arm circumference; UmA-RI = umbilical artery resistance index.

Table 3: Characteristics of infants displaying various body composition trajectories

Body composition trajectories		**n**	**Gravidity** *med (IQR)*	**Parity** *med (IQR)*	**HIV+** *n (%)*	**UmA-RIZ** [a] *mean ± SD*	**Abnormal UmA-RI** [b] *n (%)*	**Gestational age** *mean ± SD*	**Birth weight z-score** [c] *mean ± SD*	**SGA** [c,d] *n (%)*	**Asymmetric** [e] *n (%)*	**EBF 6 months** *n(%)*
			N=79	*N=79*	*N=79*	*N=79*	*N=79*	*N=79*	*N=79*	*N=79*	*N=76*	*N=73*
FMZ	**Upper**	45	3 (2, 3)	2 (2, 3)	17 (37.8)	0.44 ± 1.00	13 (28.9)	39.6 ± 1.1	-0.07 ± 0.98	4 (8.9)	21/43 (48.8)	12/43 (27.9)
	Lower	34	2 (2, 3)	2 (1, 3)	8 (23.5)	0.68 ± 1.40	12 (35.3)	39.0 ± 1.2	-0.91 ± 0.89	13 (38.2)	20/33 (60.6)	15/31 (48.4)
	p		**0.428**[g]	**0.344**[g]	**0.002**[h] *****	**0.688**[g]	**0.545**[h]	**0.014**[i] *****	**<0.001**[g] *****	**0.004**[j] *****	**0.308**[h]	**0.071**[h]
FMIZ	**Upper**	28	3 (2, 4)	3 (2, 3)	23 (82.1)	0.24 ± 0.90	6 (21.4)	39.8 ± 1.1	-0.18 ± 1.16	5 (17.9)	15/26 (57.7)	8/26 (30.8)
	Lower	51	2 (2, 3)	2 (1, 3)	20 (39.2)	0.71 ± 1.29	19 (37.3)	39.1 ± 1.2	-0.57 ± 0.92	12 (23.5)	26/50 (52.0)	19/48 (39.6)
	p		**0.190**[g]	**0.101**[g]	**0.076**[j]	**0.133**[g]	**0.148**	**0.013**[i] *****	**0.116**[g]	**0.776**[j]	**0.776**[h]	**0.452**[h]
FFMZ	**Upper**	19	2 (2, 3)	2 (1, 3)	5 (26.3)	0.27 ± 0.88	3 (15.8)	39.9 ± 1.2	0.20 ± 0.97	1 (5.3)	10/18 (55.6)	5/17 (29.4)
	Middle	45	3 (2, 3)	2 (2, 3)	10 (22.2)	0.34 ± 1.02	12 (26.7)	39.4 ± 1.1	-0.42 ± 0.94	8 (17.8)	21/44 (47.7)	17/43 (39.5)
	Lower	15	2 (1.5, 3)	2 (1, 2.5)	5 (33.3)	1.50 ± 1.52	10 (66.7)	38.5 ± 0.9	-1.28 ± 0.72	8 (53.3)	10/14 (71.4)	5/14 (35.7)
	p		**0.657**[k]	**0.409**[k]	**0.895**[j]	**0.014**[k] *****	**0.007**[j] *****	**0.002**[l] *****	**<0.001**[k] *****	**0.002**[j] *****	**0.291**[j]	**0.846**[j]
FFMIZ	**Upper**	17	3 (2, 4)	3 (1, 3)	8 (47.1)	0.31 ± 0.97	4 (23.5)	39.7 ± 1.3	0.01 ± 1.10	2 (11.8)	11/16 (68.8)	4/16 (25.0)
	Lower	62	2 (2, 3)	2 (1, 3)	17 (27.4)	0.61 ± 1.23	17 (27.4)	39.3 ± 1.0	-0.55 ± 0.97	15 (24.2)	30/60 (50.0)	23/55 (41.8)
	p		**0.018**[g] *****	**0.047**[g] *****	**0.123**[j]	**0.328**[g]	**0.560**[j]	**0.198**[i]	**0.047**[g] *****	**0.338**[j]	**0.260**[j]	**0.383**[j]

[a] *Calculated using INTERGROWTH-21ST UmA Doppler reference values (27).*
[b] *Abnormal UmA-RI: UmA-RI exceeds the 75th percentile for gestational age on the Pattinson et al reference curves (25), classified using the Umbiflow™ device.*
[c] *Calculated using the INTERGROWTH-21ST Newborn Size Standards (28).*

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[d] *SGA: small-for-gestational age, birth weight <10th percentile.*
[e] *Asymmetric fetal growth: birth HC z-score exceeds birth weight z-score by more than 1 (HCZ-BWZ>1).*
[f] *Body composition z-scores calculated using reference data from Wells et al. (34).*
[g] *Wilcoxon Mann-Whitney test*
[h] *Chi-squared test.*
[i] *Independent t-test*
[j] *Fisher's exact test.*
[k] *Kruskal-Wallis test.*
[l] *ANOVA.*
** P <0.5*
No significant (p<0.05) or near-significant (p<0.10) differences for any body composition index for maternal age, maternal height, infant sex, birth length z-score, birth HC z-score, difference between birth HC and birth weight z-scores, breastfeeding initiated, total months of exclusive breastfeeding, total months of breastfeeding, or age at first introduction of solid foods, or solid foods introduced at <6 months.
Abbreviations: BMI = body mass index; EBF = exclusive breastfeeding; HC = head circumference; HIV = human immunodeficiency virus; MUAC = mid-upper arm circumference; UmA-RI = umbilical artery resistance index.

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Table 4: Statistically significant predictors of trajectory group membership according to uni- and multivariable analysis

Trajectory	Analysis using continuous variables for birth weight z-score, UmA-RI z-score, and difference between birth HC and birth weight z-scores			Analysis using dichotomised variables for SGA vs not SGA, normal vs abnormal UmA-RI, and symmetric vs asymmetric fetal growth		
	Predictor Variable	**Univariable OR (95% CI)**	**Multivariable OR (95% CI)**	**Predictor Variable**	**Univariable OR (95% CI)**	**Multivariable OR (95% CI)**
Weight-for-age (WAZ) – compared to the middle trajectory						
Odds of Lower Trajectory	↓ Birth weight z-score [a]	5.60 (2.32-13.55)	9.32 (2.32-37.50)	SGA [b]	5.56 (1.67-20.00)	9.09 (1.75-50.00)
	↓ Gestational age [c]	1.12 (1.04-1.22)	NS	↓ Gestational age [c]	1.12 (1.04-1.22)	1.15 (1.02-1.29)
Odds of Upper Trajectory	↑ Birth weight z-score [a]	2.94 (1.28-6.67)	4.55 (1.23-16.67)	SGA [a]	NS	NS
	↑ Gestational age [c]	1.10 (1.01-1.19)	1.12 (1.01-1.25)	↑ Gestational age [c]	NS	NS
	↑ Maternal gravidity	2.04 (1.16-3.57)	2.50 (1.14-5.56)	↑ Maternal Gravidity	2.04 (1.16; 3.57)	1.96 (1.08; 3.70)
Weight-for-length (WLZ) – compared to the middle trajectory						
Odds of Lower Trajectory	↓ Birth weight z-score [a]	2.20 (1.16-4.16)	2.95 (1.33-6.55)	SGA [a]	NS	NS
Body mass index (BMI)-for-age (BMIZ) – compared to the middle trajectory						
Odds of Lower Trajectory	↓ Birth weight z-score [a]	3.22 (1.59-6.66)	3.70 (1.56-9.09)	SGA [a]	10.61 (2.47-45.55)	NS
Odds of Upper Trajectory	↑ Gestational age [c]	NS	NS	↑ Gestational age [c]	1.09 (1.02-1.17)	1.09 (1.01-1.19)
Mid-upper arm circumference (MUAC)-for-age (MUACZ) – compared to the lower trajectory						
Odds of Upper Trajectory	↑ Birth weight z-score [a]	2.27 (1.30-3.95)	2.41 (1.22-4.77)	SGA [a]	NS	NS
Length-for-age (LAZ) – compared to the middle and upper trajectories combined						
Odds of Lower Trajectory	↑ UmA-RI z-score [d]	1.69 (1.14-2.52)	1.95 (1.15-3.30)	Abnormal UmA-RI [e]	3.74 (1.44-9.75)	4.85 (1.39-16.95)
	↑ Birth length z-score [a]	NS	NS	↓ Birth length z-score	2.00 (1.39-2.94)	1.96 (1.30-2.94)
Fat mass z-score (FMZ) – compared to the upper trajectory						
Odds of Lower Trajectory	↓ Birth weight z-score [a]	2.86 (1.54-5.26)	2.78 (1.37-5.55)	SGA [a]	6.35 (1.84-21.88)	6.86 (1.77-26.69)
	Maternal HIV	4.62 (1.67-12.80)	3.74 (1.17-11.99)	Maternal HIV	4.62 (1.67-12.80)	4.30 (1.32-14.05)
Fat-free mass z-score (FFMZ) – compared to the middle and upper trajectories combined						
Odds of Lower Trajectory	↑ UmA-RI z-score [d]	1.78 (1.19-2.64)	1.78 (1.13-2.80)	Abnormal UmA-RI [e]	4.91 (1.76-13.65)	6.45 (2.05-20.24)
	↓ Birth weight z-score [a]	2.94 (1.72-5.00)	2.63 (1.45-4.76)	SGA [a]	6.89 (2.17-21.87)	8.54 (2.37-30.78)

NS = not significant. Only significant odds ratios (where the 95% confidence interval does not include 1 are displayed.

[a] Calculated using the INTERGROWTH-21ST Newborn Size Standards (28). OR calculated per 1 unit increase.

[b] SGA: small-for-gestational age, birth weight <10th percentile.

[c] OR calculated per 1 week increase in gestational age.

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[d] *Calculated using INTERGROWTH-21ST UmA Doppler reference values (27). OR calculated per 1 unit increase.*
[e] *Abnormal UmA-RI: UmA-RI exceeds the 75th percentile for gestational age on the Pattinson et al reference curves (25), classified using the Umbiflow™ device.*
Abbreviations: HIV = human immunodeficiency virus; SGA = small-for-gestational age; UmA-RI = umbilical artery resistance index.

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Body composition

The two FMZ trajectories converged by 2 years, following an initial increase and decrease. Infants in the lower FMZ trajectory had significantly (P<0.5) lower GA, BWZ, and birth HCZ, and higher rates of SGA and maternal HIV (Table 3). In multivariable analysis, the lower trajectory was associated with maternal HIV and SGA, while the upper trajectory was predicted by higher BWZ (Table 4).

The FMIZ trajectories echoed the FMZ trajectories. Birth GA was slightly, but significantly (P<0.05), higher in the upper trajectory group (Table 3), but multivariable analysis did not identify any significant predictors.

The FFMZ model described three declining trajectories, losing approximately 1.2 FFMZ units by 24 months. This decline started earlier in the lower trajectory (~4 months) than in the middle trajectory (~10 months) or upper trajectory (~12 months). Infants in the lower trajectory had significantly (P<0.05) higher UmA-RIZ and more abnormal UmA-RI, lower GA, lower BWZ and a higher rate of SGA (Table 3). In multivariable analysis, the lower trajectory was predicted by a combination of higher UmA-RIZ and lower BWZ, or abnormal UmA-RIZ and SGA (Table 4).

The two FFMIZ trajectories similarly lost ~2 z-score units over the first two years. The upper FFMIZ trajectory had significantly higher BWZ, maternal gravidity and parity (Table 3), but multivariable analysis identified no significant predictors.

DISCUSSION

This study shows the various growth and BC trajectories within a single sample of healthy, full-term infants over the first two years of life. Actual data trajectories for WAZ, LAZ, MUACZ and HCZ showed little net change (<0.5 z-scores) over the course of two years, with a tendency to more rapid growth in the first 6-12 months, followed by slower growth thereafter. FMZ and FMIZ trajectories converged over time. Trajectories for WLZ and BMIZ decreased slightly over two years, while FFMZ and FFMIZ decreased markedly. The period of most rapid FFMZ and FFMIZ decline is echoed by declining MUACZ and WAZ trajectories in the second year of life. The small net two-year decreases in anthropometric trajectories do not convey the magnitude of FFM depletion suggested by the FFMZ and FFMIZ trajectories. This supports previous research reporting that anthropometric indices such as BMI and WLZ are inadequate predictors of BC in infancy and childhood (36).

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Of the potential indicators of FGR we investigated (summarized in Figure 2), BWZ (and, in some cases, SGA and birth length z-score) and prenatal placental function (UmA-RI) predicted certain anthropometric and BC trajectories, while asymmetry at birth was not a useful predictor. Overall, the study sample had a lower mean BWZ (-0.45 ± 1.02 vs. the expected 0.00 ± 1.00) and a higher rate of SGA (22.2%, vs. the expected 10%) than would be expected in a healthy population. While many social, environmental, nutritional, and health-related factors contribute to birth size, the potential contribution of placental insufficiency should not be ignored (11). The large mean difference between birth HCZ and BWZ (0.98 ± 1.25) and high rate of asymmetry (>50%) in the study sample, alongside its inability to predict growth trajectories, suggest that this is not an appropriate indicator of FGR in the study population.

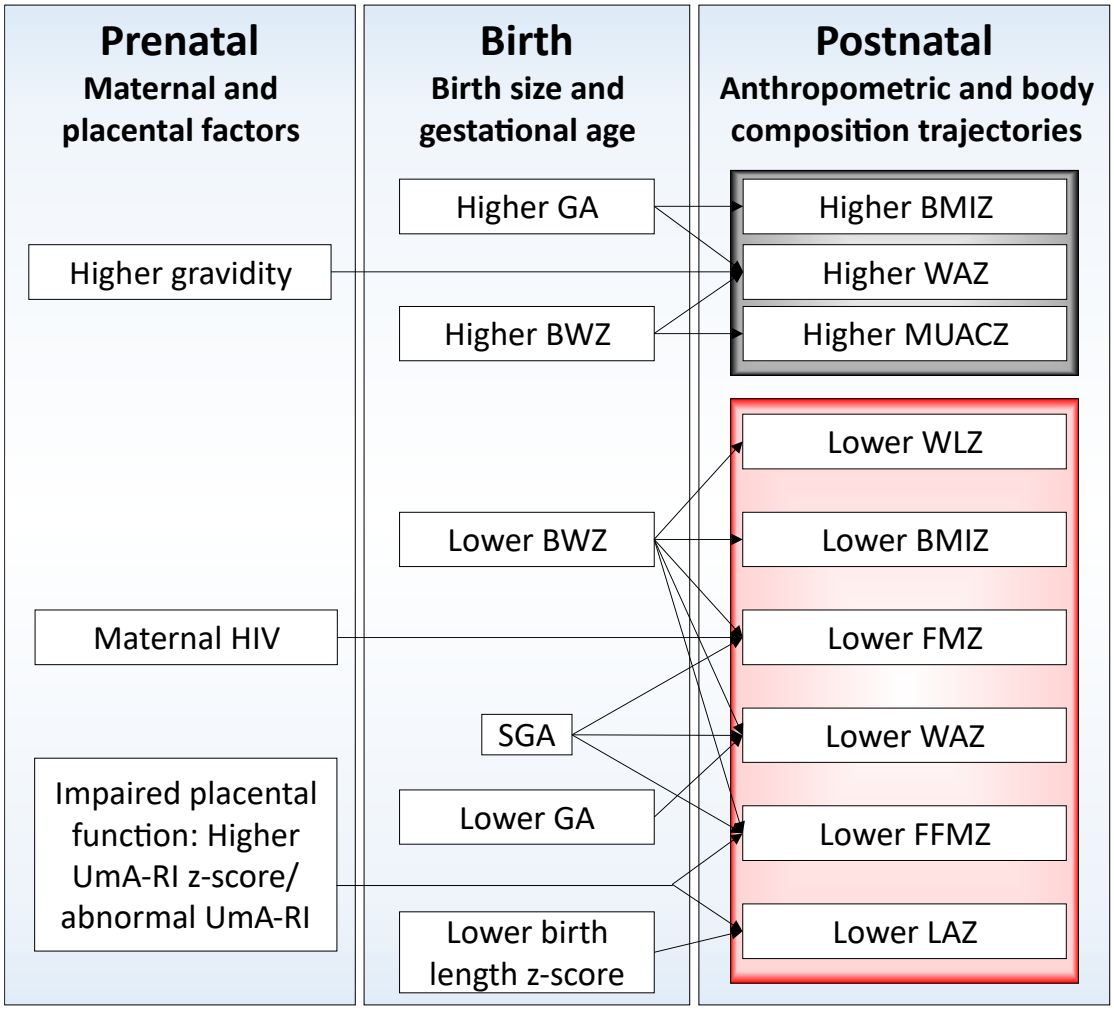

Figure 2: Summary of factors predicting anthropometric and body composition trajectories

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BWZ was strongly associated with weight-related (WAZ, WLZ, BMIZ) anthropometric trajectories, MUACZ, FFMZ and FMZ. Other research has reported birth weight indices to be associated with both FM and FFM (37,38). FFMZ and LAZ trajectories were associated with UmA-RI in multivariate analyses. Numerous studies have reported associations between LAZ and FFM (37,90-41), even into adulthood (41,42). Our results suggest that impaired placental function may be a common factor predisposing infants to restricted length growth and FFM accretion.

Our study is not the first to suggest that intrauterine growth and nutrition affect growth and BC in childhood and infancy. In low- and middle-income countries, especially, SGA or low birth weight often results in persistent growth deficits and high levels of stunting, wasting and underweight (43-46). Conflicting trends have been described for BC: one systematic review found that fetal growth restriction and SGA were both associated with lower infant FM and FFM (47), while other research associated SGA with excess accumulation of FM, particularly intra-abdominal fat (48). Part of the explanation for these differences may lie in the inability of SGA to distinguish true FGR from constitutional smallness. Doppler screening may be useful for distinguishing between these two groups, as demonstrated by a recent Austrian cohort study (49): in preterm infants assessed at term-equivalent age, SGA infants with abnormal Doppler findings (i.e. true FGR) had significantly lower FFM and FFMZ than AGA infants, while SGA infants with normal Doppler findings (i.e. constitutionally small infants) did not differ significantly from AGA infants (49). This indicates that placental insufficiency, rather than simply SGA, places infants at risk of FFM depletion – a finding supported by our results. Postnatally, nutrition and growth in infancy also affect BC outcomes. Rapid early weight gain, especially in SGA infants, is associated with higher FM (50), whereas length growth is more strongly associated with FFM accretion (41). Therefore, nutrition interventions and growth targets need to focus on linear growth and not simply weight gain.

One of this study's main strengths is the inclusion of much of the first thousand days of life. Multiple measurements over time allowed for longitudinal growth trajectory analysis, increasing the translatability of the results to individual level. Supporting optimal growth and BC in children requires a life-course approach (51,52), with the first thousand days being especially important (53,54). This research adds to the evidence that early-life exposures have long-term effects, stressing the need for interventions targeting pre- and peri-conception maternal nutrition (55), supporting fetal growth (56), and optimizing infant feeding from birth through complementary feeding and beyond (57). Interventions with strong evidence for improving pregnancy/ perinatal outcomes and fetal/ infant growth include prenatal multiple micronutrient supplementation, kangaroo mother care (particularly for small

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vulnerable newborns), delayed cord clamping, supporting breastfeeding according to WHO recommendations, provision of high-quality complementary food, routine vitamin A supplementation and the appropriate management of moderate and severe malnutrition (57). Additionally, moderate quality evidence suggests that prenatal calcium supplementation, targeted maternal protein-energy supplementation, caregiver education on improved complementary feeding, preventative zinc supplementation and provision of micronutrient powders can all support improved growth outcomes (57). Public health policies and practice need to focus on consistently implementing these interventions in the health system, while research is needed to track both the implementation and the effect on outcomes related to infant and child growth. Much less is known about how early interventions affect infant and child body composition, making this an important area of research (36). For growth in later childhood and adolescence, the evidence suggests that obesity prevention is key, as this not only supports the health of the current generation but also the next, through improving the nutrition status of young women of reproductive age (57).

Our study is limited by the sample size, which likely introduced some statistical volatility, and the exclusion of preterm infants from the sample. The use of routine birth anthropometry measurements presents a quality control challenge, especially for birth length measurement (58). Nonetheless, the results suggest important avenues to be explored in larger studies. The associations between abnormal UmA-RI, LAZ and FFM deserve further examination, particularly considering South Africa's high prevalence of both stunting (~27% of children under five years (59)) and placental insufficiency (11-13% of healthy pregnancies (11,12)). Moreover, previous research has described associations between FFM and neurodevelopmental outcomes, particularly (but not exclusively) in preterm infants (36). As early BC often tracks into adulthood (36,38), future research should investigate the possible effects of widespread FFM depletion on educational capacity and long-term earning potential, an association that has been well described in relation to poor linear growth (60,61). Routine prenatal Doppler screening could help identify infants at risk of stunting. Finally, the long-term effects of placental insufficiency in preterm infants deserve further investigation, particularly since preterm birth is itself a risk factor for poor growth outcomes. The emergence of GA as a significant predictor of outcomes even in term infants support this.

CONCLUSION

Prenatal placental insufficiency, identified using UmA-RI Doppler screening, predicted lower FFMZ and LAZ trajectories in term infants, while lower BWZ predicted lower WAZ, WLZ,

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BMIZ, FFMZ and FMZ trajectories. Optimizing infant and child growth will require improved maternal nutrition and healthy pregnancies to optimize placental function and fetal growth.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Anthropometry and body composition per visit

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	birth	6 weeks	10 weeks	14 weeks	6 months	9 months	12 months	18 months	24 months
Anthropometry									
N	81	58	71	72	71	72	64	56	50
Weight (kg)	3.06 ± 0.48	4.74 ± 0.68	5.73 ± 0.80	6.44 ± 0.93	7.89 ± 1.13	8.97 ± 1.31	9.53 ± 1.38	10.69 ± 1.45	11.52 ± 1.43
WAZ	-0.45 ± 1.02	-0.22 ± 1.09	-0.03 ± 1.09	0.05 ± 1.10	0.20 ± 1.18	0.30 ± 1.18	0.09 ± 1.18	-0.04 ± 1.16	-0.35 ± 1.08
Length (cm)	50.0 ± 2.56	54.4 ± 2.6	58.2 ± 2.6	60.7 ± 2.6	66.8 ± 3.0	71.2 ± 3.1	75.1 ± 2.7	80.3 ± 3.5	85.5 ± 4.1
LAZ	0.49 ± 1.43	-0.79 ± 1.27	-0.43 ± 1.21	-0.38 ± 1.15	0.01 ± 1.31	0.02 ± 1.28	-0.01 ± 1.09	-0.52 ± 1.24	-0.38 ± 1.30
WLZ	N/A	0.75 ± 1.04	0.56 ± 1.00	0.56 ± 1.09	0.35 ± 1.19	0.39 ± 1.12	0.16 ± 1.19	0.27 ± 1.13	-0.25 ± 1.06
BMIZ	N/A	0.27 ± 0.99	0.30 ± 1.01	0.40 ± 1.08	0.23 ± 1.18	0.31 ± 1.14	0.16 ± 1.17	0.38 ± 1.12	-0.18 ± 1.10
MUAC (cm)	N/A	12.9 ± 1.0	13.8 ± 1.1	14.4 ± 1.1	15.2 ± 1.19	15.8 ± 1.3	16.0 ± 1.4	16.1 ± 1.2	16.0 ± 1.3
MUACZ	N/A	N/A	N/A	0.89 ± 0.96	1.00 ± 0.94	1.22 ± 0.97	1.27 ± 1.08	1.09 ± 0.95	0.73 ± 1.03
HC (cm)	34.4 ± 1.58	38.5 ± 1.5	40.2 ± 1.4	41.5 ± 1.4	44.3 ± 1.3	45.8 ± 1.6	47.1 ± 1.4	48.2 ± 1.7	49.1 ± 1.3
HCZ	0.55 ± 1.22	0.61 ± 1.22	0.74 ± 1.07	0.84 ± 1.01	1.18 ± 1.00	1.03 ± 1.11	1.21 ± 0.98	0.97 ± 1.18	0.90 ± 0.87
Body Composition									
N	N/A	44	57	47	56	66	50	47	42
FM (kg)	N/A	0.72 ± 0.26	1.07 ± 0.32	1.36 ± 0.47	2.11 ± 0.73	2.05 ± 0.72	1.90 ± 0.86	2.20 ± 0.78	2.42 ± 0.74
% FM	N/A	14.62 ± 4.41	18.33 ± 4.59	20.33 ± 5.44	25.98 ± 6.02	22.54 ± 5.79	19.41 ± 6.59	20.21 ± 5.62	20.68 ± 5.32
FMZ	N/A	-0.74 ± 1.10	-0.57 ± 0.81	-0.45 ± 1.04	0.053 ± 0.99	-0.38 ± 1.01	-0.78 ± 1.08	-0.32 ± 0.59	-0.61 ± 0.68
FMI (kg/m^2)	N/A	2.36 ± 0.71	3.14 ± 0.90	3.63 ± 1.21	4.60 ± 1.40	3.93 ± 1.16	3.35 ± 1.41	3.41 ± 1.14	3.27 ± 1.04
FMIZ	N/A	-0.80 ± 0.88	-0.49 ± 0.81	-0.37 ± 1.05	0.08 ± 0.95	-0.39 ± 0.95	-0.75 ± 1.08	-0.50 ± 0.88	-0.53 ± 0.75
FFM (kg)	N/A	4.15 ± 0.52	4.79 ± 0.60	5.21 ± 0.59	5.88 ± 0.66	6.91 ± 0.86	7.71 ± 1.07	8.53 ± 1.04	9.23 ± 1.20
% FFM	N/A	85.38 ± 4.41	81.67 ± 4.59	79.67 ± 5.44	74.03 ± 6.02	77.46 ± 5.79	80.59 ± 6.59	79.79 ± 5.62	79.32 ± 5.32
FFMZ	N/A	0.46 ± 1.01	1.04 ± 0.99	1.12 ± 0.85	0.77 ± 0.92	0.88 ± 1.05	0.74 ± 1.10	0.00 ± 0.96	-0.54 ± 1.08
FFMI (kg/m^2)	N/A	13.77 ± 1.34	13.99 ± 1.23	14.01 ± 1.20	13.10 ± 1.33	13.52 ± 1.26	13.70 ± 1.33	13.22 ± 1.10	12.45 ± 1.18
FFMIZ	N/A	1.48 ± 1.09	1.47 ± 0.91	1.42 ± 0.88	0.53 ± 1.10	0.87 ± 1.05	0.95 ± 1.03	0.51 ± 0.90	-0.22 ± 1.06

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BRIDGING TEXT

The results of this final paper clearly show the value of longitudinal analysis of growth trajectories in illuminating trends that are obscured by repeated cross-sectional analysis of samples containing different participants. In particular, some of the differences which lost significance at later ages in the cross-sectional analysis remained clear in the trajectory analysis – particularly the differences in body length, FFM and FFMI z-scores. This suggests that the lack of significance observed was, indeed, due to the small and inconsistent samples rather than a true lack of difference. Conversely, the models also showed clearly that the trajectories of FM and FMI z-scores converge at two years of age, suggesting that differences in FM at birth do not persist over time.

The associations between placental insufficiency, BWZ and postnatal growth trajectories are an important finding of this paper. Lower BWZ (and, in some cases, SGA) were predictive of growth trajectories over the first 24 months of life for weight-related indices (WAZ, WLZ, BMIZ) as well as FFMZ and FMZ, while lower birth length z-score predicted LAZ trajectory. These associations are all intuitive and expected. The most important and novel finding was that abnormal prenatal UmA-RIZ was strongly predictive of lower trajectories for both LAZ and FFMZ. This plays into important public health problems. Stunting remains the most prevalent form of child malnutrition in South Africa and has been relatively resistant to change. Considering the high prevalence of abnormal UmA-RI found in the various Umbiflow studies, placental insufficiency may be contributing substantially to the stunting burden in South Africa, particularly since postnatal nutrition is rarely adequate to support catch-up growth. Secondly, the consistent decline in FFM is a concern. The finding that FFMI declines similarly (while FM and FMI do not) suggests that there may be a real change in body composition over time that is not attributable to faltering length growth. Thus, at the end of the first thousand days, the children in the study sample had a relatively low FFM that was continuing to decline, with no concomitant decrease in FM. From a physiological perspective, this may have the effect of lowering the resting energy expenditure and predisposing the child to weight gain and fat deposition.

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CHAPTER 9: GENERAL DISCUSSION AND CONCLUSION

The overall aim of this thesis was to describe the postnatal growth and body composition up to two years of age of two cohorts of small and vulnerable infants in Tshwane District, Gauteng Province. “Small and vulnerable” was defined as meeting any one of three independently applied criteria:

1. Gestational age at birth: preterm birth at <37 weeks gestation.
2. Size at birth, assessed as:
    a. Birth weight-for-GA: SGA if birth weight <10th percentile for GA.
    b. Asymmetric growth restriction: more than one z-score unit difference between birth head circumference (HC) and birth weight (BW) z-scores.
3. History of placental insufficiency (assessed by third-trimester Doppler screening of the umbilical artery).

To achieve this aim, it was first necessary to develop an integrated cross-disciplinary understanding of growth throughout the first thousand days (including the methods, reference values and cut-offs used to assess and classify growth) and to determine which of the commonly used growth charts for preterm infants would be superior. This was done in the first and second publications (i.e. chapters 3 and 4) respectively. The rest of the publications then investigated postnatal growth outcomes and their early-life predictors in two cohorts of infants. Publications 3 and 4 (chapters 5 and 6) reported on the preterm infant cohort, focusing particularly on birth weight as a predictor of growth outcomes. Publications 5 and 6 (chapters 7 and 8) focused on a cohort of term infants and, in addition to birth size indices, included third trimester Doppler screening of the umbilical artery as a novel measure of placental insufficiency. The additional paragraphs at the end of chapters 3-8 summarise the logical flow linking the separate publications. An integrated summary of the results of these investigations is presented in **Error! Reference source not found.** 9-1.

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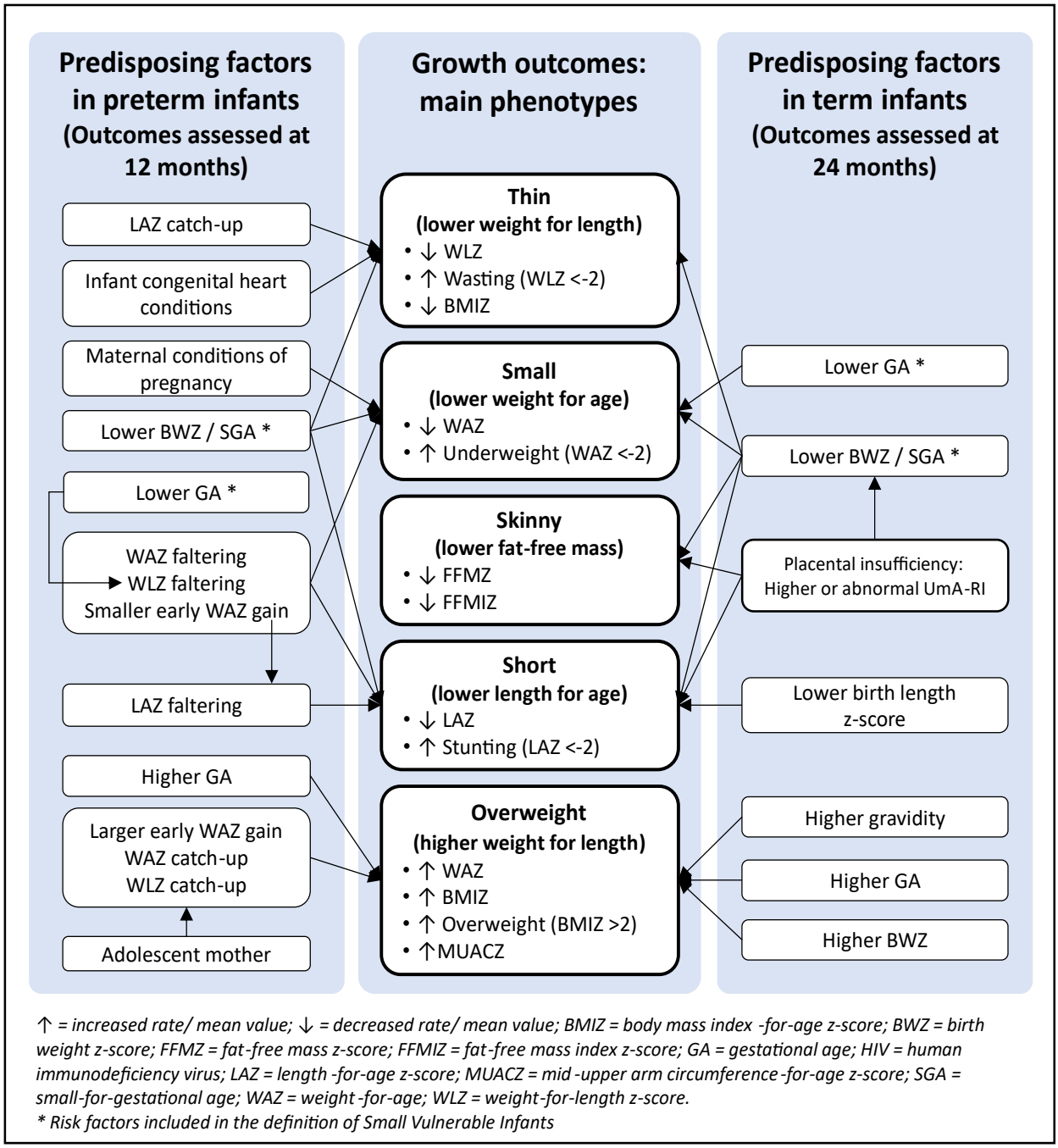

Figure 9-1: Summary of results

The totality of the research clearly shows that events in early life – i.e. *in utero* and in the early postnatal period – have strong associations with growth throughout the first two years of life. This basic concept is well-supported by a large body of literature, which has been extensively reviewed in the preceding publications. However, the indices and indicators of foetal growth used in research have thus far mostly been limited to measurements of size at birth. The Lancet framework for small vulnerable newborns, originally introduced in Chapter 2 (Figure 2-1) highlights two of these early-life risk factors: lower gestational age (i.e.

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preterm birth) and lower birth weight (i.e. SGA and/ or low birth weight).[1] This research suggests that two more risk factors are of particular importance: the presence of an abnormal Doppler (UmA-RI) in the third trimester of pregnancy (i.e. placental insufficiency), and abnormal (faltering or excessive) early weight gain, particularly in preterm infants.

An interesting finding from the multivariable analyses performed in both cohorts was that continuous variables were generally more strongly predictive of outcomes than when the same variables were dichotomised. For example, birth weight z-score performed better than SGA, and UmA-RIZ performed better than a simple classification of normal/ abnormal UmA-RI. This may be in part because classifying a continuous variable necessarily reduces the amount of information available, particularly in "borderline" cases where individuals fall close to the cut-offs. Mismatch between an individual's classification and clinical phenotype is possible, for example in the constitutionally small SGA infant that is meeting their full genetic potential and has no growth restriction. Thus, some individuals in the "normal" categories may also be at risk of poor outcomes: for example, in the preterm infant cohort, 7.2% of the AGA infants were underweight (age-corrected WAZ <-2) at one year, despite starting off at a BWZ above the 10th percentile (i.e. BWZ >-1.28). This argues for a more nuanced assessment of birth size than a simple 10th percentile cut-off.

Some researchers have argued that asymmetry at birth, assessed using the proportion or difference between birth HC and birth weight z-scores, could be a useful predictor of risk.[2,3] In the UmbiBaby study (publications 5 and 6, chapter 7 and 8), asymmetry was not predictive of growth outcomes in univariate or multivariable analysis. Therefore, this parameter was not a useful indicator of FGR in the study sample of term infants and would not add value to neonatal assessment. Though the preterm sample did not have HC measurements available, previous research conducted in preterm infants suggests that SGA is a more important predictor of growth and neurodevelopmental outcomes, and that indicators of asymmetry have limited added value.[4]

The UmbiBaby study was set up to investigate whether prenatal UmA-RI Doppler screening would be useful for identifying infants at risk of growth anomalies in children born to women assessed to otherwise have had low risk pregnancies. This is the first study to report such longitudinally collected data. The most important finding was the strong association of UmA-RI with growth trajectories for LAZ and FFMZ. Though FFMZ trajectory was also associated with BWZ, LAZ trajectory was not (at least in the term-born UmbiBaby cohort), suggesting that the UmA-RI screening can identify a group of at-risk infants that would be missed if only birth weight were considered. Of course, the predictive value of birth length z-score cannot be ignored: numerous studies have found that birth length is a key predictor of childhood

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length growth.[5,6] This also emphasises the need for reliable length measurements in maternity units.[7]

In both the preterm sample and the UmbiBaby sample, maternal HIV had little association with postnatal growth outcomes. In the UmbiBaby sample, maternal HIV was associated with increased likelihood of a low FMZ trajectory, but since the trajectories for FMZ converged by two years of age the practical value of this is debatable. Previous research that also included the UmbiBaby participants has shown that, while HIV and UmA-RI individually did not significantly predict LAZ at 18 months, the combination of both insults was associated with significantly lower LAZ and higher risk of stunting.[8] It is plausible that the UmbiBaby cohort sample was too small to detect this effect. In the cohort of preterm infants, maternal HIV without any ART in pregnancy was associated with stunting in univariate analysis, but this association disappeared in the multivariable analysis, suggesting that it was confounded by another variable (e.g. BWZ). The general lack of association of HIV with growth outcomes may be due to the high antenatal ART coverage (81% of the preterm sample mothers and 100% of the UmbiBaby mothers where ART history was recorded), which achieves virologic suppression in most mothers. The fact that no infant in either cohort contracted HIV supports this possibility. The published literature on growth outcomes in HIV exposed but uninfected infants is mixed, with some reviews reporting impaired length growth[9] but others finding no consistent difference in growth outcomes.[10]

A final risk factor that emerged as an important predictor of growth outcomes in preterm infants is early WAZ growth. The change in WAZ up to 50 weeks PMA was associated with both undernutrition (underweight and stunting, with smaller early WAZ gains) and overweight (with greater early WAZ gain). This has profound implications for clinical practice since early postnatal follow-up visits offer an excellent opportunity for growth-supporting interventions. No exact guidelines exist for the limits of acceptable WAZ changes in this period, but this series of studies suggests that a change of no more than one z-score unit from the birth weight up to 50 weeks PMA may be used as a rough guideline. A recent expert opinion guide also suggested a loss of more than one WAZ unit (excluding the first two weeks after birth) as a suitable cut-off for growth faltering.[11] In the preterm infant sample, compared to infants who lost or gained more than one z-score unit, those who maintained a weight-for-PMA z-score within ±1 z-score of their birth weight z-score had comparatively low rates of underweight (13-14% *vs*. 25-31%), stunting (17-18% *vs*. 26-28%), wasting (5-6% *vs*. 12-15%) and overweight (4-6% *vs*. 18-25%). Periods of accelerated growth may necessitate more careful assessment than periods of faltering growth since catch-up growth is normal and expected in neonates with FGR. Cooke *et al.* define catch-up growth as a physiologic

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period of increased growth velocity following a period of growth faltering, during which the infant ideally returns to their original growth percentile/ z-score.[11] Undesirable accelerated growth, conversely, occurs without any preceding growth faltering; a gain of ≥1 WAZ unit is suggested as an indicator.[11] Cooke *et al.* classify rapid growth in SGA infants as spontaneous accelerated growth. In reality, true FGR (as opposed to constitutional smallness) represents a period of faltering growth, implying that rapid postnatal growth may rather represent normal, physiologic catch-up.[11] Monitoring length growth alongside weight gain may help distinguish between physiologic catch-up growth and problematic growth acceleration.[12]

In summary, then, this work shows that if the aim is timeous identification of infants at risk of medium to longer-term growth anomalies, the small vulnerable newborn framework[1] could be usefully expanded to include a prenatal component (placental insufficiency) and an early postnatal component (early postnatal growth). Furthermore, while dichotomous indicators are clinically useful, it must be acknowledged that risk occurs on a spectrum, and that application of a hard cut-off will inevitably misclassify some infants. Figure 9- shows three simplified frameworks that attempt to illustrate this.

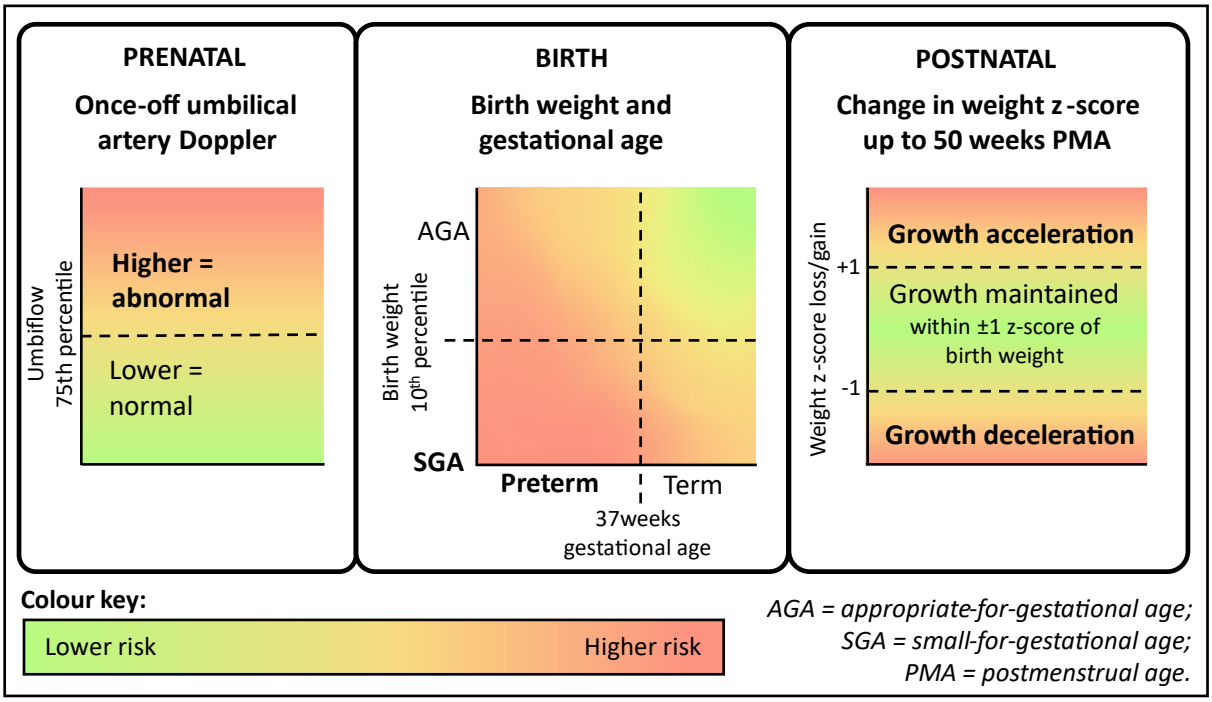

Figure 9-2: Risk factors for sub-optimal childhood growth trajectories anthropometric outcomes in the first one to two years of life.

The central schematic (birth) is a simplified version of the Lancet framework for the Small Vulnerable Newborn, while the other two schematics illustrate the prenatal element

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(umbilical artery resistance index, as assessed by once-off prenatal Umbiflow Doppler screening) and the postnatal element (early growth, operationalised as the change in weight-for-PMA z-score up to 50 weeks PMA). The graduated colours and dashed cut-off lines signify the fact that there is no clear, abrupt demarcation of “risk” versus “no risk”. Rather, risk occurs on a spectrum, and an individual’s overall condition may not strictly agree with their position relative to the cut-off. For example, an infant born extremely SGA may be at lower risk of overweight from large postnatal weight gains than one born AGA. Similarly, an infant born AGA but with an abnormal prenatal Doppler may be at greater risk of stunting and FFM depletion than an infant born slightly SGA but with a normal Doppler. These examples underscore that assessment must not only be individualised but should also consider events in the prenatal period. Each instance where an infant falls in a “red” area (i.e. beyond the cut-off) or “orange” area (i.e. near the cut-off) on any of the schematics should be considered a sign of increased risk, indicating a need to pay closer attention to postnatal growth.

The research presented here has several implications for clinical practice, some of which are more immediately attainable than others. Improved collaboration between the antenatal care services, delivery services and infant/ child health services is important. In practice, this may involve record-based communication, with clear documentation on the patient-retained child record (Road-to-Health Booklet (RtHB) in the South African context) of antenatal and perinatal information such as Doppler/ Umbiflow results (if available), acute and chronic maternal health conditions (including HIV and its treatment), gestational age at birth and the certainty thereof, and accurate birth measurements of weight, length, and HC. Repeating length and HC measurements at the first postnatal visit at 3-6 days (or at the time of discharge, for infants born via Caesarean section) could greatly improve the accuracy of these measurements since it does not disrupt early skin-to-skin contact and breastfeeding, both mother and baby are likely to be calmer and the effect of cranial moulding on HC would be reduced. These measurements, too, should be documented on the RtHB.

This research adds to the argument for incorporating Umbiflow Doppler screening into routine antenatal care across all primary health care clinics – a strategy which is currently being trialled in primary health care clinics across Tshwane District (Gauteng province, South Africa). In addition to the significant reduction in stillbirth rates (a compelling argument on its own), Doppler screening can also help identify infants at risk of poor linear growth and stunting, providing a target for interventions to reduce this prevalent form of malnutrition. Alongside this, the importance of accurate pregnancy dating cannot be overemphasised. Accurate estimates of gestational age are not only important for interpreting neonatal size

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and maturity, but also for correctly interpreting Umbiflow measurements. South African maternity care guidelines recommend that, if possible, all women who present for antenatal care with a symphysis-fundal height <24cm (i.e. before 24 weeks' gestation) should undergo one basic ultrasound examination.[13] The recent development of lower-cost handheld point-of-care ultrasound devices mean that basic ultrasound examinations (e.g. for pregnancy dating) may become accessible at primary health care level in the near future.[14,15]

The accuracy of infant anthropometric measurements – both at birth and at postnatal visits – needs urgent attention. A wealth of published research has shown that frontline health workers struggle not only with taking accurate measurements but also with interpreting these measurements and taking appropriate action.[7,16-18] In the future, electronic health records incorporating automated growth assessment could help improve the situation while simultaneously facilitating inter-disciplinary and inter-facility communication and enabling the simultaneous assessment of different risk factors.[19] In the meantime, initiatives to ensure equipment availability, sufficient staff and adequate training are needed to fill the gap. Finally, growth monitoring cannot simply stop at measuring and plotting, it must also include appropriate feedback, guidance, and support for caregivers – the success of Growth Monitoring and Promotion as a public health programme hinges on this *promotion* aspect. Resources to support mothers of infants with growth concerns do exist, including screening guidelines in the Integrated Management of Childhood Illness protocols, educational materials in the RtHB and referral pathways to dietitians in the public sector; these must be recognised and correctly utilised to achieve optimal outcomes.

Several questions remain to be addressed by future research. A WHO working group recently identified a list of research priorities for preterm and LBW infants, many of which included growth as an outcome of interest.[20] Priority nutrition-related research questions that extend beyond the neonatal period include the scaling-up and duration of exclusive breastfeeding, long-term effects of KMC, and supplementation with probiotics, iron, zinc, vitamin A and vitamin D.[20] These research questions all contribute to the complex picture of ensuring optimal growth and long-term outcomes in this vulnerable population of infants.

One area which has not yet been studied is the effect of prenatal placental insufficiency on growth outcomes in preterm infants. The UmbiBaby cohort only recruited 10 preterm infants, who were excluded from the analyses due to their small number, and due to a lack of guidelines on how body composition parameters should be interpreted in preterm infants. Future Umbiflow studies should therefore specifically aim to also recruit preterm infants.

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The observed decline in FFMZ trajectories over the first two years of life has not previously been described in the literature, raising the question of to what extent this finding is true in other (South African) populations. Furthermore, robust longitudinal studies are needed to examine the effects of this early FFM depletion on long-term outcomes relating to neurodevelopment and educational achievement, physical performance, risk of obesity and metabolic health.

Finally, interventions to address the root causes of poor growth – i.e. placental insufficiency, FGR, preterm birth, and early growth faltering or excess – need to be developed and tested in the local context. Published literature describes several interventions to support maternal health, improved pregnancy outcomes and foetal and infant growth in LMICs. These include:

- In the prenatal period: routine multiple micronutrient supplementation, screening for and treating asymptomatic maternal urinary tract infections, and syphilis screening and treatment. Additionally, targeted protein and energy supplantation, low-dose aspirin, and vaginally delivered progesterone are valuable in high-risk women. Smoking cessation, if indicated, and use of insecticide-treated bed nets in malaria-endemic areas are also proven to improve pregnancy outcomes.[21]
- For pregnant women at risk of preterm delivery, antenatal corticosteroids significantly improved infant outcomes after preterm birth.[21]
- In the neonatal period, delayed cord clamping, vitamin K administration and kangaroo mother care improve neonatal nutrition status and reduce mortality.[22] Early skin-to-skin care for all infants also supports successful breastfeeding initiation.[23]
- In infancy and early childhood, growth can be supported by supporting breastfeeding according to WHO guidelines, improved quality of complementary feeding, and routine preventative vitamin A supplementation, with supplementation of iron, zinc and multiple micronutrients as indicated.[22] Additionally, disease prevention in important through water, sanitation and hygiene (WASH) interventions, regular deworming, and malaria prophylaxis in malaria endemic areas.[22]

Many (if not most of) these interventions are already incorporated in the guidelines used by public health facilities in South Africa,[13,24-26] though implementation may be inconsistent and results in the reduction of child malnutrition (particularly stunting) are not yet evident. This research identified placental insufficiency as a potentially important contributing factor; however, little is known about the causes or potential interventions for the widespread placental insufficiency observed in otherwise healthy pregnant women. As a first step, then, aetiological studies are needed to determine the causes of placental insufficiency, whereafter appropriate interventions can be developed and trialled. There is also a need for

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clearer guidelines for distinguishing appropriate catch-up growth from undesirable growth acceleration (and a lack of catch-up growth where it is indicated), particularly in a population where stunting is prevalent. Furthermore, healthy growth requires adequate nutrition: locally appropriate strategies to support infant and child nutrition for within a socioeconomically constrained context are urgently needed. This is particularly true from the complementary feeding phase onward, when breast milk alone can no longer provide adequate nutrition, but access to nutrient-dense foods may be limited. These larger problems go beyond the scope of the health system, once again bringing into sharp focus the need for interdisciplinary and inter-sectoral collaboration.

CONCLUSION

The assessment of growth in the first thousand days of life is complex and nuanced, but critically important. Improving the nutrition status of South African children – particularly reducing the incidence of stunting and stemming the rising tide of overweight/ obesity – will require a life-course approach starting from the moment of conception. Foetal nutrient supply (indicated by Doppler screening of placental function) and attained intrauterine growth (indicated by size at birth) are invaluable for identifying infants at risk of growth and body composition anomalies, while early growth patterns can indicate a need for timeous intervention to prevent longer-term problems. Current practice would benefit from clearer cross-discipline communication, routine antenatal Doppler and more meticulous measurement and recording of birth anthropometry. Interventions to support healthy pregnancies (particularly placental function) and optimal foetal growth should take the forefront in future research.

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APPENDIX A: ETHICS CLEARANCE CERTIFICATES

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ETHICS CLEARANCE FOR UMBIBABY STUDY: UP FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through February 28, 2022 and Expires: 03/04/2023.

11 February 2021

Approval Certificate
Amendment

Ethics Reference No.: 283/2019
Title: Early child outcomes of in utero growth restricted and premature babies - a prospective cohort study in South Africa (the UmbiBaby study)

Dear Dr UD Feucht

The **Amendment** as supported by documents received between 2021-01-27 and 2021-02-10 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2021-02-10 as resolved by its quorate meeting.

Please note the following about your ethics approval:
- Please remember to use your protocol number (283/2019) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

Research Ethics Committee
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Tel +27 (0)12 356 3084
Email: deepeka.behari@up.ac.za
www.up.ac.za

Fakulteit Gesondheidswetenskappe
Lefapha la Disaense tša Maphelo

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ETHICS CLEARANCE FOR UMBIBABY STUDY: KALAFONG HOSPITAL

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

KALAFONG HOSPITAL
PRIVATE BAG X396
PRETORIA
0001

ENQUIRIES : MS P MONYEPAO
TEL : 012 318 6929
FAX : 012 373 6791
EMAIL : Patricia.Monyepao@gauteng.gov.za
REF : KPTH 31/2019

TO: Dr UD Feucht

RE: PERMISSION TO CONDUCT RESEARCH

TITLE: EARLY CHILD OUTCOMES OF IN UTERO GRWTH RESTRICTED AND PREMATURE BABIES - A PROSECTIVES COHORT STUD IN SOUTH AFRICA

Permission is hereby granted for the research to be conducted at **Kalafong Provincial Tertiary Hospital.**

This is done in accordance to the "Promotion of Access to Information Act. No 2 of 2000".

Please note that in addition to receiving approval from the hospital research committee, you are still required to seek permission from the relevant departments.

Furthermore, collecting of data and consent for participation remains the responsibility of the researcher.

You are also required to submit your final report or summary of your findings and recommendations to the office of the CEO.

Approved:

DR K.E LETEBELE-HARTELL
SENIOR MANAGER: MEDICAL SERVICES
DATE: 09/07/2019

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ETHICS CLEARANCE FOR PHD STUDY: UP FACULTY OF HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
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- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through February 28, 2022 and Expires: 03/04/2023.

Faculty of Health Sciences **Research Ethics Committee**

27 May 2021

Approval Certificate
New Application

Dear Mrs S Nel

Ethics Reference No.: 227/2021
Title: Postnatal growth and body composition up to two years of age of term and preterm infants with placental insufficiency and/or small size for gestational age at birth

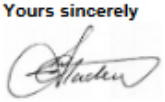
The **New Application** as supported by documents received between 2021-04-29 and 2021-05-26 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2021-05-26 as resolved by its quorate meeting.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year and needs to be renewed annually by 2022-05-27.
- Please remember to use your protocol number (227/2021) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely



On behalf of the FHS REC, Professor Werdie (CW) Van Staden
MBChB, MMed(Psych), MD, FCPsych(SA), FTCL, UPLM
***Chairperson**: Faculty of Health Sciences Research Ethics Committee*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health)

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2024 RENEWAL

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

Institution: The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567. Approved dd 18 March 2022 and Expires 18 March 2027.
- IORG #: IORG0001762 OMB No. 0990-0279 Approved for use through June 30, 2025 and Expires 07/28/2026.

Faculty of Health Sciences **Research Ethics Committee**

16 May 2024

Approval Certificate
Annual Renewal

Dear Mrs S Nel,

Ethics Reference No.: 227/2021 – Line 4
Title: Postnatal growth and body composition up to two years of age of term and preterm infants with placental insufficiency and/or small size for gestational age at birth

The **Annual Renewal** as supported by documents received between 2024-04-12 and 2024-05-15 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on 2024-05-15 as resolved by its quorate meeting.

Please note the following about your ethics approval:

- Renewal of ethics approval is valid for 1 year, subsequent annual renewal will become due on 2025-05-16.
- The Research Ethics Committee (REC) must monitor your research continuously. To this end, you must submit as may be applicable for your kind of research:
  a) annual reports;
  b) reports requested *ad hoc* by the REC;
  c) all visitation and audit reports by a regulatory body (e.g. the HPCSA, FDA, SAHPRA) within 10 days of receiving one;
  d) all routine monitoring reports compiled by the Clinical Research Associate or Site Manager within 10 days of receiving one.
- The REC may select your research study for an audit or a site visitation by the REC.
- The REC may require that you make amendments and take corrective actions.
- The REC may suspend or withdraw approval.
- Please remember to use your protocol number (227/2021) on any documents or correspondence with the Research Ethics Committee regarding your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

On behalf of the FHS REC, Dr R Sommers
MBChB, MMed (Int), MPharmMed, PhD
Deputy Chairperson *of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria*

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

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ETHICS CLEARANCE FOR PHD STUDY: KALAFONG HOSPITAL

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

KALAFONG HOSPITAL
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PRETORIA
0001

ENQUIRIES : MS PM MONYEPAO
TEL : 012 318 6995
EMAIL : Patricia.Monyepao@gauteng.gov.za
REF : KPTH 23/2021

TO: Ms S Nel

RE: CONDITIONAL PERMISSION TO CONDUCT RESEARCH

TITLE: POSTNATAL GROWTH AND BODY COMPOSITION UP TO TWO YEARS OF AGE OF TERM AND PRETERM INFANTS WITH PLACENTAL INSUFFICIENCY AND/OR SMALL SIZE FOR GESTATIONAL AGE AT BIRTH.

Conditional permission is hereby granted for the research to be conducted at **Kalafong Provincial Tertiary Hospital**. Please note that full approval will be granted on receipt of Ethics approval.

This is done in accordance to the "Promotion of Access to Information Act. No 2 of 2000".

Please note that in addition to receiving approval from the hospital research committee, you are still required to seek permission from the relevant departments. You are obliged to inform this committee in writing of any amendments made to this protocol. Importantly, you require full approval (not conditional approval) before data collection can commence.

Furthermore, collecting of data and consent for participation remains the responsibility of the researcher.

You are also required to submit your final report or summary of your findings and recommendations to the office of the Chief Executive Officer.

Kind regards

DR K.M HTWE
MEDICAL MANAGER

DATE:

Ethics approval submitted: YES NO

Approved.

DR K.M HTWE
MEDICAL MANAGER
DATE:

GAUTENG PROVINCIAL GOVERNMENT
KALAFONG HOSPITAL
17 JUN 2021
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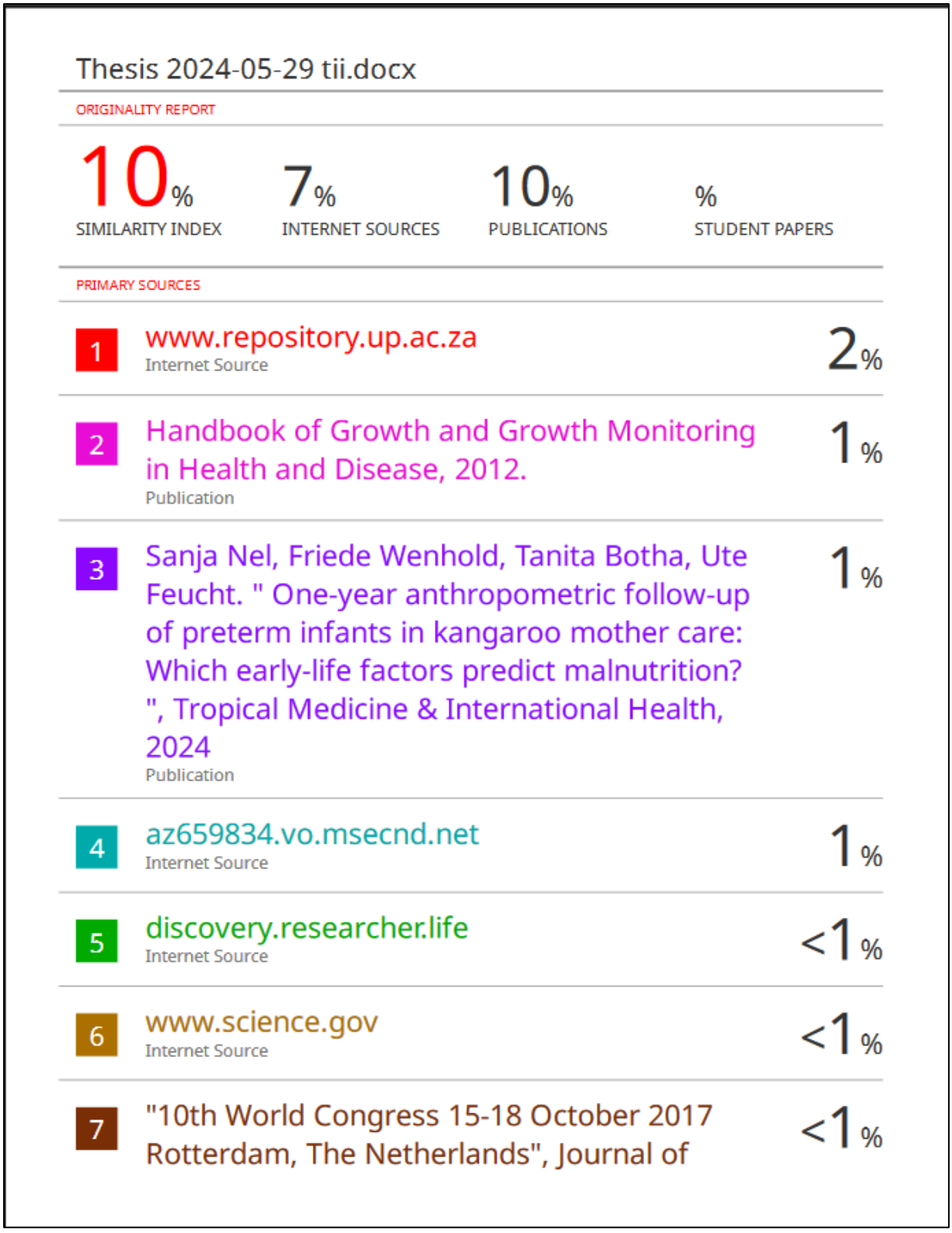
APPENDIX B: TURNITIN SIMILARITY REPORT



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PRIMARY SOURCES

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3	Sanja Nel, Friede Wenhold, Tanita Botha, Ute Feucht. " One-year anthropometric follow-up of preterm infants in kangaroo mother care: Which early-life factors predict malnutrition? ", Tropical Medicine & International Health, 2024 Publication	1%
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