The effect of early childhood growth trajectories on nutritional status and body composition at 2 years of age

Elizabeth Masiakwala

Student number: 0302371G

A Dissertation submitted to the Faculty of Health Science, University of the Witwatersrand, in fulfilment of the requirements for the degree of Master of Science.

Supervisors:

Dr. Lukhanyo Nyati

Prof. Shane Norris

Master of Science in Medicine

Johannesburg, 2022

Declaration

I, Elizabeth Masiakwala student number: 0302371G declares that this dissertation is my own work; it is being submitted for the Master of Science degree at the University of the Witwatersrand, Johannesburg. It has never been submitted for any other degree or examination at any other university.

(Signature of candidate)

…… …… …….

Day of……22 June 2022…

Publications

Masiakwala E, Nyati LH, Norris SA. 2022. The effect of infant growth patterns and nutritional status on body composition between birth and 2 years. European Journal of Clinical Nutrition; Submitted on 30 March 2022.

Abstract

Background Paediatric obesity is rising globally, and the prevalence is rising faster in low-middle income countries (LMIC) than other regions. Early life growth patterns play critical role in shaping risks of chronic diseases later in life. However, the association between early childhood growth and adult disease risk may be mediated by body composition. However, there are few studies assessing the relationship between growth patterns and body composition during early childhood. The assessment of body composition early in infancy affords discernment into the fat mass and lean mass distribution; important factors for subsequent metabolic diseases. There is limited data on early childhood body composition in LMIC settings undergoing transition.

Aims Therefore, the aims of this dissertation were to; (i) describe fat mass and fat-free soft tissue mass by air displacement plethysmography at birth, 1, 2, 3, 4 and 6 months, (ii) describe fat mass and fat-free soft tissue mass using deuterium dilution technique at 3, 6, 9, 12, 18 and 24 months; and to (iii) assess the association between childhood growth from birth to 24 months and fat mass and fat-free mass at 24 months in a cohort of South African urban infants.

Methods The data for this dissertation was a secondary analysis of data drawn from the International Atomic Energy Agency Multicentre Body Composition Reference Study on singleton infants born in Soweto, South Africa between 2014 and 2019. The anthropometric measurements weight and length, skinfold thicknesses, and arm circumferences were collected at each visit. Fat mass (FM) (kg), fat free mass (FFM) (kg), Fat mass index (FMI), fat free mass index (FFMI), and percentage fat mass (%FM) were measured using Air displacement plethysmography (ADP) and isotope dilution method (Deuterium Oxide) from birth to 24 months. The birthweights were classified as: Small-for-gestational age (SGA) (below 10th percentile), appropriate-for-gestational age (AGA) (between 10th and 90th percentile) and

large-for-gestational age (LGA) (above 90th percentile) using Intergrowth-21st growth standards. Age and sex adjusted height-for-age (HAZ), weight-for-age (WAZ) and weight-for-height (WHZ) z-scores were generated using the 2009 WHO child growth references (0 – 5 years) to assess nutritional status from birth to 2 years. The analyses of variance were used to assess differences in body composition between categories of birth weight. T-tests were used to assess differences in anthropometric measurements and body composition between sexes and levels of nutritional status. The multiple linear regression analyses were used to estimate the association between conditional growth 0-6months and 6-24months and body composition at 24 months.

Results Boys had significantly higher weight at all ages, and were taller up to 15 months of age. Girls had higher FM at birth ($p<0.001$) and 1 month ($p<0.001$) of age. There were no differences in FFM, FMI, and FFMI between sexes at all time points. SGA and AGA both had significantly higher %FM than LGA at 12 months. LGA had higher FM at 24 months. Children with stunting had significantly lower FM and FFM at 12 and 24 months. At 6 months, FFMI was significantly higher in children with stunting. Conditional relative weight 6-24 months had a stronger association with FM and FMI than conditional relative weight 0-6 months and birth weight. Conditional length in both 0-6 and 6-24 months was significantly associated with FM and FMI in females.

Conclusion The assessment of growth pattern and body composition early in infancy may prove valuable in understanding factors associated with prevalence of childhood obesity. Rapid weight gain beyond 6 months of age had a stronger associated with toddler body fat. SGA and LGA are disadvantaged extremes in infancy, likely to increase the risk for obesity.

Acknowledgements

All glory and honour go to the Almighty God for this work.

I would like to thank my supervisors; Dr Lukhanyo Nyati and Prof Shane Norris for an opportunity to pursue my Masters under their supervision; and for their guidance and expertise that contributed to my journey.

Thanks to the research team at the Developmental Pathways for Health Research Unit for their contribution in data collection. To Kgadi, Portia, Palesa, Gladys, and Nsiki, thank you for your dedication during data collection. Yusuf, Prudence and Onke thank you for your laboratory support when I was analysing samples for this study.

To my family: My mother, my pillar of strength, my brother Tebogo, and my sister in-law; thank you for your support and love and walking with me through this journey; and for giving me strength to keep pushing even through the difficult time of losing my younger brother Thabang who passed on in 2021; may he continue to rest well!

To my biggest cheerleader, my son Motsiri who believes that I am a Superwoman, thank you for your unconditional love.

Finally, I would like to acknowledge the Centre of Excellence (CoE) for funding my Masters bursary; this Masters would not have been possible without their financial support.

This work is in honour of a strong woman who raised me; my late grandmother koko Nthatisi. She never went to school but she believed in education and would always encourage me to pursue my studies.

Table of content

Declaration i

Publications ii

Abstract iii

Acknowledgements v

Abbreviations ix

List of tables xi

List of figures xi

Preface xii

Chapter 1: Background and literature review 1

1.1 Problem statement 1

1.2 Conceptual frameworks 3

1.3 Aims and objectives 5

1.3.1 Aims 5

1.4 Objectives 6

1.5 Hypotheses 6

1.6 Literature review 8

1.6.1 Biology of body composition 8

1.6.2 Measurement of body composition 12

1.6.3 Infant body composition in LMIC 14

1.6.4 Factors that influence infant body composition 16

1.6.5 Intrauterine growth restriction (IUGR) 17

Chapter 2: Methodology 19

2.1 Study setting 19

2.2 Study design 20

2.3 Ethics 21

2.4 Data collection 23

2.4.1 Infant Anthropometry 23

2.4.2 Body composition 24

2.5 Sample analysis 27

2.6 Data Processing 29

2.7 Data Management 30

2.8 Data analysis 30

Chapter 3: Submitted Manuscript 32

Introduction 34

Methods and study design 35

Study design 35

Anthropometric Measurements 36

Body composition measurement 36

Data Analysis 38

Results 38

Maternal Characteristics 38

Sex differences in anthropometric characteristics and body composition 39

Association between size at birth and body composition 39

Association of nutritional status with body composition 40

Association of birth weight, conditional relative weight, and conditional length with body composition 40

Discussion 41

Conclusion 44

Supplementary Tables 49

Chapter 4: Additional Results 53

4.1 Introduction 53

4.2 Methods 53

4.3 Results 54

4.3.1 Correlations between anthropometric measurement and infant body composition 54

4.3.2 Positive predictive values of overweight and obesity 60

4.3.3 Comparison of the current study with Fomon 62

Chapter 5: Integrated discussion and conclusion 63

5.1 Summary of key findings 63

5.2 Revisiting the hypotheses 67

5.3 Emerging themes 67

5.3.1 Early childhood effects of SGA compared to mid-childhood effect of LGA 68

5.3.2 Critical periods for the development of body composition during infancy 69

5.3.3 Risk of obesity emerges during infancy in South African children 70

5.4 Implications of the study 71

5.5 Strengths and limitations 71

5.6 Recommendation and future research 72

5.7 Conclusion 73

References 74

Abbreviations

ADP: air-displacement plethysmography

AGA: Appropriate for gestational age

BAT: Brown adipose tissues

BC: Body composition

BMI: Body Mass Index

BW: Birth weight

CVD: Cardiovascular disease

DOHaD: Developmental Origins of Health and Disease

DPHRU: Developmental Pathways for Health Research Unit

DXA: dual energy x-ray absorptiometry

FFM: Fat free mass

FFMI: Fat free mass index

FM/FFM: Fat mass: Fat free mass ratio

FM: Fat mass

FMI: Fat mass index

FTIR: Fourier transform infrared

HAZ: Height-for-age z-score

HIC: High-income countries

IAEA-MBCRS: International Atomic Energy Agency Multicentre Body Composition Reference Study

IUGR: Intrauterine growth restriction

LGA: Large for gestational age

LAZ: Length-for-age z-score

LMIC: Low-middle income countries

MRC: Medical Research Council

MUAC: Mid-upper arm circumference

NCD: Non-communicable diseases

PPV: Positive Predictive Value

ROC: Receivers operating characteristic

SANHAHES-1: South African National Health and Nutrition Survey

SGA: Small for gestational age

SSA: sub-Saharan Africa

TBW: Total body water

T2D: Type 2 diabetes

UWW: Underwater weighing

WAT: White adipose tissues

WHO: World Health Organization

WHZ: Weight-for-height z-score

%FM: Percentage fat mass

List of tables

Table 3-1 Maternal characteristics stratified by child sex (boys and girls) 45

Table 3-2 Relationship between birthweight z-score, conditional relative weight, and conditional length at 0-6 and 6-24 months with fm, fmi, ffm and ffmi at 24 months.....47

Table 4-1 Correlation between fm and anthropometry measurements 55

Table 4-2 Correlation between ffm and anthropometry measurements.....56

Table 4-3 Correlations between fmi and anthropometry measurements 57

Table 4-4 Correlation between ffmi and anthropometry measurements 58

Table 4-5 Correlation between fm:ffm ratio and anthropometry measurements.....59

Table 4-6 Positive predictive values (95 % confidence interval) of the 85th and 95th percentiles (determined by lms for the sample) of anthropometric measurements to predict overweight (>85th percentile) and obesity (>95th centile) by fmi and %fm. 61

Table 5-1 Summary of key findings 63

Table S 3-1 Sex difference in infant anthropometry from birth to 24 months 49

Table S3-2 Body composition from birth to 6 months by adp peapod method.....49

Table S3-3 Body composition from 3-24 months by deuterium oxide dilution method.....51

Table S3-4 Sex differences in the relationship between birthweight z-score, conditional relative weight, and conditional length at 0-6 and 6-24 months with FM, FMI, FFM and FFMI at 24 months.....52

List of figures

Figure 1-1 The conceptual framework describing relationship between early life and later outcomes mediated by body composition.....4

Figure 1-2 Changes in body composition during fetal and neonatal stage (56). 10

Figure 1-3 Hyperplasia starts early in infancy and remain constant in adulthood. pink (individuals with obesity), blue (lean individuals). (57).....12

Figure 1-4 Models of body composition. reprinted from (ellis, 2000) .....**ERROR! BOOKMARK NOT DEFINED.**

Figure 1-5 The influence of breastfeeding on infant body composition. (107).....17

Figure 2-1 Soweto on south africa map (124) 19

Figure 2-2 Picture 1 and 2 of showing the inequality in income distribution between households (126).....20

Figure 2-3 Study flow diagram.....22

Figure 2-4 PEA POD system (133) 25

Figure 2-5 Saliva sampling using deuterium dilution method (134).....26

Figure 2-6 Agilent 4500 series tumbl-ir portable fourier transform infrared (ftir) spectrometer (agilent technologies, ca, usa) (136) 28

Figure 3-1 Relationship between birthweight categories at 6, 12, and 24 months with body composition at 2 years 46

Figure 3-2 Relationship between nutritional status at 6, 12, and 24 months with body composition at 2 years 47

Preface

"If you want to measure the classlessness of a society, and you are not interested in rhetoric but in actual conditions and facts, then looking at the growth of children ... is perhaps the best way" ~ James Tanner

My interest in infant body composition began when I was given an opportunity to be part of the International Atomic Energy Agency Multicentre Body Composition Reference Study (IAEA-MBCRS) support team at the Developmental Pathways for Health Research Unit (DPHRU). I joined the DPHRU in 2015 as a laboratory technician processing and analysing samples for different projects in the unit. In 2018, I was assigned to the IAEA-MBCRS as a lab technician to administer deuterium oxide doses and collect saliva samples from the infants, and to measure their total body water using the new Agilent 4500 series Tumbl-IR portable Fourier transform infrared (FTIR) spectrometer. This was an exciting opportunity for me as this technology was not only new in our unit, but in South Africa. Not only did I learn to operate new laboratory equipment, I was also privileged to be trained by Christine Slater on how to interpret the results. While analysing the saliva samples in the laboratory, the changes in the body composition of those infants evoked my curiosity and I was determined to understand the association between those changes and the rising prevalence of childhood obesity in Soweto.

When the door opened, I grabbed the opportunity to be mentored by great academics Professor Shane Norris and Dr Lukhanyo Nyati and to and learn from their expertise in this field. This journey gave me an opportunity to learn how to clean and analyse data using the statistical program Stata. It was my first time using Stata and learning all the statistical language and terms was difficult, but was all worth it.

This work highlighted and promised to fill the research gaps in the area of early childhood nutritional status and infant body composition particularly in South Africa where there is a paucity of data of early childhood body composition. This is a dissertation by publication which produced an article which was submitted for publication to the European Journal for Clinical Nutrition. Chapter one of my dissertation outlines the problem statement and the adopted conceptual frameworks, overall aims and objectives, as well as the literature review on my topic. Chapter 2 provides the methods that were used in the study including the design, the participants and the methods used. Chapter 3 presents a manuscript that describes the objectives 1 to 4, and chapter 4 presents the additional results for objective 5. Lastly, chapter 5 gives the overall discussion and the conclusion from this dissertation.

Chapter 1: Background and literature review

1.1 Problem statement

The increasing prevalence of childhood overweight and obesity has become an urgent public concern in both developed and the developing countries (1,2). Obesity in childhood is considered a public health problem due to its association with risk of early onset of obesity related diseases in adulthood such as diabetes, cardiovascular diseases and others (3,4). According to the World Health Organization (WHO) 2019 report, the estimated number of overweight and obese children under the age of five years globally was 38.2 million in 2019 (5). It is also estimated that by 2025, 268 million school-aged children will be overweight and 91 million will be obese globally (6). Low-middle income countries (LMIC) contribute 87% of the total global number of childhood overweight and obesity under the age of five years, although high-income countries (HIC) still have the highest within-country proportion of children with overweight and obese (7). Africa has seen a drastic rise from 6.6 million in 2000 to 9.7 million in 2017 of overweight and obese children under the age of five years (7). Of particular concern, is the rising prevalence of overweight and obesity in children under the age of 5 years in South Africa (8). Data from the South African National Health and Nutrition Survey (SANHAHES-1) showed that approximately 25% of South African young children (2-4 years) were overweight or obese (9).

Obesity is the fifth leading cause of mortality and one of the contributing factors for a number of chronic illnesses and psychosocial challenges globally (10). Childhood obesity tends to persist into adulthood where it is a contributing factor to wide range of noncommunicable diseases (NCD) (3). Globally, the rising burden of NCD is recognised as a health issue (11), accountable for over half of all global health problems (12) and significantly contributing to mortality and morbidity (13). Moreover, children who are obese or overweight are more likely to suffer from series of psychological comorbidities such as anxiety and low self-esteem (14,15) as well as metabolic and cardiovascular diseases like type-2 diabetes (T2D) and high blood pressure (16,17). Obesity is defined as a physical manifestation of chronic excess energy characterised by an excess body fat (18). Not much is known of the exact cause of obesity, however it is perceived to be the result of complex interplay of genetic makeup, socioeconomic status, cultural influences, biological and behavioural factors (19,20).

Obesity has its origin traced back in early life and tracks throughout life course such that birthweight and infant weight were reported to be associated with lifelong overweight and obesity (3,21). Similarly, low birthweight has been reported to be linked to type 2 diabetes and cardiovascular disease later in life (22,23). However, majority of studies assessing early childhood nutritional status are based on anthropometric measurements and there is a paucity of data of early childhood body composition in LMIC settings undergoing transition (24). Anthropometric measurements are useful markers of physiological changes during critical periods of growth, given that they are easily attainable and non-invasive (25). However, anthropometric measurements have limitations due to the inability to discriminate fat mass (FM) from fat free mass (FFM) (26,27). Body Mass Index (BMI) has a low sensitivity in detecting excess fat or extreme muscle mass in children which is likely to give inaccurate

classification (28). Similarly, skinfolds thickness do not reflect total amount of body fat (29), making it difficult to predict FFM (30). To better understand how infant growth and nutrition are associated with adverse health risks throughout the life course, data on the accurate assessment of drivers of infant body composition is crucial (31,32).

1.2 Conceptual frameworks

It is purported that early life growth patterns play a critical role in shaping risks of chronic diseases later in life (33). This concept was first introduced by David Barker in what is now widely known as the Developmental Origins of Health and Disease (DOHaD) or "foetal origin" hypothesis (33). The hypothesis provides a theoretical framework emphasizing the importance of early childhood growth and development in the prevention of adult diseases. It postulates that most adult chronic diseases have their origin from foetal adaptation to a nutrition compromised environment during antenatal life (23,34,35). This means that the developing foetus under intrauterine stress resorts to developing predictive adaptive responses which foster immediate response and brace for similar environmental encounters later in life (36). However if later that infant is exposed to an environment contradictory to that *in utero* such as overnutrition it could have dire effects such as predisposition to NCD risks (33,36).

Hales and Barker in their development of first conceptual NCD model termed "thrifty phenotype" reported that low birth weight and foetal undernutrition are associated with high risk of cardiovascular disease and type 2 diabetes later in life (22,23). The aetiological pathways 1 to 6 as illustrated in **Error! Reference source not found.** show the association between early life growth (the first 1000 days) and later outcomes. It is believed that the

relationship between early life growth and later adult outcomes is mediated by infant body composition. Thus, accurate assessment of body composition is crucial to better understand how infant growth and nutrition are associated with adverse health risks throughout the life course (31,32). However, there is a limited data on the relationship between early life growth patterns and infant body composition, particularly in LMIC.

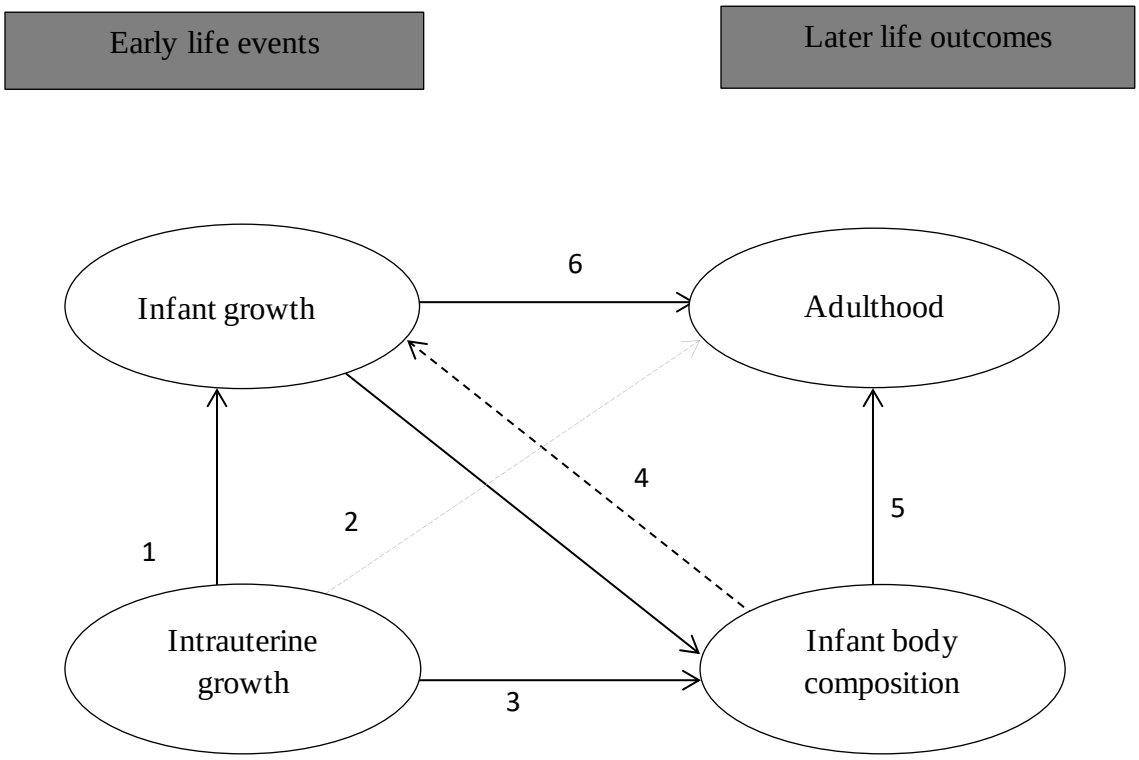

Figure 1-1 The conceptual framework describing relationship between early life and later outcomes mediated by body composition

Assessment of body composition affords the discernment into fat mass and lean mass distribution, which are important factors for subsequent metabolic diseases (31). Therefore, the conceptual framework adopted for this study looks to investigate pathways 1-3 as shown in Figure 1-1. The DOHaD framework forms the foundation for this dissertation in assessment of

infant body composition in order to evaluate drivers of childhood obesity in LMIC. The association of birthweight, a proxy for intrauterine growth, and early growth patterns with body composition in the first 2 years of life is described in this study. The association of birthweight and early growth patterns with body composition is well documented in HIC (37–40). Studies have demonstrated a positive relationship between birthweight and rapid weight gain during early infancy with later adiposity (41,42). Low birthweight was reported to be associated with morbidity and mortality and increased risk of childhood obesity at 8 years (43), CVD and T2D later in life (44,45), while rapid weight gain between birth to 6 months and from 9 months has also been reported to be associated with body fat and lean mass in childhood (46,47). Other studies in developed countries suggest that faster weight gain in infancy is associated with later obesity (46,48), and consequent risk of multiple non-communicable diseases (22,49).

1.3 Aims and objectives

Data for this study were collected from 757 black infants born at Chris Hani Baragwanath Academic Hospital, South Africa, between 2014 and 2019.

1.3.1 Aims

Therefore, the overall aims of this present dissertation are:

(i) To assess critical periods in the first 1000 days during which growth patterns may independently influence body composition ;

(ii) To assess whether poor nutritional status is associated with increased fat mass.

1.4 Objectives

The objectives were to assess:

a) Age-related changes in fat mass and fat-free soft tissue mass between birth and 24 months.
b) The association between birthweight categories (SGA, AGA and LGA) and body composition;
c) The relationship between infant growth from birth to 6 months and 6 to 24 months and body composition at 24 months;
d) The relationship between stunting and body composition at 24 months
e) The association between anthropometric measurement and fat mass, and fat-free mass

1.5 Hypotheses

The association between early life events and later life health outcomes has been well demonstrated. The nutritional programming hypothesis by Hales et al. proposed that an organism is able to adapt to poor environment by programming its body size and metabolism to expect similar depleted environment later in life, therefore permanently affecting its normal growth (23). Wells et al. in their programming of body composition by early growth and nutrition hypothesis stated that during nutritional deprivation in infancy, FM may be preserved at the expense of height for optimum metabolic function (50). Given the high prevalence of early childhood overweight and obesity in South African black children and adolescent girls (51), we hypothesize that:

H_1: Rapid weight gain is associated with higher FM

H_2: Children who experienced undernutrition (characterised by SGA and stunting) will have higher body fat than children who experienced normal growth

H_3: Weight gain in the first 6 months of age has a stronger association with body fat at 2 years of age than weight gain after 6 months.

1.6 Literature review

This section serves to explain the rationale for assessing body composition as well as to review several concepts related to infant body composition as well as challenges and gaps, particularly in LMIC settings. Firstly, it gives the background on the biology of body composition in infancy. Secondly, it covers components and models of body composition. Thirdly, it explores available methods employed in assessing body composition; and finally, the available literature on body composition, particularly in LMICs.

1.6.1 Biology of body composition

Body composition is a term used to describe different components within the body (52). There are numerous ways to define it, such as partitioning body weight into two components; FM and the rest of the tissues being compressed as one component (FFM) (53). This is called the two-component (2C) model. FFM is then further divided into 2 components, water content and the remaining solids which are largely minerals and proteins to make it a three-component (3C) model. On a more complex level, FFM is further partitioned into three more chemical components, water, proteins and minerals making it a four-component (4C) or multi-component model, as shown in Figure 1-2 (54). The advantage of a multi-component model over 2C model is that it yields smaller errors when the proportions of body composition components vary and it also produces more reliable results of changes in body composition in a variety of circumstances (55).

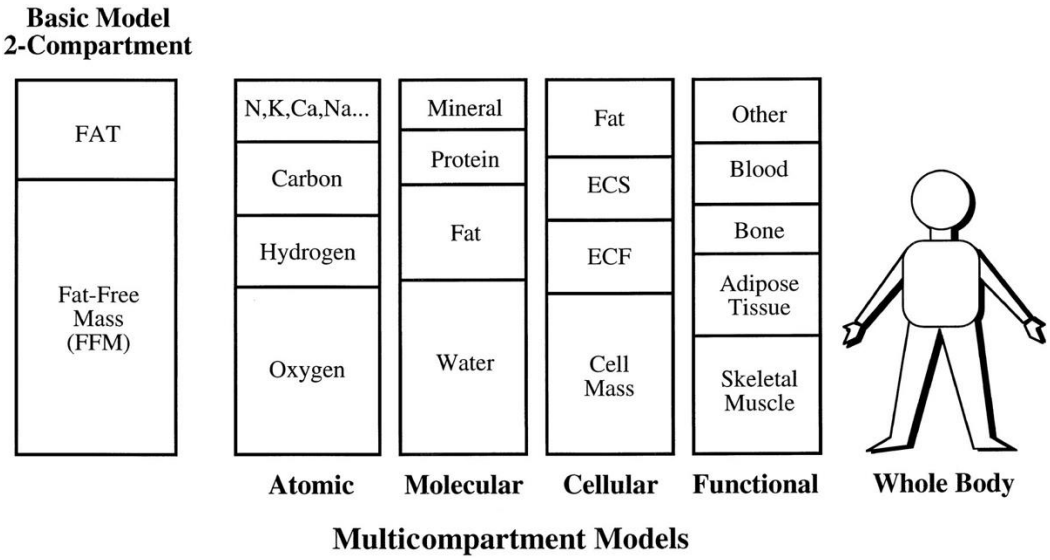

Figure 1-2 Models of Body composition. Reprinted from (Ellis, 2000)

ECS: Extracellular solids; ECF: Extracellular fluids

During foetal development and neonatal stage, all components of body composition increase with fat mass increasing at a faster rate such that mass of fat equals that of protein at full term, as shown in Figure 1-3 (56). However, after birth as individual ages, there is an increase in body fat specifically on the abdominal region and a decrease in lean mass and bone mass density (57). Body water is an important constituent of human body composition and it takes a large part of FFM (58). FFM is about 80% of water at birth and throughout childhood. The hydration then gradually starts to decrease from the age of 3 years to 73% during adolescent and remains constant in adulthood (59,60).

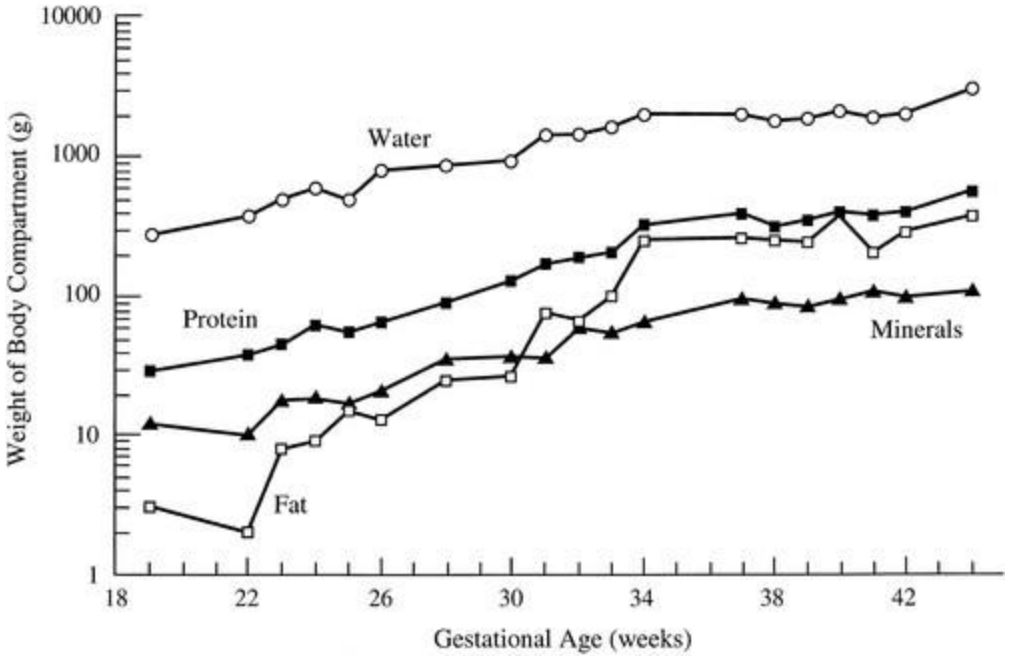

Figure 1-3 Changes in body composition during foetal and neonatal stage (56)**.**

Adipose tissue develops *in utero* and throughout life (61). During the third trimester of pregnancy fat deposits start to appear, in a process known as adipogenesis (62). During this process, preadipocytes are developing into mature adipocytes and rapidly develop into a fat mass which is about 15% of body weight at birth (62,63). In the first 4 to 6 months of life 40-65% of total body weight gain is accounted for by fat deposition (64). Babies usually reach a peak in adiposity during infancy followed by dramatic decline by 5 years of age (65). Adipose tissue is the largest endocrine organ in the body responsible for many aspect of physiology including hormonal secretion (adipokines) (66), aiding central interconnection of metabolic communications, and thermal regulation control against colds and trauma (67).

There are two main classes of adipose tissues, white and brown adipose tissues. The white adipose tissues (WAT) are designed to store energy, while brown adipose tissues (BAT)

generate heat by disintegrating energy (67). BAT which are located in the interscapular region are primarily prominent in the infancy period and decline shortly after birth (66). WAT which are mainly for fat storage are divided into subcutaneous and visceral and are disguised based on their locations (66). Fat distribution plays a critical role in metabolic risk, such that visceral or central fat depots promote metabolic risk while subcutaneous fat exert minimal or no risk (68). This distribution of fat can be measured by assessing body composition using various available methods.

Obesity is regarded as the accumulation of excess fat mass and is often linked to adipose tissue impairment (69). Expansion of adipose tissue can be accomplished by either increased number of adipocytes (hyperplasia) or the enlargement of existing ones (hypertrophy) (70). This adipose tissue dysfunction in adipose tissue is a key contributor of adverse metabolic and cardiovascular consequences of obesity (71). Adipocyte hyperplasia is a trademark for enlarged adipose tissue in obesity (72). Hypertrophy of adipocytes is as a consequence of increased adipokine secretion, fatty acid flux and adipocyte cell death which lead to macrophage inflammation (73). Increase in number of adipocytes is determined early in childhood and adolescent periods and remains constant during adulthood, meaning that obesity in later life started during infant hypertrophic growth, seen in Figure 1-4 (61). In children, it has been reported that there is rapid increase in hypertrophy versus hyperplasia before the age of 2 years (74), which was associated with inflammation and insulin resistance in children with obesity (70). Adipose tissue altercations, diet, as well as genetics influence adipose tissue obesity phenotypes (75,76).

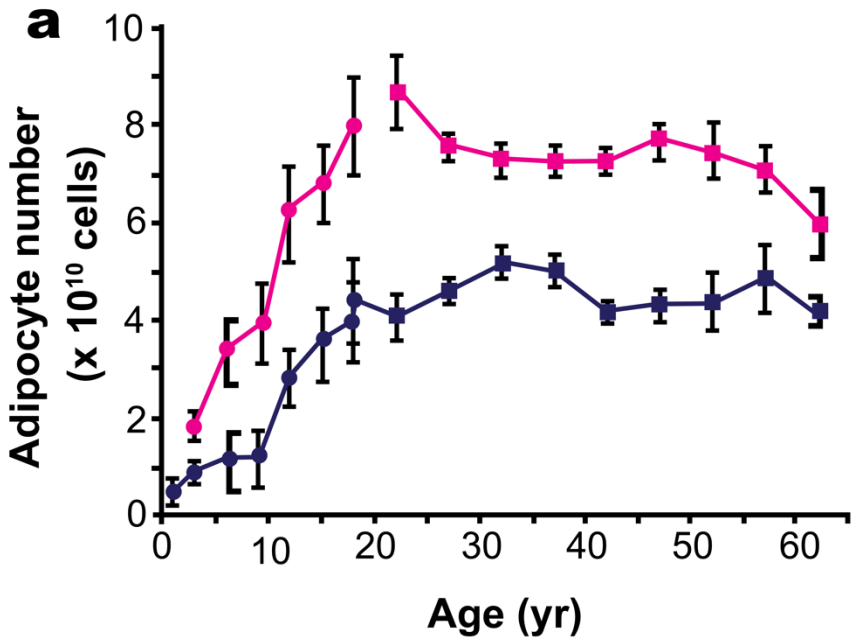

Figure 1-4 Hyperplasia starts early in infancy and remain constant in adulthood. Pink (individuals with obesity), Blue (lean individuals). (61)

1.6.2 Measurement of body composition

Assessment of body composition early in infancy is a key part of public health intervention for the prevention of obesity related adverse health later in life. Historically, body fatness has been measured using anthropometric measurements such as weight-for-length, skinfold thickness measurements, and BMI (77,78). Anthropometry is an inexpensive, simple and widely used method for assessing infant growth. However, anthropometric parameters have limitations. Although BMI is used in most clinical and epidemiological studies as a useful proxy for body fatness, it does not discriminate between the FM and the FFM (26,27). Additionally, BMI had been reported to have low sensitivity in detecting excess fat or extreme muscle mass in children which is likely to give inaccurate classification (28). Similarly, one limitation of skinfolds is

that they do not reflect total amount of body fat (29), making it difficult to predict FFM from skinfold thickness (30). In infancy, classification of nutritional status using anthropometric measurements becomes complicated due to continually changing body composition (79).

The concept of body composition in paediatrics is not a new phenomenon. In the 1960s Fomon published chemical composition estimates of a reference child from birth to one year using deuterium method (80). In 1982 with his colleagues in their classic study presented gender and age references modelling components of fat mass, lean mass and lean tissues from birth to 10 years using deuterium oxide method (81). In 1989 Lohman provided a review on methods and equations of assessing body composition from birth to 17 years (82). Subsequently in 2000, Butte et al. (83) published their body composition data from 0.5 weeks to 2 years of age using deuterium dilution, body counting, and dual energy x-ray absorptiometry (DXA) methods. In the intervening years, studies continued to upgrade and expand on Fomon's classic model. In 2011, Fields et al. (84) presented a longitudinal data in exclusively breast-fed infants from birth to 6 months of age assessed by ADP. Subsequently, in 2014 Jonathan Wells presented body composition reference data using the four component model in UK infants, children and adolescents aged from 5 to 20 years (85).

Methods that apply a multicompartmental approach for measurement of body composition include isotope dilution, ADP, DXA, and others. Isotope dilution method is considered a gold standard in estimating body composition in infants (56). The use of deuterium dilution isotope for body composition analysis in paediatrics has increasingly become an area of interest, fundamentally in studying nutritional and metabolic status (32,50). This method has gained its

advantage for safety to use in infants as it requires little amount of biological specimen for analysis (86). It is more feasible in a field setting and trusted to have produced quality data in LMIC such as Ethiopia, India, and Gambia (87–89). ADP method which is based on 2 component model is non-invasive, low cost, low maintenance, fast (approximately 2 minutes), easy to operate and has demonstrated high accuracy in infants (56,90). Hydrostatic weighing which required the subject to be fully immersed under water was considered a gold standard for estimating body composition (91). However, due to its limitations in children, DXA has been widely used as an alternative method. DXA method uses three component model to measure FM, FFM and bone minerals where each component differently absorbs non radiation x-ray beams so they can effortlessly be discriminated from one another (25). DXA has the ability to show distribution of body components, unlike the aforementioned methods. This method is considered safe in the sense that the exposure to radiation during measurement is similar to that occurring in nature (92). Limitations for using DXA in infancy have been reported. Firstly, an infant is required to remain still during the process which is mostly difficult, and secondly there are limits for repeating of measurements in infants for monitoring of growth patterns (25). Additionally, the four-component model employs different methods for the measurement of body mass, total body water (TBW) by deuterium dilution, bone minerals using DXA and total body volume by ADP to allot tissues into FM and FFM (54). It is considered to be more robust and accurate model, however it is costly and limited to large clinical studies. These methods afford better discernment into body composition than using anthropometric method alone.

1.6.3 Infant body composition in LMIC

Amidst the persistence of double burden malnutrition in LMIC where growth impairment is common (93), data on infant body composition in LMIC is still very limited (24). A study

conducted on Gambian children from 3 to 18 months using stable isotope method reported Gambian infants to have lean mass deficits that increased with age when compared with UK infants (87). Body composition data in 2011 on Ethiopian newborns reported a positive linear relationship between birthweight and relative FM for boys and girls (94). And later the same Ethiopian cohort presented SSA urban context body composition reference charts for healthy infant population (88). Similarly, a study on Ugandan children with severe acute malnutrition found low levels of leptin, suggestive of low FM and a major biochemical factor predicting mortality (95). In contrast, a study done on Brazilian adolescents reported that in this population, rapid weight gain in infancy was rather associated with larger size in adolescence than increased adiposity (96). Similarly, data from a collaboration of five longitudinal cohort studies in LMIC settings including South Africa reported a positive relationship between birth weight and linear growth from 0 to 2 years of age as well as rapid weight gain at infancy with adult overweight (97). These studies showed that there is an association between early growth factors and body composition, and that there is a need for more infant body composition assessment studies in LMIC.

1.6.4 Factors that influence infant body composition

Factors influencing infant body composition such as gender, maternal obesity and feeding practices have been well documented (98,99). Gender plays a significant role in influencing body composition early in life. Girls have been reported to have higher percentage body fat at birth than boys (98).

One other factor that influences infant body composition and increases risk of infant overweight and obesity is maternal obesity (100). Infants of mothers with pre-pregnancy obesity estimated by BMI have been reported to have significantly higher FM and %FM at birth compared to average weight groups (101). Likewise, women with obesity have been reported to deliver infants with higher adiposity but not lean mass (102,103). This provides evidence that body composition is programmed *in utero* through the metabolic status of the mother.

Postnatally, factors such as breastfeeding have also been reported to influence infant body composition. Breastfeeding beyond 6 months have been reported to lower the adverse effect of early rapid weight gain from 0 to 5 months on FMI at 3 years (104). However, one study (with sample size of only 20 participants) reported that among breastfed infants, those who were breastfed frequently in a 24 hour period over the first 12 months of life had higher FM, %FM, and FMI and lower FFM and FFMI as compared to less frequent feeders, shown in Figure 1-5 (105). It is therefore crucial to monitor maternal pre-pregnancy nutritional status and postpartum factors for the prevention of adverse body composition in children.

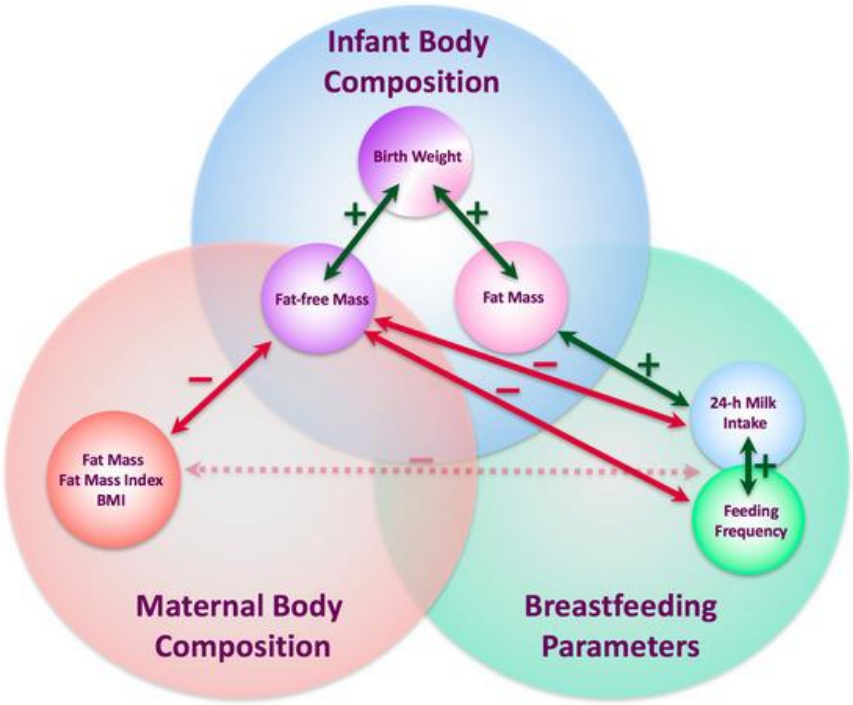

Figure 1-5 The influence of breastfeeding on infant body composition (105)

1.6.5 Intrauterine growth restriction (IUGR)

The relation between foetal life and adverse adult outcomes must be attributed to infant body composition. Thus, this section reviews the influence of IUGR on early infant body composition. Infants who experiences IUGR have been reported to have lower FM and FFM at neonatal period (3 to 10 postnatal days) and also significantly lower FM and FFM at 6 weeks to 12 months compared to those without IUGR (106,107). It has been shown that poor foetal growth constrains FFM which eventually limits metabolic capacity to tolerate rich diet (108). Early FFM deficit has been reported to be primary determinant of neurological impairment at 2 years in preterm infants which experienced IUGR (109). The aforementioned studied showed that IUGR infants are shorter and lighter than normal growth in the first year of life.

Chapter 2: Methodology

Figure 2-1 Soweto on South Africa map (110)

2.1 Study setting

This study was carried out in Soweto Township in South Africa. Soweto is the largest township in South Africa which covers an area of 200.3 km² with a population of approximately 1,271,628, which is predominantly black (98.5%) (111). Soweto was established during the apartheid era as a racial segregated residential area for displaced black people and migrant mine workers (111). This township is located 15 km south west of the City of Johannesburg, a metropolitan municipality in Gauteng province as shown in Figure 1-1. Gauteng is South Africa's biggest economic and financial hub contributing 34% of South Africa's gross domestic products and 10% of Africa's GDP (111). Although situated within economically advancing province, inequality in income distribution between households is evident, Figure 2-2. The study was conducted at Chris Hani Academic Baragwnath Hospital situated in

Soweto. Chris Hani Baragwanath Academic Hospital is the world's third largest hospital with approximately 17 000 babies delivered annually (112).

Figure 2-2 Picture 1 of a double storey house and picture 2 of squatter camp, both from Soweto showing the inequality in the income distribution between households (113)**.**

2.2 Study design

Data for this dissertation was a secondary analysis of data drawn from the International Atomic Energy Agency Multicentre Body Composition Reference Study (IAEA-MBCRS). IAEA-MBCRS is a longitudinal study on singleton infants born in Soweto between 2014 and 2019. The main objective of the IAEA-MBCRS study was to develop references to describe changes in body composition in infants from birth to 24 months in 9 geographically diverse populations including South Africa. This study recruited pregnant women living in Soweto who came for routine check- up in antenatal ward, and/or mothers who just delivered live neonates in the maternity ward at Chris Hani Baragwanath Academic Hospital.

Women who already gave birth at maternity ward at Chris Hani Baragwanath Academic Hospital we randomly approached and those eligible were recruited for the IAEA- MBCRS study. Eligibility was assessed using a screening questionnaire based on the following inclusion criteria: healthy singleton term infants born within 37 and 42 weeks of gestation, 18 years or older mother living in Soweto, a non-smoker with at least secondary school education level and willing to breastfeed for at least up to 6 months (see Appendix 1). Infants were to be without morbidity and congenital abnormalities. Exclusion criteria were: infants with significant morbidity such as cardiorespiratory illnesses and congenital abnormalities which might affect infant growth, and mothers living with HIV/AIDS. The sample size was 747 mothers who provided written informed consent. A longitudinal flow diagram showing follow up study events is described in Figure 2-3.

2.3 Ethics

Ethical permission for IAEA-MBCRS was granted by the University of the Witwatersrand Human Research Ethics Committee (M200997) as seen in Appendix 2. Caregivers or mothers gave informed signed consent before being enrolled in the study. All data collected was treated as confidential and a unique study number was assigned to the participant upon enrolment to the study.

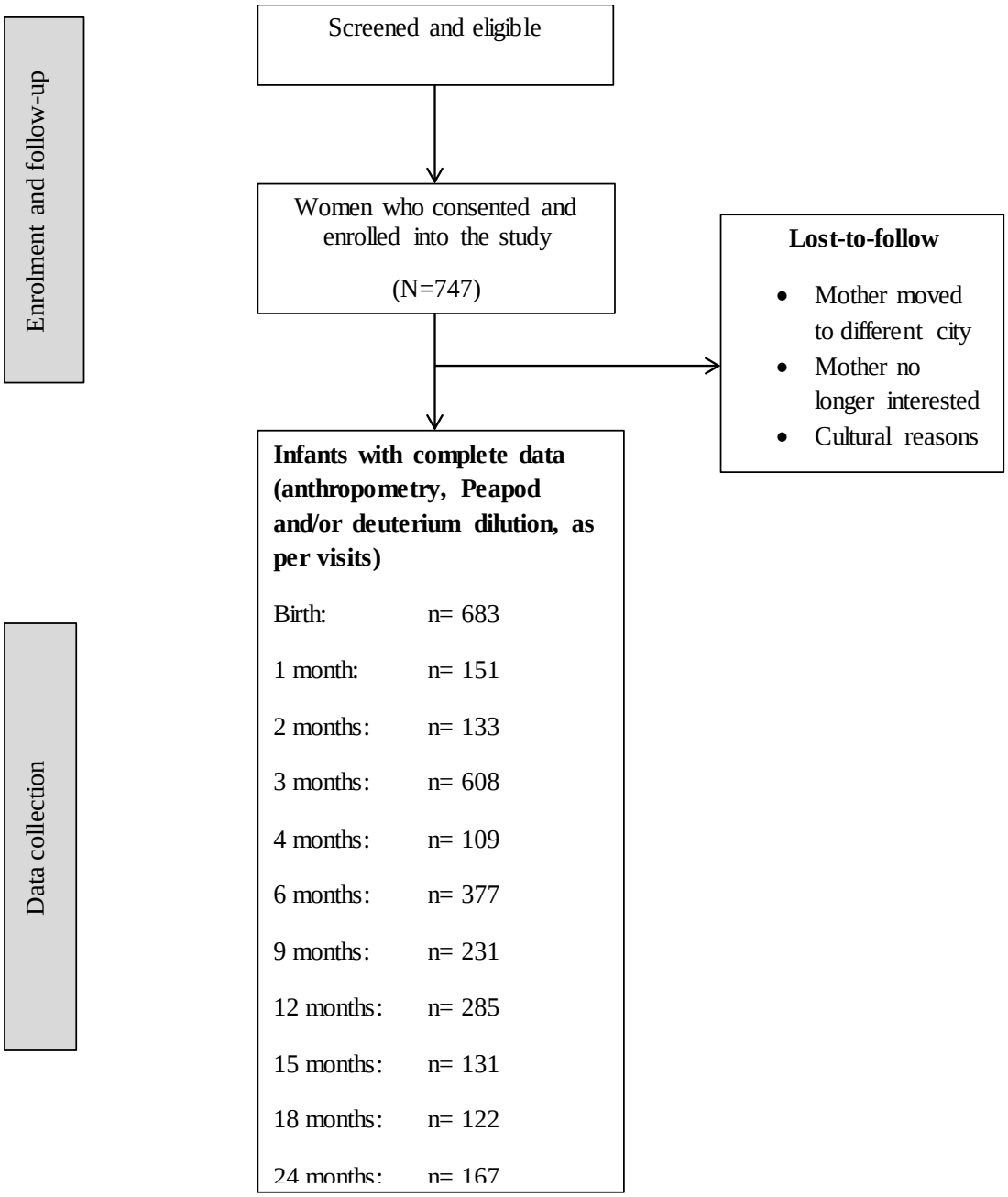

Figure 2-3 Study flow diagram

Note: Data collection for the primary study was done in 2 phases namely: IAEA 1 (at 0-24 months) and IAEA 2 (at 0-6 months) hence the variations in sample sizes at different time points

2.4 Data collection

Data collection for the primary study occurred from 2014 to 2019. Structured questionnaires were used by a trained research assistant at a baseline visit to gather information from mothers on demographics and maternal characteristics such as marital and occupational status, number of years of formal education, gestational age as well as the number of previous births.

2.4.1 Infant Anthropometry

Anthropometric measurements weight and length were taken at birth, 1, 2, 3, 4, 6, 9, 12, 15, 18, and 24 months follow-up visits. Measurements were taken according to WHO MGRS standardized standard operating procedures (SOP) (114,115). Anthropometric parameters for the IAEA-MBCRS study were weight, length, triceps and subscapular skinfolds thickness, and mid-upper arm circumferences. For measurement reliability, all infant measurements were taken and recorded independently (blinded) by the researcher and research assistant measuring the baby one after the other to give more reliable results. Standardization and training for anthropometric measurements took place every 3 months or as needed for validation and to obtain consistent results. For quality assurance, all anthropometry instruments were calibrated daily during data collection for accurate results. Weighing scale (Seca) was calibrated using different weights of 0.5kg, 1kg, 2kg, and 5kg. Harpenden infantometer was calibrated using two aluminium metallic rods of 75cm and 40cm.

Skinfold thickness was measured using Holtain Tanner, UK caliper graded in millimetres with 0.2 mm precision. Measurements were done on the left triceps and the left subscapular

skinfolds. During measurements, the mother was asked to put the baby on her lap with the baby's left arm hanging relaxed on the side or supported by the mother. The research assistant then gently picked up the skinfold and mark at about 1cm above the midpoint. The caliper was then placed below the finger and the thumb at the marked area maintaining a gentle grip, and then released to allow the pressure of the caliper to be exerted on the fold. Measurements were then recorded after 2 seconds of the grip. The same instructions were followed for the measurements of subscapular skinfolds which are located below the inferior angle of the scapula.

2.4.2 Body composition

IAEA-MBCRS study used two methods of infant body composition assessment. ADP method was used to describe body composition from birth to 6 months using PEA POD (COSMED, 2014) This method is based on the densitometry principle which was initially used in underwater weighing (UWW) where the subject was immersed in water (56,116). ADP uses body mass and body volume to derive total body density and estimate FM and FFM (117). Measurements are not affected by the crying and movement of the baby (118). During PEA POD measurement, a naked infant was placed inside the closed testing chamber, shown in Figure 2-4. The pressure and volume changes within the chamber were used to measure body volume. Body density was then calculated to derive FM and FFM. One of the limitations is that the instrument can only measure infants with body weight less than 8kg (25).

Figure 2-4 PEA POD system. Picture taken from the internet (119)

The deuterium dilution method was used to measure total body water (TBW) using a non-radioactive stable isotope (99.8 atom % deuterium oxide). To estimate TBW quantity in infants, a safe dose of stable isotope was orally administered, allowed to distribute and exchange with the subject water pool until it reaches equilibrium. TBW value can then be used to estimate FFM (kg) (58,59). FM (kg) is then obtained by calculating the difference between body weight and FFM (25). Although this method is time consuming, it is straight forward, easy to perform and suitable for large field settings making it a gold standard in the assessment of body composition in infants (25). The choice of isotope (deuterium oxide and Oxygen-18) and type of sample (blood, urine or saliva) are mostly determined by the type of instrument (56). This method is based on the following suppositions:

(i) There is distribution of tracer only in the exchangeable pool,

(ii) There is an equal distribution within this pool,

(iii) During the equilibration time, tracer is not metabolized, and

(iv) Equilibrium is reached rapidly (92).

The present study used the plateau method which was based on three steps:

(i) Establishment of infant baseline level of deuterium oxide by collecting of pre-dose saliva sample,

(ii) Administration of deuterium oxide dose,

(iii) Collection of post-dose saliva sample after equilibration of the dose with the body water pool was completed after 3 hours (117).

The first sample was done at least 15 minutes after the baby was last feed. Making sure that the baby was seated comfortably on the mother's lap, the nurse started by cleaning the baby's mouth by cotton wool making sure that there were no milk residues. Saliva was then collected by patiently moving a new clean swab around the baby's mouth until it is soaked with saliva, Figure 2-5. The swab was carefully removed and placed in the 20ml syringe and then squeezed into 2ml sample collection tube. Several attempts were needed to collect using new clean cotton swab each time until acceptable volume was reached. Amount of time for collection varied as some infants were more cooperative than the others. All dates and times of saliva collection were recorded on a data entry form as well as on sample vials.

Figure 2-5 Saliva sampling using deuterium dilution method. Source: Image publicly available from IAEA (120)

An accurately weighed dose of 1ml of 99.8% deuterium oxide was given to an infant using a 3ml syringe. A dose was drawn to 1ml using a clean new 3ml syringe; it was then weighed on the tared scale and the value recorded. The dose was carefully administered to the infant slowly to make sure that no spillage occurred. The empty syringe was weighed again and the value was recorded. In order to estimate how much dose the baby consumed, the value of the empty syringe was then subtracted from the value of the syringe when it had the dose. Mothers were advised to wait 30 minutes after dose administration to feed the infants.

The second saliva sample was collected 3 hours post dose administration. Samples were stored in clearly labelled cryoboxes individual for each collection point to avoid cross contamination. Sample inventory was created on the spreadsheets to keep track on samples. Samples were stored in -20 degree Celsius freezer until analysis.

For accurate results, sample collection was performed by a trained nurse. Sample vials were labelled with the participant unique study number and a collection date before starting the saliva sampling to avoid errors. Each sampling time had different sampling tubes with different colours for easy identification. Leak-proof cryotubes were used and caps were closed tightly to prevent evaporation. Precautions were taken to avoid cross-contamination between baseline and post-dose saliva samples by storing them in separate cryoboxes. New clean gloves, syringes and cotton wool were used for each baby and each dose time.

2.5 Sample analysis

Samples were analysed at DPHRU laboratory by a qualified and trained laboratory technician and handled according to good clinical laboratory practice. The enrichment of deuterium was

measured using an Agilent 4500 series Tumbl-IR portable Fourier transform infrared (FTIR) spectrometer (Agilent Technologies, CA, USA) shown in Figure 2-6. The instrument is fitted with optics suitable for absorbance measurements on liquid samples in the mid-infrared range, and only takes about 20-30 microliters of sample. Sample analysis and handling standard operating procedure was adopted from the IAEA Recommended Operating Procedure (121). Samples were centrifuged at 3000rpm for 10min before the analysis. Quality control standards were performed daily, in the morning before and in the afternoon after sample analysis. Each sample was analysed in duplicate for precision, and the results were recorded in the laboratory book and on the spreadsheet provided by the IAEA. To prevent cross-contamination between samples, the sampling window was gently cleaned with 100% ethanol after each analysis. For reliability and accuracy, quality control standards were used as a day-to-day check for variation in the analysis of deuterium analysis. The FTIR instrument was maintained daily by using a water dampened cloth to wipe the exterior.

Figure 2-6 Agilent 4500 series Tumbl-IR portable Fourier transform infrared (FTIR) spectrometer (Agilent Technologies, CA, USA) (122)

2.6 Data Processing

Data processing for this dissertation was performed by the author under the guidance of the supervisors. Birthweight categories were derived using an online gestational weight gain calculator accessed from the International Foetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) project (123). The calculations were based on sex, gestational age in weeks, and weight at birth to derive birth percentiles. Birthweight categories were then defined as SGA (birthweight below 10th percentile), AGA (birthweight between 10th and 90th percentiles), and LGA (birthweight above 90th percentile).

Age and sex adjusted HAZ, WAZ and WHZ z-scores were generated using the 2006 WHO child growth standards for children from birth to 5 years. Z-scores were used to define stunting (<-2 z-score HAZ), wasting (<-2 z-score WHZ) and underweight (<- z-score WAZ) (124). The BMI-for-age z-scores cut-offs +1.04 (~85th percentile) for overweight and +2 (95th percentile) for obesity were used. The lamba mu sigma method was used to generate percentiles for FMI and %FM for the sample. Excess adiposity was defined using the anthropometric cut-offs as FMI or %FM >85th percentile for overweight and > 95th percentile for obesity. The positive predictive values (PPV) were calculated to how much the cut-offs (85th and 95th percentiles) for BMI, MUAC, triceps skinfold thickness, subscapular skinfold thickness, and sum of skinfold thickness predicted similar cut-offs for FMI and %FM. Receivers operating characteristic (ROC) curves were used to assess BMI as a proxy to predict overweight and obesity by FMI and %FM.

2.7 Data Management

All data collected for IAEA-MBCRS study was captured on to the University of the Witwatersrand Research Electronic Data Capture (REDCap) system stored on the DPHRU server. Access for the usage and extraction of data for the purpose of this dissertation was granted by the principal investigator for IAEA-MBCRS. Data cleaning and analysis by the author included:

(i) Quality checks: All incorrectly captured or missing data on the REDCap were re-entered correctly as per the original form;

(ii) All data were evaluated for accuracy and any outliers emerged were rechecked and corrected where possible. Clean dataset was reviewed and approved by the supervisors and imported on to statistical software (Stata) for further analysis. Graphs and tables described in this dissertation were created using Microsoft Excel.

2.8 Data analysis

All data for this dissertation were analysed using Stata 14.2 version (Stata-Corp LP, College Station, Texas, USA). Statistical differences were accepted at $p<0.05$, $p<0.01$, and $p<0.001$. To produce normal distribution and reduce skewness, variables (FM, FFM, FMI, FFMI, and FM/FFM) were transformed by logarithmic transformation. Chi-square tests were used to assess sex differences between groups. Conditional variables (weight and length) were obtained as standardised residuals by regressing weight at 6 and 24 months on previous measures (97). Conditional relative weight is the weight at current age accounting for current

height and previous weight, while conditional length does not account for current weight (97). The Shapiro-Wilk test was used to test normality for FM, FFM, FMI, FFMI, %FM, and FM/FFM. Independent t-test and Mann-Whitney U test were used to assess differences between groups for continuous normally and non-normally distributed variables from birth to 2 years, respectively.

Multiple linear regression analysis was used to assess the association of birthweight z-scores, conditional relative weight at 0-6 and 6-24 months and conditional length at 0-6 and 6-24 months with body composition (FM, FMI, FFM, and FFMI). This dissertation investigated whether there were critical periods (before 6 or after 6 months) that influence the relationship between growth patterns and body composition using multiple linear regression analysis. To assess prenatal influences on body composition, one-way analyses of variance (ANOVA) was used to assess differences in body composition between birth weight groups.

Chapter 3: Submitted Manuscript

The following manuscript has been submitted to the European Journal of Clinical Medicine. Submission date: 30 March 2022

Title: The effect of infant growth patterns and nutritional status on body composition between birth and 2 years

Abstract

Objective A trade-off between body fat and size may exist during periods of nutritional deprivation. Therefore the objectives of this study were to assess the (i) relationship between birthweight, postnatal growth and nutritional status and body composition, and (ii) critical periods for the development of body composition in early childhood.

Methods Weight and length were measured between birth and 24 months on 757 infants (419 boys, 338 girls). Fat mass and fat-free mass were measured by isotope dilution method (Deuterium Oxide) from 3 to 24 months. Analyses of variance (ANOVA) were used to assess differences in body composition between categories of birth weight. T-tests were used to assess differences in body composition between levels of nutritional status. Multiple linear regression analyses were used to estimate the association between conditional growth 0-6 months and 6-24 months and body composition at 24 months.

Results There were differences in FFM and not in FM in terms of AGA and LGA with SGA. SGA and AGA had higher %BF than LGA. There were no differences in FMI but differences in FFMI, with stunted having more FFMI. Conditional relative weight (CRW) 6-24 months was strongly and positively associated with FM and FMI while conditional length 6-24 months was negatively associated with FFMI. Birth weight was weakly associated with FM and FFM but not with the indices.

Conclusion SGA and LGA are disadvantaged extremes in infancy likely to increase the risk for obesity. Changes in weight gain beyond 6 months may have a stronger influence on subsequent body fat.

Introduction

Paediatric obesity is rising globally, and the prevalence is rising faster in low- and middle-income countries (LMIC) than other regions (125–128). Globally, 35 of the estimated 43 million overweight or obese preschool children in 2010 were from developing countries (129). By 2030, it is estimated that 28% of children between 5 and 9 years of age will be obese in South Africa, which is higher than the estimated prevalence in the United States of America (130). Obesity tracks through the life course, and infant weight and length gain are associated with lifelong overweight and obesity (3,21). Additionally, rapid weight gain in childhood is associated with increased risk of early onset chronic diseases as well as adverse psychosocial outcomes through the developmental life course (131–133). However, the relationship between early childhood growth and adult health outcomes may be mediated by body composition.

Obesity has a multifactorial aetiology and growth patterns in infancy play a key role in laying the foundation for excess fat accrual. The period between birth and 6 months is considered a critical period as it is associated with more rapid weight gain than any other period in infancy (134). Weight growth velocity at 3 months is associated with the greatest odds of overweight among 8-17 year old adolescent girls and boys (135). Additionally, rapid weight gain in the first 12 months of life is a stronger predictor of later adiposity than rapid weight gain between birth and 2 years (136). A large proportion of children from LMIC also experience nutritional deprivation in utero and in infancy, which may promote catch up growth in weight and length. However, it has been suggested that the acceleration in postnatal fat gain precedes the acceleration in body mass, subsequent to intrauterine growth restriction (137), leading to a mismatch between body fat and body size among malnourished children.

Wells et al. hypothesised that there is a trade-off between linear growth and body fat, such that fat mass is preserved at the expense of height during periods of deprivation (50). Few studies have investigated the relationship between growth and obesity using the components of body composition, fat mass and fat-free mass in LMIC. Thus, the aims of this longitudinal study of infants from a middle-income country were to assess the (i) relationship between birthweight, postnatal growth and nutritional status and body composition, and (ii) critical periods for the development of body composition in early childhood. We hypothesised that children who experienced undernutrition will have higher body fat than children who experienced normal growth.

Methods and study design

Study design

Data for this study were from 757 black infants born at Chris Hani Baragwanath Academic Hospital, South Africa, between 2014 and 2019. Mothers who were 18 years and above living in Soweto urban township, which is part of the Johannesburg Metropolitan Council Area in South Africa, were randomly approached and recruited at the maternity ward at Chris Hani Baragwanath Academic Hospital. Eligibility was based on the following criteria; (i) mothers had to be residents of Soweto, 18 years and above, must have delivered a full term (between 37 and 42 weeks gestation) singleton healthy baby; (ii) A non-smoker and willing to breastfeed for up to 6 months and must have attained at least secondary school

education level. Eligible mother-baby pairs were then followed up from birth until they reached 24 months. Infants with significant morbidity and congenital abnormalities and mothers living with HIV/AIDS were excluded from the study. All mothers provided written informed consent, and ethics approval was obtained from the University of the Witwatersrand Committee for Research on Human Subjects (M200997).

Anthropometric Measurements

Anthropometric measurements were taken as per WHO MGRS standardized methodology (114,115). A portable electronic scale (Seca 376) placed on a flat surface and covered with a soft paper towel to protect the baby from direct contact with the cold surface was used to measure weight. The scale was then tared before placing a naked baby and measurement was recorded when the baby was calm. The supine length was measured from the crown of the head to the heels using a calibrated Harpenden Infantometer (Range 300-1100mm) with digital counter readings to the nearest 0.1 cm. For measuring of length, the Infantometer with a perpendicular fixed headboard and a movable footboard was placed on a flat surface with a soft paper towel on top to prevent the baby from direct contact with the cold surface. The measurement was taken with the head touching an immovable heard board, positioned in the Frankfort vertical plane, secured by the supporting research assistant standing at the head position. The lead measurer stood on the side to hold the baby's legs together making sure that the knees were straightened and the footboard moved gently towards the heels of the baby.

Body composition measurement

Air displacement plethysmography method, PEA POD (Cosmed, Concord, CA, USA) was used to measure infant body composition from birth up to 8kg. The first sets of measurements were taken within the first 72 hours of birth. The principles and standard operating procedures have been described elsewhere (90). In brief, this method is based on whole body densitometry to estimate FM and FFM. The machine was calibrated daily before assessment by a trained staff and passed all quality control checks as per instructions by the manufacturer. A naked infant was placed inside the closed testing chamber in which the pressure and volume changes within the chamber were used to estimate body volume. Sex-specific FM, FFM and percentage fat were then derived from body density. The duration of the test was only 2 minutes and the mother was allowed inside the room during measurements.

Body composition of infants above 8kg was measured by stable isotope dilution method using 99.8 atom % D, Sigma-Aldrich deuterium oxide isotope as outlined in the IAEA standard operating procedures (117). This method required sample collection and analysis. Sample collection was a 3-hour process that was based in three stages: Baseline sample collection, dose administration and post dose collection. Baseline saliva sample was collected 20 minutes after the baby's last feed by placing a ball of clean cotton wool inside the baby's mouth until it was soaked wet. The soaked cotton wool was carefully removed and transferred into 20ml syringe, saliva sample was then squeezed out into a 2ml vial labelled with a unique infant identification code. The baby was slowly given 1ml dose of undiluted deuterium oxide making sure that no spillages occurred.

Another saliva sample was then collected 3 hours post dose administration, assuming the enrichment distribution reached equilibrium. Samples were stored in -20 degrees Celsius until analysis.

Saliva samples were analysed in duplicate using portable 4500 Tumbl-IR Fourier transform infrared (FTIR) spectrometer (Agilent Technologies, CA, USA) according to manufactures instructions. The instrument is fitted with optics suitable for absorbance measurements on liquid samples in the mid-infrared range, and only takes about 20-30 microliters of sample. To prevent cross-contamination between samples, the sampling window was cleaned with 99.9% ethanol after each analysis.

Data Analysis

Continuous data were assessed for normality and where appropriate presented as means (± SD) and as percentages for categorical variables. Multiple linear regression analyses were used to assess the association of birthweight z-score, conditional relative weight, and conditional length at 2 age intervals (0-6 months and 6-24 months) with FM, FMI, FFM, and FFMI. We also explored the relationship between size at birth and body composition trajectories from birth to 2 years. Birth size categories were classified as SGA, AGA, and LGA using INTERGROWTH-21 standards (123). Lastly, nutritional status at 2 years was assessed by length-for age z-scores (LAZ). Stunting was defined as LAZ <-2 and LAZ >-2 as non-stunting using WHO standards (138). Independent t-tests were used to compare body composition between boys and girls. Comparison by

nutritional status (e.g. stunting vs. non-stunting) was assessed using the independent t-tests. Age- and-sex specific associations between anthropometric and clinical variables and FM and FFM were assessed using a Pearson Correlation. To assess prenatal influences on body composition, one-way analyses of variance (ANOVA) was used to assess differences in body composition between birth weight groups. The study data were analysed using the latest version of Stata (Stata-Corp LP, College Station, Texas, USA). All analyses were performed at the 5% level of significance.

Results

Maternal Characteristics

Maternal characteristics (*n*= 419 boys and *n*= 338 girls) are described in Table 3-1. The average age of the mothers was 25.8 (6.0) years and they had an average of 12 (0.8) years of schooling. A majority of the mothers were in skilled manual work occupation (43.6% & 49.2 % for mothers with boys and girls respectively), with less than 10% in unskilled positions for both sexes. Before the birth of the study participant, a majority of mothers were nulliparous with 48.6% & 40.3% having no previous live births among mother of boys and girls respectively.

Sex differences in anthropometric characteristics and body composition

Sex difference in anthropometry is presented in Table S 3-1. Boys had significantly higher weight at all ages, and were taller up to 15 months of age. Body compositions by PEA POD and deuterium dilution methods are presented in Supplementary Sample size **in square brackets [n]**

***p<0.05 **p<0.01 ***p<0.001**

Table S3-2 and

Table S3-3 respectively. Girls had higher FM at birth ($p<0.001$) and 1 month ($p<0.001$) of age and higher FM-to-FFM ratio between birth and 6 months as measured by PEA POD and between 3 and 24 months as measured by deuterium.

Association between size at birth and body composition

The association of birthweight categories and body composition at 2 years is described in Figure 3-1. There were no significant differences in FM and FFM between categories of birth weight. At 12 months, both SGA and AGA had significantly higher %FM than LGA ($p<0.05$). AGA had higher FFM than SGA at 6 ($p<0.05$), 12 ($p<0.01$) and 24 ($p<0.001$) months. Additionally, LGA had higher FFM ($p<0.001$) than SGA, at 12 months. Similarly, LGA had higher FFMI ($p<0.01$) at 12 months than SGA, while AGA had higher FFMI ($p<0.05$) at 24 months than SGA.

Association of nutritional status with body composition

Associations between stunting and body composition at 6, 12, and 24 months are described in Figure 3-2. Children with stunting had lower FM ($p<0.001$) and FFM ($p<0.01$, $p<0.001$) at 12 and 24 months and additionally at 6 months for FFM ($p<0.05$) than children without stunting. Conversely, children with stunting had higher FFMI ($p<0.01$) at 6 months than children without stunting.

Association of birth weight, conditional relative weight, and conditional length with body composition

Association of birth weight, conditional relative weight, and conditional length with body composition is described in Table 3-2. Birth weight and condition relative weight gain 0-6 months and 6-24 months were significantly associated with FM (crw 0-6: ($p<0.01$, SE 0.09) FMI (crw 0-6: ($p<0.05$, SE 0.11) crw 6-24: ($p<0.001$ SE 0.11) FFM (crw 0-6: ($p<0.001$, SE 0.08) crw 6-24: ($p<0.001$ SE 0.08), and FFMI (crw 0-6: ($p<0.001$, SE 0.12) crw 6-24: ($p<0.05$ SE 0.11). However, only conditional length at 0-6 ($p<0.01$, SE 0.09) and 6-24 ($p<0.05$, SE 0.09) months were associated with FFM

Sex differences are described in supplementary

Table S3-4. In boys, conditional relative weight gain 6-24 months was significantly associated FM ($p<0.001$, SE 0.17) and FMI ($p<0.001$, SE 0.19). In girls, birth weight, condition relative weight (crw) gain and conditional length (cl) gain 0-6 months and 6-24 months were significantly associated with FM (crw 0-6: ($p<0.001$, SE 0.07), cl 0-6: ($p<0.01$, SE 0.08); crw 6-24: ($p<0.001$ SE 0.07), cl 6-24: ($p<0.01$ SE 0.08) and FFM (crw 0-6: ($p<0.001$, SE 0.09), cl 0-6: ($p<0.01$, SE 0.10); crw 6-24: ($p<0.001$ SE 0.09), cl 6-24: ($p<0.05$ SE 0.11). However, only conditional relative weight gain 0-6 ($p<0.05$, SE 0.12) and 6-24 ($p<0.001$, SE 0.12) months were associated with FMI, while only conditional relative weight gain 0-6 months ($p<0.05$, SE 0.17) was associated with FFMI.

Discussion

This study investigated the relationship between birthweight, nutritional status, and postnatal growth and body composition. Additionally, we investigated whether the weight gain during the first 6 months of postnatal life may have a stronger influence on body composition in the toddler period than later weight gain. There were significant differences between categories of birth weight and levels of nutritional status. Children born SGA and AGA both had significantly higher %BF than children born LGA at 12 months of age. Conversely, children born LGA had higher FFM and FFMI than SGA at 12 months. Additionally AGA had higher FFM at 12 and 24 months and higher FFMI at 24 months than SGA. Stunting was associated with lower FM and FFM at 12 and 24 months; and additionally at 6 months for FFM. Growth patterns throughout infancy and the toddler period were significantly associated with body composition at 24 months.

SGA is a proxy for intrauterine growth restriction, which may adversely influence fat metabolism. Children born SGA have a tendency towards higher fat absorption than AGA (139). Consequently, SGA may have a greater propensity to accruing body fat (140), especially in abdominal depots (141), which may increase the risk of later cardiometabolic disease. Conversely, being LGA is considered a marker of in utero overnutrition, which is likely to predispose children to postnatal obesity (142). Our findings also confirmed that SGA and LGA are disadvantaged extremes in infancy, likely to increase the risk for obesity. Our results show that SGA had higher %FM than LGA. However %FM has limitations as it is not an independent index of body fatness meaning that high values might either reflect high FM or low FFM (143). A Swedish study reported that both term SGA and LGA infants had higher body fat than AGA in the first 4 months of life (144). Although not significantly different, LGA tended to have higher body fat at 24 months, suggesting the effects of LGA on obesity may emerge later in the early childhood period. Hediger et al found that differences in body fat between SGA and LGA only emerged at 6 years of age, with LGA having higher body fat at this age (145). We found that AGA had higher FFM and FFMI at 24 months, affirming the metabolic advantage of this group.

In contrast to intrauterine growth restriction; postnatal nutritional deprivation was not associated with significantly higher body fat. It has been suggested that during nutritional deprivation in infancy, FM may be preserved at the expense of height for optimum metabolic function (50). To this end, it would be expected that children with stunting would have higher FM than those without stunting. We found that children with stunting had lower FM and FFM than children with no stunting. Notwithstanding, there was a tendency towards higher FMI at 6 months for children with stunting than those with no stunting, albeit it was not statistically different. Surprisingly, infants with stunting in the present study had significantly higher FFMI at 6 months compared to children with no stunting. Others found that stunting was not

associated with FFMI at 6 months (146), while stunting at 2 years was negatively associated with total fat-free soft tissue mass at 22 years (147).

Intrauterine growth restriction plays a key role in influencing postnatal growth patterns. It has been suggested that there is a differential rate of growth between body size and composition among SGA, such that the acceleration in subcutaneous fat deposition precedes acceleration in weight during catch-up growth (137). Early infancy is a critical window for the development of adiposity early in life. Previous studies reported that weight gain at 6 months of life was a better predictor of fat mass later in life, than weight gain after 6 months (135,148). We could not establish that rapid growth at 0-6 months was a better predictor of FM than growth at 6- 24 months. In contrast, rapid weight gain beyond 6 months of age had a stronger association with toddler body fat. Our findings in girls also show that rapid linear growth was associated with higher adiposity at 24 months. These findings may conversely highlight the effect of adiposity on linear growth during childhood. Forbes et al. hypothesised that childhood adiposity accelerates linear growth; meaning that in childhood heavier children are generally taller (149). A previous Birth to Twenty cohort study reported an association between rapid linear growth in infancy with increased visceral adipose tissues at 22 years (147).

This was the first longitudinal study to investigate the effect of growth patterns on nutritional status and body composition from birth to 2 years using the gold standard method in our setting. Our data were from healthy infants of healthy educated mothers who were within the upper socioeconomic status. One limitation was that we did not have enough data on maternal pre-pregnancy BMI status, which would have shed a light on whether LGA and high birthweight infants were born of women with obesity. The second limitation was that our findings were not representative of all infants and were biased to urban black infants. Due to our small sample size, stunting and size at birth categories could not be stratified by sex. Nonetheless, this

provides the groundwork for subsequent studies on infant body composition in LMIC, particularly SSA. Understanding how growth patterns influence body composition in LMICs undergoing dual burden of malnutrition is pivotal.

Conclusion

In conclusion, we found significant differences by birth weight categories and nutritional status. SGA had a higher body fat in infancy while LGA tended towards higher body fat in the toddler period. Both SGA and LGA are disadvantaged extremes in infancy likely to increase the risk for obesity. Conversely, stunting was associated with lower body fat. Thus, intrauterine growth restriction and not postnatal nutritional deprivation may trigger fat preservation. Additionally, our findings showed that growth patterns beyond 6 months of age had stronger associations with toddler body fat. Therefore, nutrition interventions should be targeted towards women of child bearing age at pre conception, to optimise intra uterine growth and birth weight outcomes since this forms the basis for early growth and development of which the effects reach well into the adult years.

Table 3-1 Maternal characteristics stratified by child sex (boys and girls)

Maternal variable	Total	Boys	Girls	P value
	N= 757	n = 419	n = 338	
Age (years) (n=757)	25.8 (6.0)	26.1 (6.3)	25.5 (5.7)	0.162
Pre-pregnancy weight (kg) (n=193)	70.6 (19.6)	69.6 (18.2)	71.6 (20.9)	0.494
Gestational age at birth (weeks) (n=693)	38.8 (1.35)	38.8 (1.3)	38.8 (1.4)	0.806
Maternal education (years) (n=753)	12.05 (0.8)	12.1 (1.4)	12.0 (0.2)	0.645
Parity (n=698)				0.844
None	157 (44.5)	191 (48.6)	123 (40.3)	
One	91 (26.4)	94 (23.9)	88 (28.8)	
Two+	100.5 (29)	107 (27.2)	94 (30.8)	
Marital status (n=708)				0.203
Single/divorced/widowed	274.5 (77.3)	238.0 (75.3)	311.0 (79.3)	
Married/cohabiting	79.5 (22.7)	78.0 (24.7)	81.0 (20.7)	

Standard errors in parentheses: *** p<0.001, ** p<0.01, * p<0.05

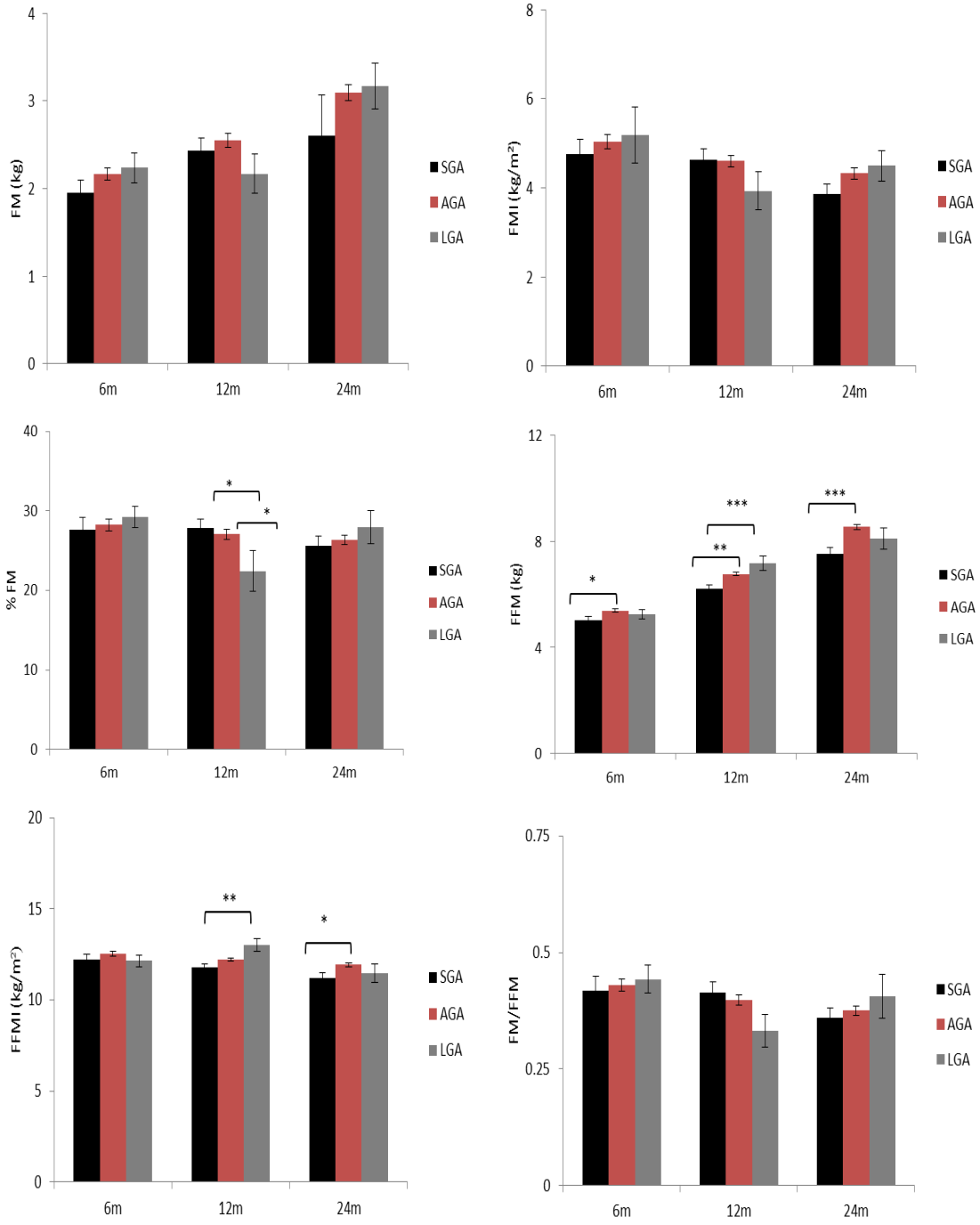

Figure 3-1 Relationship between birthweight categories at 6, 12, and 24 months with body composition at 2 years

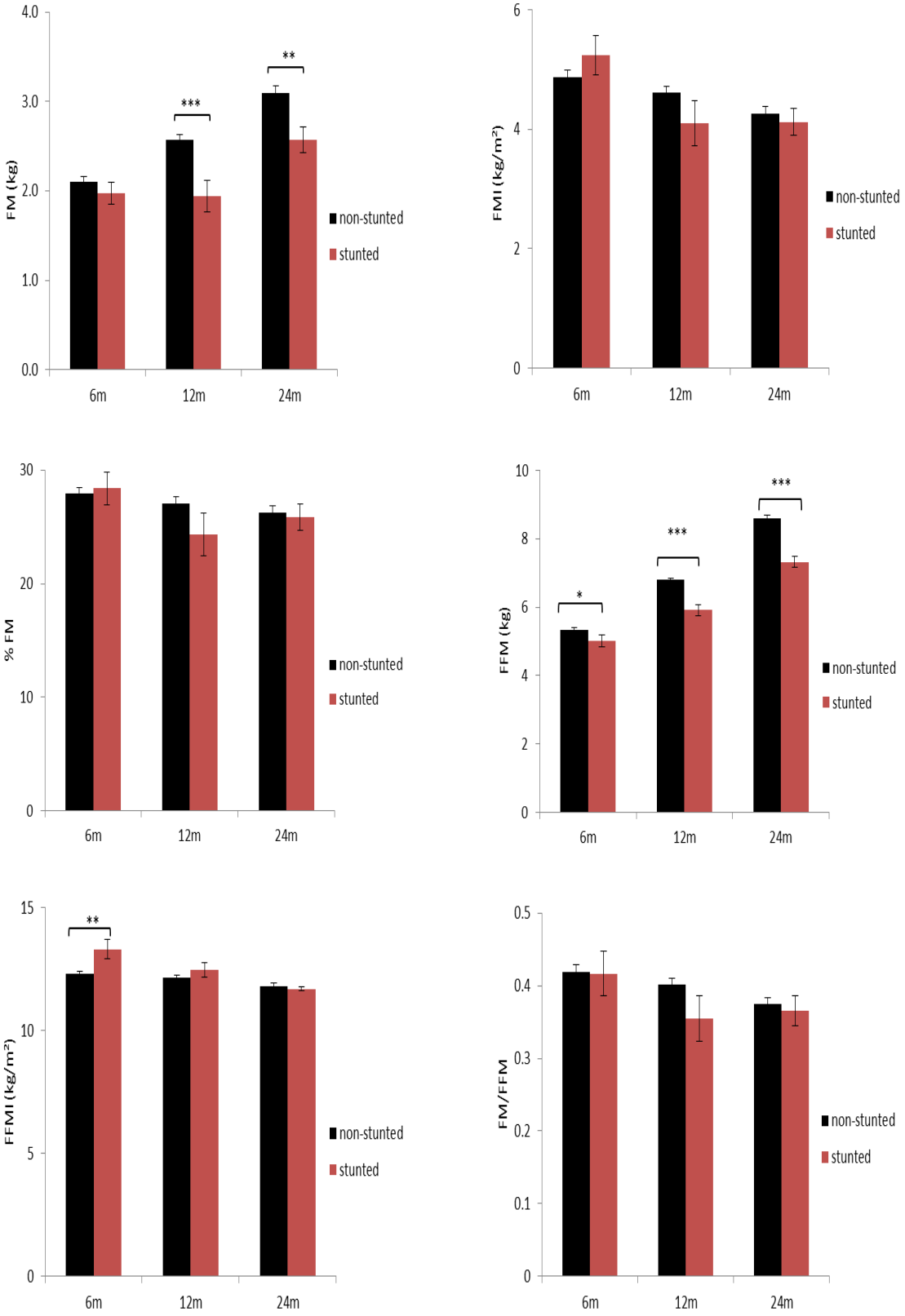

Figure 3-2 Relationship between nutritional status at 6, 12, and 24 months with body composition at 2 years

Table 3-2 Relationship between Birthweight z-score, conditional relative weight, and conditional length at 0-6 and 6-24 months with FM, FMI, FFM and FFMI at 24 months

Variables	FM (kg)	FMI (kg/m²)	FFM (kg)	FFMI(kg/m²)
Birthweight z-score	0.14* (0.07)	0.14 (0.09)	0.20** (0.07)	0.10 (0.09)
Conditional relative weight (0-6 months)	0.27** (0.09)	0.29* (0.11)	0.46*** (0.08)	0.41*** (0.12)
Conditional length (0-6 months)	0.17 (0.09)	0.13 (0.12)	0.25** (0.09)	0.02 (0.12)
Conditional relative weight (6-24 months)	0.53*** (0.09)	0.64*** (0.11)	0.33*** (0.08)	0.28* (0.11)
Conditional length (6-24 months)	0.05 (0.10)	-0.16 (0.12)	0.24* (0.09)	-0.33* (0.13)
R-squared	0.42	0.38	0.49	0.26

Standard errors in parentheses: *** p<0.001, ** p<0.01, * p<0.05

Supplementary Tables

Table S 3-1 Sex difference in infant anthropometry from birth to 24 months

	Weight (kg)		Length (cm)	
Age	Boys	Girls	Boys	Girls
Birth	3.2 (0.4)** *[322]*	3.1 (0.4) *[301]*	50.4 (2.8)*** *[320]*	49.5 (2.9) *[294]*
1 month	4.3 (0.6)** *[69]*	4.0 (0.6) *[79]*	53.4 (3.0)** *[69]*	52.1 (2.6) *[79]*
2 months	5.3 (0.5)** *[62]*	5.0 (0.7) *[67]*	56.0 (2.2)* *[62]*	55.1 (2.5) *[67]*
3 months	6.3 (0.8)*** *[314]*	5.8 (0.9) *[277]*	59.8 (3.1)*** *[306]*	58.1 (3.4) *[275]*
4 months	6.9 (0.8)* *[48]*	6.5 (1.0) *[58]*	62.8 (2.6)*** *[48]*	60.8 (2.4) *[58]*
6 months	7.8 (1.1)** *[189]*	7.4 (1.1) *[191]*	66.7 (3.0)*** *[187]*	64.7 (2.7) *[188]*
9 months	8.9 (1.2)*** *[109]*	8.3 (1.1) *[106]*	71.0 (3.6)* *[109]*	69.9 (3.8) *[105]*
12 months	9.7 (1.2)*** *[155]*	9.1 (1.3) *[133]*	75.0 (3.4)*** *[152]*	73.5 (3.9) *[129]*
15 months	10.3 (1.4)* *[64]*	9.7 (1.3) *[59]*	77.6 (2.9)** *[69]*	75.9 (3.3) *[61]*
18 months	10.8 (1.6) *[62]*	10.2 (1.4) *[55]*	79.6 (3.5) *[64]*	78.7 (3.3) *[57]*
24 months	11.9 (1.7)* *[83]*	11.3 (1.5) *[72]*	84.8 (4.1) *[90]*	83.7 (3.4) *[81]*

Sample size in square brackets [n] *p<0.05 **p<0.01 ***p<0.001

Table S3-2 Body composition from birth to 6 months by ADP Peapod method

	FM (kg)		FFM (kg)		FM%		FMI (kg/m²)		FFMI (kg/m²)		FM/FFM	
Age	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birth	0.3 (0.2)***	0.4 (0.2)	2.7 (0.3)	2.6 (0.3)	10.4 (4.5)	11.8 (4.1)	1.4 (0.7)	1.6 (0.7)	11.8 (1.3)	11.6 (1.5)	0.1 (0.1)**	0.1 (0.1)
1 month	0.8 (0.2)***	0.8 (0.3)	3.4 (0.4)	3.2 (0.4)	19.4 (4.1)	20.1 (4.9)	2.9 (0.8)	3.0 (1.0)	11.9 (1.2)	11.7 (1.1)	0.2 (0.1)***	0.3 (0.1)
2 months	1.3 (0.3)	1.3 (0.4)	4.0 (0.4)	3.7 (0.4)	24.4 (4.4)	25.5 (4.9)	4.2 (1.1)	4.2 (1.2)	12.8 (1.1)	12.1 (1.3)	0.3 (0.1)***	0.3 (0.1)
3 months	1.7 (0.4)	1.7 (0.5)	4.6 (0.4)	4.2 (0.4)	26.8 (4.3)	27.9 (5.6)	4.8 (1.0)	4.9 (1.5)	12.9 (1.2)	12.3 (1.2)	0.4 (0.1)***	0.4 (0.1)
4 months	1.8 (0.5)	1.9 (0.7)	4.9 (0.4)	4.5 (0.5)	26.5 (5.3)	28.5 (6.8)	4.7 (1.3)	4.9 (1.7)	12.7 (0.9)	12.2 (1.2)	0.4 (0.1)***	0.4 (0.1)
6 months	1.9 (0.5)	2.0 (0,0)	5.4 (0.4)	5.2 (0.4)	25.9 (4.3)	27.7 (5.3)	4.4 (1.2)	5.0 (1.4)	12.4 (1.1)	12.7 (1.2)	0.4 (0.1)***	0.4 (0.1)

***p<0.05 **p<0.01 ***p<0.001**

Table S3-3 Body composition from 3-24 months by deuterium oxide dilution method

	FM (kg)		FFM (kg)		FM (%)		FFMI (kg/m^2)		FMI (kg/m^2)		FFM/FM	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
3 months	1.7 (0.5)	1.7 (0.5)	4.6 (0.6)	4.3 (0.6)	26.6 (5.9)	28.1 (6.6)	13.3 (2.5)	12.5 (2.0)	4.9 (1.6)	4.9 (1.5)	0.4 (0.1)***	0.4 (0.1)
6 months	2.2 (0.7)	2.3 (0.7)	5.7 (0.7)	5.1 (0.7)	27.2 (7.0)	30.7 (7.3)	12.9 (1.8)	12.2 (1.7)	5.0 (1.5)	5.5 (1.7)	0.4 (0.1)***	0.5 (0.2)
9 months	2.7 (0.8)	2.6 (0.7)	6.3 (0.8)	5.8 (0.8)	29.3 (6.7)	30.5 (6.6)	12.5 (1.6)	11.8 (1.6)	5.2 (1.5)	5.3 (1.5)	0.4 (0.1)***	0.5 (0.1)
12 months	2.7 (0.8)	2.6 (0.9)	7.0 (0.9)	6.4 (0.8)	27.3 (6.3)	28.6 (7.4)	12.7 (3.1)	11.8 (1.6)	4.8 (1.5)	4.8 (1.6)	0.4 (0.1)***	0.4 (0.2)
15 months	2.8 (0.8)	2.9 (1.0)	7.6 (1.0)	7.1 (0.9)	26.6 (5.3)	28.9 (7.3)	12.5 (1.1)	11.8 (1.1)	4.6 (1.2)	4.9 (1.7)	0.4 (0.1)***	0.4 (0.2)
18 months	2.8 (1.1)	2.9 (0.7)	7.9 (1.1)	7.3 (0.9)	25.8 (7.0)	28.3 (5.5)	12.6 (1.5)	11.7 (1.3)	4.4 (1.5)	4.7 (1.1)	0.4 (0.1)***	0.4 (0.1)
24 months	3.2 (1.1)	3.2 (0.9)	8.8 (1.1)	8.1 (1.0)	26.2 (5.9)	27.9 (5.1)	12.1 (1.3)	11.7 (1.2)	4.4 (1.4)	4.5 (1.1)	0.4 (0.1)***	0.4 (0.1)

***p<0.05 **p<0.01 ***p<0.001**

Table S3-4 Sex differences in the relationship between Birthweight z-score, conditional relative weight, and conditional length at 0-6 and 6-24 months with FM, FMI, FFM and FFMI at 24 months

Variables	FM (kg)		FMI(kg/m²)		FFM (kg)		FFMI (kg/m²)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Birthweight z-score	0.34	0.11*	0.37	0.10	0.48**	0.16*	0.36*	0.07
	(0.20)	(0.05)	(0.23)	(0.08)	(0.16)	(0.06)	(0.17)	(0.12)
Conditional relative weight (0-6 months)	0.25	0.26***	0.25	0.27*	0.37*	0.49***	0.32*	0.43*
	(0.17)	(0.07)	(0.20)	(0.12)	(0.14)	(0.09)	(0.14)	(0.17)
Conditional length	0.06	0.26**	-0.02	0.25	0.22	0.31**	-0.06	0.11
(0-6 months)	(0.17)	(0.08)	(0.20)	(0.14)	(0.14)	(0.10)	(0.15)	(0.20)
Conditional relative weight (6-24 months)	0.67***	0.43***	0.85***	0.49***	0.31*	0.38***	0.40**	0.21
	(0.17)	(0.07)	(0.19)	(0.12)	(0.13)	(0.09)	(0.14)	(0.18)
Conditional length (6-24 months)	-0.15	0.26**	-0.38	0.07	0.15	0.24*	-0.34*	-0.38
	(0.17)	(0.08)	(0.19)	(0.14)	(0.14)	(0.11)	(0.14)	(0.21)
R-squared	0.40	0.67	0.45	0.42	0.46	0.65	0.41	0.24

***p<0.05 **p<0.01 ***p<0.001**

Chapter 4: Additional Results

4.1 Introduction

This chapter present results that were not submitted for publication but contributed to this dissertation. Broadly, this chapter presents results that investigated the relationship between anthropometric measurement and infant body composition. Anthropometry is the most commonly used method for assessing infant body composition in under-resourced settings. However, the extents to which anthropometric measurement reflect body fat is not well understood. BMI has been reported to be associated with body fat and related risk of adverse health in children at the age of 5 years (150). However there have been concerns in the use of BMI as a proxy for body fatness in infancy (151). This dissertation investigated which of the indices best reflected FM, FFM, FMI, and FFMI from birth to 2 years.

4.2 Methods

Age and sex adjusted HAZ, WAZ, and WHZ were generated using the 2006 WHO child growth standards for children from birth to 5 years (138). Correlation analysis was performed to investigate the association between HAZ, WAZ, and WHZ and FM, FFM, FFM, FFMI, and FM/FFM using Stata. Anthropometric classification were used to predict overweight and obesity as defined by FMI and %FM. WHO growth standard derived z-scores were assessed as independent variables: weight-for-age (kg), length-for-age (cm), weight-for-length (kg/cm), triceps-for-age (mm) and subscapular-for-age (mm). Overweight was defined at >85th and obesity at 95th percentiles, respectively.

4.3 Results

4.3.1 Correlations between anthropometric measurement and infant body composition

The relationship between anthropometric indices HAZ, WAZ, and WHZ and FM, FFM, FMI, FFMI, and FM/FFM at different ages, shown in Table 4-1, Table 4-2, Table 4-3, Table 4-4, and Table 4-5. At birth to 24 months there was stronger correlation between FM, FFM and FMI with WAZ than HAZ and WHZ in both boys and girls. There was a correlation between FM, FFM, FMI, and FFMI and WHZ at birth to 18 months in girls. FMI and FFMI showed no correlation with HAZ in girls at birth to 2 years, and moderate correlation at 15 and 18 months in boys. At 3 months, there was a strong correlation between FM and HAZ in boys.

Table 4-1 The correlation between FM and HAZ, WAZ and WHZ in boys and girls from birth to 24 months

***p<0.05 **p<0.01 ***p<0.001**

FM	Length-for-age		Weight-for-age		Weight-for-length	
Visit	Boys	Girls	Boys	Girls	boys	girls
Birth	0.1729	0.3461***	0.5145***	0.5597***	0.3177**	0.3236**
1 month	0.1786	0.2952**	0.5245**	0.7707***	0.1629	0.4113***
2 months	0.2413	0.4508***	0.6528***	0.8142***	0.3593**	0.3789**
3 months	0.226***	0.1724*	0.6762***	0.6315***	0.3925***	0.2998***
4 months	0.1698	0.2132	0.7544***	0.7792***	0.5958***	0.6323***
6 months	0.2136*	0.0174*	0.7364***	0.7281***	0.5783***	0.6599***
9 months	0.0734	0.2064*	0.6909***	0.6161***	0.0237	0.5405***
12 months	0.2829**	0.2657**	0.6793***	0.6778***	0.5838***	0.5164***
15 months	0.3977**	0.2104	0.7798***	0.7822***	0.7429***	0.724***
18 months	0.4638**	0.333*	0.7397***	0.6431***	0.6881***	0.597***
24 months	0.3286**	0.4127***	0.7514***	0.773***	0.7486	0.0364***

Table 4-2 The correlation between FFM and HAZ, WAZ and WHZ in boys and girls from birth to 24 months

***p<0.05 **p<0.01 ***p<0.001**

FFM	Length-for-age		Weight-for-age		Weight-for-length	
Visit	Boys	Girls	Boys	Girls	boys	girls
Birth	0.4273***	0.6179***	0.7922***	0.8514***	0.2979*	0.3876***
1 month	0.3403**	0.4382***	0.6963***	0.8524***	0.0703	0.3331**
2 months	0.4603***	0.5506***	0.802***	0.8454***	0.2401	0.4116***
3 months	0.4195***	0.3731***	0.7288***	0.6985***	0.1886**	0.1798**
4 months	0.2945	0.4932***	0.6094***	0.7627***	0.2972	0.3386*
6 months	0.2848***	0.4939***	0.6599***	0.6939***	0.4344***	0.4457***
9 months	0.4059***	0.4567***	0.7215***	0.7733***	0.1372	0.4888***
12 months	0.6085***	0.5402***	0.7476***	0.7083***	0.4386***	0.4162***
15 months	0.7413***	0.6383***	0.8775***	0.6908***	0.7258***	0.3706**
18 months	0.4138**	0.5563***	0.7281***	0.8072***	0.6785***	0.6599***
24 months	0.6225***	0.6211***	0.786***	0.8287***	0.5875***	-0.0248

Table 4-3 The correlation between FMI and HAZ, WAZ and WHZ in boys and girls from birth to 24 months

FMI	Length-for-age		Weight-for-age		Weight-for-length	
Visit	Boys	Girls	Boys	Girls	boys	girls
Birth	0.0363	0.1665	0.4492***	0.4707***	0.4193***	0.3864***
1 month	-0.095	0.0665	0.3865**	0.6837***	0.389**	0.5668***
2 months	-0.0715	0.2138	0.5286***	0.7412***	0.5707***	0.5925***
3 months	-0.0548	-0.192	0.4904***	0.4792***	0.6531***	0.5892***
4 months	-0.093	-0.0805	0.6455***	0.6287***	0.7394***	0.7598***
6 months	-0.0734	-0.015	0.6018***	0.6309***	0.6912***	0.7462***
9 months	-0.1216	-0.144	0.5902***	0.4468***	0.0145	0.6194***
12 months	0.0276	-0.0086	0.5326***	0.5079***	0.7208***	0.6179***
15 months	0.1375	-0.1227	0.6288***	0.5532***	0.6912***	0.7787***
18 months	0.3358*	-0.0057	0.6785***	0.4511**	0.689***	0.5795***
24 months	0.1166	0.1299	0.6314***	0.5824***	0.7444***	-0.0292

***p<0.05 **p<0.01 ***p<0.001**

Table 4-4 The correlation between FFMI and HAZ, WAZ and WHZ in boys and girls from birth to 24 months

***p<0.05 **p<0.01 ***p<0.001**

FFMI	Length-for-age		Weight-for-age		Weight-for-length	
Visit	Boys	Girls	Boys	Girls	boys	girls
Birth	-0.1769	0.0178	0.4177***	0.4208***	0.6546***	0.4597***
1 month	-0.363	-0.3959	0.3343**	0.4711***	0.6441***	0.8349***
2 months	-0.3247	-0.1841	0.514***	0.4222***	0.8022***	0.7717***
3 months	-0.331	-0.4554	0.2333***	0.3038***	0.7643***	0.7526***
4 months	-0.4439	-0.2559	0.2133	0.3883**	0.6154***	0.6605***
6 months	-0.4354	-0.0244	0.2397**	0.4347***	0.6569***	0.6095***
9 months	-0.1149	-0.1962	0.4595***	0.495***	0.1165	0.6789***
12 months	0.0007	-0.1368	0.2488**	0.2309*	0.41***	0.5389***
15 months	0.2925*	-0.0752	0.7324***	0.1727	0.7572***	0.4174**
18 months	-0.1185	-0.1341	0.39**	0.4504**	0.5726***	0.6651***
24 months	-0.0677	-0.0138	0.446***	0.3437**	0.6386***	-0.2071

Table 4-5 The correlation between FM:FFM and HAZ, WAZ and WHZ in boys and girls from birth to 24 months

FM/FFM	Length-for-age		Weight-for-age		Weight-for-length	
Age(months)	Boys	Girls	Boys	Girls	boys	girls
0	0.0599	0.2071	0.2994*	0.3857***	0.2347	0.2451*
1	0.0475	0.1925	0.2743*	0.6023***	0.1498	0.3664***
2	0.0546	0.3091*	0.3442**	0.641***	0.2773*	0.2925*
3	0.0799	0.0262	0.3985***	0.3364***	0.3138***	0.2173**
4	0.0735	-0.0127	0.5698***	0.4926***	0.5118***	0.5443***
6	0.0841	-0.0104	0.4725***	0.4441***	0.416***	0.484***
9	-0.1417	-0.0432	0.3414**	0.2041*	-0.0293	0.2816**
12	0.0246	0.0423	0.3523***	0.3839***	0.3828***	0.3428***
15	0.0067	-0.0568	0.3403*	0.5118***	0.3983**	0.6228***
18	0.3384*	0.0366	0.5259***	0.2274	0.4745***	0.2617
24	0.1021	0.124	0.4691***	0.4214***	0.539***	0.0507

***p<0.05 **p<0.01 ***p<0.001**

4.3.2 Positive predictive values of overweight and obesity

The current study assessed how much overweight and obesity as defined by anthropometric measurements could predict excess adiposity (>85th & 95th percentiles) defined by FMI and %FM at the age of 2 years, using the positive predictive value. Positive predictive values (PPV) presented as percentages at 95% confidence interval in Table 4-6. In overweight by BMI classification; the PPVs for identifying excess adiposity were 28.1% & 32.5% by FMI and 14.1% & 26.6% by %FM. MUAC prediction of obesity by FMI was 45.8% & 57.7%. Girls generally presented significantly higher PPV in BMI and arm circumference classifications by both FMI and %FM. Subscapular skinfolds (47.6% & 36.4%) showed better obesity prediction by FMI than triceps (29.2% & 24.0%). In overweight and obesity classification by sum of skinfolds, boys presented higher values by FMI at 21.4% & 57.1% as compared to girls at 17.2% & 36.4%, respectively. %FM generally showed lower overweight and obesity predictions as compared to FMI.

Table 4-6 Positive predictive values of anthropometric measurements to predict overweight (>85th percentile) and obesity (>95th centile) by FMI and %FM.

Classification	Boys		Girls	
	FMI	%FM	FMI	%FM
Overweight (>85th centile)				
BMI	28.1 (17.6-40.8)	14.1 (6.64-25.0)	32.5 (22.2-44.1)	26.6 (16.3-39.1)
Arm circumference	12.9 (5.70-23.9)	11.1 (4.59-21.6)	26.7 (17.1-38.1)	22.2 (12.7-34.5)
Triceps skinfold	14.8 (6.98-26.2)	16.7 (8.29-28.5)	21.7 (12.7-33.3)	21.1 (11.4-33.9)
Subscapular skinfold	20.0 (10.4-33.0)	18.2 (9.08-30.9)	15.6 (7.76-26.9)	25.0 (14.0-38.9)
Sum of skinfolds	21.4 (11.6-34.4)	20.0 (10.4-33.0)	17.2 (8.90-28.7)	25.0 (14.0-38.9)
Obesity (>95th centile)				
BMI	50.0 (29.1-70.9)	23.3 (9.93-42.3)	57.7 (36.9-76.6)	23.3 (9.93-42.3)
Arm circumference	45.8 (25.6-67.2)	26.7 (12.3-45.9)	57.7 (36.9-76.6)	30.0 (14.7-49.4)
Triceps skinfold	29.2 (12.6-51.1)	13.3 (3.46-30.7)	24.0 (9.36-45.1)	10.3 (2.19-27.4)
Subscapular skinfold	47.6 (25.7-70.2)	26.9 (11.6-47.8)	36.4 (17.2-59.3)	20.8 (7.13-42.2)
Sum of skinfolds	57.1 (34.0-78.2)	26.9 (11.6-47.8)	36.4 (17.2-59.3)	16.7 (4.74-37.4)

4.3.3 Comparison of the current study with Fomon

The current study compared %FM with HIC findings from Fomon et al (81). The findings are presented in Figure 4-1. Infants in the current study showed a rapid increase in %FM with the highest peak at 6 months for girls and 9 months for boys than the Fomon study. In both studies %FM was higher in girls than boys, however the difference was the widest in the current study.

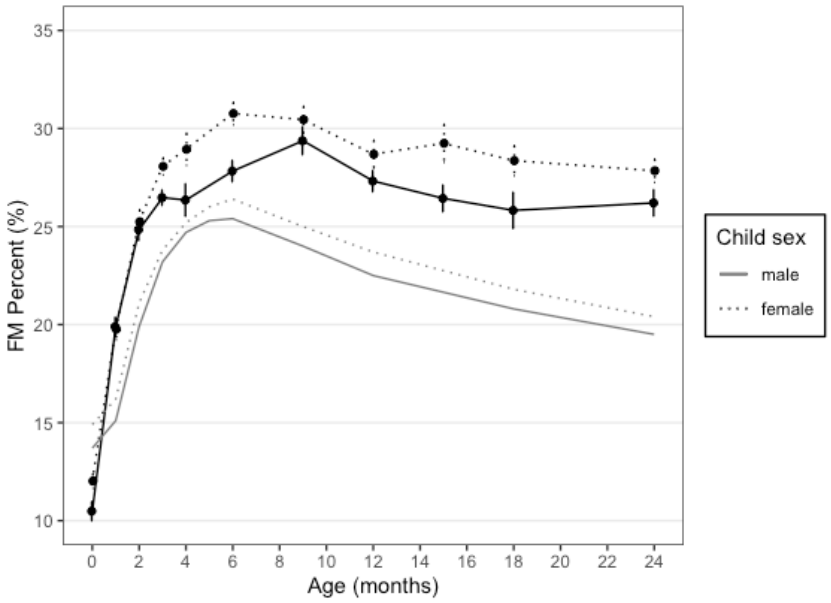

Figure 4-1 Comparing %FM of South African infants with Fomon study. Black (South African infants), Blue (Fomon infants)

Chapter 5: Integrated discussion and conclusion

5.1 Summary of key findings

This chapter discusses key findings which emerged from the main objectives of this dissertation, and further revisits the conceptual framework and hypotheses, as well as the implications of the study and recommendations for future research. Key findings emerged from the analyses are described in Table 5-1

Table 5-1 Summary of key findings

Objectives	Chapter	Summary of key finding
1. To assess age and sex-related changes in fat mass and fat-free soft tissue mass between birth and 24 months	3	• FM and FFM increased with age from birth to 24 months • %FM, FMI, and FFMI increased with age from birth to 6 months and remained constant from 9 to 24 months • FM/FFM remained constant throughout • Girls had higher FM at birth than boys

		• There were no differences in FMI, %FM, FFM and FFMI between different sexes
2. To assess the relationship between birthweight categories and body composition	3	• SGA and AGA had significantly higher %FM than LGA at 12 months • LGA had higher FFM ($p<0.001$) than SGA, at 12 months • LGA had higher FFMI ($p<0.01$) at 12 months than SGA • AGA had higher FFMI ($p<0.05$) at 24 months than SGA. • no significant differences in FM and FFM between categories of birth weight
3. To assess the relationship between infant growth and infant body composition	3	• Conditional relative weight gain at 0-6 months and 6-24 months were significantly associated with FM, FMI, FFM, and FFMI • Conditional length 0-6 ($p<0.01$, SE 0.09) and 6-24 ($p<0.05$, SE 0.09) months were associated with FFM

4. To assess the relationship between nutritional status and body composition	3	• Children with stunting had lower FM ($p<0.001$) at 12 months and FFM ($p<0.001$) at 24 months than non-stunted children • Children with stunting had higher FFMI ($p<0.01$) at 6 months than children without stunting
5. To assess the association between anthropometric measurement and fat mass, and fat-free mass	4	• WAZ showed stronger correlation between FM, FFM and FMI at birth to 2 years than HAZ and WHZ in both boys and girls • FM strongly correlated with WHZ (association coefficient range: 0.04-0.72) and FFM strongly correlated with HAZ (association coefficient range: 0.37-0.64) in girls than in boys

The overall aim of this dissertation was to assess critical periods during which growth patterns in the first 1000 days may independently influence body composition and whether poor nutritional status is associated with increased fat mass. Additionally, this dissertation explored the correlation between anthropometric measurements and the components of body composition. WAZ was more strongly correlated with FM (rho: 0.51-0.78 for WAZ vs. 0.02-

0.74 for WHZ) in boys, and (rho: 0.56-0.81 for WAZ vs. 0.30-0.72 for WHZ) in girls and FFM (rho: 0.61-0.88 for WAZ vs 0.07-0.73 for WHZ) in boys and (rho: 0.69-0.85 for WAZ vs 0.18-0.49 for WHZ) in girls. Conversely, WAZ was more strongly correlated with FMI (rho: 0.39-0.65 vs 0.01-0.74 for WHZ) in boys and (rho: 0.45-0.74 for WAZ vs 0.39-0.78 for WHZ) in girls. HAZ was more correlated with FFMI (rho: 0.42-0.83) in girls than in boys (rho: 0.12-0.80). Generally, BMI had a higher positive predictive value for excess FM than MUAC, and skinfolds thickness. Among participants with overweight, the PPV of BMI in predicting FMI was 28.1% in boys and 32.5% in girls, while it was 50.0% in boys and 57.7% in girls among participants with obesity. The growth rate in percent body fat was considerably higher among South African infants than the Fomon references.

This dissertation also explored the relationship between birthweight, postnatal growth patterns and infant body composition as shown in the conceptual framework. Path 1 assessed the relationship between birthweight and body composition at 6, 12 and 24 months using birthweight categories. Path 2 investigated the association of nutritional status at 6, 12, and 24 months with body composition. Path 3 investigated the association of rapid weight gain and linear growth 0-6 months and 6-24 months with body composition. The dissertation showed that SGA and AGA had significantly higher %FM than LGA at 12 months. LGA had higher FFMI ($p<0.01$) at 12 months than SGA. Rapid weight gain beyond 6 months of age had a stronger associated with toddler body fat. Children with stunting had lower FM ($p<0.001$) at 12 months and FFM ($p<0.01$, $p<0.001$) at 24 months than non-stunted children. Subscapular skinfold showed better prediction of overweight and obesity by percentage body fat than BMI.

5.2 Revisiting the hypotheses

There were three hypotheses (H) which were tested in this dissertation. The response (R) is provided below each of the hypotheses:

H_1: Rapid weight gain in infancy (characterised by conditional relative weight gain) is a predictor of overweight and obesity in childhood

R: Rapid weight gain in infancy could be a predictor of overweight and obesity as measured by FM. The hypothesis is accepted

H_2: Children who experienced undernutrition (characterised by SGA and stunting) will have higher body fat than children who experienced normal growth,

R_1: SGA children had higher percentage body fat than LGA. The hypothesis is accepted

R_2: Children with stunting exhibited lower FM and FFM than non-stunted children: The hypothesis is not accepted

H_3: Weight gain in the first 6 months of age has a stronger association with body fat at 2 years of age than weight gain after 6 months.

R: The period of 6 to 24 months was a better predictive period for positive association between growth patterns and body fat later in childhood. The hypothesis is not accepted

5.3 Emerging themes

There were three main themes which emerged from this dissertation. The themes were as follows:

(i) Early childhood effects of SGA vs mid-childhood effects of LGA

(ii) Critical period for development of body composition during infancy

(iii) Risk of obesity emerges during infancy in South African children

5.3.1 Infancy period (0-6 months) effects of SGA compared to toddler period (9-24 months) effect of LGA

Size at birth offers an early opportunity to assess in detail growth rate and body composition (152). Birth weight in particular is mostly used as a proxy for intrauterine over- or undernutrition risks. Children born at the extremes of birth size are at a greater disadvantage of risk of short or long term health problems (153). This study showed that SGA accumulate more body fat earlier in postnatal while LGA accumulated more in later infancy. SGA infants in this study exhibited faster gain in %FM than LGA and AGA. Although %FM has been reported to overestimate FM and underestimate FFM in infancy as it is not an independent index of body fatness, the findings in this study are important to monitor catch-up growth in children who are born small for their age as compared to their AGA peers. In agreement with these findings, Hediger et al reported that SGA infants had lower body fat at birth and show relative increase in body fat from 2 to 12 months compared to AGA (154).

Children born small for their gestational age usually exhibit catch-up growth in their first 6 months of life (155–157). However there has been a debate on whether it is being born small or the subsequent catch-up growth that is important in determining adiposity predisposition. There is evidence that accelerated growth during critical window periods has unfavourable effect on long term health, particularly the risk of cardiovascular disease and obesity (158). Findings from this dissertation showed that rapid weight gain was a stronger independent

predictor of adiposity than birthweight. Rapid weight gain after 6 months, independent of birthweight, was strongly correlated with FM, FMI, and FFM. These findings show that it is size at birth followed by subsequent postnatal catch-up growth from 6-24 months period that influence adiposity.

This dissertation also revealed that birthweight z-score were significantly associated with FFM. One study reported that the positive association between birthweight z-score and FFM could program more central subcutaneous adiposity in adolescence (159). This study supports the concept that there is a differential rate of growth between body size and composition among SGA, such that the acceleration in subcutaneous fat deposition precedes acceleration in weight during catch-up growth (137).

Likewise, this dissertation highlighted the effect of LGA on body composition. Our findings showed that the effect of LGA is more relevant in the toddler period (24 months). LGA infants have been reported to have increased chances of developing metabolic risks in childhood (age 11 years) (160). These findings elicit the need for interventions to prevent these birthweight extremes by promoting normal postnatal growth.

5.3.2 Critical periods for the development of body composition during infancy

The period between birth and 6 months is considered a critical period as it is associated with more rapid weight gain than any other period in infancy (134). Additionally, close to 40-65% of weight gain in this period is attributable to fat mass gain (65). Studies reported that weight gain at 6 months of life was a better predictor of fat mass later in life, than did after 6 months

(135,148). Rapid weight gain in the first 6 months was reported to be a predictor of metabolic risk in adolescent (161). Similarly rapid weight gain in the first 3 months of life was reported to be associated with central adiposity and lower insulin sensitivity in early adulthood (162). A recent systematic review on the association between rapid weight gain from birth to 2 years and later adiposity reported that rapid weight gain in the first 12 months period was associated with greater odds of obesity (136). This dissertation revealed that growth patterns after the first 6 months of life influence body composition at 2 years. Therefore this dissertation suggests that the entire first 2 years of life may be the critical window of developmental plasticity in adipose tissue.

5.3.3 Risk of obesity emerges during infancy in South African children

The increased prevalence of overweight and obesity particularly in the sub-Saharan Africa (SSA) has become a public concern. On average, the prevalence of obesity between the ages on 5-17 years in SSA is about 15.4% in girls and 7,6% in boys (163). In South Africa black adolescent girls experienced faster gain in BMI velocity than white girls of the same age (164). BMI references of South African adolescent black girls were reported to be higher than the American references. In comparison with Fomon study, the infants in this dissertation experienced more rapid increase in %FM in the first 6 months of life and a slower decline after 6 months than their study. In 1982 Fomon et al. in their classic study presented gender and age body composition reference data from birth to 10 years. The finding in the current study showed that girls in particular accumulated more %FM which remained steady after 6 months. Therefore the risk of obesity in South Africa emerges in infancy. However the limitation with

this comparison is that data from Fomon study dates back to 1982 and there has been a secular change in BMI which may have in this comparison.

5.4 Implications of the study

DOHaD pointed out the origin of cardiovascular diseases back to preconception and postnatal environmental factors. This study contributes in highlighting key early life factors that may be the link to improve healthy infant growth and ultimately lower overweight and obesity epidemic. Most importantly the study shows that the assessment of infant body composition is imperative as it will assist policy makers in creating targeted intervention strategies and ultimately reduce future childhood obesity. This dissertation highlights the need to monitor and manage rapid weight gain among South African infants. In the National Strategy for the Prevention and Control of Obesity in South Africa (2015-2020) to reduce obesity prevalence by 10% by 2020, the minister of health acknowledged that: *"Research will guide and influence important inter-sectoral action at the national, district and provincial levels"*. The Department of Basic Education in the same report admitted that the double burden of malnutrition is a national concern in schools, and committed to come on board for the success of the strategy (165). I therefore believe that the population-based study conducted in this dissertation should be an essential component of the national strategy in fighting obesity epidemic in South Africa.

5.5 Strengths and limitations

There are notable strengths of this study as well as limitations for consideration. Firstly, the strength is that the study was done on urban black children and this would be an advantage in development of population targeted obesity prevention interventions. Second was the use of ADP and deuterium dilution methods to directly measure FM and FFM. These methods are more reliable and yielded more accurate results than if this study had used BMI as a tool to assess body composition. The third strength of the current study is the timing of infants' measurements, the critical window period of between birth and 2 years. Although previously stated as the strength, a predominantly black population sample might be a limitation. South Africa is a racially diverse nation insomuch that these findings cannot be extended beyond black urban population and therefore should not represent the entire population of South African children. Given the large proportion of infants born in South Africa, exclusion of HIV-exposed infants is another limitation in this study. The second limitation was the sample size. Due to our small sample size and different sample at different time points, stunting could not be stratified by sex.

5.6 Recommendation and future research

This dissertation recommends interventions such as improving pre-pregnancy maternal and paternal nutritional status to improve normal growth and help manage childhood undernutrition and obesity (166). Similarly, assessing body composition early in infancy would have long term benefits in ensuring that healthy infants grow to become healthy adults. Effective interventions such as providing nutrition counselling to mothers by the healthcare

workers may reduce stunting and SGA- and LGA-related obesity risk in children under 5 years (167), particularly in South Africa.

As acknowledged in the preceding section, the findings are biased to urban population and cannot represent the entire South African children. Therefore more population based studies on the association between infant growth patterns and nutritional status and body composition should be conducted in order to implement population specific policies to reduce the childhood obesity epidemic. Further research on other groups, such as adolescents, is necessary to assess the relationship between body composition in infancy and later growth.

5.7 Conclusion

This dissertation provides further evidence that later outcomes have their origins in early life. Additionally the study provides the foundation for more population studies on infant body composition in LMIC, particularly SSA, for targeted childhood obesity prevention interventions. Infancy is an important period in which preventative interventions may help prevent later health risks. In conclusion this dissertation showed that assessing the association of growth patterns and body composition early in infancy may prove valuable in understanding factors associated with prevalence of childhood obesity.

References

1. Kim S, Popkin BM. Commentary: Understanding the epidemiology of overweight and obesity - A real global public health concern. International Journal of Epidemiology. 2006.
2. Popkin BM. Nutrition Transition and the Global Diabetes Epidemic. Curr Diab Rep. 2015;15(9):1–8.
3. Simmonds M, Burch J, Llewellyn A, Griffiths C, Yang H, Owen C, et al. The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: A systematic review and meta-analysis. Health Technol Assess (Rockv). 2015;
4. Singh AS, Mulder C, Twisk JWR, Van Mechelen W, Chinapaw MJM. Tracking of childhood overweight into adulthood: A systematic review of the literature. Obesity Reviews. 2008.
5. WHO. Facts and figures on childhood obesity. Comm End Child Obes. 2019;
6. Lobstein T, Jackson-Leach R. Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. Pediatr Obes. 2016;
7. World Health Organization. WHO | Joint child malnutrition estimates - Levels and trends (2017 edition). WHO. 2018.
8. Mbogori T, Kimmel K, Zhang M, Kandiah J, Wang Y. Nutrition transition and double burden of malnutrition in Africa: A case study of four selected countries with different social economic development. AIMS Public Heal. 2020;
9. Shisana, O., Labadarios, D., Rehle, T., Simbayi, L., Zuma, K., Dhansay, A., Reddy, P.,

Parker, W., Hoosain, E., Naidoo, P. and Hongoro, C. 2014. The South African National Health and Nutrition Examination Survey, 2012: SANHANES-1: the health and nutritional status of the nation. :55.

10. World Health Organization (WHO). Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity. World Health Organization. 2016.

11. Glasgow S, Schrecker T. The double burden of neoliberalism? Noncommunicable disease policies and the global political economy of risk. Heal Place. 2016;

12. Benziger CP, Roth GA, Moran AE. The Global Burden of Disease Study and the Preventable Burden of NCD. Global Heart. 2016.

13. Kengne AP, Bentham J, Zhou B, Peer N, Matsha TE, Bixby H, et al. Trends in obesity and diabetes across Africa from 1980 to 2014: An analysis of pooled population-based studies. Int J Epidemiol. 2017;

14. Sagar R, Gupta T. Psychological Aspects of Obesity in Children and Adolescents. Indian Journal of Pediatrics. 2018.

15. Moradi M, Mozaffari H, Askari M, Azadbakht L. Association between overweight/obesity with depression, anxiety, low self-esteem, and body dissatisfaction in children and adolescents: a systematic review and meta-analysis of observational studies. Critical Reviews in Food Science and Nutrition. 2020.

16. Fang X, Zuo J, Zhou J, Cai J, Chen C, Xiang E, et al. Childhood obesity leads to adult type 2 diabetes and coronary artery diseases: A 2-sample mendelian randomization study. Med (United States). 2019;

17. Wühl E. Hypertension in childhood obesity. Acta Paediatrica, International Journal of Paediatrics. 2019.

18. Chaput JP, Doucet É, Tremblay A. Obesity: A disease or a biological adaptation? An update. Obes Rev. 2012;

19. Kansra AR, Lakkunarajah S, Jay MS. Childhood and Adolescent Obesity: A Review. Frontiers in Pediatrics. 2021.

20. Skelton JA, Irby MB, Grzywacz JG, Miller G. Etiologies of obesity in children: Nature and nurture. Pediatric Clinics of North America. 2011.

21. Gibson LY, Allen KL, Davis E, Blair E, Zubrick SR, Byrne SM. The psychosocial burden of childhood overweight and obesity: evidence for persisting difficulties in boys and girls. Eur J Pediatr. 2017;

22. Barker DJP, Eriksson JG, Forsén T, Osmond C. Fetal origins of adult disease: Strength of effects and biological basis. Int J Epidemiol. 2002;31(6):1235–9.

23. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia. 1992.

24. Steyn NP, Mchiza ZJ. Obesity and the nutrition transition in Sub-Saharan Africa. Ann N Y Acad Sci. 2014;1311(1):88–101.

25. Demerath EW, Fields DA. Body composition assessment in the infant. Am J Hum Biol. 2014;26(3):291–304.

26. Wells JC. A critique of the expression of paediatric body composition data. Arch Dis Child. 2001;85(1):67–72.

27. Wells JCK. A Hattori chart analysis of body mass index in infants and children. Int J Obes. 2000;24(3):325–9.

28. Lazarus R, Baur L, Webb K, Blyth F. Body mass index in screening for adiposity in children and adolescents: Systematic evaluation using receiver operating characteristic

curves. Am J Clin Nutr. 1996;

29. Jones PRM, Davies PSW, Norgan NG. Ultrasonic measurements of subcutaneous adipose tissue thickness in man. Am J Phys Anthropol. 1986;

30. Wells JCK, Fewtrell MS. Measuring body composition. Arch Dis Child. 2006;91(7):612–7.

31. Wells JCK, Fewtrell MS. Is body composition important for paediatricians? Arch Dis Child. 2008;93(2):168–72.

32. Ellis KJ. Evaluation of body composition in neonates and infants. Semin Fetal Neonatal Med. 2007;12(1):87–91.

33. Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE. Lancet. 1989;

34. Barker DJP, Osmond C. Infant Mortality, Childhood Nutrition, and Ischaemic Heart Disease in England and Wales. Lancet. 1986;327(8489):1077–81.

35. Gluckman PD, Hanson MA, Buklijas T. A conceptual framework for the developmental origins of health and disease. Vol. 1, Journal of Developmental Origins of Health and Disease. 2010. p. 6–18.

36. Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol. 2005;

37. K.R. Kjøllesdal M, Holmboe-Ottesen G. Dietary Patterns and Birth Weight—a Review. AIMS Public Heal. 2014;

38. Carberry AE, Colditz PB, Lingwood BE. Body composition from birth to 4.5 months in infants born to non-obese women. Pediatr Res. 2010;

39. Carberry AE, Raynes-Greenow CH, Turner RM, Askie LM, Jeffery HE. Is body fat

percentage a better measure of undernutrition in newborns than birth weight percentiles? Pediatr Res. 2013;

40. Ong KK, Dunger DB. Birth weight, infant growth and insulin resistance. In: European Journal of Endocrinology, Supplement. 2004.

41. Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk Factors for Childhood Obesity in the First 1,000 Days: A Systematic Review. American Journal of Preventive Medicine. 2016.

42. Kain J, Martínez M, Close M, Uauy R, Corvalán C. The association of excessive growth with development of general and central obesity at 7 years of age in every period after birth in Chilean children. Nutrition. 2016;

43. Casey PH, Bradley RH, Whiteside-Mansell L, Barrett K, Gossett JM, Simpson PM. Evolution of obesity in a low birth weight cohort. J Perinatol. 2012;

44. Ashworth A. Effects of intrauterine growth retardation on mortality and morbidity in infants and young children. In: European Journal of Clinical Nutrition. 1998.

45. Shrimpton R. Preventing low birthweight and reduction of child mortality. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2003.

46. Chomtho S, Wells JCK, Williams JE, Davies PSW, Lucas A, Fewtrell MS. Infant growth and later body composition: Evidence from the 4-component model. Am J Clin Nutr. 2008;87(6):1776–84.

47. Ong KK, Emmett P, Northstone K, Golding J, Rogers I, Ness AR, et al. Infancy weight gain predicts childhood body fat and age at menarche in girls. J Clin Endocrinol Metab. 2009;

48. Ong KK. Size at birth, postnatal growth and risk of obesity. Horm Res. 2006;65(SUPPL. 3):65–9.

49. Barker DJP. Journal of the American College of Nutrition The Developmental Origins of Adult Disease. 2013;(September):37–41.

50. Wells JCK, Chomtho S, Fewtrell MS. Programming of body composition by early growth and nutrition. Proc Nutr Soc. 2007;66(3):423–34.

51. Nyati LH, Pettifor JM, Norris SA. The prevalence of malnutrition and growth percentiles for urban South African children. BMC Public Health. 2019;19(1):1–14.

52. Wang ZM, Pierson RN, Heymsfield SB. The five-level model: A new approach to organizing body-composition research. Am J Clin Nutr. 1992;

53. William E. Siri. Body Composition From Fluid Spaces and Density: Analysis of Methods. Adv Biol Med Phy. 1956;

54. Heymsfield SB, Ebbeling CB, Zheng J, Pietrobelli A, Strauss BJ, Silva AM, et al. Multi-component molecular-level body composition reference methods: Evolving concepts and future directions. Obes Rev. 2015;

55. Elia M. Body composition analysis: an evaluation of 2 component models, multicomponent models and bedside techniques. Clinical Nutrition. 1992.

56. Ellis KJ. Human body composition: In vivo methods. Physiological Reviews. 2000.

57. St-Onge MP, Gallagher D. Body composition changes with aging: The cause or the result of alterations in metabolic rate and macronutrient oxidation? Nutrition. 2010.

58. Lukaski C. Review Methods traditional Article for the assessment and new13 of human body composition : Am J Clin Nutr. 1987;46(February):537–56.

59. Lee SY, Gallagher D. Assessment methods in human body composition. Current Opinion in Clinical Nutrition and Metabolic Care. 2008.

60. FRIIS-HANSEN B. Body water compartments in children: changes during growth and

related changes in body composition. Pediatrics. 1961;

61. Spalding KL, Arner E, Westermark PO, Bernard S, Buchholz BA, Bergmann O, et al. Dynamics of fat cell turnover in humans. Nature. 2008;

62. Ali AT, Hochfeld WE, Myburgh R, Pepper MS. Adipocyte and adipogenesis. European Journal of Cell Biology. 2013.

63. Spray CM, Widdowson EM. The Effect of Growth and Development on the Composition of Mammals. Br J Nutr. 1950;

64. Davies PSW. Estimates of body fatness in infancy and childhood. Am J Hum Biol. 1992;

65. Kuzawa CW. Adipose Tissue in Human Infancy and Childhood: An Evolutionary Perspective. Yearb Phys Anthropol. 1998;

66. Gesta S, Tseng YH, Kahn CR. Developmental Origin of Fat: Tracking Obesity to Its Source. Cell. 2007.

67. Berry DC, Stenesen D, Zeve D, Graff JM. The developmental origins of adipose tissue. Development (Cambridge). 2013.

68. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiological Reviews. 1994.

69. Ahmadian M, Wang Y, Sul HS. Lipolysis in adipocytes. International Journal of Biochemistry and Cell Biology. 2010.

70. Landgraf K, Rockstroh D, Wagner I V., Weise S, Tauscher R, Schwartze JT, et al. Evidence of early alterations in adipose tissue biology and function and its association with obesity-related inflammation and insulin resistance in children. Diabetes. 2015;

71. Lee YH, Mottillo EP, Granneman JG. Adipose tissue plasticity from WAT to BAT and

in between. Biochimica et Biophysica Acta - Molecular Basis of Disease. 2014.

72. Pellegrinelli V, Carobbio S, Vidal-Puig A. Adipose tissue plasticity: how fat depots respond differently to pathophysiological cues. Diabetologia. 2016.

73. Chan P-C, Hsieh P-S. The Role of Adipocyte Hypertrophy and Hypoxia in the Development of Obesity-Associated Adipose Tissue Inflammation and Insulin Resistance. In: Adiposity - Omics and Molecular Understanding. 2017.

74. Häger A, Sjöström L, Arvidsson B, Björntorp P, Smith U. Body fat and adipose tissue cellularity in infants: A longitudinal study. Metabolism. 1977;

75. Comuzzie AG, Allison DB. The search for human obesity genes. Science (80-). 1998;

76. Marti A, Martinez-González MA, Martinez JA. Interaction between genes and lifestyle factors on obesity. In: Proceedings of the Nutrition Society. 2008.

77. Ong KKL, Ahmed ML, Dunger DB, Emmett PM, Preece MA. Association between postnatal catch-up growth and obesity in childhood: Prospective cohort study. Br Med J. 2000;

78. Wells JCK. Body composition in infants: Evidence for developmental programming and techniques for measurement. Rev Endocr Metab Disord. 2012;13(2):93–101.

79. Koo WWK. Body composition measurements during infancy. In: Annals of the New York Academy of Sciences. 2000.

80. Fomon SJ. Body composition of the male reference infant during the first year of life. Pediatrics. 1967;

81. Fomon SJ, Haschke F, Ziegler EE, Nelson SE. Body composition of reference children from birth to age 10 years. Am J Clin Nutr. 1982;35(5 Suppl.):1169–75.

82. Lohman TG, Hingle M, Going SB. Body Composition in Children Assessment of

Body Composition in Children in 1989 (25 Years Ago). Pediatr Exerc Sci. 1989;

83. Butte NF, Hopkinson JM, Wong WW, Smith EO bria., Ellis KJ. Body composition during the first 2 years of life: An updated reference. Pediatr Res. 2000;

84. Fields DA, Gilchrist JM, Catalano PM, Gianní ML, Roggero PM, Mosca F. Longitudinal body composition data in exclusively breast-fed infants: A multicenter study. Obesity. 2011;

85. Wells JCK. Toward body composition reference data for infants, children, and adolescents. Adv Nutr. 2014;

86. Koletzko B, Sauerwald T, Demmelmair H. Safety of stable isotope use. 1997;12–7.

87. Wells JCK, Hawton K, Darch T, Lunn PG. Body composition by 2H dilution in Gambian infants: Comparison with UK infants and evaluation of simple prediction methods. Br J Nutr. 2009;102(12):1776–82.

88. Andersen GS, Girma T, Wells JCK, Kæstel P, Leventi M, Hother AL, et al. Body composition from birth to 6 mo of age in Ethiopian infants: Reference data obtained by air-displacement plethysmography. Am J Clin Nutr. 2013;98(4):885–94.

89. Jain V, Kurpad A V., Kumar B, Devi S, Sreenivas V, Paul VK. Body composition of term healthy Indian newborns. Eur J Clin Nutr [Internet]. 2016;70(4):488–93. Available from: http://dx.doi.org/10.1038/ejcn.2015.152

90. Urlando A, Dempster P, Aitkens S. A new air displacement plethysmograph for the measurement of body composition in infants. Pediatr Res. 2003;53(3):486–92.

91. McGarty JM, Butts NK, K L, Fletcher RA. COMPARISON OF THREE HYDROSTATIC WEIGHING METHODS. Med Sci Sport Exerc. 1983;

92. Heymsfield S, Lohman T, Wang Z, Going S. Multicomponent molecular-level models

of body composition analysis. In: Human Body Composition. 2005.

93. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, et al. Maternal and child undernutrition: consequences for adult health and human capital. The Lancet. 2008.

94. Andersen GS, Girma T, Wells JCK, Kastel P, Michaelsen KF, Friis H. Fat and fat-free mass at birth: Air Displacement plethysmography measurements on 350 ethiopian newborns. Pediatr Res. 2011;

95. Bartz S, Mody A, Hornik C, Bain J, Muehlbauer M, Kiyimba T, et al. Severe acute malnutrition in childhood: Hormonal and metabolic status at presentation, response to treatment, and predictors of mortality. J Clin Endocrinol Metab. 2014;

96. Wells JCK, Dumith SC, Ekelund U, Reichert FF, Menezes AMB, Victora CG, et al. Associations of intrauterine and postnatal weight and length gains with adolescent body composition: Prospective birth cohort study from Brazil. J Adolesc Heal. 2012;

97. Adair LS, Fall CHD, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: Findings from five birth cohort studies. Lancet. 2013;

98. Wiechers C, Kirchhof S, Balles L, Avelina V, Weber R, Maas C, et al. Neonatal body composition: crossectional study in healthy term singletons in Germany. BMC Pediatr. 2019;

99. Pirilä S, Saarinen-Pihkala UM, Viljakainen H, Turanlahti M, Kajosaari M, Mäkitie O, et al. Breastfeeding and determinants of adult body composition: A prospective study from birth to young adulthood. Horm Res Paediatr. 2012;

100. Catalano PM, Farrell K, Thomas A, Huston-Presley L, Mencin P, De Mouzon SH, et

al. Perinatal risk factors for childhood obesity and metabolic dysregulation. Am J Clin Nutr. 2009;

101. Sewell MF, Huston-Presley L, Super DM, Catalano P. Increased neonatal fat mass, not lean body mass, is associated with maternal obesity. Am J Obstet Gynecol. 2006;

102. Moussa HN, Alrais MA, Leon MG, Abbas EL, Sibai BM. Obesity epidemic: Impact from preconception to postpartum. Future Science OA. 2016.

103. Castillo-Laura H, Santos IS, Quadros LCM, Matijasevich A. Maternal obesity and offspring body composition by indirect methods: a systematic review and meta-analysis. Cad Saude Publica. 2015;

104. Ejlerskov KT, Christensen LB, Ritz C, Jensen SM, Molgaard C, Michaelsen KF. The impact of early growth patterns and infant feeding on body composition at 3 years of age. Br J Nutr. 2015;

105. Gridneva Z, Rea A, Hepworth AR, Ward LC, Lai CT, Hartmann PE, et al. Relationships between breastfeeding patterns and maternal and infant body composition over the first 12 months of lactation. Nutrients. 2018;

106. Verkauskiene R, Beltrand J, Claris O, Chevenne D, Deghmoun S, Dorgeret S, et al. Impact of fetal growth restriction on body composition and hormonal status at birth in infants of small and appropriate weight for gestational age. Eur J Endocrinol. 2007;

107. Mazarico E, Martinez-Cumplido R, Díaz M, Sebastiani G, Ibáñez L, Gómez-Roig MD. Postnatal anthropometric and body composition profiles in infants with intrauterine growth restriction identified by prenatal Doppler. PLoS One. 2016;

108. Wells JCK. The programming effects of early growth. Early Hum Dev. 2007;

109. Frondas-Chauty A, Simon L, Flamant C, Hanf M, Darmaun D, Rozé JC. Deficit of Fat Free Mass in Very Preterm Infants at Discharge is Associated with Neurological

Impairment at Age 2 Years. J Pediatr. 2018;

110. CNN.com - Inside Africa: Soweto Uprising Remembered - June 15, 2001 [Internet]. [cited 2022 Mar 18]. Available from: http://edition.cnn.com/2001/WORLD/africa/06/15/inside.africa/

111. Forced Removals in South Africa | South African History Online [Internet]. [cited 2022 Mar 18]. Available from: https://www.sahistory.org.za/article/forced-removals-south-africa

112. The Chris Hani Baragwanath Hospital, South Africa | The World's 3rd Biggest Hospital, in South Africa - Contact Details (Address, Phone Numbers, Email Address) and Map [Internet]. [cited 2022 Mar 18]. Available from: https://www.chrishanibaragwanathhospital.co.za/

113. Good free photos - free stock photos and free images [Internet]. [cited 2022 Feb 17]. Available from: https://www.goodfreephotos.com/

114. de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: Planning, study design, and methodology. Food Nutr Bull. 2004;25(1 SUPPL. 1):15–26.

115. De Onis M. Reliability of anthropometric measurements in the WHO Multicentre Growth Reference Study. Acta Paediatr Int J Paediatr. 2006;95(SUPPL. 450):38–46.

116. Behnke AR, Feen BG, Welham WC. The specific gravity of healthy men: Body weight ÷ volume as an index of obesity. J Am Med Assoc. 1942;

117. IAEA. Introduction to Body Composition Assessment Using the Deuterium Dilution Technique with Analysis of Urine Samples by Isotope Ratio Mass Spectrometry. IAEA Hum Heal Ser no 13. 2011;

118. Wrottesley S V., Pisa PT, Micklesfield LK, Pettifor JM, Norris SA. A comparison of

body composition estimates using dual-energy X-ray absorptiometry and air-displacement plethysmography in South African neonates. Eur J Clin Nutr. 2016;70(11):1254–8.

119. COSMED - PEA POD: Gold standard for non-invasive Infant Body Composition [Internet]. [cited 2022 Mar 18]. Available from: https://www.cosmed.com/en/products/body-composition/pea-pod

120. Using Isotopic Techniques to Accurately Assess Exclusive Breastfeeding | IAEA [Internet]. [cited 2022 Mar 18]. Available from: https://www.iaea.org/newscenter/news/using-isotopic-techniques-accurately-assess-exclusive-breastfeeding

121. International Atomic Energy Agency. Introduction to body composition assessment using the deuterium dilution technique with analysis of saliva samples by Fourier transform infrared spectrometry. IAEA Human Health Series; no. 12. 2010.

122. Portable FTIR Spectrometer, Rugged Non-Lab Analyzer | Agilent [Internet]. [cited 2022 Mar 18]. Available from: https://www.agilent.com/en/product/molecular-spectroscopy/ftir-spectroscopy/ftir-compact-portable-systems/4500-series-portable-ftir

123. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857–68.

124. de Onis M, Garza C, Onyango AW, Rolland-Cachera M-F. Les standards de croissance de l'Organisation mondiale de la santé pour les nourrissons et les jeunes enfants. Arch Pédiatrie. 2009;16(1):47–53.

125. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J

Pediatr Obes. 2006;

126. Popkin BM, Slining MM. New dynamics in global obesity facing low- and middle-income countries. Obesity Reviews. 2013.

127. Tzioumis E, Kay MC, Bentley ME, Adair LS. Prevalence and trends in the childhood dual burden of malnutrition in low- and middle-income countries, 1990-2012. Public Health Nutrition. 2016.

128. Di Cesare M, Sorić M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: A worldwide epidemic requiring urgent action. BMC Medicine. 2019.

129. De Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010 Nov 1;92(5):1257–64.

130. Tim Lobstein and Hannah Brinsden. Atlas of Childhood Obesity. www.worldobesity.org (Access date 20/11/2021). 2019.

131. Baker JL, Olsen LW, Sørensen TIA. Childhood Body-Mass Index and the Risk of Coronary Heart Disease in Adulthood. N Engl J Med. 2007;

132. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years: The GBD 2015 Obesity Collaborators. N Engl J Med. 2017;

133. Reilly JJ, Kelly J. Long-term impact of overweight and obesity. Int J Obes. 2011;

134. Li YF, Lin SJ, Chiang TL. Timing of rapid weight gain and its effect on subsequent overweight or obesity in childhood: Findings from a longitudinal birth cohort study. BMC Pediatr. 2020;

135. Botton J, Heude B, Maccario J, Ducimetière P, Charles MA, Basdevant A, et al.

Postnatal weight and height growth velocities at different ages between birth and 5 y and body composition in adolescent boys and girls. Am J Clin Nutr. 2008;

136. Zheng M, Lamb KE, Grimes C, Laws R, Bolton K, Ong KK, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. Obes Rev. 2018;19(3):321–32.

137. Okada T, Takahashi S, Nagano N, Yoshikawa K, Usukura Y, Hosono S. Early postnatal alteration of body composition in preterm and small-for-gestational-age infants: implications of catch-up fat. Pediatr Res. 2015;77(1):136–42.

138. WHO MULTICENTRE GROWTH REFERENCE STUDY GROUP. WHO Child Growth Standards : Length/height-for-age, weight-for-age, weight-for-length, weight-forheight and body mass index-for-age: methods and development. Geneva, Switzerland. Acta Pædiatrica. 2006;

139. Picaud J -C, Putet G, Rigo J, Salle B, Senterre J. Metabolic and energy balance in small- and appropriate-for-gestational-age, very low-birth-weight infants. Acta Pædiatrica. 1994;83(6):54–9.

140. Cho WK, Suh BK. Catch-up growth and catch-up fat in children born small for gestational age. Korean Journal of Pediatrics. 2016.

141. Cho K, Suh B-K. Catch-up growth and catch-up fat in children born small for gestational age. Korean J Pediatr. 2016;59(1):1–7.

142. Lawlor DA. The society for social medicine John Pemberton Lecture 2011. Developmental overnutrition-an old hypothesis with new importance. International Journal of Epidemiology. 2013.

143. Wells JCK, Cole TJ. Adjustment of fat-free mass and fat mass for height in children aged 8 y. Int J Obes. 2002;

144. Larsson A, Ottosson P, Törnqvist C, Olhager E. Body composition and growth in full-term small for gestational age and large for gestational age Swedish infants assessed with air displacement plethysmography at birth and at 3-4 months of age. PLoS One. 2019;

145. Hediger ML, Overpeck MD, McGlynn A, Kuczmarski RJ, Maurer KR, Davis WW. Growth and fatness at three to six years of age of children born small- or large-for-gestational age. Pediatrics. 1999;

146. Skau JKH, Grenov B, Chamnan C, Chea M, Wieringa FT, Dijkhuizen MA, et al. Stunting, wasting and breast-feeding as correlates of body composition in Cambodian children at 6 and 15 months of age. Br J Nutr. 2019;

147. Prioreschi A, Munthali RJ, Kagura J, Said-Mohamed R, Rolfe EDL, Micklesfield LK, et al. The associations between adult body composition and abdominal adiposity outcomes, and relative weight gain and linear growth from birth to age 22 in the Birth to Twenty Plus cohort, South Africa. PLoS One. 2018;13(1):1–11.

148. Sachdev HS, Fall CHD, Osmond C, Lakshmy R, Biswas SKD, Leary SD, et al. Anthropometric indicators of body composition in young adults: Relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. Am J Clin Nutr. 2005;

149. FORBES GB. LEAN BODY MASS AND FAT IN OBESE CHILDREN. Pediatrics. 1964;

150. Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. Body mass index as a measure of adiposity among children and adolescents: A validation study. J Pediatr. 1998;

151. Freedman DS, Sherry B. The validity of BMI as an indicator of body fatness and risk

among children. Pediatrics. 2009.

152. World Health Organization. World Health Organization. Training Course on Child Growth Assessment. Geneva. World Health Organization. Training Course on Child Growth Assessment. Geneva. 2008.

153. Lei X, Zhao D, Huang L, Luo Z, Zhang J, Yu X, et al. Childhood Health Outcomes in Term, Large-for-Gestational-Age Babies with Different Postnatal Growth Patterns. Am J Epidemiol. 2018;

154. Hediger ML, Overpeck MD, Kuczmarski RJ, McGlynn A, Maurer KR, Davis WW. Muscularity and fatness of infants and young children born small- or large-for-gestational-age. Pediatrics. 1998;

155. Tenovuo A, Kero P, Piekkala P, Korvenranta H, Sillanpää M, Erkkola R. Growth of 519 small for gestational age infants during the first two years of life. Acta Paediatr Scand. 1987;

156. Albertsson-Wikland K, Wennergren G, Wennergren M, Vilbergsson G, Rosberg S. Longitudinal follow-up of growth in children born small for gestational age. Acta Pædiatrica. 1993;

157. Fitzhardinge PM, Inwood S. Long-term growth in small-for-date children. Acta Paediatr Scand Suppl. 1989;

158. Singhal A, Lucas A. Early origins of cardiovascular disease: Is there a unifying hypothesis? Lancet. 2004.

159. Labayen I, Moreno LA, Ruiz JR, González-Gross M, Wärnberg J, Breidenassel C, et al. Small birth weight and later body composition and fat distribution in adolescents: The AVENA study. Obesity. 2008;

160. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood:

Association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;

161. Ekelund U, Ong KK, Linné Y, Neovius M, Brage S, Dunger DB, et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J Clin Endocrinol Metab. 2007;92(1):98–103.

162. Leunissen RWJ, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA - J Am Med Assoc. 2009;

163. Muthuri SK, Francis CE, Wachira LJM, LeBlanc AG, Sampson M, Onywera VO, et al. Evidence of an overweight/obesity transition among school-aged children and youth in Sub-Saharan Africa: A systematic review. PLoS ONE. 2014.

164. Nyati LH, Pettifor JM, Ong KK, Norris SA. Adolescent growth and BMI and their associations with early childhood growth in an urban South African cohort. Am J Hum Biol. 2021;

165. National Strategy for prevention and Control of Obesity [Internet]. [cited 2022 Feb 25]. Available from: https://extranet.who.int/ncdccs/Data/ZAF_B10_NationalStrategy

166. Barker M, Dombrowski SU, Colbourn T, Fall CHD, Kriznik NM, Lawrence WT, et al. Intervention strategies to improve nutrition and health behaviours before conception. The Lancet. 2018.

167. Mistry SK, Hossain MB, Arora A. Maternal nutrition counselling is associated with reduced stunting prevalence and improved feeding practices in early childhood: A post-program comparison study. Nutr J. 2019;