EARLY LIFE RISKS AND CHILD DEVELOPMENT

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DECLARATION

I, Wiedaad Slemming, declare that this thesis is my original work. Where there has been contribution from other people, this has been duly acknowledged. This thesis is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any degree or examination at this or any other university.

Name: Wiedaad Slemming

Signature: Date: 28 July 2017

DEDICATION

To my nearest and dearest who has accompanied and supported me on this journey… I would not have been able to do this without you cheering me along, being there to take up the slack and believing that I could do this.

To those I have loved and lost along the way…I will be forever grateful that you were an integral part of my life and helped me to become the person I am today.

THESIS MATERIAL

In the process of completing this PhD thesis, the research was reported and published in a series of scientific publications in international, peer-reviewed journals. Results from this study were also presented in the form of oral and poster presentations at various academic and scientific conferences.

Peer-reviewed publications

I. Slemming W, Bello B, Saloojee H, Richter L. Maternal risk exposure during pregnancy and infant birth weight. *Early Human Development.* 2016; 99:31-6.

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III. Slemming W, Kagura J, Norris S, Saloojee H and Richter L. Child development at age 5 years: The effects of maternal education, socio-economic status and early life growth examined prospectively in a low resourced setting (under revision; for submission to *Paediatrics and International Child Health*).

Student's contribution to publications

The student was primarily responsible for the conceptualisation of the papers, data management, statistical analyses and writing of the manuscripts. The co-authors provided guidance on the conceptualisation of the manuscripts, the methods and statistical analyses employed, as well as reviewing and/or editing manuscript drafts. All co-authors have agreed that the scientific papers that they have co-authored may be presented in the results section of this PhD thesis (Appendix 8).

Conference proceedings

I. Slemming W, Bello B, Saloojee H, Richter LM. Early exposure to risks to child development. Oral presentation at the 9th PHASA Conference in collaboration with the AFPHA; 24-27 September 2013, Cape Town, South Africa.

II. Slemming W, Bello B, Saloojee H, Richter LM. Maternal risk exposure during pregnancy and infant birthweight. Poster presentation at the 9th World Congress Developmental Origins of Health and Disease; 8-11 November 2015, Cape Town, South Africa.

III. Slemming W, Bello B, Saloojee H, Richter LM. The effects of maternal risk exposure during pregnancy and the first year of life on early childhood growth. Oral presentation at the International Developmental Paediatrics Congress; 2-5 December 2015, Istanbul, Turkey.

IV. Slemming W, Kagura J, Saloojee H, Richter LM. The influence of maternal risk exposure during pregnancy on stunting and linear growth in early childhood. Oral presentation at the Faculty of Health Sciences Research Day; 1 September 2016, University of the Witwatersrand, South Africa.

V. Slemming W, Kagura J, Saloojee H, Richter LM. The influence of risk exposure during pregnancy and the first year of life on stunting in urban South African 2-year olds. Poster presentation at the Second World Nutrition Conference; 30 August-2 September 2016, Cape Town, South Africa.

Other

Wits Health Sciences Research News (August 2016). *Maternal risk exposure during pregnancy and infant birthweight* - See more at: http://www.wits.ac.za/health/research/research/research-articles/august-2016/#sthash.tvcuJLOq.dpuf

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ABSTRACT

Background

Exposure to biological and psychosocial risks, particularly during the first three years of life, affects brain development and compromises the short- and long-term health and development of children, as well as their educational achievement and long-term productivity. This study sought to determine the effects of maternal and child environmental and psychosocial exposures during pregnancy and the first two years of the child's life on growth and development outcomes in early childhood (up to 5 years) in an urban South African birth cohort.

Methods

Data used for this study was from the Birth to Twenty Plus (Bt20+) longitudinal birth cohort study, initiated in 1990 in the greater Johannesburg metropolitan area, South Africa. First, the associations between exposure to nine maternal risks, assessed in 1228 women, and subsequent infant birth weight was assessed. Second, the study examined the effects of risk exposure to the mother (and child) during pregnancy and the first year of a child's life on stunting at age 2 years in 1098 mother–child pairs. Finally, the associations between ten demographic and psychosocial exposures occurring during the third trimester of pregnancy and the first two years of a child's life and child development age 5 were examined in 636 mother-child pairs. Multivariable regression analyses were used to investigate associations between exposures and outcomes. Further analysis was undertaken to assess whether early life growth mediated the associations between maternal and household exposures and child development outcome at age 5.

Results

Unwanted pregnancy (or ambivalence) was associated with a ~156 g reduction in infant birth weight (β = −0.32, 95% confidence interval (CI): −0.51, −0.14). Tobacco use during pregnancy was negatively associated with BWZ (β = −0.32, 95% CI: −0.59, −0.05). Exposure to both these risks was associated with cumulative reductions in birth weight.

Approximately 1 in 5 children were stunted at age 2 years, with males at greater risk than females. Higher maternal education was protective for females (adjusted odds ratio (AOR) = 0.35; 95% CI: 0.14, 0.87), while higher household SES was protective for males (AOR for richest SES group = 0.39; 95% CI: 0.16, 0.92).

Males scored significantly lower than females on the developmental measure at age 5. Improved child developmental outcome was associated with higher birthweight for both sexes and superior linear growth in males. R-DPDQ scores increased by 0.84 units for every 1 SD increase in relative linear growth between birth and two years (β = 0.84 [95% CI 0.30, 1.39]). Socio-economic status (for both sexes) and maternal education for males were significant predictors of better child development. Growth status did not mediate the effects of socio-economic status (either sex) or maternal education (males) on developmental outcome.

Conclusion

Social factors, especially social determinants such as household SES and maternal education, were associated with early childhood growth and development in this context. Prenatal (using birthweight as a proxy) and postnatal growth were important for child development. Males were particularly vulnerable to poor growth and development in this cohort. The effects of household SES and maternal education on child development at 5 years were not mediated by linear growth between birth and 4 years.

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I wish to thank my supervisors, Professor Linda Richter and Professor Haroon Saloojee for accompanying me on this journey. I have learnt so much from both of you and thank you for your continued support, encouragement and mentorship.

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I'd like to thank my parents, who taught me the value of hard work and who encouraged me to pursue my dreams and aspirations. To my sisters, my greatest supporters, you inspire me…

To my children – you encourage me to be the best version of myself. Thank you for making it all worthwhile …

TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
THESIS MATERIAL iv
ABSTRACT vii
ACKNOWLEDGEMENTS ix
TABLE OF CONTENTS x
LIST OF APPENDICES xiii
LIST OF FIGURES xiv
LIST OF TABLES xv
DEFINITION OF TERMS xvi
LIST OF ABBREVIATIONS xx
PREFACE xxii
PART 1: INTRODUCTION 1
CHAPTER 1: BACKGROUND AND LITERATURE REVIEW 2
1.1 Background 2
1.1.1 Why early childhood development is important 3
1.1.2 The global picture 5
1.1.3 Study context: South Africa in transition 6
1.1.4 Conceptual framework for this study 8
1.2 Literature review 12
1.2.1 Defining ‘risk factors’ 12
1.2.2 Risks to early child growth and development 12
1.2.3 Early childhood growth and child development 26
1.2.4 Pathways influencing the effect of risk exposure on child development 29
1.2.5 Pathways linking early life risk exposures, growth and child development 30
1.2.6 Child development measures 33
1.2.7 Summary of literature review 36
1.2.8 Relevance and justification for the study 37
1.3 Overall aim 38
1.3.1 Specific objectives 38

1.3.2 Research questions and study hypotheses 39
CHAPTER 2: METHODOLOGY 40
2.1 Study design and data source 40
2.1.1 Study design: Birth to Twenty Plus 40
2.1.2 Bt20+ study recruitment 40
2.2 Study setting: Bt20+ 43
2.3 Data collection and management 44
2.3.1 Data collection instruments 44
2.3.2 Measures and procedures 45
2.3.3 Data management 50
2.4 Analytical strategy 50
2.5 Ethical considerations 54
PART 2: EMPIRICAL CHAPTERS 55
CHAPTER 3: MATERNAL RISK EXPOSURE DURING PREGNANCY AND INFANT BIRTHWEIGHT 56
3.1 Introduction 56
3.2 Methods 57
3.3 Results 60
3.4 Discussion 65
3.5 Conclusion 69
CHAPTER 4: EARLY LIFE RISK EXPOSURE AND STUNTING IN URBAN SOUTH AFRICAN 2-YEAR OLD CHILDREN 71
4.1 Introduction 71
4.2 Methods 72
4.3 Results 77
4.4 Discussion 80
4.5 Conclusion 85
CHAPTER 5: CHILD DEVELOPMENT AT AGE 5 YEARS: THE EFFECTS OF MATERNAL EDUCATION, SOCIO-ECONOMIC STATUS AND EARLY LIFE GROWTH EXAMINED PROSPECTIVELY IN A LOW RESOURCE SETTING 87
5.1 Introduction 87
5.2 Methods 88
5.3 Results 92
5.4 Discussion 97
5.5 Conclusion 102

PART 3: DISCUSSION AND CONCLUSION 103
CHAPTER 6: DISCUSSION AND CONCLUSION 104
6.1 Summary of thesis findings 104
6.1.1 Review of hypotheses (H0) 106
6.2 Emerging themes from the study findings 107
6.2.1 Social factors are important for early child growth and development 107
6.2.2 Prenatal and postnatal growth are important for child development 109
6.2.3 Growth as a mediating factor for child development 110
6.2.4 Sex differences are evident in growth and development 111
6.3 Conceptual relevance 112
6.4 Contextual relevance 115
6.4.1 Implications of study findings for national policies and programmes 115
6.4.2 International relevance 118
6.5 Strengths and limitations of the study 118
6.6 Research recommendations 121
6.7 Conclusions 122
REFERENCES 124
APPENDICES 151

LIST OF APPENDICES

Appendix 1 Relevant sections from the Bt20+ questionnaires used for thesis.....152
Appendix 2 Differences between analytical sample and excluded sample (Objective 1 analysis) ……174
Appendix 3 Differences between analytical sample and excluded sample (Objective 2 analysis)…….175
Appendix 4 Differences on key variables between analytical sample and excluded sample (Objective 3 analysis)……177
Appendix 5 Bivariate analysis of factors associated with child development scores at 5 years of age……..178
Appendix 6 Ethics clearance……..179
Appendix 7 Change of title……..180
Appendix 8 Co-author agreement form…….181

LIST OF FIGURES

Figure 1.1 Brain plasticity reduces with age and more effort is required to intervene later in life - adapted from Levitt (2009)[Levitt, 2009 #1079] 5
Figure 1.2 Pathways from poverty to poor child development (adapted from Walker *et al*.)[18].....8
Figure 1.3 Adapted conceptual framework for this study.[18] 11
Figure 1.4 Illustration of the overlap of major risk factors for child survival and development (adapted from Jensen *et al*.[54]) 13
Figure 1.5 Pathways linking poverty to developmental inequities (adapted from Walker *et al.*[87]).....30
Figure 1.6 Brain development in the first five years (adapted from Nelson[292]) 32
Figure 2.1 Geographical area of the Bt10 study population showing position of major public health clinics and hospitals (adapted from Yach[313]).....41
Figure 2.2 Map showing location where the Bt20+ study is located 44
Figure 2.3 Data analysis strategy for the study 52
Figure 3.1 Sex-specific mean birthweight z-score for study sample.....62
Figure 3.2 Relationship between number of significant risk factors (tobacco use in pregnancy and pregnancy wantedness) and reduction in infant mean birthweight z-score. 65
Figure 3.3 Relationship between number of significant risk factors (tobacco use in pregnancy and pregnancy wantedness) and reduction in infant mean birthweight z-score for males and females. 65
Figure 4.1 Selection of study sample 76
Figure 5.1 Path diagram for mediation analysis 92
Figure 6.1 Modified conceptual framework for thesis. 114

LIST OF TABLES

Table 1.1 Categorisation of child development domains[298-300] 34
Table 2.1 Maternal and household factors used in this study.....46
Table 2.2 Variable definitions used in the study 46
Table 3.1 Descriptive statistics and differences in mean birthweight for study sample 60
Table 3.2 Multiple linear regression analysis: Significant determinants of birthweight z-score 63
Table 3.3 Multiple linear regression analysis: Significant determinants of birthweight z-score in boys and girls.....64
Table 4.1 Characteristics of study sample (*n*=1098) 77
Table 4.2 Factors associated with stunting in children at age 2 years.....79
Table 5.1 Socio-demographic, maternal, household and growth characteristics in the study sample 93
Table 5.2 Sex-stratified regression analysis showing β and 95% CI of the association between early life growth and R-DPDQ.....96
Table 5.3 Effects of household SES and maternal education on R-DPDQ at age 5: influence of birthweight and relative linear growth.....97
Table 6.1 Consolidated study findings.....104

DEFINITION OF TERMS

Conditional/ relative growth	Conditional growth is the difference between observed and predicted body size. The predicted body size is estimated based on body size at earlier ages and the growth of the population/cohort. Conditional growth variables are conditional weight or height measures and are uncorrelated with all previous growth measurements.[1]
Cumulative/multiple risk	Terms are often used interchangeably and refer to the presence of more than one risk factor. It may also refer to the accumulating influences of continuous exposure to adversity. It can be used in methodological terms, i.e. cumulative risk models/ indices operationalize multiple risk exposure in an additive manner and define exposure to singular risks dichotomously (0 = absence of risk; 1 = presence of risk).[2,3]
Developmental screening	Screening is a "brief assessment procedure aimed at identifying children who may need more comprehensive diagnosis or assessment."[4]
Differential reactivity	Some individuals are not only more vulnerable to adverse environments but also more susceptible to both negative and positive experiences.[5]
Direct developmental assessment	Involves assessing children by presenting stimuli (such as objects/sounds) to evoke responses or by requiring children to complete specific tasks/activities. Usually completed by trained assessors in a clinical environment.[6]

Early childhood	In this thesis, refers to the period between birth and 5 years of age.
Early child/hood development	In this thesis, refers to the development – the attainment of skills and competencies in the physical, sensori-motor, cognitive, language and social–emotional domains - of children between birth and 5 years of age.[7]
Epigenome	The epigenome is made up of chemical compounds and proteins that can attach to DNA and direct such actions as turning genes on or off, controlling the production of proteins in particular cells.[8]
Fetal alcohol spectrum disorder	Fetal alcohol spectrum disorder is an umbrella term used to describe the range of effects (from mild to severe) on an individual as a result of maternal prenatal alcohol use. These effects include physical, cognitive/learning and behavioural deficits which may have lifelong impacts. The term is not intended for use as a clinical diagnosis.[9]
First 1 000 days	Refers to the period from conception until a child's second birthday, i.e. encompasses the 270 days of pregnancy and the 730 days of the first two years of a child's life.
Life course	A life course developmental perspective addresses the sequencing of events or processes (e.g. biological, behavioural, and psychosocial) that influence risk of later health and disease (and other outcomes) over the life span and also considers intergenerational influences.[10]

Low birthweight	Low birthweight is defined as weight at birth of less than 2 500 grams.[11]
Observational measures of development	Observational measures require a trained observer to document the behaviours displayed by a child in a familiar environment (e.g. home or school). These can be observations that require the observer to follow the child during the normal course of the day and observe and record his/her behaviour. They are often used to complement standardised assessment.[12]
Plasticity	Plasticity refers to the potential for change in intrinsic characteristics in response to environmental stimuli.[13] Developmental plasticity refers to the capacity of the brain to reorganise its structure or function in response to environmental stimuli.[14]
Preterm birth	Preterm is defined as babies born alive before 37 weeks of pregnancy are completed.[15]
Risk/exposure	Risk is commonly defined as a probability of an adverse outcome, or a factor that raises this probability. These predictors of undesirable outcomes are usually supported by evidence that a status or condition is statistically associated with higher probability of 'poorer' outcomes. In the context of child development, the term risk factor is used to refer to particular biological and psychosocial hazards that can compromise outcomes across any of the developmental domains.[16-18]
Sensitive period	A broad term that refers to limited periods in

	development when the effects of experience on the brain are unusually strong.[19]
Small-for-gestational age	This is a term used to describe infants born with a birthweight below the 10% percentile of the recommended gender-specific birthweight for gestational age reference curves.[20]
Stunting	Stunting is defined as a length- or height-for-age less than minus two standard deviations (or z-scores) of the World Health Organization growth standards median and indicates failure to attain linear growth potential as a result of suboptimal health and/or nutrition.[21]

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ANAs	Annual National Assessments
ASQ	Ages and Stages Questionnaires
Bt10	Birth to Ten
Bt20	Birth to Twenty
Bt20+	Birth to Twenty Plus
BWZ	Birthweight *z*-score
CFI	Comparative Fit Indices
COHORTS	Consortium of Health-Orientated Research in Transitioning Societies
DDST	Denver Developmental Screening Test
DHS	Demographic and Health Survey
DPME	National Department of Performance Monitoring and Evaluation
ECD	Early child/hood development
FASD	Fetal alcohol spectrum disorder
HAZ	Height-for-age *z*-score
HIV	Human immunodeficiency virus
HOME	Home Observation for Measurement of the Environment
inCLASS	Individualized Classroom Assessment Scoring System
IQ	Intelligence quotient
LAZ	Length-for-age *z*-score

LMIC	Low and middle income countries
PDI	Pitt Depression Inventory
PEDS	Parents’ Evaluations of Developmental Status
R-DPDQ	Revised Denver Pre-screening Developmental Questionnaire
RMSEA	Root Mean Square Error of Approximation
SANHANES	South African National Health and Nutrition Survey
SD	Standard deviation
SDGs	Sustainable Development Goals
SEM	Structural equation modelling
SES	Socio-economic status
SGA	Small-for-gestational-age
SRMR	Standardized Root Mean Square Residual
TB	Tuberculosis
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

PREFACE

"*What we are learning about all the elements that affect the development of children's brains – whether their bodies are well nourished, whether their minds are stimulated, whether they are protected from violence – is already changing the way we think about early childhood development. Now it must change the way we act*." Anthony Lake, UNICEF Executive Director, April 14, 2016.

Over the last two decades, scientific evidence has confirmed the importance of the early years of life and led to a renewed global commitment to invest, not only in child survival strategies but also in early child development programmes that support young children to grow and develop optimally. Countries across the world are developing and implementing early childhood development (ECD) policies in an effort to promote equitable development and economic growth.

My path to this PhD started in 2011, when the National Department of Performance Monitoring and Evaluation (DPME) in the Presidency, in collaboration with the Inter-Governmental Steering Committee on ECD, commissioned a diagnostic review of ECD in South Africa. Professor Linda Richter was commissioned to lead the review. The Division of Community Paediatrics at the University of the Witwatersrand (where I work) was approached to be part of the expert team conducting the review.

The same team then went on to develop a National Policy and Programme on ECD. These processes highlighted many questions regarding our understanding of the associations between the social and environmental risks to which many children in South Africa are exposed to and their developmental outcomes, particularly in the early years of life. The associations between prevalent biological risks and infant growth and development had been well-described in the South African context, but less is known about the effects of 'non-biological' risks on infant and child outcomes, as well as the interactions between biological and non-biological risks. Through my own broader understanding of ECD, I became interested in exploring the interdependence and interaction between the biological (including genetic) factors and the social and environmental exposures on child growth and development,

particularly in contexts such as South Africa where there are both high levels of poverty or adversity, and inequity. Through my interactions with Prof Richter and others, I was granted access to a rich, longitudinal dataset, the Birth-to-Twenty cohort, that had data on approximately 3 200 urban, South African children and their mothers, across many of the domains that were relevant to my research questions.

This dataset formed a strong basis for the exploration of these research questions in a South African birth cohort. Despite the data having been collected in the early 1990's, many of these risks are still prevalent in our society and affect many children on a daily basis. It is my hope that the results of this analysis will contribute towards the development of more effective ECD programmes for young children across the life-course, particularly during pregnancy and the first years of life.

The outline of the thesis is illustrated below.

Part 1: Introduction

Chapters 1 and 2 include the background of the study comprising the problem statement and conceptual framework, literature review and methods for the study.

Part 2: Empirical Chapters

Chapters 3-5 contain details of the studies undertaken for this project, utilising data from the South African Birth to Twenty Plus (Bt20+) birth cohort study:

a) Associations between selected maternal psychosocial and environmental risk factors during pregnancy and subsequent infant birthweight;
b) Effects of psychosocial and environmental exposures affecting the mother (and child) during pregnancy and the first year of the child's life on stunting at age 2 years;
c) The effects of maternal education, socio-economic status and early life growth on child development at age 5 years.

Part 3: Integrated Discussion and Conclusion

Chapter 6 comprises an integrated discussion of the thesis, synthesising the main research findings and concludes with an evaluation of the study strengths and limitations, the relevance and implications of these findings for early childhood policy

and programme development and implementation, as well as future research considerations.

PART 1: INTRODUCTION

"The debate between nature and nurture as determinants of early child development is over. Today, we understand that the two are inextricably linked. The degree of their interdependence—and the impact of this interplay on the developing brains of children—is even greater than we previously imagined. This knowledge has tremendous implications for how we design and deliver early child development interventions."

World Health Organization Director-General, Margaret Chan, 2014

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1.1 Background

Complex interactions between a child's personal experiences (e.g. family and social relationships), environmental influences (e.g. exposures to extreme poverty), his/her biological and genetic predispositions, beginning before conception, directly affect his/her health, growth, brain development and the establishment of important regulatory systems.[22] Scientific evidence confirms that the period from conception to age three years is a specifically sensitive and vulnerable period for child growth and development.[7] This is due to the rapid physical and neurological growth that occurs during this time, rendering children's brain and physiological systems highly receptive to influences from their physical and psychosocial environments.[23] This period is also a unique window of opportunity, during which a child's development is affected both positively and negatively. It is recognised that early exposure to adversity can result in physiological disruptions or embedded biological "memories" that persist into adulthood and result in lifelong impairments in both physical and mental health.[22]

There is increasing scientific evidence emphasising the importance of early child development (ECD) and South Africa is one of a growing number of countries that are investing in interventions to promote both child survival and development. The identification of risk factors for early child development is important to provide a framework for understanding aetiology as well as a means to target at-risk individuals and evaluate interventions in order to improve child outcomes.[24] This requires a deeper understanding of the distribution, effects and interaction between significant risk factors (particularly during the early critical developmental periods), in a local context, in order to develop relevant and appropriate policies and programmes. Some study findings may also be generalisable to other similar settings.

Most of the research examining the relationships between early life risks, and/or growth and child development are from high-income settings. Globally there is a call for increased investment in ECD but, in order to do this effectively, context-specific evidence in countries in which children face challenges to optimum development is required, advancing the identification of and interactions between key risk factors and

improving understanding of the burden of disease in order to implement more effective interventions. This chapter aims to provide an overview of the effects and relationships between early psychosocial and environmental exposures affecting the mother and her child and her child's subsequent growth and development.

1.1.1 Why early childhood development is important

Children's development is shaped by dynamic and continuous interaction between their genetic inheritance and biology *(nature)* and their experiences which are largely influenced by their physical and psychosocial environments *(nurture)*. Although, children receive approximately 23 000 genes from their parents, not every gene does what it is intended to do. The experiences children have early in life leave a chemical 'signature' on their genes (collectively called the epigenome) that can determine how these genes are turned on and off, i.e. whether and how genes are expressed.[14] Gene expression occurs in the context of the intra- and extracellular environments within the body and in the context of experience with the external environment.

Brain development is particularly responsive to environments and experiences early in life, with the first three years being especially important as this is the period of the most rapid growth for brain development and learning.[14,25] During this period of heightened plasticity, the brain and other physiological systems are highly receptive to a variety of environmental influences, whether positive or negative.[26] It is a time during which risk and adversity have the most potential for harm, and effective preventive and protective interventions have the greatest benefit.[27]

Although the developmental process is quite robust, the rate of progression and quality of a child's development can be modified by both risk and protective factors in their early environment.[28] Extreme poverty, early nutritional deprivation, exposure to toxins and psychosocial stressors (e.g. as a result of abuse or severe maternal depression) can significantly influence short- and long-term brain function, cognitive development, behaviour and health outcomes for children.[7,26,29]

Scientific evidence suggest that for children experiencing severe adversity, environmental influences may be as, or more, significant than genetic predispositions in their effect on the odds of developing chronic health conditions years or even decades later.[14] New evidence also shows that deficits and disadvantage persist and

extend into subsequent generations, thereby creating an intergenerational cycle of poverty, as well as lost developmental potential and human capital.[30,31]

Nurturing, caring, developmentally stimulating and protective interactions between children and caregivers can ameliorate or counterbalance the negative effects of these adverse exposures on child development.[32] Nurturing care comprises a home environment that is sensitive to a child's needs, responsive and emotionally supportive and that provides appropriate early learning and play opportunities, as well as protection against harm.[7] These positive interactions mainly takes place in the immediate home and family context but extends to other child care and service providers, across a number of sectors, such as health, education and social protection.[7,23]

Disadvantaged children in low and middle income countries (LMIC) who do not reach their developmental potential are less likely to be productive adults.[25] Evidence, mainly from longitudinal cohort studies, suggests that the long-term productivity of these children is reduced through fewer years of schooling and less learning per year in school.[25] It is estimated that, on average, each year of schooling increases wages by nearly 10%.[33] The recent Lancet series on ECD estimated that there are approximately 43% of children in LMIC who are at risk of suboptimal development as a result of extreme poverty and stunting.[27] For this group of children, the analysis suggested that there is an estimated average deficit in adult yearly income of approximately 26%.[27] Thus, beyond health and development, early adversity also negatively affects children's educational attainment and sets a critical foundation for their entire life course, including their later adult productivity.

Inequities in child development start prenatally and continue through the life course and can persist into subsequent generations.[25] Child development, like health, follows a social gradient with increasing socio-economic status (SES) associated with progressively better health and development outcomes for children with the converse being true for decreasing SES.[34,35] Differences between children that are based upon social inequities are evident as early as the first year of life in a range of developmental domains and tend to increase as they get older.[36,37] It is likely that a child and family facing adversity in one context is also facing it in others. Adverse

exposures tend to be cumulative and exposure to adverse experiences early in life also increases the probability of adverse exposures later in the life course.[35]

The science is clear. Availability and access to the structural and nurturing interventions required to mitigate these risks must start early.[23] It is easier, less costly and more effective to establish strong foundations in health and development early in life than it is to try to intervene or 'fix' them later (Figure 1.1).[26] Thus, strong biological, psychosocial and economic arguments all point to the need for early intervention and increased investment to protect, promote and support early child development, starting with a particular emphasis on the first three years of life.[27]

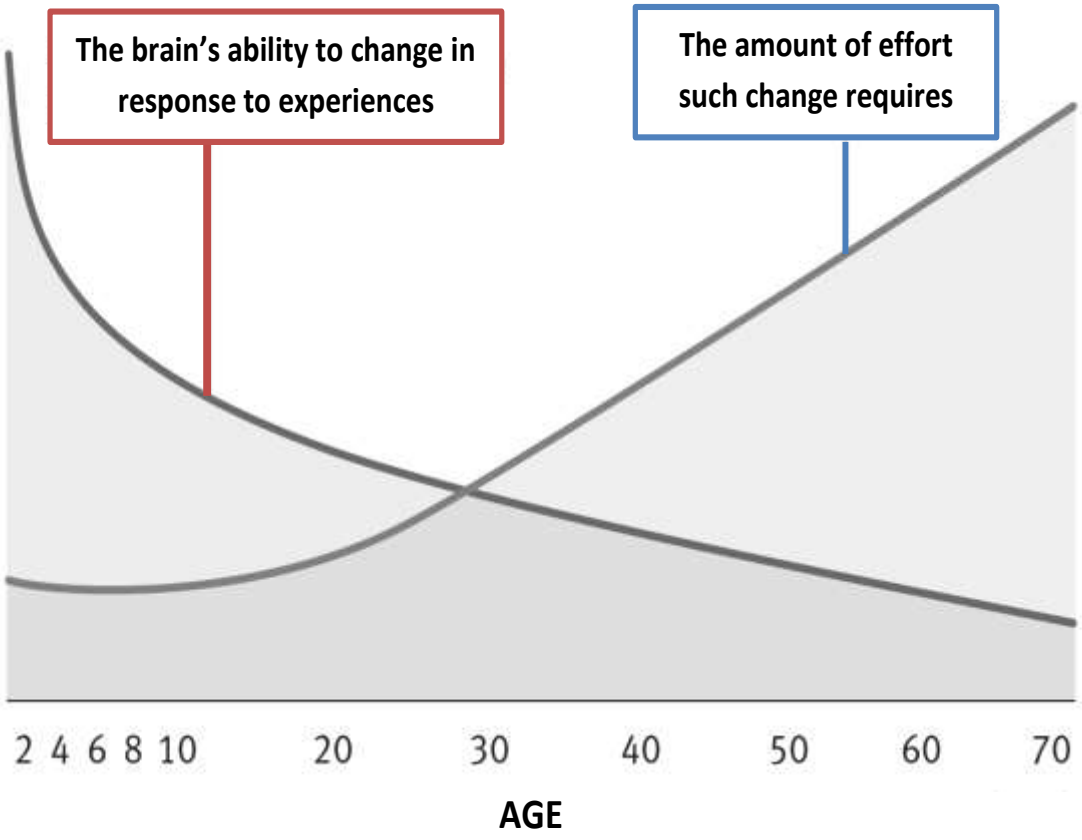


Figure 1.1 Brain plasticity reduces with age and more effort is required to intervene later in life - adapted from Levitt (2009)[38]

1.1.2 The global picture

Significant improvements in child mortality have occurred over the past two decades, with a reported 53% decline in the under-5 mortality rate between 1990 and 2015.[39] However, global estimates from a recent Lancet series on ECD, shows that although

fewer than 6 million under-5 child deaths occur each year, approximately 250 million children (43%) in LMIC are at elevated risk of poor developmental outcomes because of stunting or exposure to extreme poverty. Over two-thirds of these children reside in sub-Saharan Africa.[27]

Globally, the momentum and commitment to improving ECD has grown. In 2008, the World Health Organization (WHO) Commission on the Social Determinants of Health identified support for children's early development as a key factor to achieving global health equity.[34] Since 2000, there has been increased global investment in ECD in light of strong scientific and economic evidence that this is a means to give children the best start in life but, also at a population level, redress inequity and promote health and economic prosperity across the life course.[7] By July 2014, 45% of LMIC had national multisectoral ECD policies in place. This is a significant increase from only seven LMIC in 2000.[7] In many countries, this has also resulted in increased funding for ECD.[23] Between the 2007 and 2016, three Lancet series on ECD were published that were instrumental in not only providing a strong scientific and economic evidence base for increased focus and investment in ECD as part of the broader global development agenda but, more recently, in mapping pathways for action to step up integrated effective interventions at scale.

For the first time, ECD has been included as part of the foremost global development framework, the Sustainable Development Goals (SDGs),[40] and is reflected in the new Global Strategy for Women's, Children's and Adolescents' Health (2016-2030),[41] which aims to ensure that children have an equal chance to not only survive but also go on to thrive. These global initiatives have highlighted the close links between survival and development and the synergistic impacts of suboptimal environments and poor growth in the early years on short term and long-term child development outcomes and the need for relevant and comprehensive ECD policies and programmes.

1.1.3 Study context: South Africa in transition

Over the past two decades, South Africa has experienced significant political, economic and socio-demographic transitions. It is also simultaneously experiencing a complex health transition and is faced with a quadruple burden of disease.[42] Infant and child mortality rates are declining. Simultaneously, the morbidity profile

comprising of coexisting infectious diseases (such as HIV and TB) and non-communicable diseases, such as childhood malnutrition, interpersonal violence and unintentional injuries are persisting or are on the increase.[42]

Although there has been significant progress in child survival, child morbidity remains high and it is estimated that approximately 20-30% of South African children are experiencing either a development difficulty/disability or are 'at risk' of a developmental difficulty.[43] Despite the economic progress that has been made post-democracy, there are still high levels of poverty and income inequality between the top and bottom 20% of the population.[44] Four million children below 6 years of age live in the poorest 40% of households. This figure has remained unchanged since 2003.[45] In addition, almost a third of these young children fall below the food poverty line, which makes them likely to be food insecure and at greater risk of malnutrition.[45] The most prevalent form of malnutrition in South Africa is stunting, with approximately 22% of children below 6 years of age reported as having a height-for-age measurement below minus two standard deviations from the reference median.[46] The youngest children (0-3 years) have the highest prevalence of stunting (~26%) and this has increased by 3% between 2005 and 2012.[46]

Latest available estimates show that approximately one in eight infants is born low birthweight in South African public health facilities and this statistic has been fairly consistent since 2005.[45] Antenatal and postnatal depression are of significant concern, affecting approximately one-third of women in South Africa.[45] There are no national assessments of cognitive development conducted in the preschool years, but considering the Annual National Assessments (ANAs) as a proxy measure, only 56% and 57% of children at Grade 3 level achieved more than 50% in mathematics and language respectively in the latest results.[45] Thus, it is evident that many South African children are exposed to adverse exposures that may predispose them to poor health and developmental outcomes. Unfortunately, many of these risk factors tend to cluster in the same individuals. New scientific insights into the transgenerational transmission of these environmental effects further highlight the need for effective health and social interventions.[31,47]

1.1.4 Conceptual framework for this study

As previously discussed, children do not grow up in isolation, nor in vacuums. Rather, interaction between factors in a child's biology, immediate family/community environment, and broader society steers and shapes his/her development over time. These interactions (relationships and processes) can support, sustain or hinder optimal child development.[48] Various types of risk factors interact to influence child development outcomes across different developmental domains, i.e. cognitive, sensori-motor and social-emotional development (Figure 1.2).

As depicted, poverty and socio-cultural risk factors, such as low maternal education, increase young children's exposure to biological and psychosocial risks that subsequently affect developmental outcomes through changes in brain structure and function, as well as behaviour.[18] Biological risks include prenatal and postnatal growth, nutrient deficiencies, and environmental toxins and psychosocial risks refer to parenting factors, maternal depression and exposure to violence.[18]

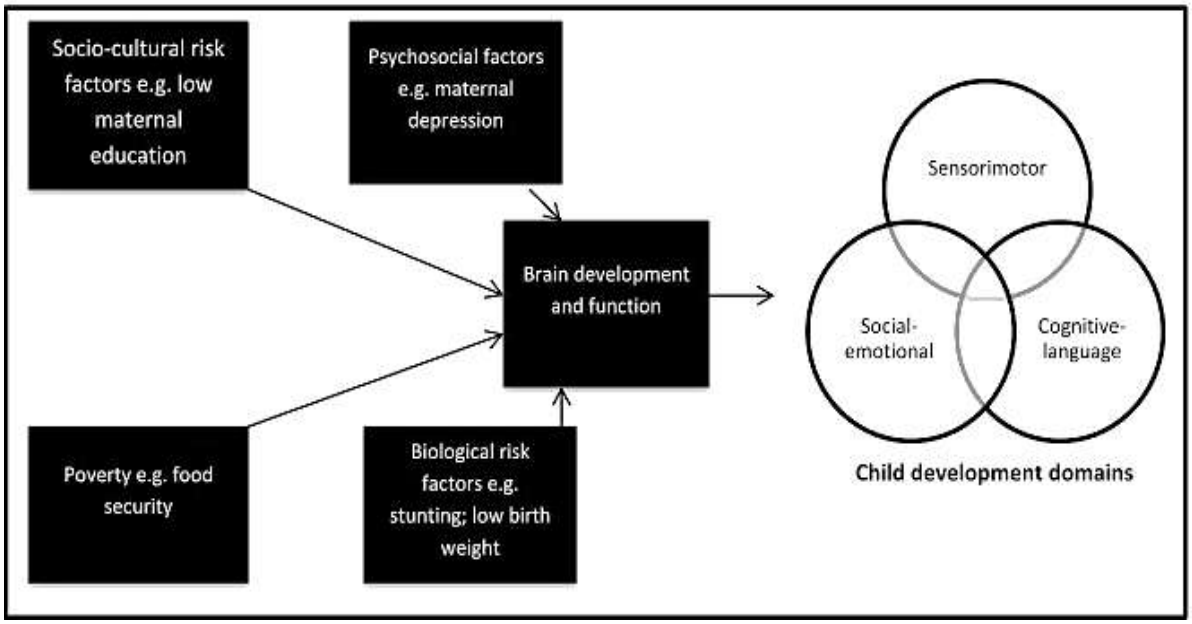


Figure 1.2 Pathways from poverty to poor child development (adapted from Walker *et al*.)[18]

This framework is applicable to this study as it considers early life exposures as well as the interactions between the various types of risks that may affect child growth and development. It also recognises that children are not exposed to single risks but are frequently exposed to multiple and cumulative risks.[49,50] The more risks that

accumulate, the more growth, health and development are compromised.[51] Increasing scientific evidence shows that these consequences of impairments in child growth and development are also likely to be intergenerational, thus continuing the pathways shown for subsequent offspring.[31]

According to the bioecological systems theory of human development, four interacting dimensions need to be considered when attempting to understand child development in context, i.e. person factors (pertaining to the child); process factors (e.g. family-level interactions); contexts (e.g. neighbourhoods); and time (i.e. changes over time in the individual or environment).[52]

Individual, interpersonal and community level influences are considered proximal factors; and structural and societal influences are considered distal factors.[52] Proximal factors are the primary processes for influencing child development as pertaining to the day-to-day experiences of the child and usually refer to measures of parent-child interactions.[48] These processes change as children develop and mature and are influenced by the characteristics of the immediate context, e.g. home environment, as well as more distant influences such as the social environment. The child is therefore at the centre of a series of proximal influences with ever extending concentric circles of distal interacting influences.

Drawing on the bioecological systems theory, some adaptations were made to the framework adapted from Walker *et al*.[18] for the purposes of this study (Figure 1.3). This study focused mainly on the immediate or proximal factors influencing child development, i.e. factors pertaining mainly to the mother and child, and the immediate household environment as these are deemed to be the most influential for the day-to-day development of children.[48]

Socio-economic status (which can be considered as both a proximal and distal determinant) was not considered separately but rather as one of the socio-cultural risk factors in this study and mainly in the context of the household (proximal) environment. Early childhood growth was considered as both an intermediate outcome but also a possible mediator between early life risk exposure and child development outcomes in the preschool years. There was a specific focus on

exposures during pregnancy and the first two years of life (the first 1 000 days), as this is a particularly vulnerable period for growth and development. Outcomes were measured within the first five years of life as these are the most critical formative developmental years that lay the foundation for future health, growth and learning.

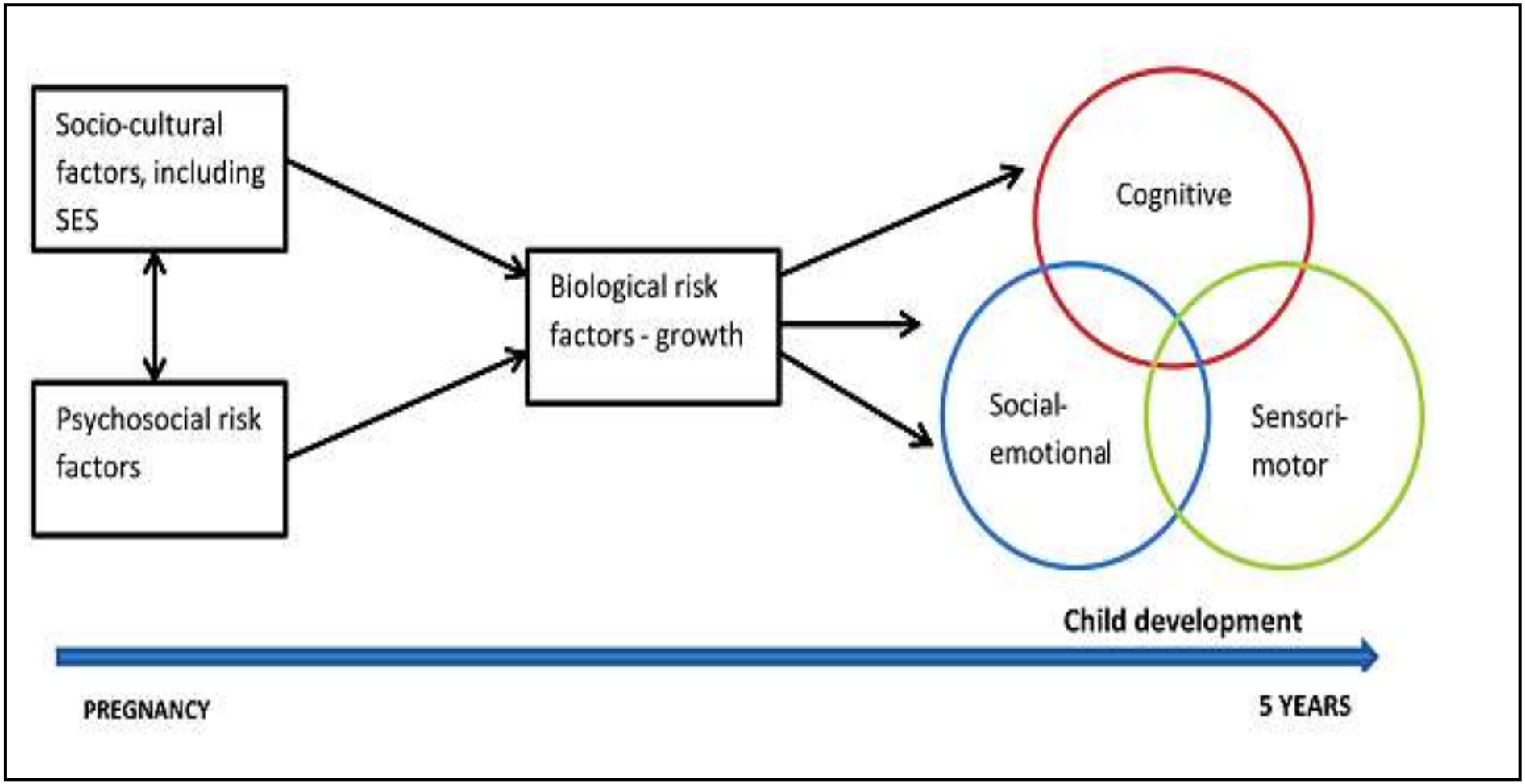


Figure 1.3 Adapted conceptual framework for this study.[18]

1.2 Literature review

This literature review includes an overview and synthesis of different measures and definitions of growth and cognitive development in early childhood, particularly the period between birth and 5 years of age. It also comprises an evaluation of the evidence on the association between the various types of early life risk factors and growth and cognitive development, with a discussion on the possible pathways of association.

1.2.1 Defining 'risk factors'

Risk is commonly defined as a probability of an adverse outcome, or a factor that raises this probability.[53] These predictors of undesirable outcomes are usually supported by evidence that a status or condition is statistically associated with higher probability of 'poorer' outcome(s).[54,17] In the context of child development, the term risk factor is used to refer to particular biological, environmental, socio-cultural and psychosocial hazards that can compromise outcomes across any of the developmental domains.[18]

1.2.2 Risks to early child growth and development

There is significant overlap of the major risk factors for child survival and development (Figure 1.4). Risk exposure starts prenatally and can adversely affect child health and development along the life course.

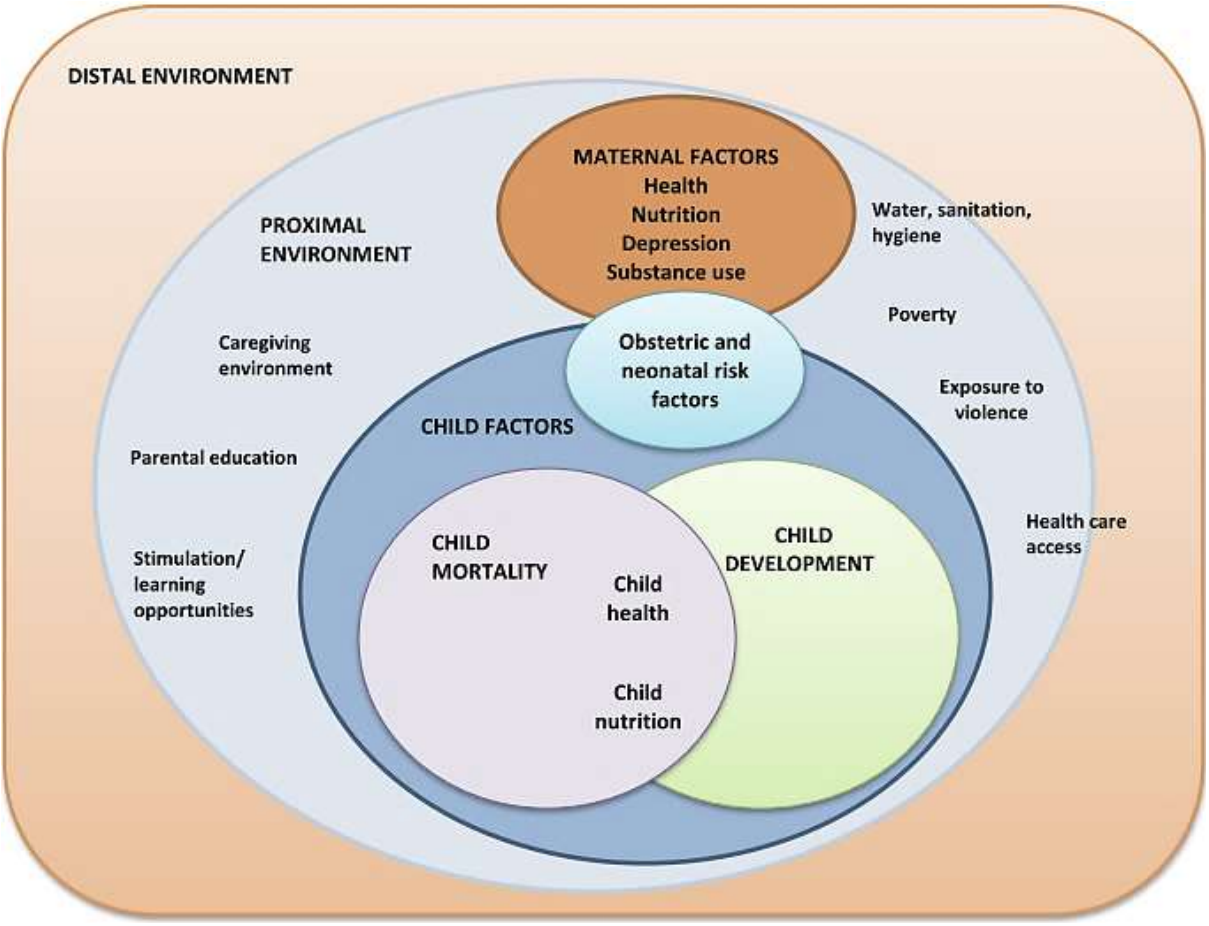


Figure 1.4 Illustration of the overlap of major risk factors for child survival and development (adapted from Jensen *et al*.[55])

1.2.2.1 Maternal factors

Numerous maternal factors have been associated with infant and child growth and development outcomes. Beyond biological factors such as maternal health and nutritional status, maternal psychosocial factors influence infant and child outcomes either directly or indirectly.

Maternal age

Young maternal age is an established risk factor for a range of adverse child outcomes. However, both advanced and younger maternal age may be associated with poorer birth and child health outcomes, although the pattern of association for older maternal age is less clear.[56]

Many studies have found significantly higher risk of low birthweight infants being born to mothers of younger maternal age (≤19 years).[56-58] Younger mothers have an

increased risk of intrauterine growth restriction, preterm birth, offspring mortality during infancy and childhood undernutrition.[56,59,60] A meta-analysis that included studies across different income settings reported evidence of a dose-response relationship between maternal age and low birthweight; the magnitude of the association decreasing with increasing maternal age.[58]

In the context of adolescent pregnancy, first-time mothers younger than fifteen years of age were particularly at risk of low birthweight and preterm birth.[58] This was reaffirmed in recent analyses of pooled data from five birth cohorts in LMIC that included 19 403 women, including from South Africa, which concluded that infants born to mothers aged 15-16 years in LMIC were more likely to be born low birthweight or at earlier gestational age compared to those born to mothers aged 19 years or older.[56,61] Furthermore, this study showed that younger maternal age (≤19 years) was associated with stunting at age 2 years, as well as failure to complete secondary schooling. Children of younger mothers had a 30–40% increased risk of stunting at 2 years and failing to complete secondary schooling.[56] In contrast, advanced maternal age (≥35 years) was protective against both these outcomes.[1]

A recent study using pooled demographic health survey data from eighteen countries found that children of younger mothers (< 19 years) were more likely to be stunted in approximately half the cases, with further growth restriction emerging after 24 months of age, particularly in African and Asian countries.[62] The associations between adolescent motherhood and poorer infant and child outcomes can be attributed to a range of biological, social and behavioural factors. There is evidence to suggest that younger mothers are less likely to breastfeed and, if they do breastfeed, might do so for a shorter duration than older mothers,[63-65] thus potentially compromising infant nutrition and growth. This association has also been shown in South Africa.[66] Younger mothers also tend to have lower socioeconomic status, fewer years of schooling, and less stable relationships than older mothers.[56,67]

However, there is local evidence that shows that advanced maternal age (>34 years) may also be detrimental for infant health outcomes. A retrospective analysis of pregnancy and birth outcomes for 1 945 women delivering in a tertiary public health facility in South Africa found that women older than 34 years were more likely to have infants born preterm or low birthweight as compared to women between 20-34 years

of age.[68] Although these findings have been supported elsewhere,[69] there have also been studies that reported marginal or no differences in perinatal outcomes for infants born to women of advanced maternal age compared to younger women.[70,71] A systematic review of the topic suggested that increased rates of adverse perinatal outcome were modest until age 40 years or older and that maternal socio-economic advantage may ameliorate some of the adverse effects of advanced maternal age on perinatal outcomes.[72]

The analysis by Fall *et al*.[56] found that gestation was significantly shorter for mothers aged 35 years and older and that they were more likely to have preterm births as compared to women of younger age groups. Conversely, having an older mother (≥35 years) was protective against early childhood stunting in the same analysis. Children of older mothers had significantly higher height-for-age *z*-score (HAZ) at age 2 years as compared to children of younger mothers.[56]

Lower cognitive performance and educational achievement for children of adolescent mothers has been reported, mainly in high-income countries.[56,73-75] Conversely, children of older mothers tend to perform better on cognitive tests at school entry.[74] As with growth, there appears to be a positive linear relationship between maternal age and child cognitive and educational performance. There is evidence that children of younger mothers do more poorly on cognitive tests, but also present with more behavioural difficulties.[76,77] However, there is some evidence to suggest that the lower cognitive performance and increased behavioural difficulties of children born to younger mothers cannot be ascribed to maternal age itself but rather to their family background or social circumstances. A large, longitudinal survey conducted in the United States found that when these factors were controlled for, the disadvantage shown by children of younger mothers was significantly reduced.[77] Thus, adverse outcomes are associated with extremes of maternal age across different income settings.[78] This is of public health interest, particularly as there may be short- and long-term consequences for child outcomes.

Maternal education

Historically, maternal education is frequently used as an indicator of socio-economic status.[79] In 1979, Caldwell[80] found that maternal education was a stronger predictor

of child survival than other characteristics related to SES. Some subsequent evidence have supported this finding, even showing that in some instances the magnitude and significance of the effect of mother's education exceeded the influence of income.[81,82]

However, there is inconsistency in the literature with some studies showing that higher maternal education only tends to benefit child health and growth in the intermediate SES groups, with less positive effects for children in the poorest or the wealthiest segments.[79,83,84] It is unlikely that higher levels of education will make a significant difference in contexts where there are insufficient resources available to women. Similarly, if abundant resources, then mother's education may be less important.[79] The observed differences across studies could also reflect the variations in the range of SES strata that were sampled. A South African study found that paternal education rather than maternal education was associated with child stunting at 2 years. However, maternal and paternal education was highly correlated and including both variables in the analysis may have attenuated the effect of maternal education on child growth.[85]

Nonetheless, studies across different income settings have shown that maternal education is an independent determinant of child health, growth and development.[79,82,86,87] One hypothesis is that more educated mothers are less likely to be depressed, and thus are more able to provide adequate nutrition and more supportive and better quality home environments for their children.[88-90] It is postulated that there are key causal pathways through which maternal education affects child nutrition.[91,92] More educated mothers may have increased knowledge of health issues,[93] greater awareness and knowledge of appropriate nutrition, as well as better utilisation of available services for child health and well-being.[94] Indirectly, maternal education promotes empowerment of women allowing them increased autonomy and control over decision making around child care.[93] It can also reduce the likelihood of household poverty, thus alleviating financial constraints and improving living conditions.[84]

Maternal education has been shown to have positive impacts both on the cognitive and behavioural development of children, with more sustained effects shown on child

behaviour.[87,95] A recent South African study, using Birth to Twenty Plus (Bt20+) cohort showed that maternal education was protective in attenuating the negative effects of early developmental delay on child development outcomes.[96] Particular parenting aspects such as caregiver warmth toward the child, maternal sensitivity and responsiveness to the child, and the ability to provide a safe and stimulating environment have been associated with cognitive and behavioural development in young children.[18] Studies have shown that lower maternal schooling (and family income) is associated with lower psychosocial stimulation in the home, as children are unlikely to have play materials and daily stimulation, thereby negatively affecting their cognitive development. Mothers with higher levels of education also tend to have better parenting practices, ability to provide materials for cognitive stimulation, and to offer variety in child stimulation activities.[79,86,87,97,98]

Marital status

Maternal marital status has been associated with infant child health and development outcomes in previous studies. The relationship between marital status and birth outcomes has been shown to vary by maternal race and age.[99,100] This association is consistent across different income settings.[100-104]

Infants born to single mothers are significantly more at risk of increased mortality, being small-for-gestational-age (SGA), born preterm or low birthweight than infants of mothers who are married or living with a partner.[105-108] These risks extend to early childhood growth, with children of single mothers at greater risk of stunted growth in the first five years of life, particularly in Sub-Saharan Africa.[103,104] Results from a large Swedish cohort showed that these negative effects go beyond health outcomes, with children of single parents having increased risks of psychiatric disease, suicidal behaviours, injury and addiction in childhood and adolescence.[109]

Children of single mothers score significantly lower on cognitive assessments than children of mother who are married or cohabiting.[110,111] However, some authors argue that maternal marital status serves as a proxy marker for a complex web of interactions that affect family and social resources, such as maternal SES, social support and child ‘wantedness’, which may all influence child health and well-being.[100,111]

Pregnancy wantedness

There are various definitions applied in the literature to measure pregnancy wantedness or intention. Unintended pregnancies are usually referred to as pregnancies that are either unwanted (i.e. when none or no more children are desired), or mistimed (i.e. occurs earlier than wanted).[112] Generally, pregnancies are referred to as intended when they occur 'at the right time' or later than anticipated, usually due to infertility or difficulties conceiving.[112] Unplanned pregnancy generally refers to a pregnancy that occurs, despite the use of contraception or when the woman did not plan or desire to get pregnant without the use of contraception.[112] These definitions usually apply in the context of live births, with terminated pregnancies assumed to be unintended or unwanted.[112,113]

Globally, more than 40% of all pregnancies are considered to be unintended, i.e. either mis-timed or unwanted, with the highest rates in sub-Saharan Africa.[114] It has been shown that infants of mothers who had an unwanted pregnancy were at increased risk of mortality before age 5 years,[115] and were more likely to be born low birthweight or preterm as compared to infants whose births were either mis-timed or intended.[116-118] A meta-analysis by Shah *et al*.,[101] showed that the odds of a low birthweight or preterm birth were approximately 50% higher for mothers with an unwanted pregnancy. This association was confirmed by a recent meta-analysis that showed that infants from unintended pregnancies had a 1.41 increased odds of being born low birthweight as compared to infants from intended pregnancies.[119] It has been postulated that this relationship may be the result of certain maternal behaviours, such as delayed antenatal care, as well as increased stress and depression or the lack of social support during the pregnancy.[117] However, a large, population-based survey in the United States found that this association was not mediated by the social support the mother and family received.[116]

Children whose conception is unwanted are also at greater risk of malnutrition.[120-122] Population-based studies in South America and Asia have shown that toddlers of mothers who had an unwanted pregnancy had a 30-40% increased risk of being stunted than offspring from intended pregnancies.[120,122]

There is also evidence to support the association between unplanned or unintended pregnancy and poorer child development outcomes, such as poor verbal ability and low educational attainment.[123-125] Findings from a nationally representative longitudinal birth cohort study in the United States showed that maternal unwanted pregnancy was associated with poorer socio-emotional development in 5-6 year olds, particularly in the areas of concentration and attention.[126] A study conducted in the United States found that these behavioural effects extend beyond early childhood, with offspring from unwanted pregnancies presenting with increased behavioural problems in adolescence.[127]

Tobacco use

Maternal cigarette smoking is a known risk factor for adverse pregnancy and infant health outcomes, such as increased risk of placental abnormalities, stillbirth, fetal growth restriction, preterm birth and sudden infant death syndrome.[128-130] Maternal smoking during pregnancy is associated with a 30% increased risk of preterm birth and is causally related to small-for-gestational age births and low birthweight in a dose-response manner.[128,131] A case-control study conducted in a farming region of South Africa found that maternal cigarette smoking during pregnancy was the strongest routine predictor of low birthweight in this population.[132] The odds were increased by nearly two-fold when combined with concurrent alcohol use during pregnancy.[132] Local estimates of maternal smoking during pregnancy in South Africa are high and range from 20% to 60%, with higher smoking rates reported among Coloured/Mixed race women, in particular.[133]

The negative effects of prenatal exposure to cigarette smoke extends beyond pregnancy and infant outcomes and has been shown to affect postnatal brain development and later cognitive and behavioural development.[128,134,135] Numerous studies have shown associations between smoke exposure and neurodevelopment, including behavioural difficulties, attention deficit disorder, hyperactivity and learning difficulties.[129] In utero second hand smoke exposure is associated with poorer cognitive development, particularly in younger children, and also increases the risk of neurodevelopmental delay.[135] However, the relationship between prenatal nicotine exposure and cognitive impairment is not as strong as the link with behavioural difficulties in childhood.[136] Infants born to mothers who smoked during pregnancy

have an approximately three-fold increased risk of attention deficit hyperactivity disorder (ADHD) as compared to infants born to non-smoking mothers.[137]

Although the effects of cigarette smoking on infant and child health and development are well-known, less is known about the health effects of smokeless tobacco (such as snuff and chewing tobacco) use during pregnancy. Smokeless tobacco use is more common among Black South African women than cigarette smoking, with an estimated national prevalence of 13.2% as compared to a smoking prevalence of 5.4%.[138] There is some evidence across income settings that suggest that the use of smokeless tobacco products during pregnancy could be as detrimental as cigarette smoking to newborn and child health.[130,139,140]

Alcohol use

Maternal alcohol consumption during pregnancy is of public health concern due to its adverse effects on short- and long-term physical, neurodevelopmental and behavioural outcomes for children.[141,142] There is robust evidence of the teratogenic effects of maternal alcohol consumption during pregnancy at high doses, characterised at the extreme end as fetal alcohol spectrum disorder (FASD).[143,144] South Africa has high levels of maternal alcohol use during pregnancy and among the highest prevalence of FASD globally.[9,145]

There is a clear dose-response relationship indicating that heavy drinking during pregnancy has negative effects on infant outcomes, including an increased risk of low birthweight, preterm birth and being born small-for-gestational-age (SGA). However, the overall dose-response relationships for low birthweight and SGA are reported to only show an effect at >10g of pure alcohol per day (approximately one drink per day) and for preterm births at >18g of pure alcohol per day (approximately 1.5 drinks per day).[146]

There are inconsistent results from studies assessing the effects of low to moderate maternal prenatal alcohol consumption on infant outcomes.[146-149] Findings from a prospective birth cohort study showed that maternal alcohol consumption in the first trimester had the strongest association with fetal growth and SGA births.[150] They also found that infants born to mothers who drank more than two units of alcohol per week

in the first trimester had a two-fold increased odds of being born SGA and three-fold increased odds of being born preterm as compared to non-drinkers. This indicates a lower threshold than previously reported by other studies.[146,150,151]

Prenatal alcohol exposure is often cited as the leading cause of non-genetic intellectual disability.[136] Children with FASD, including in South Africa, present with a range of neurodevelopmental difficulties, such as language delay, cognitive deficits in learning, attention, memory, executive function and motor skills, all of which can be detrimental to their educational achievement.[152-157,158] Moderate levels of prenatal alcohol consumption have been associated with child cognitive and behavioural difficulties.[159-161] However, this association is more consistently reported in relation to child behaviour than cognition.[141,143,158,162] Low to moderate prenatal alcohol exposure is not consistently associated with lower educational achievement.[157] The type of learning problems that children may present with depends on the dose, pattern and timing of prenatal alcohol exposure.[157]

Evidence from animals and humans confirm that behavioural changes may be seen even at low levels of maternal prenatal alcohol consumption.[141] A prospective study of 501 mother-child dyads found that child behaviour was negatively affected even when mothers consumed as little as one drink per week during pregnancy. In addition, children who were exposed to any level of alcohol in utero were three times more likely to display delinquent behaviour, even after controlling for other factors.[162]

Prenatal stress

Increasing scientific evidence in high, low and middle income settings suggest that maternal prenatal stress has adverse effects on child physical and mental health.[163] Independent of biomedical risk factors, prenatal life event stress has been associated with reductions in infant birthweight, and with significantly increased odds of being born low birthweight.[164-167] However, this has not been found consistently across studies; with some studies reporting no or little effect of maternal prenatal anxiety on neonatal outcomes, including birthweight.[168,169] A meta-analysis of 35 studies, including 31 323 women concluded that prenatal psychosocial stress during pregnancy explained a negligible to very small amount of the variance in perinatal outcomes, such as low birthweight.[169]

However, it has been shown that the timing and severity of exposure to stressful life events during pregnancy matters. Exposures during the first trimester of pregnancy, in particular, have been associated with decreased infant birthweight.[165] Thus, the variability in findings could be explained by conceptual and methodological issues, particularly in relation to how prenatal stress is defined and measured.[170,171] Prenatal stress has been assessed in some studies using questionnaire measures of anxiety/depressive symptoms or exposure to stressful life events during pregnancy.[163,172] A meta-analysis of 115 studies by Nast *et al*.[171] identified a range of definitions applied to prenatal stress and 43 different instruments that assessed a range of constructs that fell under seven categories of prenatal stress.

There is a growing evidence base indicating that maternal stress exposure during pregnancy affects not only child health but also cognitive and socio-emotional development in children.[173-178] Although the exact mechanisms of the effects of prenatal stress on infant and child health and development are unclear, it is postulated that the epigenome, through which the environment regulates gene expression, is responsible for some of the long-lasting effects of antenatal stress on brain and behavioural development.[179] It is also possible that there may be long-lasting effects from prenatal stress that may impair mother-infant interactions and could affect child cognitive and behavioural development.[163]

Exposure to increased levels of maternal pregnancy-specific stress/anxiety, particularly during early or late gestation, has been reported to be associated with delayed mental and motor development in the first year of life.[176,180,181] In contrast, Di Pietro *et al*.,[182] found that mild to moderate levels of stress experienced by mothers during pregnancy could be beneficial for fetal maturation in healthy populations.

Numerous studies, including from South Africa, have reported the link between maternal antenatal anxiety and behavioural difficulties in children, particularly within the first five years of life.[175,177,183-185]

Maternal depression

Positive associations between postpartum depression and child undernutrition have mainly been reported in low and middle income settings.[186-191] A meta-analysis of 17

studies conducted in LMIC, with a total of 14 000 mother-infant pairs, found that children of women with postnatal depressive symptoms were twice as likely to be underweight or stunted.[190]

Compared with non-depressed women, offspring of women with postnatal depression have and increased risk of insecure attachment, poor language and cognitive and behavioural development.[192-197] Longitudinal birth cohort studies suggest that children of mothers with postnatal depression are also at significantly greater risk of psychological difficulties later in life.[198,199] It is postulated that persistent (continuous) or recurrent depression rather than postnatal depression by itself is related to these later psychological effects in children.[200]

It has been reported that the relationship between postnatal depression and child behavioural outcomes are mediated by parenting/caregiving, particularly hostile caregiving behaviours.[201] Similarly, maternal childrearing behaviours mediated the association between maternal depression and infant attachment.[202] Mothers who are postnatally depressed are less responsive to infant distress signals, in interacting with their infants and provide them with less cognitive stimulation.[194,203,204]

The estimated prevalence of postnatal depression is high in low and middle income settings, ranging between 20-40%. Local studies have reported prevalence rates of postnatal depression of between 35-50% in some settings.[202,205] A systematic review including 84 articles identified that SES moderated the effects of postnatal depression on caregiving.[205] Thus, the effects of postnatal depression on maternal caregiving will be worse for children living in adverse socio-economic conditions.

1.2.2.2 Household factors

Household socio-economic status

Evidence from high income and LMIC have shown that being born into and reared in an impoverished or low SES setting is associated with adverse child health and development outcomes for children.[7,35,98,206] SES is linked with a wide range of health, cognitive and socio-emotional outcomes in children, with effects starting before birth and persisting across the life course.[35,97,207] There is an inverse relationship between SES and child mortality and morbidity, including early child

development.[35] Mortality and morbidity rates decrease, the higher up one moves on the SES ladder. This gradient is observed across most settings regardless of the construct/s used to measure SES.[35,206] However, these differences are reported to be smaller in more equal societies.[208]

Children born into low SES families are more likely to experience growth retardation and inadequate neurodevelopment in utero.[97,207,209,210] They are more likely to be born preterm, low birthweight, have stunted growth and have cognitive and emotional or behavioural difficulties in childhood.[85,86,166,211-216] The relationship between poverty and undernutrition is well-established. Disparities in stunting prevalence between and within countries across different socio-economic strata reflect this.[217,218]

SES is significantly associated with child cognitive development from infancy through mid-childhood,[97,219,220] with SES disparities wider in language ability, memory and executive function.[220,221] Studies indicate that these discrepancies in cognitive development between children from low and high SES groups may increase with age.[221] A longitudinal study from Bangladesh reported a one standard deviation increase in cognitive deficit between the top and bottom wealth quintiles from the ages of seven to 63 months.[90] Although there is some debate as to which aspects of SES are most strongly linked to cognitive development, it is clear that the timing and duration of exposure to poverty matters.[222] Early exposure and persistent hardship exert greater negative effects on child cognitive and behavioural outcomes, particularly within the first five years of life.[35,222,223] It is estimated that by 5 years of age, chronic or persistent poverty is associated with an intelligence quotient (IQ) reduction of between 6 to13 points.[222] Low SES children exhibit poorer cognitive and behavioural performance, particularly in the domains of language, memory, executive functioning, and social-emotional processing in comparison to their higher SES peers, with some studies indicating that there may be underlying neural differences.[224] These disparities in cognitive performance may potentially perpetuate the transmission of poverty across generations.[225]

An analysis conducted on a national longitudinal sample of approximately 2 000 children in the United States, indicated that cognitive stimulation in the home and parenting style were the most significant influences mediating the effect of poverty on child development.[226] This finding was also confirmed in a longitudinal study in

Bangladesh, which showed that although the effect of poverty on cognitive development was mainly mediated by parent education up to 24 months of age, the quality of the home environment had a substantial, longer-lasting effect on child cognitive outcomes up to 63 months of age.[90]

Household crowding

Crowding is typically assessed by the ratio of the number of persons living in the household per number of rooms available in the house and usually excludes the kitchen and bathroom/s.[227,228] Overcrowding is usually defined as being present if a specific threshold is exceeded, with ratios greater than one (>1 person/room) often applied in high-income settings. In LMIC, ratios of >2-3 persons/room are often regarded as being above the accepted threshold.[229]

Regardless of how crowding is defined, it has been shown to have negative effects on physical and mental health in childhood, by increasing the risk of infections and physical injury, compromising household relationships, and promoting the spread of infectious disease.[230] However, a systematic review, which included 201 studies from 32 European countries found weak evidence to support the association between household crowding and adverse child health and development outcomes.[231] Contrasting findings have been reported in low income settings. A South African study found that crowding was negatively associated with child development outcomes and also explained additional variability in growth measures, specifically child height, weight and head circumference.[229] Another study of low-income women in the United States showed that infants, born to women in crowded households, were nearly three times more likely to be born low birthweight as compared to their counterparts.[232]

The negative effects of overcrowding on child health is amplified when combined with other risk factors.[233] This may explain the variation in findings from different income settings, as children from low income settings are likely to be exposed to more risk factors, either at the same time or over longer periods.[234-236]

Studies have shown that the intensity and duration of exposure to household crowding matters.[230,235,236] There are increased detrimental effects on child health

and education outcomes when there is increased household density.[235,237,238] In addition, it has been shown that long-term crowding is a stronger predictor of adverse child outcomes than a single estimate.[238]

School-going children living in crowded homes have been shown to have greater behavioural adjustment difficulties, poorer educational performance and reported less supportive relationships with their parents.[239] For younger children, higher-density settings may be result in more distractions and less constructive play.[240] The association between household crowding and child cognitive development can be mediated by parent responsiveness; mothers in overcrowded households tend to be less responsive to young children.[97,241] Household crowding during early childhood has been shown to be negatively associated with concurrent and prospective cognitive development in the United Kingdom and the United States.[241] Although maternal responsiveness explained some of the association between overcrowding and cognition, the authors postulated that there may also be other factors that mediate this relationship.[242] Parents in high-density households tend to talk to their children less often and these households are often noisier and more chaotic; both are factors that could further impact child cognitive and behavioural development.[240,242] Negative impacts of crowding in childhood can extend into later life, with studies reporting compromised adolescent and adult health and educational outcomes when children are exposed to crowded living conditions in childhood.[230,238,243]

1.2.3 Early childhood growth and child development

Birthweight, considered a proxy for the intra-uterine interactions between the mother and fetus, has consistently been associated with child cognitive and educational performance, as well as behavioural development.[244,245] Low birthweight (birthweight <2500 g) is associated with poorer cognitive,[244,246-249] and educational,[246,249,250] outcomes and behavioural difficulties,[251,252] in the short- and long-term. However, some studies have reported no significant associations between full-term low birthweight and IQ or behavioural difficulties in school-aged children.[253,254]

Beyond extremes of birthweight, positive relationships between infant birthweight and cognitive development have been observed across the full range of birthweight.[244,246-248,255] These associations do not appear to be linear, with children at the higher end

of the birthweight range appearing to show poorer cognitive performance.[256] Associations between infant birthweight (used as a continuous measure) and behaviour in childhood or later life have also been reported less consistently. Three large longitudinal birth cohort studies, conducted in in high and middle income countries, did not find significant associations between birthweight of term infants and later behavioural outcomes.[244,247,257] This suggests that the effects of infant birthweight on child development may be more significant in children at the extremes of the birthweight distribution.[252]

It is not only birthweight, as a marker of fetal nutrition and growth, which is important for child health and development, but rather adequate nutrition and growth throughout the first three years of a child's life.[29] Linear growth in childhood, in particular, is regarded as a marker of healthy growth. Stunted growth (low length/height for age) has been associated with risk of morbidity and mortality,[258] loss of physical growth potential,[1,259] compromised neurodevelopment,[260,261] learning capacity and productivity,[1,262] as well as increased risk of non-communicable diseases in later life.[1,263] A child is considered stunted when his/her length/height-for-age is below two standard deviations of the World Health Organization (WHO) child growth standard median (<-2 z-score).[21]

Stunting is the most prevalent type of child malnutrition and considered a global health priority.[264] The process of becoming stunted typically begins early in life (in utero) and is most marked during the first two to three years of life.[218,265] The most rapid decline in length-for-age is observed between the ages of 6 months and 2 years, with some stabilisation thereafter, including the possibility of catch-up growth for some children.[218,266] A Malawian study estimated that ~20% of the observed 10cm height-deficit (as compared with the WHO Growth Standards) in their sample at age three years was already present at birth. They further estimated that another ~20% was added in the first 6 months of life, 50% between 6-24 months and the remaining 10% in the third year.[267] Although similar length/height-for-age patterns are observed across different regions, there also appears to be significant differences in stunting prevalence between and within countries. Most of the stunting burden is concentrated in LMIC, particularly in South Asia and sub-Saharan Africa.[7]

Stunting is a proxy indicator of child health and development and represents the influence of various psychosocial and biological risk factors.[18,268] There are

consistent associations between stunting during the first two years of life and cognitive function,[261,269-271] and educational performance, including grade repetition and school dropout in children.[25,250,265,272,273] Associations tend to attenuate after 24 months of age.[90] Less consistent associations have been reported between stunting and behavioural outcomes.[261,271,273] Two recent meta-analyses that included studies conducted in LMIC, did not find clear associations between stunting and socio-emotional development.[271,273]

Although the effects of early stunting on later child development outcomes are well-established, stunting throughout childhood has also been found to have an impact on child cognition.[74,274] There is also substantial evidence showing that stunting has long-term effects on later health and development, including final adult height, lower school attainment and economic productivity in adulthood.[18,259]

Beyond discrete early life growth measures, weight gain and linear growth throughout early childhood have been associated with child development outcomes and are usually quantified as conditional growth measures.[90,244,275] Conditional growth variables indicate children's deviation from the expected size based on their own previous measures and the growth of the other children (in a population or cohort) and is interpreted as representing slower or faster relative weight gain or linear growth.[1] Postnatal weight gain (measured between 4-7 years of age) was associated with IQ but not behavioural outcomes in term infants in a large, Chinese birth cohort.[244] Other studies have reported greater effects of linear growth for later cognitive development than growth in weight, particularly in the first two years of life.[1,90,275] Higher conditional height at two years of age has also been associated with long-term outcomes, such as a decreased risk of short adult height and reduced educational attainment in a pooled analysis of data on 8 362 participants from LMIC.[1]

However, links between relative weight gain and linear growth in early childhood and later health outcomes are less robust.[276,277] In a pooled analysis of the COHORTS data, relative weight gain in mid-childhood was associated with an increased likelihood of elevated blood pressure and overweight in adults. These associations were strengthened significantly with age.[1] However, contrasting results have been reported elsewhere. In Brazil, it has been shown that rapid early infancy weight gain is not associated with increased obesity risk in adolescence,[276] whereas rapid linear

growth in the first two years of life is associated with greater adult height and attained schooling.[1,249] Faster linear growth during infancy and mid-childhood has also been shown to increase the likelihood of adult overweight and elevated blood pressure.[1]

1.2.4 Pathways influencing the effect of risk exposure on child development

The pathways that influence how risk factors can affect brain and behavioural development include timing, dose, i.e. co-occurrence and cumulative influences, as well as differential reactivity (Figure 1.5).[88]

Timing

Extraneous and environmental factors have maximum effect on brain (and behavioural) development during specific life stages, i.e. sensitive periods. During early growth and development, the evolving brain architecture and other maturing organ systems are highly receptive to a variety of environmental influences, both positive and negative.[54] Adaptations due to risk factors for poor health and development can be biologically embedded in the brain and other organ systems at these times, and may result in health impairments years or even decades later.[26,278]

Dose

This refers to the duration and intensity of the exposure. Where there is a dose-response relationship between an exposure and outcome, it implies that the strength of the association varies with the level of exposure.[279] It is important to note that a single risk factor does not necessarily lead to developmental impairments; however, children exposed to one risk factor are at increased risk of exposure to others.[280] Risks, particularly in contexts of adversity, often co-occur and persist resulting in exposure to multiple and cumulative risks that interact and reinforce one another.[88,280] Exposure to increases in the number of childhood adversities or severe developmental risks significantly increases the risks of later life health, behavioural and developmental difficulties.[26,281-283]

Differential reactivity

A growing body of scientific evidence suggest that some children are not only more vulnerable to adverse experiences but also more susceptible to both negative and positive environments. The effect of risk and protective factors on the development of

the brain (and behaviour) can be moderated by specific characteristics that pertain to the child or his/her context, such as parenting experiences or social support.[5,284]

As risk factors are cumulative, interactive and tend to reinforce one another, [285] it is likely that the same children who are exposed to suboptimal physical and psychosocial environments are also more likely to experience poor growth during early life.[286,287] Thus, placing them at greater risk for adverse developmental outcomes.

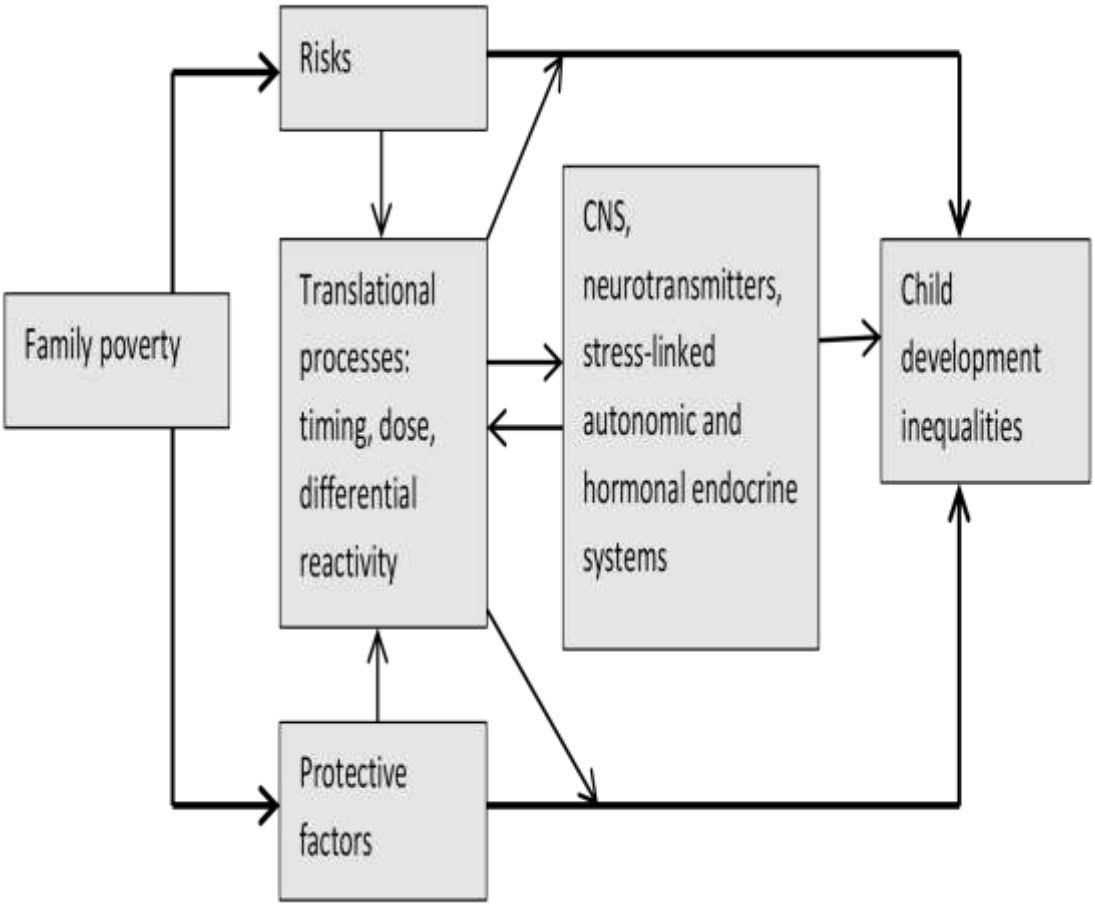


Figure 1.5 Pathways linking poverty to developmental inequities (adapted from Walker *et al.*[88])

1.2.5 Pathways linking early life risk exposures, growth and child development

Adequate nutrition, both before and after birth, is important for healthy brain, organ and musculoskeletal development. Sufficient intake of macronutrients (protein, carbohydrates, and fats) and micronutrients (vitamins, minerals and trace elements)

is essential in the early years when physical growth and brain development are occurring at a more rapid pace than during any other period in the life course.[26] Inadequate nutrition during this time can affect the structure and functions of the brain with long-lasting and sometimes irreversible effects on child cognition and behaviour.[18,288] The earlier in the lifecycle the malnutrition occurs, the greater the likelihood that brain size will be reduced and the longer the malnutrition continues, the greater the impact on the developing brain.[289]

The brain undergoes rapid development in the first five years of life through a series of events that occur in overlapping time periods in different brain areas (Figure 1.6). These processes build on each other and even small disturbances can lead to adverse effects on brain and cognitive development.[18] Various nutrients are required for specific neurodevelopmental processes. Thus the timing, as well as the degree, of nutrient deprivation is of particular importance. Nutrient deficiencies are more likely to compromise brain development if the deficit occurs at a time when there is a particular need for a specific nutrient.[288]

Although not yet clearly defined, three main pathways have been identified through which undernutrition may affect child development outcomes. The first is that nutritional deficiencies may compromise brain structure and function and lead to a reduction in the number of neurons and synapses, dendritic arborisation and myelination, resulting in smaller brain size and potentially impair the functioning of the central nervous system.[290,291]

The second pathway is through children's exploration and interaction with their environment. Malnutrition not only predisposes children to illness, which may affect how they engage with their environment, but children who lack energy, become withdrawn and seek less stimulation from their physical and social environments.[292] Third, caregivers may treat children who are small for their age differently, providing them with less age-appropriate stimulation or challenging them less, which could also lead to impaired cognitive development.[29,286]

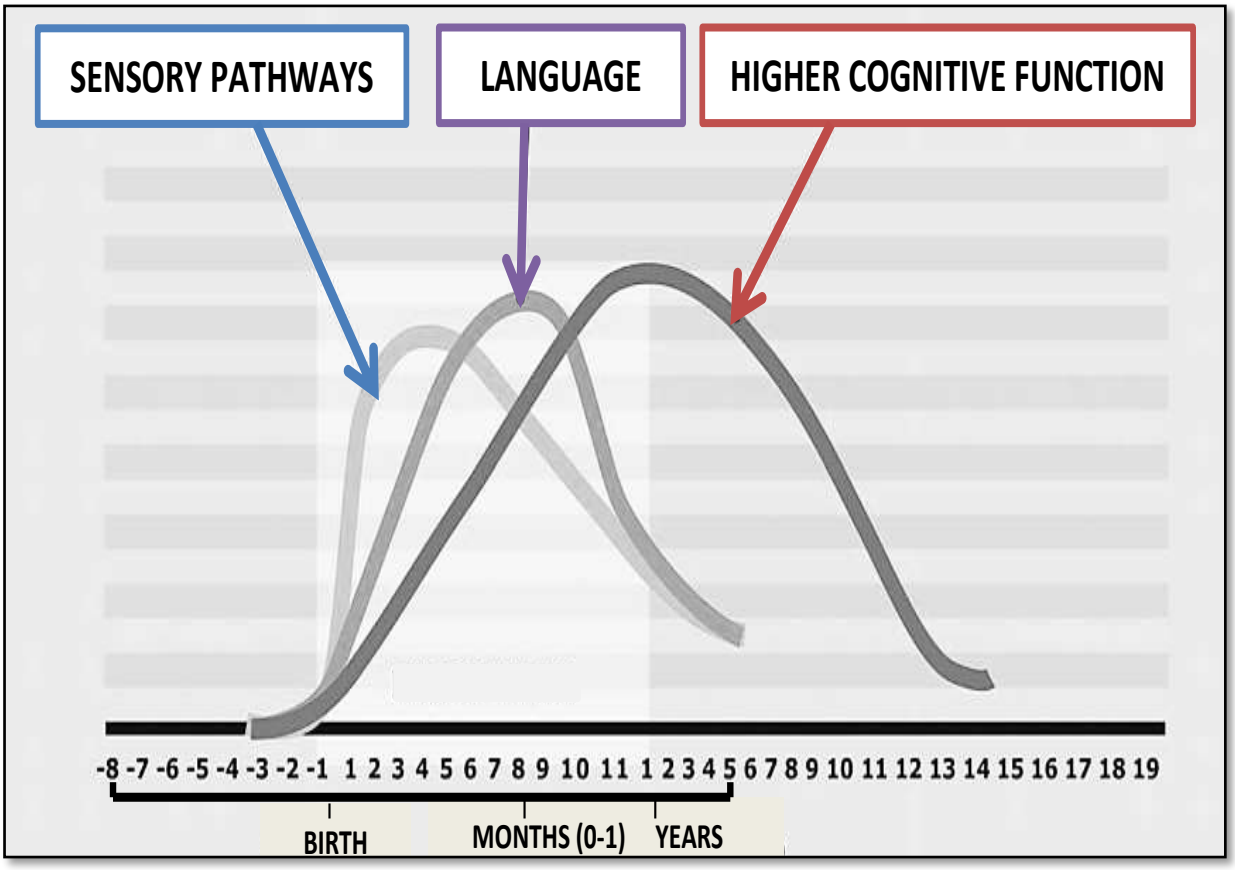


Figure 1.6 Brain development in the first five years (adapted from Nelson[293])

Healthy brain development depends on multiple experiences. The influence of experiences on brain development can be categorised as 'experience-expectant' and 'experience-dependent' processes.[294,295] Experience-expectant development refers to features of the environment that are (or should be) ubiquitous and 'expected' for development to occur normally; the absence of these experiences impairs the neurodevelopmental processes that rely on them.[295] For example, the brain relies on exposure to visual stimuli through the optic nerve for development of the visual cortex.[294] Conversely, experience-dependent development refers to experiences that can occur over the lifespan in response to environmental stimuli.[294,295] For example, the ability to read or write is dependent on exposure to specific environmental stimuli and experiences that only certain individuals may have access to.[295]

Adequate nutrition can be regarded as an aspect of the environment that is expected by the brain for healthy development to occur.[296] Similarly, an environment where the expectation for responsive and stimulating caregiving (to offset the effects of risk exposure) is not met, impairs some of the same neurodevelopmental processes as

nutritional deprivation in young children.[29] The effects of poor growth and environmental influences on brain development may operate in a number of ways, namely additive, interacting and mediating.[29] In the case of additive effects, nutritional deficiency and environmental influences may exert independent, cumulative effects on the developing brain. Alternatively, poor nutrition or environmental stimuli may only affect some children but not others. In this case, as shown in Chilean study, low birthweight infants born into high SES households were at lower risk of poor development than their counterparts born into low SES households.[297]

Possible mechanisms through which the effects of poor nutritional status on brain development may be mediated include caregiving behaviours and practices, as well as child interactions with the environment.[29] For example, poor nutritional status may lead to a withdrawn, lethargic child limiting exploration of the environment and less positive caregiver interactions, which may in turn adversely affect brain development.[29]

Thus, it is possible that the effects of growth and environmental (physical and psychosocial) influences on child development may operate through different mechanisms.

1.2.6 Child development measures

A recent global analysis of the risk of poor development in young children in LMIC, estimated that 20-39% of children younger than 5 years (who were exposed to stunting or poverty) were at risk of poor development in South Africa.[298] Thus, it is of utmost importance that children at risk of poor development are identified early to receive the necessary intervention and support.

Child development can be categorised into four major domains, namely motor, language, cognitive or adaptive and socio-emotional (table 1.1).[299] Each domain of development is assessed by the child's ability to carry out a sequence of activities that reflect the expected level of development at a specific age.[6]

Table 1.1 Categorisation of child development domains[299-301]

Developmental domains	Description
Motor	Encompasses both *fine* motor (the manipulation of objects with the hands, e.g. to draw or eat) and *gross* motor (the control of large muscle groups in order coordinate complex physical activities) ability.
Language	Refers to articulation, receptive and expressive language development.
Cognitive or Adaptive	*Cognitive:* Refers to the strategies and processes that children apply to make sense of and respond to their environment and experiences. Includes the ability to problem solve, learn, understand and retain information and apply it as required. *Adaptive:* Encompasses the conceptual, social and practical skills people use to function on a daily basis.
Socio-emotional	Ability to regulate behaviour, interact, establish and maintain relationships.

Child development can be assessed by: (1) direct assessment or testing of the child; (2) verbal report or completion of a questionnaire of the child's abilities by the parent or teacher; and (3) observation of a child, usually in an unstructured, familiar environment (e.g. at home or school) by a trained assessor.[6,302,303]

Direct assessment typically involves the use of a standardised assessment tool. Infants are presented with stimuli, e.g. sounds or objects, in order to evoke specific responses, or children are asked to complete tasks or activities, such as searching for a hidden object. Assessors are generally professionals who regularly interact with children and are usually required to complete additional training on how to administer and score the test.[299,303] Examples of direct assessments are the Bayley Scales of Infant Development and the Griffiths Mental Development Scales.[304]

Another method of assessing child development is through parent/caregiver report, which often entails the completion of a questionnaire or checklist by an informant who knows the child well, usually a parent/caregiver, or a teacher. It requires answering questions about the child's abilities based on what they know of the child, and does not involve any direct assessment of the child. This approach can offer information about how children behave in other (i.e., non-standardised or unstructured) test conditions.[302] Informants usually report whether a behaviour has occurred and how frequently or whether they have any particular developmental concerns. They may also be asked to compare their child's development with other children of the same age. Examples of this type of assessment are the Ages and

Stages Questionnaires (ASQ),[305] and the Parents' Evaluations of Developmental Status (PEDS).[306]

Observational measures require a trained observer to document the behaviours displayed by a child in a familiar environment (e.g. home or school). These can be observations that require the observer to follow the child during the normal course of the day and observe and record his/her behaviour (naturalistic observation). They are often used to complement standardised assessment.[12] These can also be conducted in structured situations, where children's behaviour, as well as their completion of specific tasks, is observed in a controlled situation. An example of this approach is the Individualized Classroom Assessment Scoring System (inCLASS) that uses multiple observations in order to determine patterns of individual child behaviours across and within classroom settings.[307]

Ideally, assessment of a child's development would include a component of each of these approaches but, more commonly, only one method is used.[6]

Developmental screening tools

Screening tests are brief tools that aim to identify children who are at risk of developmental delays or difficulties in one or more of the developmental domains.[12] Screening tools typically include the major developmental domains, but some may not include all the domains or are specific to a particular domain, such as the Pediatric Symptom Checklist which uses parent opinion to assess child behaviour.[308] Assessment of child functioning is more effective when multiple domains are measured. Screening tests are not diagnostic and are usually a first step in the assessment process to identify children 'at risk' who need a more comprehensive developmental assessment.[6,12] They are less costly, quick and relatively easy to administer, and do not require much training time. However, screening tools are less effective in assessing milder developmental difficulties that may also have a significant impact on subsequent child development. Screening tools are beneficial when used as part of a developmental surveillance programme, and where predetermined population-based cut-offs have been established. Screening tests

may involve direct child testing, parent/caregiver report or both.[12] An example of a screening tool is the Denver Developmental Screening Test (DDST).[309]

For each assessment tool there is a threshold a child must achieve that indicates the absence of developmental concerns at that time. The threshold is set by norm referencing and criterion referencing. Norm-referenced tests are standardised tests and the child's scores in each developmental domain are compared with scores from a sample of children of the same age and/or sex that are representative of the population evaluated (normative sample). Conversely, criterion-referenced tests assess whether a child has acquired a specific skill by a particular age.[6,12]

Currently, child development assessment tools that are available and have been used in LMICs typically include: (1) a standard assessment tool that has been developed in a high income setting with no adaptations; (2) a 'Western' tool that has been translated and/or adapted for the local cultural context; (3) a combination of a number of translated and/or adapted items from several different tools from 'Western' settings; or (4) a culturally-relevant tool that has been developed locally consisting of original items designed to be applicable to the study/reference population.[6,12]

Most screening tools have been developed in high income settings and there are issues related to the use of these tools in LMIC. However, screening tools are often adapted for use in lower resourced settings to identify developmental differences among groups of children as they are relatively easy to implement.

1.2.7 Summary of literature review

The literature review has highlighted that, beyond biological (and genetic) factors, there are a number of psychosocial exposures that may affect child growth and development. It also emphasises the importance of growth during the first years of life on child development and identifies potential pathways through which poor growth may affect child development outcomes.

There is consensus that the timing, intensity and duration of exposure to particular risk factors, including poor growth, are critical for brain development, as well as that

some children may be more susceptible to both positive and negative environmental influences.

Growth, particularly linear growth, within the first two years has been associated with short- and long-term health and development outcomes.[90,250] However, growth beyond this period is also important for child health and well-being.[90,244] Studies, mainly from lower resourced settings, have found that growth during early childhood may mediate the effects of poverty on child cognitive development.

1.2.8 Relevance and justification for the study

There is abundant literature on potential risk factors for poor child growth and development. However, it is unclear whether the same risk factors are associated with both growth and development and whether risk factors affect growth and development through different mechanisms. In addition, as context is important with regard to the manifestation of these risk factors, there is still uncertainty as to which are key psychosocial and environmental risk factors that impact child growth and development in settings, such as South Africa, that are not only lower resourced but also have wide socio-economic disparities.

From the literature surveyed, it is still unclear whether prenatal growth (of which birthweight is a proxy marker) or postnatal growth is the dominant influence on child development outcomes. There is also conflicting evidence as to what are key growth markers that impact child development. There is some evidence to support birthweight and/or weight gain in infancy and early childhood having a stronger impact on development outcomes, though other studies have found that linear growth is a stronger determinant of later child outcomes.

Thus, the extent to which early childhood growth (pre- and postnatal weight and linear growth) mediates the effects of social risks, such as poverty, remains unclear; especially as there has been conflicting evidence from studies conducted across different income settings.

Some inconsistencies relating to the association between early childhood growth and development may be due to methodological issues, such as the use of different indicators of growth and development across studies. Important confounders might

be omitted and there may be measurement errors, particularly with regard to the inclusion of multiple growth measures (at different time points) in the same analysis, which may raise issues of multicollinearity. This can be addressed through the use of conditional growth variables, which this study has employed. Few studies have used more powerful and flexible multivariate modelling techniques to explore the relationships (and interactions) between risks to development, growth and child development outcomes, particularly in a LMIC context. Limitations in study design are also an issue, with most studies being cross-sectional, thereby limiting causal inference.

This thesis aims to address some of the challenges highlighted above by investigating these relationships using data from a large, longitudinal birth cohort in a low resourced setting. The intention is that findings of this study will contribute to the local and international evidence base on early childhood growth and development and inform the design of timely, targeted interventions to address key risks, and promote child health and well-being, in lower resourced settings.

1.3 Overall aim

The aim of the study was to determine the effects of maternal and child environmental and psychosocial exposures during pregnancy and the first two years of the child's life ('the first 1 000 days') on growth and development outcomes in early childhood (up to 5 years) in an urban South African birth cohort.

1.3.1 Specific objectives

1. To determine the associations between maternal psychosocial and environmental risk factors assessed during pregnancy and subsequent infant birthweight.
2. To assess the effects of psychosocial and environmental exposures affecting the mother (and child) during pregnancy and the first two years of a child's life on stunting at age 2 years.
3. To determine the associations between early life psychosocial and environmental exposures, growth (between birth and 4 years of age) and child development at 5 years of age and to assess whether relative linear growth

mediates the association between key early life exposures and child development.

1.3.2 Research questions and study hypotheses

Research Question 1: Are there associations between maternal psychosocial and environmental exposures during pregnancy and subsequent infant birthweight?
Hypothesis (H0): There are no associations between maternal psychosocial and environmental exposures during pregnancy and subsequent infant birthweight.

Research Question 2: Which of the measured psychosocial and environmental exposures that a mother (and her child) is exposed to during pregnancy and the first two years of life are associated with stunting at 2 years of age?
Hypothesis (H0): There are no associations between maternal and child risk exposures during pregnancy and the first two years of life and stunting at age 2 years.

Research Question 3: Are there sex differences in relation to early life psychosocial and environmental exposures, growth (between birth and 4 years) and child development at age 5 years?
Hypothesis (H0): There are no differences between males and females in relation to psychosocial and environmental exposures, growth and development.

Research Question 4: Is early childhood growth (between birth and 4 years of age) associated with child development at 5 years of age?
Hypothesis (H0): Early childhood growth is not associated child development at 5 years of age.

Research Question 5: Does relative linear growth mediate the association between key psychosocial and environmental exposures and child development?
Hypothesis (H0): Relative linear growth does not mediate the effects of key psychosocial and environmental exposures on child development.

CHAPTER 2: METHODOLOGY

This chapter describes the study design and setting, data measurement and management techniques used, analysis plan implemented and the ethical considerations related to this thesis.

2.1 Study design and data source

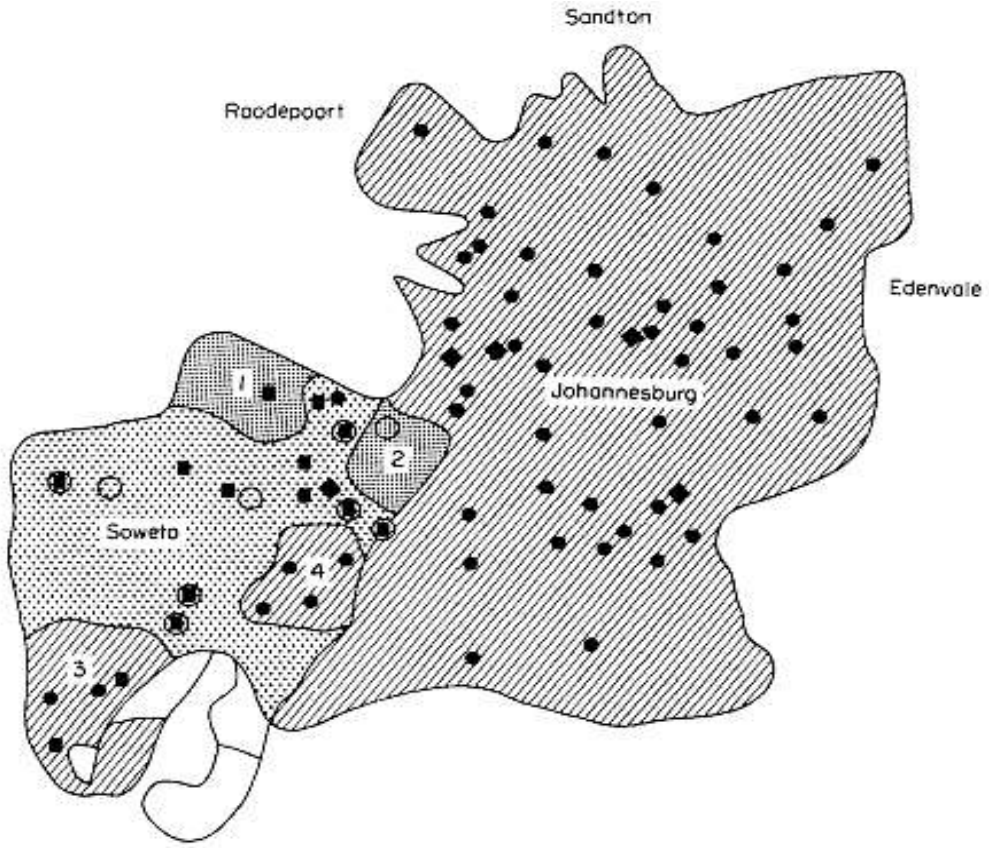
2.1.1 Study design: Birth to Twenty Plus

This series of studies involve secondary analysis of data collected in the course of the Bt20+ cohort. Bt20+ is a prospective, longitudinal birth cohort study, the largest and longest running study of child and adolescent health and development in Africa, and one of few large-scale longitudinal birth cohort studies in the world.[310] The study began in 1990, and spans the transition from the *apartheid* era to democracy in South Africa and the beginning of rapid urbanisation and wide-ranging political, legislative and socio-cultural transformation in South Africa.[311] The children enrolled into the study are the first cohort born into a free South Africa and became informally known as 'Mandela's Children' as they were born in the seven weeks following Nelson Mandela's release from prison on 11 February 1990.[312]

2.1.2 Bt20+ study recruitment

In 1988, collaboration of more than thirty researchers, academics and service providers marked the inception of the Birth to Ten (Bt10) birth cohort study, with the aim of tracking the health, growth and development of urban children born in Soweto-Johannesburg from before birth to ten years of age.[313] Pilot studies were conducted during 1989 and 1990 to estimate the number of children who could be enrolled into the study (sampling) and feasibility, such as potential for follow-up. The pilot studies showed that 20% of deliveries were immediately lost to follow-up as mothers were not found after delivery at the addresses they had provided or because they had provided false contact details.[311] These were largely non-resident women who planned to deliver their babies in Soweto-Johannesburg for personal/social reasons, and who were highly mobile within the area or were women who gave false

addresses in order to be able to deliver their babies in a hospital.[311] Thus, the cohort was defined by the timing of a singleton birth within a 7-week period in 1990, as well as residence within the designated metropolitan area for at least 6 months after the birth of the child. The study population is defined geographically as births in all extant suburbs of the Soweto-Johannesburg metropolitan area, served by the Johannesburg and Soweto City Councils (Figure 2.1).[314]



1= Meadowlands; 2 = Diepkloof; 3 = Lenasia; 4 = Eldorado Park
● Johannesburg City Health clinics ◆ Provincial Hospitals
■ Soweto City Health clinics ○ Provincial Maternity facilities

Figure 2.1 Geographical area of the Bt10 study population showing position of major public health clinics and hospitals (adapted from Yach[314])

A pre-enrolment phase was used to identify women who were likely to deliver within the specified enrolment period. A baseline questionnaire was administered by trained interviewers to collect data on pregnant women attending antenatal clinics in the Soweto-Johannesburg metropolitan area during the 26th to 32nd week of pregnancy. Enrolment took place between 23 April and 8 June 1990 and included infants (singleton births) born in the Soweto-Johannesburg metropole (n=5 449) during the specified enrolment period.[311] On commencement of the enrolment period, wide-

ranging efforts were made to identify and trace records of all births that occurred within the Soweto-Johannesburg metropole. These included placing an interviewer in the public health delivery centres (within the study area) during the enrolment period, accessing delivery records from public and private health facilities, accessing birth notification and mortuary records and retrospectively tracing of women and their infants when accessing postnatal health services in the area.[315]

Although more than 5000 births were notified in the area during the enrolment period, only 3273 children were verified as being resident in the Greater Johannesburg Metropolitan area for a minimum of 6 months after the child's birth.[313,315] Thus, the realised sample is 3 273 cases (referred to as the residential cohort). Some of the main reasons for non-enrolment included migration out of the study area within 6 months after the child's birth, false contact details, as well as stillbirths.[315] A small number of women, mainly White, declined participation due to privacy reasons.[311,313] Black children comprised the major race group in the study sample (78.5%), followed by Coloured/Mixed race (11.7%), White (6.3%) and Indian (3.5%) children.[316]

In 2000, Bt10 became Birth to Twenty (Bt20) as the study continued into its second decade.[315] Adopting a life-course approach, Bt20 continued to collect a wide range of data related to young people's health, growth and development but also focused on exploring specific questions related to risks for lifestyle-related diseases, such as cardiovascular disease and diabetes, and psychological and educational outcomes. As from October 2005, offspring of the index children started to be born and were included in the study and hence the cohort became known as Birth to Twenty Plus (Bt20+).[312]

The latest wave of data collection was completed in 2015 and focused on transitions to adulthood in relation to education, livelihoods, attained adult height and cardio-metabolic disease risk. The cohort participants are currently approximately 26 years old; with a study retention rate of nearly 70%. Attrition was due to reasons such as migration (most common), deaths of either the mother or child, and adoptions or abandonment and study fatigue among others.[315] The study currently follows more than 2 000 children and families throughout the Gauteng province.[317] Circular migration significantly influenced the longitudinal sample, for example, a child might

have been available for assessment at 5 years, but not at 7 years, but was available again at 9 years.[311]

2.2 Study setting: Bt20+

The Bt20+ study is situated in Soweto (an acronym for South Western Townships), which falls within the greater Johannesburg Metropole in Gauteng province, the wealthiest and most populous province in South Africa (Figure 2.2).[318] Soweto spans over 200km^2 and comprises approximately 72 formal suburbs and informal settlements.[319] It is the largest, predominantly black residential area in South Africa, with a population density of 6 357 persons/km^2 and close to one third of Johannesburg's 4.4 million population.[320]

Most of the population is aged between 16 and 64 years, with close to one half having completed matric or higher education.[320] The South African Census (2011) data identified 355 331 households in Soweto.[320] Approximately 90% of households had access to electricity and a flush toilet, but only 55% had access to piped water inside the dwelling.[320] Data collected from a sub-sample of this cohort in 1996, revealed that approximately 21% of mothers had completed secondary education, 25% of households had access to an inside flush toilet and 41% had access to piped water in the dwelling.[321] Thus, although there have been improvements in access to basic services, such as utilities and education, Soweto continues to have persistently high levels of poverty and socio-economic disparities.

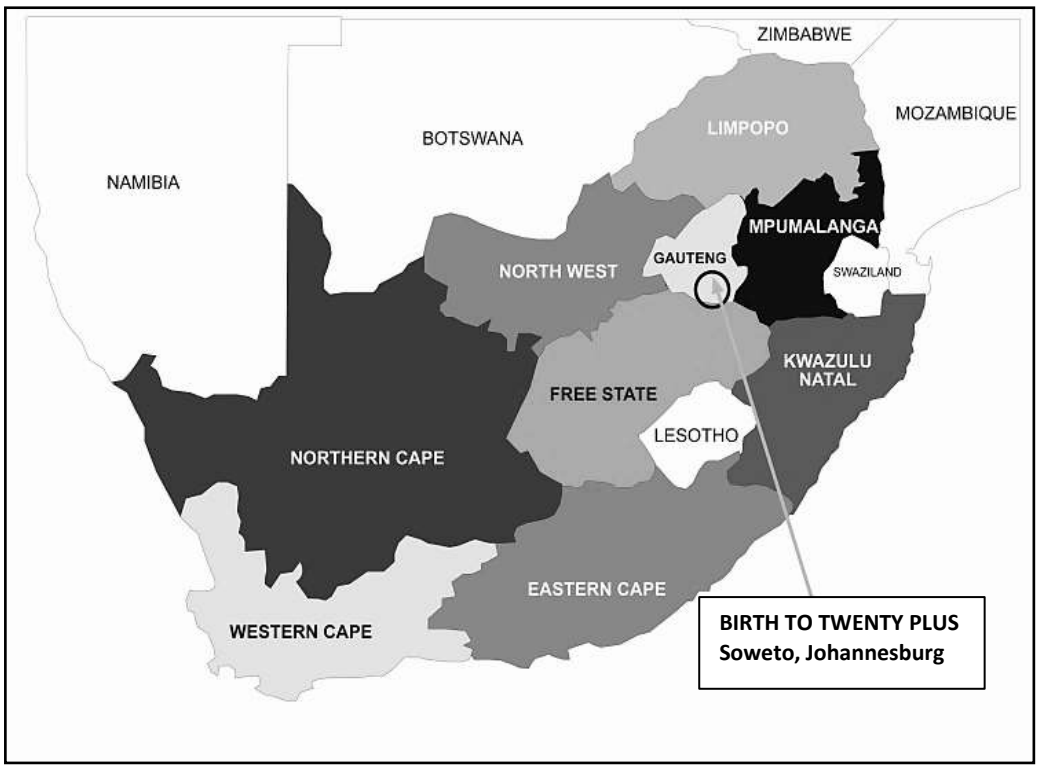


Figure 2.2 Map showing location where the Bt20+ study is located

2.3 Data collection and management

Data for the analyses that follow were collected during pregnancy, at delivery, 6 months, and between 1 and 5 years of age (between 1990 and 1995).

2.3.1 Data collection instruments

Standard Bt20+ questionnaires were administered by trained interviewers at each data collection point and were piloted and validated before commencing each data collection wave. The questionnaires were administered in the interviewee's home language, mainly English, Afrikaans, Sotho and Zulu. In instances where a participant preferred to speak their own (another South African) language, an interviewer who was proficient in that language would conduct the interview. The relevant sections of the respective questionnaires pertaining to exposure variables used in this study (antenatal, delivery, 6 months, 1 and 2 years) used in this study are presented in Appendix 1.

2.3.2 Measures and procedures

This section provides information regarding the maternal and household exposures, as well as the growth measures and development outcome used in these analyses. Further details on the respective exposure and outcome variables used to address each of the thesis objectives are presented in the ensuing Results section (chapters 3 to 5).

2.3.2.1 Maternal and household factors

Maternal demographic and psychosocial exposures were recorded using a standard questionnaire administered verbally to mothers by trained, multilingual interviewers at either antenatal clinics, the Bt10 offices at Chris Hani Baragwanath Hospital in Soweto or at home, between the third trimester of pregnancy and the first two years of the index child's life.

For objective 1, nine maternal and household exposures were examined. Maternal age at the birth of the index child, maternal education, marital status, pregnancy wantedness (mother's rating of her desire to be pregnant at the time of the interview), maternal prenatal stress, tobacco use (cigarette smoking, snuff use or chewing tobacco) and alcohol use. Overcrowding in the home (classified as present if more than 3 people per room used for sleeping) and household socio-economic status (SES) were measured between birth and 2 years of age. For objectives 2 and 3, ten maternal and household exposures were included in the analysis. These included the same exposures as for objective 1, but also included maternal depression, which was measured 6 months after the birth of the index child. Table 2.1 provides a breakdown of when data were collected for each of the included exposure variables.

Measures were treated as cross-sectional (between earliest data collection point and 2 years) where there were multiple data collection points for a specific exposure variable, in order to maximise the sample size. Data was extracted from the data collection point with the largest sample size and then gaps were filled in with data from the nearest earlier/later time points as appropriate.

Table 2.1 Maternal and household factors used in this study

Measures	Data Collection Wave				
	Antenatal	Birth	6 months	1 year	2 years
Maternal factors					
Maternal age at birth		X	X	X	X
Marital status	X		X	X	X
Maternal education	X		X	X	X
Alcohol use during pregnancy	X				
Tobacco use during pregnancy	X				
Pregnancy wantedness	X				
Prenatal stress	X				
Maternal depression			X		
Household factors					
Overcrowding	X				X
Household assets			X	X	X

Table 2.2 provides information on the variable definitions used in this study. Additional information is provided in text to explain the derivation of composite variables, scores used in the study or where further clarity is required for specific cut-offs used.

Table 2.2 Variable definitions used in the study

Variable	Variable definition
Maternal factors	
Maternal age at birth	Measured as a continuous variable; used as either a categorical or a continuous variable in the analyses
Maternal marital status *Married* *Living together* *Separated/divorced/widowed* *Single*	Married, living with a partner, separated/divorced/widowed or single
Maternal education *≤ Grade 7* *Grades 8 -10* *Grades 11-12* *Post school training*	Grade 7 or lower; completed Grades 8-10; Grades 11-12; or had post school training (diploma or university degree)
Maternal alcohol use during pregnancy *No* *Yes*	Mother drank any alcohol during pregnancy
Maternal tobacco use in pregnancy (any) *No* *Yes*	Mother used any cigarettes, snuff or chewing tobacco during pregnancy
Pregnancy wantedness *Yes* *No/Unsure*	Mother was not sure or did not want to be pregnant at time of interview (third trimester)
Prenatal stress	Sixteen stressors were surveyed at interview

Scores <4 *Scores ≥4*	during pregnancy, with yes/no replies indicating the presence/absence of each stressor. Scores were summed across all responses to produce an overall stress score.
Maternal depression *<20* *≥20*	Scores of ≥20 indicated a self-report consistent with postnatal depression
Household factors	
Crowding *≤3 people/room* *>3 people/room*	Ratio of people/rooms used for sleeping. Overcrowding was classified as present in this study if the ratio was >3, as the mean ratio for the sample was 3.25.
Household assets *0* *1* *2* *3* *4* *5* *6* *7*	Asset scores were generated through an additive index, by attributing a score of 0 to unavailable assets and a score of 1 to assets present in the household.

Sixteen stressors women were exposed to in the previous 6 months were enquired about during the pregnancy interview in order to assess for prenatal stress. Yes/no responses indicated the presence/absence of each stressor. An overall score was determined by the sum of all sixteen responses. The scale had reasonable internal consistency ($\alpha = 0.64$). As stress scores were not normally distributed, participants with the top 15% of scores were considered to be high scorers, in line with previous studies.[184] A score of 4 was the closest cut-off point to yield the top 15%, therefore scores of 4 or more were considered suggestive of high prenatal stress.

Symptoms of maternal depression were assessed 6 months postnatally using the Pitt Depression Inventory (PDI).[322] The PDI comprises 24 items and every item is coded as either no (0), don't know (1) or yes (2). Total scores range from 0 to 48; with a score of 20 or more indicating a self-report consistent with postnatal depression.[322] The PDI has been used extensively locally and internationally and is highly correlated with other depression measures such as the Edinburgh Postnatal Depression Scale.[189,199,323]

Ownership of material assets at a household level (i.e. home ownership, electricity, television, car, fridge, washing machine and telephone) was used as a measure of SES as these were common to all relevant time points for the study. The use of these assets was based on the Demographic and Health Survey (DHS) household questionnaire that is used in LMIC, including South Africa.[324] Use of a household

asset indicator as a proxy measurement for SES has become increasingly popular and has been validated in low and middle income countries.[325,326]

The crowding ratio is obtained by dividing the number of people (in the household) by the number of rooms occupied by the household.[327] There is no standard measure of overcrowding in South Africa. The average household size in South Africa was 4.5 at the time of the 1996 population census.[328] The mean ratio for the Bt20+ sample was 3.25 per room (used for sleeping). It is for this reason that a ratio of >3 people per room was used as an indicator of crowding for these analyses instead of the lower United Nations ratio of >2 people per room.

2.3.2.2 Early childhood growth

Weight and length/height measures were collected at three months, 6 months, and yearly between 1 and 4years of age using standard procedures.[21] Reliability was confirmed by test-retest evaluation and quality control throughout the study. Only infant weight was measured at birth. All weight and height measures were converted to *z*-scores by comparing them to the WHO growth standards.[21]

Stunting at age 2 years was defined as a length-for-age *z*-score (LAZ)/HAZ of >2 standard deviations below the WHO Child Growth Standards median.[21]

To investigate growth between birth and 4 years of age, it was important to differentiate the effects of linear growth and weight gain because they are strongly correlated, as are repeat growth measurements of the same individual. For this reason, relative linear growth variables (for linear growth between 0-2 years and between 2-4 years) were computed as residuals obtained by regressing present length/height on previous length/height and weight measures (excluding present weight).[259] Infant birthweight was used as a proxy in these calculations as birth length was not measured. Relative weight gain variables (between 0-2 years and 2-4 years) were defined as present weight accounting for present length/height and all previous weight and length/height measures. These variables are expressed in standard deviation units to allow direct comparison of regression coefficients.

2.3.2.3 Child development at 5 years of age

The measure used to assess child cognitive and behavioural development in this study was based on the Revised Denver Pre-screening Developmental Questionnaire (R-DPDQ).[329] The measure comprised 32 culturally-appropriate items and covers the child's personal-social, fine motor, gross motor, language and cognitive abilities at age 5 years (Appendix 1). During the assessment, parents were asked a set of questions and children were required to complete a series of simple tasks. Thus, a combination of parent report and direct assessment were used to assess child development. Where necessary, some items were modified to be culturally appropriate, for example, the word 'hedge' was changed to 'fence'. The R-DPDQ was assessed for feasibility and appropriateness prior to inclusion in the Bt20+ study.[330]

Internal consistency for the R-DPDQ measure in the Bt20+ sample was 0.72, measured by Cronbach's α. The study did not use externally derived age-specific norms as these may not be applicable to South African children but rather utilised within-sample variation on the scores, which were adjusted for the child's age.[261] An overall developmental score was calculated by adjusting the total raw score by the child's chronological age, and replacing missing values on individual items by the series mean.[96,331] The majority of participants (73%) had complete data on all 32 items. Cases with missing data only had three or fewer items missing; with most only missing one item.[96,331]

2.3.2.4 Covariates

Maternal parity, maternal height and gestational age were adjusted for in analyses for objectives 1, 2 and 3. For objectives 2 and 3, whether the child was ever breastfed and duration of breastfeeding were also controlled for. In addition, infant birthweight was adjusted for in the stunting analysis for Objective 2.

Parity was defined as the number of viable pregnancies. Maternal height (in cm) was measured using standardised techniques. Gestational age was obtained from medical records derived from the mother's report of her last menstrual period. Information on breastfeeding included whether the infant was ever, exclusively or

predominantly breastfed (no other food or fluids) and duration of breastfeeding. Data collected at six months and at 1 and 2 years were interpreted to establish the appropriate answer.

2.3.3 Data management

All relevant variables to be used in the following analyses were extracted from the Bt20+ datasets and variables from separate datasets were merged into one dataset using participants' identification numbers. Checks were implemented to validate that the datasets were merged correctly. Data management by the author included conducting cleaning and quality checks on data pertaining to all key variables at relevant time points for this study. Data were evaluated for consistency, accuracy and outliers. Random checks of 10% of the original response forms were conducted when a high frequency of coding errors or missing or improperly defined data was detected. In such a case, the dataset as a whole was checked. Recoding errors were corrected and where data was incorrectly captured from the original response forms, data were re-entered correctly.

Prior to statistical analyses, data manipulation techniques were employed in order to achieve more meaningful results. Data manipulation for the study included the creation of new variables (e.g. dummy variables and composite variables) and the recoding of existing variables (e.g. reverse coding), as well as converting or transforming variables (e.g. continuous variables to categorical variables). The cleaned datasets for each study objective were then imported into the statistical software used for analysis, Stata 13.1 (Stata Corporation, College Station, Texas, USA).

2.4 Analytical strategy

Although, details of the analytical approaches used for these analyses are described in each of the Results chapters, additional information about specific analytical components for each research question is provided in this section. The data analysis plan for the thesis is presented in Figure 2.3.

Research Question 1 aimed to address Objective 1, Research Question 2 addressed Objective 2, and Research Questions 3 to 5 aimed to address Objective 3.

Research Question 1: *Are there associations between maternal psychosocial and environmental exposures during pregnancy and subsequent infant birthweight?*
Bivariate statistical analyses were undertaken to estimate the unadjusted association between each of the exposure variables and the outcome, birthweight. Following bivariate analyses, multiple regression analysis was conducted to determine risk factors that were independently associated with infant birthweight in the full sample, as well as in sex-stratified analyses, and to estimate the strength of the adjusted associations. The variables that were significant in bivariate analysis at $p<0.15$ were considered for inclusion in the model. Estimation of the regression model parameters for the 'final model' was based on the ordinary least squares method. Variables that were statistically significant were included in the final model if $p< 0.05$. In addition, a quantile regression model was built to compare the results.

Research Question 2: *Which of the measured psychosocial and environmental exposures that a mother (and her child) is exposed to during pregnancy and the first two years of life are associated with stunting at 2 years of age?*
Bivariate analyses were conducted to determine the unadjusted association between each exposure and stunting at age two years. Thereafter, sex-stratified multiple logistic regression models were used to determine risk factors that were independently associated with stunting at 2 years and the pseudo R^2 for model fit. Possible covariates, selected on the level of significance in bivariate analysis ($p<0.10$) and theoretical relevance, were adjusted for in the analyses. Variables were included into the regression models using a stepwise approach.

Research question 3: *Are there sex differences in relation to early life psychosocial and environmental exposures, growth (between birth and 4 years) and child development at age 5 years?*
Descriptive statistics were used to summarise early life exposures, growth and child development variables by sex of the child. Following bivariate analyses, sex-stratified multiple linear regression models were used to determine the associations between birthweight and relative linear growth (0-2 years and 2-4 years) and child development in males and females, respectively.

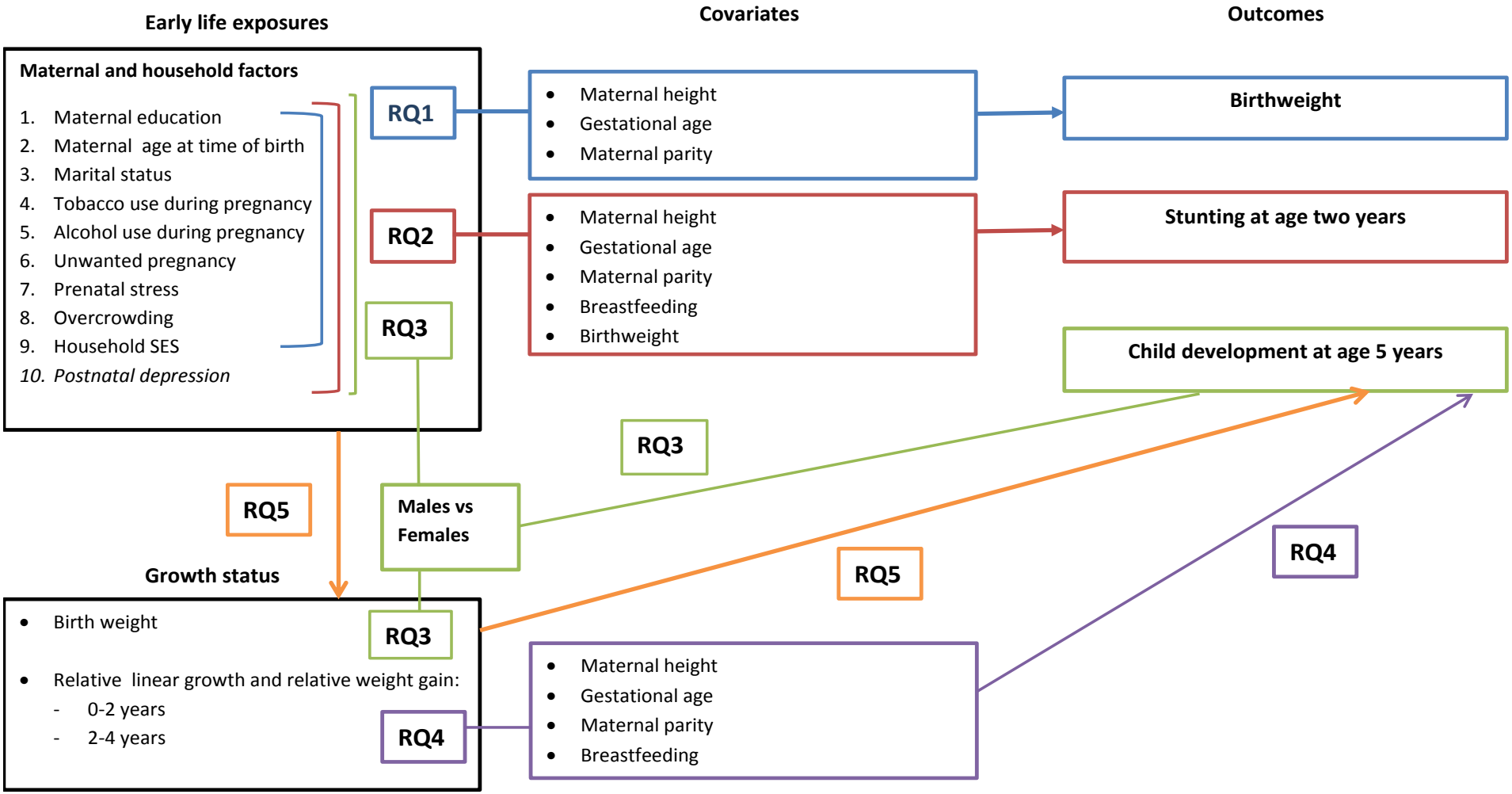


Figure 2.3 Data analysis strategy for the study

Abbreviations: Research Question (RQ)

Research Question 4: *Is early childhood growth (between birth and 4 years of age) associated with child development at 5 years of age?*

Statistical methods were required to differentiate the effects of linear growth and weight gain because they are strongly correlated, as are repeat measurements taken in the same individual. For this reason, conditional growth variables were derived to deal with the multicollinearity. Relative linear growth variables (for linear growth between 0-2 years and between 2-4 years) were computed as residuals obtained by regressing present length/height on previous length/height and weight measures (excluding present weight). Relative weight gain variables (between 0-2 years and 2-4 years) were defined as present weight accounting for present length/height and all previous weight and length/height measures. These variables are expressed in standard deviation units to allow direct comparison of regression coefficients.

Bivariate analyses were conducted to determine the unadjusted association between individual exposures and the R-DPDQ. Thereafter, sex-stratified multiple linear regression models were used to determine the associations between early life growth variables and the outcome and to estimate the strength of the adjusted associations. Variables with a $p<0.10$ in bivariate analysis were included in the regression models using a stepwise approach. Individual factors, i.e. growth variables were added first (model 1), followed by maternal factors (model 2) and then household factors (model 3).

Research Question 5: *Does relative linear growth mediate the association between key psychosocial and environmental exposures and child development?*

We conducted mediation analysis using structural equation modelling (SEM) to assess the extent to which early childhood growth affected the relationship between maternal and household factors and child development outcomes at age 5 years. Mediation assumes causality and a temporal ordering among the variables under study, i.e. exposures significant in regression models, mediators (birthweight, and relative linear growth between 0-2 years and 2-4 years) and the outcome (child development scores at 5 years of age).[332]

As variables in a causal relationship can be both causes and effects, the standard regression methods are inappropriate for modelling such a relationship due to the *a*

priori assignment of each variable as either a cause (independent variable) or an effect (dependent variable).[332] In SEM, a dependent variable in one model equation can become an independent variable in other components of the SEM model. Thus, the causal relationships in a hypothesized mediation process are more appropriately assessed using a more flexible and powerful multivariable technique such as SEM.

SEM models are best represented by path diagrams, which consist of nodes representing the variables and arrows showing relations among these variables. Measured or observed variables are represented by rectangles. The variables are related by single-headed arrows that are hypothesized causal paths estimated by linear regression coefficients, and double headed arrows indicating covariance.

Presentation of the results decomposes the influences of one variable on another into direct, indirect and total effects. The direct effects represent the pathway from the exogenous (exposure) variable (household SES and maternal education) to the outcome (R-DPDQ) that does not pass through the mediators (growth status variables). The indirect effects depict the pathways from the exogenous variables to the outcome through the mediators. The total effects equal the sum of the direct and mediation (indirect) effects of the exogenous variables on the outcome.[332,333]

We tested the model fit using several standardised fit statistics, to test the consistency between the predicted and observed data matrix. A good-fitting model is indicated by Comparative Fit Indices (CFI) values at or above 0.95, Root Mean Square Error of Approximation (RMSEA) of at or less than 0.05, and Standardized Root Mean Square Residual (SRMR) of less than 0.08.[332,334]

2.5 Ethical considerations

Parents or primary caregivers gave written informed consent for their children to participate in Bt20+ at each data collection point. Each participant was provided with a unique identification number (which was used on all questionnaires) and this maintained confidentiality. Ethical approval for this thesis was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (certificate no: M120609 – Appendix 6).

PART 2: EMPIRICAL CHAPTERS

"But we now know that it takes more than education for a child's brain to develop – a lot more… We already knew how critical the first years of a child's life are to the healthy development of her brain. During those early years, almost 1000 brain cells connect every second – a pace never matched again. These connections are the building blocks of a child's life… They help define her capacity to learn, her future success … even her future happiness. But now we know that those connections are deeply affected not only by genetics but also by the conditions of a child's young life. The two are inextricably intertwined."

Anthony Lake, UNICEF Executive Director, October 7, 2015

CHAPTER 3: MATERNAL RISK EXPOSURE DURING PREGNANCY AND INFANT BIRTHWEIGHT

Wiedaad Slemming, Braimoh Bello, Haroon Saloojee and Linda Richter

Slemming W, Bello B, Saloojee H, Richter L. Maternal risk exposure during pregnancy and infant birth weight. *Early Human Development* 2016; 99:31-6

3.1 Introduction

Birthweight is well-established as a determinant of an infant's immediate and future health, influencing infant and adult morbidity and mortality.[335,336] Low birthweight (birthweight < 2500g) results from complex interactions between a range of individual, psychosocial and environmental factors. The link between low birthweight and stressful life events immediately preceding or during pregnancy is well-established.[337,338] Psychosocial factors, such as prenatal stress or poor social support, are postulated to impact on birth outcomes via biological (neuroendocrine, immune or vascular) mechanisms.[339] Health behaviours, such as inadequate maternal nutrition and substance use, are also known to increase risk of low birthweight through similar mechanisms.[340]

Birthweight itself may affect an individual's risk for positive and negative short- and long-term health outcomes. Increases in birthweight are related to increased years of schooling, decreased risk of grade failure and reduced likelihood of short adult stature.[250] Risk for chronic diseases in later life, such as adult-onset diabetes, among others, increases continuously as birthweight decreases, even for infants born within the normal birthweight range.[341] Thus, it is important to consider the full continuum of birthweight and not only categorisations of birthweight (such as low birthweight) in epidemiological research.

The relationship between maternal risk exposure and infant birthweight has mostly been studied in high income countries and by categorising birthweight, rather than using it as a continuous variable.[100] This study aimed to address these gaps by identifying the associations between selected maternal psychosocial and

environmental risk factors assessed during pregnancy and subsequent infant birthweight in a large, urban prospective South African cohort.

3.2 Methods

Data and study population

Data for this study were drawn from the Birth to Twenty Plus (Bt20+) study, a longitudinal birth cohort study, initiated in 1990 in the greater Johannesburg metropolitan area, South Africa.[310] Pregnant women deemed likely to deliver within a specified period were recruited through public health antenatal facilities and all singletons born within a 7-week period in 1990 were enrolled. The study prospectively follows 3 273 children and their families throughout the Gauteng province. The enrolment methods, attrition, and profile of the Bt20+ cohort have been well described elsewhere.[310,313] Black children comprised the major race group in the study sample (78.5%), followed by Coloured/Mixed race (11.7%), White (6.7%) and Indian (3.5%) children. These groupings refer to the *apartheid* system of population group classification and continues to be used as a measure for redressing past inequities. It is the largest and longest running study of child and adolescent health and development in Africa, tracking outcomes in several domains, i.e. physical, educational, social and psychological. The study spans South Africa's transition from *apartheid* to democracy and adopts a life course approach.[310]

The full Bt20+ sample comprises 3 273 singleton births. In our analysis we use data from the antenatal period (n = 1 595) and delivery reports. A total of 1 228 women had complete data for all exposure variables (measured prenatally) and had infants who were delivered within the greater Johannesburg metropolitan area over the specified 7-week period, between April and June of 1990. These 1 228 mother-infant pairs comprised the analytical sample for this study.

Measures

Individual risk exposures

Maternal demographic, and psychosocial, risk exposure was explored using a verbal questionnaire administered to mothers by trained, multilingual interviewers during the third trimester of pregnancy. Infant outcomes were collected immediately after birth.

Nine maternal psychosocial and environmental risk factors were assessed: 1) maternal education; 2) maternal age at birth; 3) marital status; 4) pregnancy wantedness; 5) alcohol use during pregnancy; 6) tobacco use (cigarettes, snuff or chewing tobacco) during pregnancy; 7) crowding in the home (more than 3 people per room used for sleeping); 8) maternal prenatal stress; and 9) household socio-economic status (SES).

Household SES was categorised based on an asset index derived from a listing of household assets (home ownership, electricity, television, car, fridge, washing machine and telephone). Use of a household asset indicator as a proxy measurement for SES has been validated in developing country contexts.[326] Asset scores were generated through an additive index, by attributing a score of *1* to assets present in the household and a score of *0* to unavailable assets. Asset scores were then grouped into tertiles, i.e. 1 (poorest) to 3 (wealthiest) for analysis; these groupings were relative to the study sample.

For prenatal stress, sixteen stressors were surveyed at interview during pregnancy, with yes/no responses indicating the presence or absence of each. Scores were summed across all sixteen responses to yield an overall stress score. The scale had reasonable internal consistency ($\alpha = 0.64$). As stress scores were not normally distributed, participants with the top 15% of scores were considered to be high scorers, in congruence with previous studies.[184] The closest cut-off point to yield the top 15% was a score of 4. Thus, scores of 4 or more were taken as indicative of high levels of stress.

In addition, demographic variables such as ethnicity and sex of the child were also collected (table 3.1).

Control variables

In addition to the nine risk factors, maternal parity, maternal height and gestational age were adjusted for as possible covariates. Maternal height (in cm) was measured using standardized techniques.[56] Gestational age was obtained from medical records and estimated based on the mother's report of her last menstrual period.

Outcome measure

The outcome variable was birthweight. Electronic weighing scales were used to weigh the infant. Reliability was confirmed by test-retest evaluation and monitoring of quality control throughout the study. *Z*-scores were calculated using the World Health Organization Child Growth Standards.[21] *Z*-scores in anthropometry are widely used to analyse the nutritional status and growth of young children and are recommended for several reasons.[21] *Z*-scores are calculated based on the distribution of the reference population (both the mean and the standard deviation) and thus reflect the birthweight distribution of that population.[21] As standardised measures, *z*-scores are useful for comparing weight at birth across age and sex (i.e. measures of males vs females).[21,342]

Statistical analyses

Appropriate descriptive statistics were used to summarise the outcome and risk variables. Frequencies and percentages were used for categorical variables, while means and standard deviations (SD) were used for continuous variables. Bivariate statistical analyses were undertaken to estimate the unadjusted association between each of the exposure variables and birthweight (using birthweight *z*-score (BWZ)). Pearson's χ^2- test was used to check for differences between the analytical study sample and other participants in the Bt20+ cohort who were not included in the analyses (Appendix 2).

Following bivariate analyses, multiple linear regression models were used to determine risk factors independently associated with infant birthweight and to estimate the strength of the adjusted associations.

A probability value of $p<0.05$ was designated for statistical significance and all analyses were conducted using Stata 13.1 (Stata Corporation, College Station, Texas, USA).

Ethical considerations

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa (Certificate no: M120609). Informed consent was obtained from mothers antenatally and again at delivery.

3.3 Results

Sample characteristics

A summary of key characteristics of the study sample (n = 1228) is shown in table 3.1. In comparison with the Bt20+ participants who were not included in the analysis for this study, study participants were more likely to be Black, single, unsure or did not want to be pregnant, and also had infants with a higher birthweight ($p < 0.001$ for all) (Appendix 2).

Table 3.1 Descriptive statistics and differences in mean birthweight for study sample

Variable	n(%) / mean±SD	Mean birthweight (g)	*p*-value
Demographic variables			
Child sex			
Male	639 (52)	3174	0.008**
Female	589 (48)	3101	
Ethnicity			
Black	940 (76.6)	3162	0.109
White	87 (7.1)	3225	
Coloured	132 (10.8)	3077	
Indian	69 (5.6)	2826	
Explanatory variables			
Smoked cigarettes during pregnancy			
No	1133 (93.0)	3151	0.013*
Yes	85 (7.0)	3015	
Snuff use during pregnancy			
No	1031 (91.2)	3154	0.398
Yes	99 (8.8)	3112	
Chewed tobacco during pregnancy			
No	1116 (99.4)	3150	0.726
Yes	7 (0.6)	3086	
Tobacco use in pregnancy (any)			

No	1037 (84.9)	3153	0.028*
Yes	184 (15.1)	3067	
Drank alcohol during pregnancy			
No	1066 (88.5)	3143	0.444
Yes	138 (11.5)	3109	
Pregnancy wantedness			
Yes	512 (42.8)	3187	0.004**
No/Unsure	685 (57.2)	3104	
Marital status			
Married	497 (40.5)	3156	0.627
Living together	22 (1.8)	3013	
Separated/divorced/widowed	20 (1.6)	3223	
Single	689 (56.1)	3128	
Maternal education			
≤ Grade 7	171 (14.0)	3187	0.686
Grades 8 -10	478 (39.1)	3129	
Grades 11-12	371 (30.3)	3120	
Post school training	203 (16.6)	3157	
Prenatal stress			
Scores <4	1048 (85.3)	3140	0.774
Scores ≥4	180 (14.7)	3129	
Maternal age at birth	26.2 ± 5.7		
<20 years	145 (11.8)	3016	0.681
20-35 years	974 (79.3)	3156	
≥35 years	109 (8.9)	3153	
Crowding			
≤3 people/room	770 (62.8)	3159	0.064
>3 people/room	456 (37.2)	3106	
Household assets			
0	45 (3.7)	3128	0.044*
1	100 (8.1)	3169	
2	145 (11.8)	3154	
3	198 (16.1)	3117	
4	281 (22.9)	3131	
5	212 (17.3)	3130	
6	147 (12.0)	3189	
7	100 (8.1)	3100	
Control variables			
Gestational age (weeks)	38.2±1.6		
Parity	2.2±1.3		
Maternal height (cm)	159.5 ± 6.3		
Outcome variables			
Birthweight (g)	3139 ± 486		

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

The mean infant birthweight was 3139 g (SD 486 g), with a significant advantage in mean birthweight for male infants of 73 g (p = 0.008) (table 3.1). Both boys and girls had BWZ below the WHO reference standard (Figure 3.1).

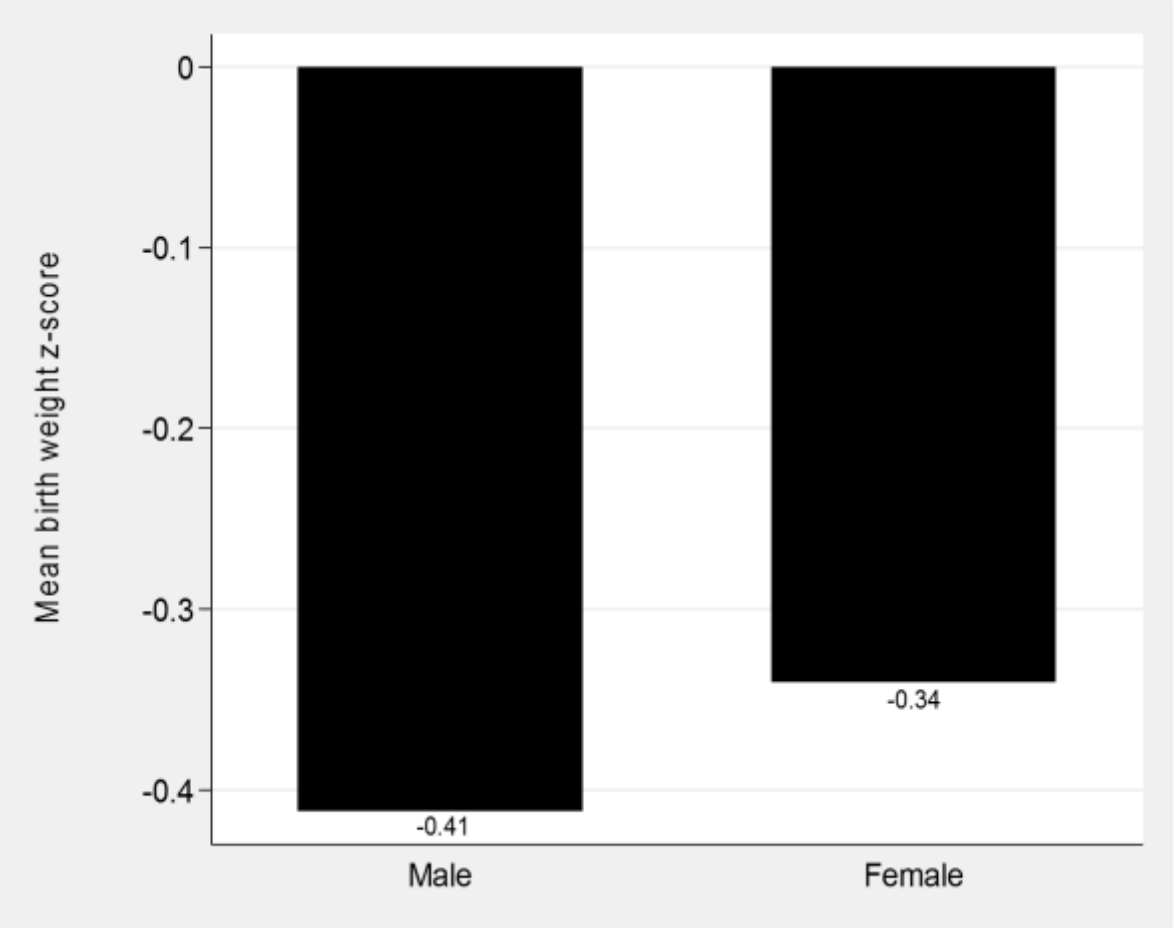


Figure 3.1 Sex-specific mean birthweight z-score for study sample

Determinants of birthweight

Fifteen percent of women either smoked cigarettes or used smokeless tobacco products (snuff or chewing tobacco) during pregnancy. Approximately 7% of women in this sample reported smoking cigarettes and were predominantly of Coloured/Mixed race (32.8%) or White (27.6%). The use of smokeless tobacco products (mostly snuff) was limited to a small number of Black women. Significant differences were found in the mean birthweight of infants whose mothers used any tobacco products during pregnancy (mean difference = 86 g; 95% CI: 10, 162 g), particularly those mothers who smoked cigarettes (mean difference = 136 g; 95% CI 28, 244 g). The use of snuff did not result in a significant difference (table 3.1).

Infants born to mothers who were unsure, or did not want to be pregnant (57%), had a significantly lower birthweight (mean difference = 83 g; 95% CI: 27, 139 g) as

compared to women who wanted to be pregnant at the time of interview. More than a third of these women lived in households with low asset scores.

Multiple linear regression analysis, after adjusting for possible covariates, showed that gestational age, pregnancy wantedness (β = -0.32; 95% CI: -0.51, -0.14), maternal parity and tobacco use (β = -0.32; 95% CI: -0.59, -0.05) during pregnancy were independently associated with birthweight, with maternal height showing borderline significance (table 3.2).

Table 3.2 Multiple linear regression analysis: Significant determinants of birthweight z-score

Variable	Category	Regression coefficient	95% CI	*p*-value
Gestational age (weeks)		0.31	0.26, 0.36	0.000***
Pregnancy wantedness	Yes	Ref		
	No/Unsure	-0.32	-0.51, -0.14	0.001**
Maternal parity		0.12	0.02, 0.23	0.019*
Tobacco use during	No	Ref		
pregnancy	Yes	-0.32	-0.59, -0.05	0.021*
Maternal height (cm)		0.01	0.00, 0.03	0.062

N = 456; R^2 of the model = 0.3002

ref. is the reference category; **p<0.05; **p<0.01; ***p<0.001*

† *Adjusted for maternal age, maternal education, overcrowding, sex of the child, maternal prenatal stress, marital status, household assets and alcohol use during pregnancy*

In sex-stratified analysis, pregnancy wantedness was negatively associated with BWZ for boys (β = -0.31; 95% CI -0.57; -0.05) and girls (β = -0.27; 95% CI -0.54; -0.00). Gestational age was positively associated with BWZ for both sexes, and increased maternal height and parity was associated with a higher BWZ among boys (table 3.3).

Table 3.3 Multiple linear regression analysis: Significant determinants of birthweight z-score in boys and girls

Variable	Category	Regression coefficient	95% CI	*p*-value
Boys				
Gestational age (weeks)		0.33	0.26, 0.40	0.000***
Maternal height (cm)		0.03	0.01, 0.05	0.003**
Maternal parity		0.16	0.03, 0.30	0.019*
Pregnancy wantedness	Yes	ref		
	No/Unsure	-0.31	-0.57, -0.05	0.019*
Girls				
Gestational age (weeks)		0.27	0.19, 0.35	0.000***
Pregnancy wantedness	Yes	ref	-0.54, 0.00	0.047
	No/unsure	-0.27		

Boys: N = 215; R^2 of the model = 0.4007/ Girls: N = 241; R^2 of the model = 0.2356
ref. is the reference category; **p<0.05; **p<0.01; ***p<0.001*
† *Adjusted for maternal age, tobacco use during pregnancy, maternal education, overcrowding, maternal prenatal stress, marital status, household assets and alcohol use during pregnancy*

Cumulative risk

Exposure to both of the significant risk factors (tobacco use and pregnancy wantedness) was associated with a reduction of ~306 g (95% CI 204; 413 g) in infant birthweight (Figure 3.2).

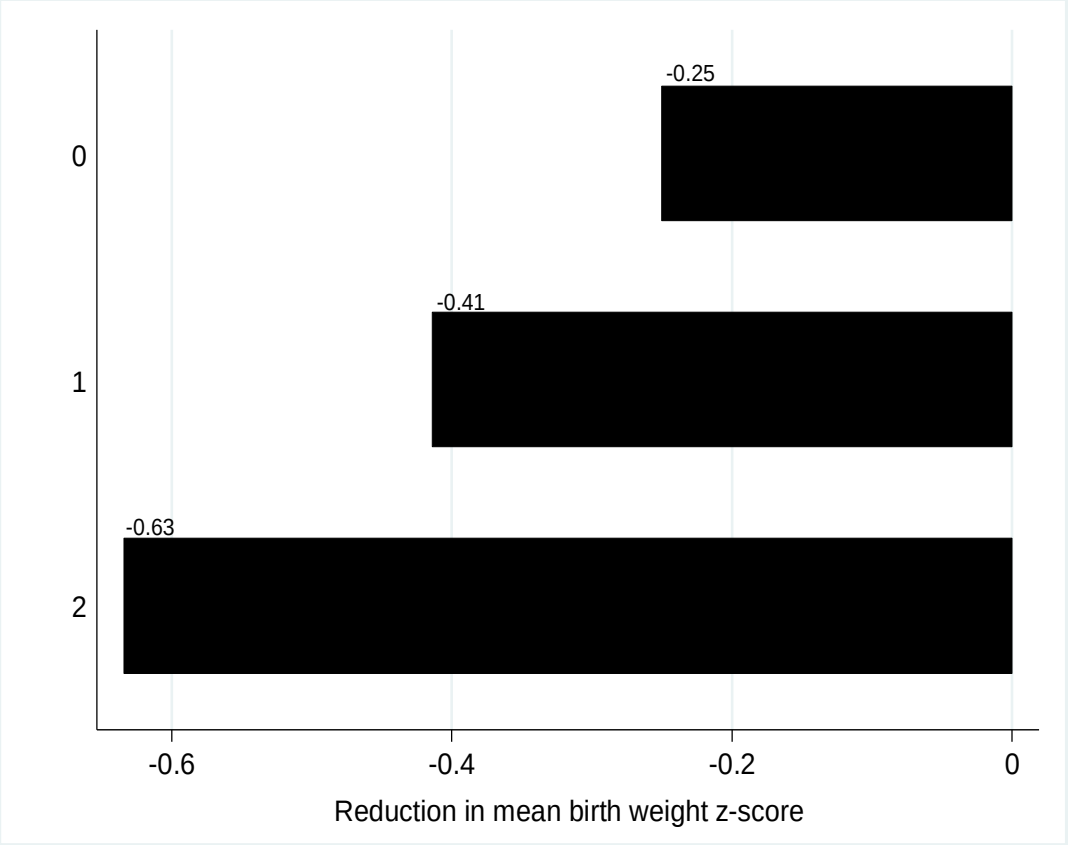


Figure 3.2 Relationship between number of significant risk factors (tobacco use in pregnancy and pregnancy wantedness) and reduction in infant mean birthweight z-score.

3.4 Discussion

The study offers three central findings. First, in concordance with Bronfenbrenner's ecological theory of child development,[52] this study reinforces the importance of the psychosocial and physical qualities of a child's immediate care and home environments, particularly in early (intrauterine) life. Second, having a mother who had previously given birth was found to be protective and associated with an increase in infant birthweight. Third, this study confirmed that exposure to multiple relative to single risks prenatally resulted in greater reductions in infant birthweight.

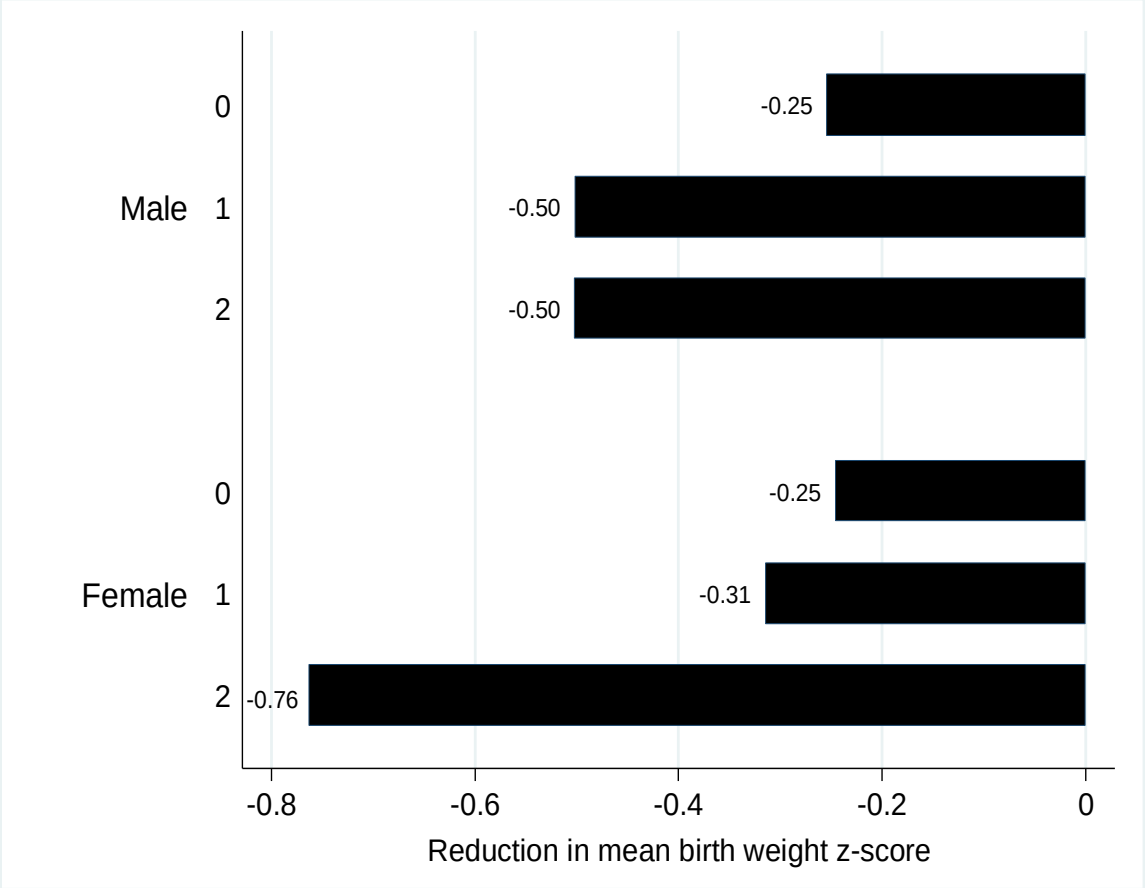


Figure 3.3 Relationship between number of significant risk factors (tobacco use in pregnancy and pregnancy wantedness) and reduction in infant mean birthweight z-score for males and females.

Concurrent with findings from previous studies mostly conducted in high-income countries, this study found that risks related to maternal attitudes and behaviours during pregnancy, namely unwanted pregnancy and tobacco use, significantly lowered birthweight. There were a high proportion of unwanted pregnancies, including ambivalence toward the pregnancy, in this sample; mostly in single mothers. In this study, unwanted pregnancy was negatively associated with birthweight. This is consistent with previous studies that showed that pregnancy wantedness is a key determinant of newborn health and well-being, particularly in the context of low socio-economic status and single parenthood.[116,117,343]

However, there is some uncertainty in the literature regarding the impact of pregnancy intentions on pregnancy and infant outcomes, mainly related to methodological challenges. One debate is whether it is the intention status (intended, mistimed and unwanted pregnancy) of the pregnancy or the socio-demographic characteristics of these mothers that account for observed differences in outcomes.[344] This study reinforces the importance of the psychosocial context toward this debate but does not clarify the relative contributions of intention status as compared to maternal socio-demographic characteristics in determining infant outcomes, as intention status was not explored in enough detail.

Maternal use of any tobacco products had significant detrimental effects on infant birthweight, with girls more affected than boys. This is in line with other studies on the effects of cigarette-smoking and tobacco use internationally and in the Bt20+ cohort.[128,345] While the role of cigarette-smoking on birthweight is well-documented, the study showed that the use of snuff and tobacco-chewing, which may be more common than cigarette-smoking in some Black communities, also have negative effects on birthweight.

Higher parity was associated with higher infant birthweight. Some evidence suggests that higher parity (parity ≥5) leads to higher rates of negative neonatal outcomes (including birthweight).[346] Other studies that have reported a positive association similar to our findings, attributed this to women being economically stable and having access to proper care.[347] However, this hypothesis is not necessarily valid in our context as most women were living in poor households.

This study did not find an association between maternal prenatal stress and birthweight. This may be due to the study only exploring associations of prenatal stress as a dichotomous variable (high vs low prenatal stress scores) with infant birthweight. Similar studies conducted previously on this cohort and that have found associations between prenatal stress and later child outcomes (such as behaviour), separated stressful events into sub-categories of prenatal stress to investigate whether specific types of stressors were associated with the child outcome.[184] Thus, more in-depth analysis of the effects of particular prenatal stressors on earlier child outcomes (such as birthweight) may add value in the South African context.

Maternal cumulative risk exposure was negatively correlated with infant birthweight. This finding is consistent with international literature on maternal cumulative risk exposure and infant health and well-being but requires further research in the South African context.[209] Nearly all the available evidence on cumulative risk exposure, and infant and child outcomes, emanates from economically developed countries, whereas the greatest convergence of multiple adverse psychosocial environments that may lead to serious health consequences for children occurs in LMIC.[348]

Strengths and limitations of the study

This study is one of the first to explore the influence of psychosocial and environmental risks that mothers are exposed to prenatally on subsequent infant birthweight, particularly prospectively, in a middle income setting. The study used information from a large prospective, urban cohort study based in South Africa with data that was collected prospectively during the antenatal period and shortly after delivery, thus reducing the risk of maternal reporting bias across the measures explored in this study.

The risk factors studied were limited to those that were measured in the Bt20+ study and thus did not include factors that may affect infant birthweight, such as maternal access to antenatal care and particular biological risks (such as maternal nutrition, pregnancy and birth complications), among others.

Only pregnancy wantedness (or ambivalence) was captured in this study and not whether the pregnancy was un-/intended or mistimed. The latter would have provided

more insight into the mothers' intention status, as it may influence women's ability or compliance with seeking health care before, during and after the pregnancy.[349]

The status of pregnant mothers' tobacco use was based solely on self-report. No information on daily consumption levels was obtained and, therefore, the dose-response relationship of tobacco use on infant birthweight could not be explored in more detail.

Adjustment for gestational age as a mediating variable is standard practice in perinatal epidemiology. However, there is an emerging debate regarding whether gestational age at birth should be adjusted for when investigating the associations of risk factors with neonatal outcomes, as subsequent adjustment may affect the reliability of the model estimates.[350] By including gestational age in the regression analysis, it may remove the significance of variables that are associated with gestational age, as well as birthweight, as these two variables are closely related. When conducting multiple regression analyses with, and without, gestational age in this study, the same variables were significantly associated with infant birthweight.

This study did not include ethnicity in the final analysis as the under-representation of minority race groups due to the differential enrolment, retention and attrition of White and Black families (in particular) in the Bt20+ study, made it difficult to conduct valid population group comparisons. More meaningful comparisons based on other stratification criteria, such as SES, were explored.

The conclusions from the findings are limited as the underlying aetiologies, and the mechanisms of the associations between each of the significant risks found in this study and fetal growth, requires more rigorous consideration, particularly in similar contexts.

Implications for research, policy and practice

This study reinforces the importance of psychosocial and environmental contexts in determining child health outcomes and the need for further research to better understand the aetiologies of these associations.

Despite the study data being collected 25 years ago, the most recently available South African national estimates indicate that the prevalence of unwanted pregnancy,[113] and maternal tobacco use during pregnancy,[351] remain high. Both maternal tobacco use and unwanted pregnancy are amenable to preventative interventions. Often, unwanted pregnancy is associated with adolescent motherhood. However, in this study, the majority of mothers who had indicated ambivalence or unwanted pregnancy were living in poorer households and were aged 20 to 35 years. This emphasises the importance of assessing and addressing the psychosocial factors that may negatively impact pregnant mothers and their unborn children during antenatal care and reinforces the importance of interventions, such as contraception and family planning, social assistance and interventions that advance the empowerment and autonomy of women beyond current initiatives aimed largely at adolescents.

There has been a steady decline in cigarette consumption since the tobacco control legislation was enacted in South Africa in the 1990's.[351] However, overall national trends indicate that smoking rates still remain high in certain population groups, including pregnant women, with reported rates of approximately 20-40% amongst Coloured/Mixed race women.[352]

Quitting smoking early in pregnancy will produce the greatest benefits, but stopping at any stage during pregnancy is beneficial to the mother and infant pre- and postnatally. The impacts of maternal smoking extend beyond pregnancy and child birth. Women who smoke are less likely to initiate breastfeeding, and those who do, are more likely to discontinue breastfeeding early in infancy.[353]

3.5 Conclusion

The study findings are particularly important from a policy and practice perspective as the significant risks in this study are still prevalent and are amenable to intervention in the South African (and many LMIC) context. There is a need for more focused primary prevention initiatives which are provided along a continuum of care. This points to the need for interventions that are accessible and that start at pre-conception, with health, education and empowerment initiatives aimed at adolescents and which follow them through their life course (and that of their unborn children).

Such systems of care should identify and support women to address adverse psychosocial influences during pregnancy, and to adopt beneficial health behaviours, decisions and attitudes for both themselves and their infants.

CHAPTER 4: EARLY LIFE RISK EXPOSURE AND STUNTING IN URBAN SOUTH AFRICAN 2-YEAR OLD CHILDREN

Wiedaad Slemming, Juliana Kagura, Haroon Saloojee and Linda Richter

Slemming W, Kagura J, Saloojee H, Richter LM. Early life risk exposure and stunting in urban South African 2-year old children. *Journal of Developmental Origins of Health and Disease* 2017:1-0.

4.1 Introduction

Linear growth in early childhood is one of the most sensitive indicators of child health and well-being. Stunting (defined as a height of more than two standard deviations below the World Health Organization growth standards median),[21] is an anthropometric measure that strongly correlates with social and economic deprivation and is widely used a proxy for inequalities in child health.[354] Linear growth faltering commences in the fetal period and continues after birth, with the period between conception and two years of life (the 'first 1 000 days') recognised as a sensitive period for childhood growth and development.[355]

Stunting is associated with susceptibility to infection, impaired cognitive development and lower educational performance in childhood,[18,356] reduced adult stature (in the absence of compensatory growth),[263,357] lower productivity and earnings in adulthood,[358] and increased risk of childhood and adult obesity and cardio-metabolic diseases. There is increasing evidence to support the view that these effects may be transmitted to subsequent generations.[262,278]

Stunting is considered to have both proximal determinants such as the availability of sufficient quantity, quality and diversity of food, hygiene, water and sanitation, recurrent infections and access to high-quality primary care, and distal determinants such as poverty and low maternal education.[217] It is acknowledged that the biological (including genetic), psychosocial and environmental determinants of stunting operate in tandem via epigenetic mechanisms and longer-term selection strategies.[359] It is estimated that approximately 20% of stunting may be attributed to in utero origins,[264] with social, human development and economic factors contributing to the remaining 80%.[360]

Although the determinants of stunting are well recognised, the relative contributions of these are influenced by contextual factors such as the distribution and intensity of exposures and the interactions between them.[264,268] The most common reported differences in stunting prevalence are between wealth quintiles (particularly in countries with high inequality), maternal age and education level, place of residence and, to a lesser extent, child sex.[361] Previous studies examining the association between early life risk exposures and subsequent stunting in this and other low and middle income settings have been either cross-sectional in design or considered only a limited number or types of risk, usually at birth and/or postnatally.

The aim of this study was to investigate the effects of selected biological, psychosocial and environmental risk factors affecting the mother (and her child) during pregnancy and the first two years of life in an urban South African setting to better understand the determinants of stunting in this context.

4.2 Methods

Data and study population

Data for this study were drawn from the Birth to Twenty Plus (Bt20+) study, a longitudinal birth cohort study, initiated in 1990 in the greater Johannesburg metropolitan area, South Africa.[310] Pregnant women deemed likely to deliver within a specified period were recruited through public health antenatal facilities and all singletons born within a 7-week period (23 April – 8 June 1990) were enrolled. The study continues to prospectively follow 3 273 children and their families throughout the Gauteng province. The enrolment methods, attrition, and profile of the Bt20+ cohort have been well described elsewhere.[316] Black children comprised the major race group in the study sample (78.5%), followed by Coloured/Mixed race (11.7%), White (6.3%) and Indian (3.5%) children.[310] These groupings refer to the *apartheid* system of population group classification and continue to be used as a measure for approximating the enduring effects of *apartheid* and redressing past inequities.

Measures

Individual risk exposures

Maternal demographic and psychosocial risk exposures were recorded using a questionnaire administered verbally to mothers by trained, multilingual interviewers during the third trimester of pregnancy and at six months postnatally. This analysis used infant data collected at birth, 6 months, 1 year and 2 years.

Ten maternal and child risk exposures were examined. Pregnancy wantedness (mother's rating of her desire to be pregnant at the time of the interview), maternal prenatal stress, tobacco use (cigarette smoking, snuff use or chewing tobacco) and alcohol use were measured during pregnancy. Maternal age at the birth of the index child, maternal education, marital status, overcrowding in the home (classified as present if more than 3 people per room used for sleeping) and household socio-economic status (SES) were measured between birth and 2 years of age. Maternal depression was measured six months after the birth of the index child.

Prenatal stress was assessed by enquiring about sixteen stressors women were exposed to in the previous 6 months. Yes/no responses indicated the presence/absence of each stressor; with the sum of the sixteen responses yielding and overall stress score. Scores of 4 or more were considered suggestive of high prenatal stress.

Household SES was derived from a listing of household assets (house, radio, television, car, refrigerator, washing machine and landline telephone). The use of household assets as a proxy measure of SES has been validated in low and middle income countries and used previously in this cohort.[326] For analysis, principal components analysis was used to create a SES index on the basis of household assets. Using this method, study participants were categorised into one of five groups for socioeconomic status; with quintile one corresponding to the lowest SES group.

Symptoms of maternal depression were assessed six months postpartum using the Pitt Depression Inventory (PDI). The PDI primarily assesses a mother's current feelings and change in mood manifestations.[322] It comprises 24 items and every item is answered and coded as either no (0), don't know (1), or yes (2). Total scores range from 0 to 48, with a score of 20 or higher indicating a self-report consistent with

postnatal depression. The measure has been used in studies internationally and in South Africa and is highly correlated with measures such as the Edinburgh Postnatal Depression Scale.[199]

In addition, demographic variables such as the ethnicity and sex of the child were collected.

Control variables

Maternal height, infant birthweight, gestational age and infant breastfeeding (ever breastfed and duration of breastfeeding) were identified as possible covariates. Maternal height (in cm) was measured using standardised techniques.[21] Electronic weighing scales were used to weigh the infant at birth. Birthweight *z*-scores were calculated using the 2006 World Health Organization growth standards.[21] Length was not measured at birth. Gestational age was obtained from the medical records and estimated based on the mother's report of her last menstrual period. Breastfeeding data were measured during the first two years of life through maternal/caregiver report.

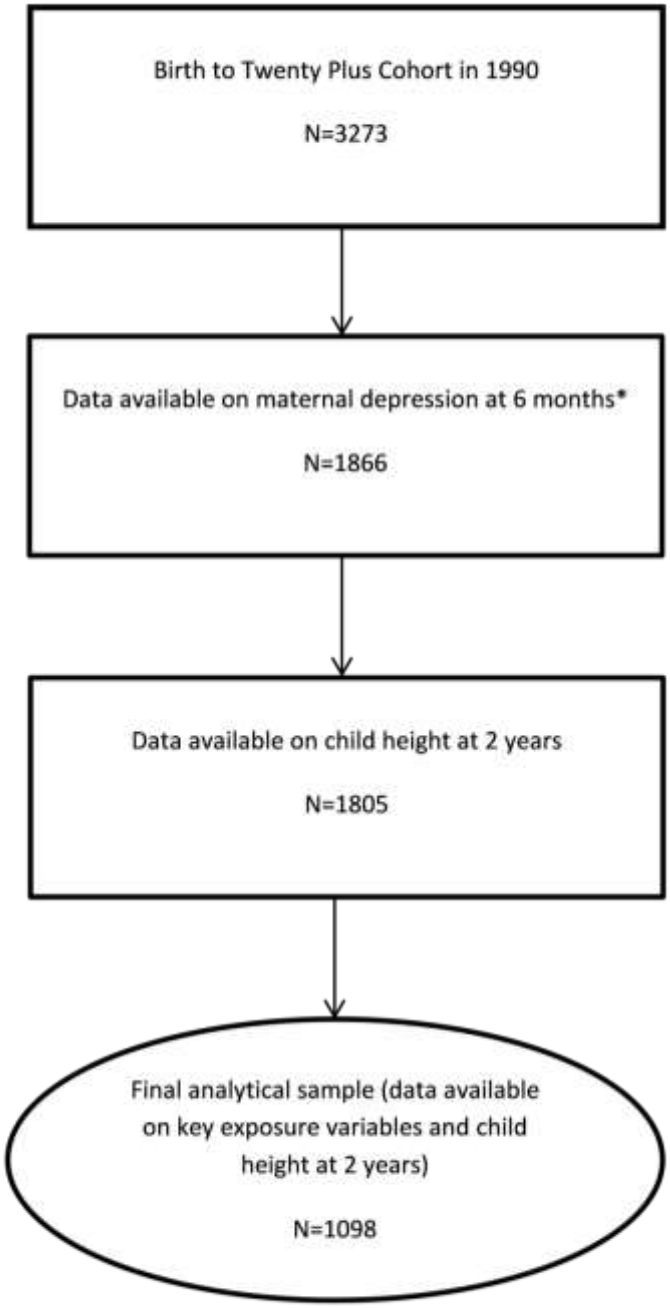
Outcome measures

Child height was measured at age 2 years using a Harpenden stadiometer and recorded to the nearest 0.1 cm, according to the standard procedures recommended by the World Health Organization (WHO).[21] All weight and height measures were converted to *z*-scores by comparing them to the 2006 World Health Organization (WHO) growth standards.[21] Stunting was defined as a length/height-for-age *z*-score (L/HAZ) of < –2 standard deviations of the WHO Child Growth Standards median.[21]

Statistical analyses

Descriptive statistics were used to summarise the outcome and risk variables by sex of the child. Frequencies and percentages were used for categorical variables while means and standard deviations (SD) were used for continuous variables. Pearson's χ^2- test was used to check for differences between the analytical study sample (and participants in the Bt20+ cohort who were not included in the analyses (Figure 4.1).

Statistical analyses were undertaken to estimate the association between the exposure variables and stunting at age 2 years. Bivariate analyses were conducted to determine the unadjusted association between each exposure and stunting at age 2 years. Thereafter, sex-stratified multiple logistic regression models were used to determine risk factors that were independently associated with stunting at 2 years and the pseudo R^2 for model fit. Possible covariates, selected on the level of significance in bivariate analysis ($p<0.1$) and theoretical relevance, were adjusted for in the analyses. Variables were included into the regression models using a stepwise approach. A probability value of $p<0.05$ was considered to be statistically significant and all analyses were conducted using Stata 13.1 (Stata Corporation, College Station, Texas, USA).



**Maternal depression at 6 months was used as the base variable for determining the final analytical sample for the study as this was the data collection time point (for this study) at which there was the lowest number of observations*

Figure 4.1 Selection of study sample

4.3 Results

A total of 1866 women completed both the antenatal questionnaire and the Pitt Depression Inventory six months postnatally. Height-for-age measurements were available for 1805 children at age 2 years. The analytical sample for this study included 1098 mother-infant pairs who had exposure and outcome data at all relevant study time points (Figure 4.1). A summary of key characteristics of the study sample is shown in table 4.1.

Table 4.1 Characteristics of study sample (*n*=1098)

Variables	Males (*n*=540, *n* %)	Females (*n*=558; *n* %)	*p*-value
Outcome variable			
Stunted at age 2y			0.029*
No	406 (75.2)	450 (80.7)	
Yes	134 (24.8)	108 (19.4)	
Height at 2y (cm)	83.68±3.4	82.69±3.5	0.000***
Demographic variables			
Ethnicity			0.693
Black	426 (78.9)	432 (77.4)	
White	24 (4.4)	27 (4.8)	
Coloured/mixed race	66 (12.2)	79 (14.2)	
Indian	24 (4.4)	20 (3.6)	
Exposure variables			
Maternal and child characteristics			
Maternal age (years)	25.4±6	25.6±6	0.581
Marital status			0.175
Married/living together	214 (39.6)	199 (35.7)	
Single/separated/ divorced/ widowed	326 (60.4)	359 (64.3)	
Maternal education			0.833
≤Grade 7	60 (11.1)	69 (12.5)	
Grades 8-10	228 (42.3)	238 (43.1)	
Grades 11-12	178 (33.0)	177 (32.1)	
Post school training	73 (13.5)	68 (12.3)	
Any tobacco use			0.396
No	277 (84.7)	269 (87.1)	
Yes	50 (15.3)	40 (12.9)	
Alcohol use			0.840
No	286 (89.1)	267 (89.6)	
Yes	35 (10.9)	31 (10.4)	
Pregnancy wantedness			0.417
Yes	131 (41.2)	114 (38.0)	
No/ unsure	187 (58.8)	186 (62.0)	
Prenatal stress			0.970
<4	500 (92.6)	517 (92.7)	
≥4	40 (7.4)	41 (7.4)	

Postnatal depression (Pitt score)			0.606
<20	408 (75.6)	429 (76.9)	
≥20	132 (24.4)	129 (23.1)	
Household characteristics			
Overcrowding			0.335
<3 people/ room	306 (60.8)	329 (63.8)	
≥3 people/ room	197 (39.2)	187 (36.2)	
Household assets			0.818
Radio	62 (12.2)	62 (11.8)	
No	445 (87.8)	465 (88.2)	
Yes			
			0.023*
Television	120 (23.8)	95 (18.0)	
No	385 (76.2)	432 (82.0)	
Yes			
			0.036*
Car	342 (67.7)	324 (61.5)	
No	163 (32.3)	203 (38.5)	
Yes			
			0.551
Fridge	120 (22.8)	117 (22.2)	
No	385 (76.2)	410 (77.8)	
Yes			
			0.249
Washing machine	402 (79.5)	403 (76.5)	
No	104 (20.6)	124 (23.5)	
Yes			
			0.001**
Telephone	229 (45.4)	187 (35.5)	
No	276 (54.7)	340 (64.5)	
Yes			
			0.075
Own house	360 (67.8)	398 (72.8)	
No	171 (32.2)	149 (27.2)	
Yes			
Control variables			
Birthweight (g)	3144±495	3038.6±508.6	0.000***
Gestational age (weeks)	38.3±1.7	38.12±1.9	0.706
Maternal height (cm)	157.3±5.3	157.5±4.9	0.862
Ever breastfed			0.953
No	19 (3.5)	20 (3.6)	
Yes	521 (96.5)	538 (96.4)	
Duration of breastfeeding (months)	12.6±8.97	12.9±8.7	0.632

*Values are presented as mean± SD for continuous variables and number (%) for categorical variables; *p<0.05; **p<0.01; ***p<0.001*

Women included in the analytical sample were more likely to be younger, shorter, Black, live in households with fewer assets, breastfeed their infants and have infants with lower mean length for age z-scores at age 2 years ($p \leq 0.01$ for all) compared to the sample not included in the analysis (Appendix 3). This inclusion of more vulnerable groups is consistent with previous attrition analyses conducted on the Bt20+ cohort and is likely due to a desire by these groups to receive services.[316]

Two hundred and forty-two children (22%) were stunted at age 2 years. Although males, on average, were taller than females at age 2 years ($p < 0.001$); significantly more males (24.8%) than females (19.4%) were stunted at age 2 (table 4.1). The odds of being stunted were 38% higher among males (OR = 1.38; 95% CI: 1.03, 1.83) (table 4.2).

In bivariate analysis (table 4.2), being male, Black or Coloured/Mixed race, having a lower socio-economic status (quintile 1 or 2), living in overcrowded households, lower maternal education (< Grade 11), maternal age, single motherhood, lower birthweight *z*-score, shorter gestational age and shorter duration of infant breastfeeding all significantly increased the risk of stunting at age 2 years.

Multivariable logistic regression analysis (table 4.2) showed that higher household SES was protective against stunting at age 2 for males; with males in SES quintile 4 (AOR = 0.39; 95% CI: 0.19, 0.81) and 5 (AOR = 0.39; 95% CI: 0.16, 0.92) having a 61% decreased likelihood of being stunted as compared to males in quintile 1. Higher maternal education was associated with a lower likelihood of stunting among females, particularly for infants of mothers with a Grade 11-12 education (AOR = 0.35; 95% CI: 0.14, 0.87). Birthweight *z*-scores showed the strongest association with stunting in both sexes; with a one-standard deviation increase in birthweight associated with a 43% and 36% decreased likelihood of being stunted at age 2 years for males (AOR = 0.57; 95% CI: 0.45, 0.73) and females (AOR = 0.64; 95% CI: 0.50, 0.82), respectively.

Table 4.2 Factors associated with stunting in children at age 2 years

Variable	**Total sample (*n*=1098)**	**Males (*n*=416)**	**Females (*n*=447)**
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Child sex			
Female	1.00		
Male	1.38 (1.03, 1.83)*		
Ethnicity			
White	1.00		
Black	0.14 (1.10,7.13)*		
Coloured/Mixed race	0.15 (1.12, 8.23)*		
Indian	-0.08 (0.02, 1.91)		
Maternal characteristics			
Maternal age	0.97 (0.95, 0.99)*		
Marital status			
Married/living together	1.00		

Single/separated/divorced/widowed	1.32 (0.98, 1.79)		
Maternal education			
≤Grade 7	1.00		1.00
Grades 8-10	0.97 (0.63, 1.49)		0.81 (0.37, 1.77)
Grades 11-12	0.51 (0.32, 0.83)**		0.35 (0.14, 0.87)*
Post school training	0.43 (0.23, 0.79)**		0.32 (0.10, 1.10)
Any tobacco use			
No	1.00		
Yes	0.93 (0.51, 1.68)		
Alcohol use			
No	1.00		
Yes	0.54 (0.24, 1.23)		
Pregnancy wantedness			
Yes	1.00		
No/ unsure	1.36 (0.88, 2.12)		
Prenatal stress			
<4	1.00		
≥4	0.72 (0.40, 1.31)		
Postnatal depression (Pitt score)			
<20	1.00		
≥20	0.72 (0.40, 1.31)		
Household characteristics			
Overcrowding			
<3 people/ room	1.00		
≥3 people/ room	1.72 (1.28, 2.32)***		
Household SES			
Quintile 1 (poorest)	1.00	1.00	
Quintile 2	0.84 (0.58, 1.21)	0.52 (0.26, 1.06)	
Quintile 3	0.66 (0.46, 0.96)*	0.42 (0.20, 0.88)*	
Quintile 4	0.58 (0.40, 0.84)**	0.39 (0.19, 0.81)*	
Quintile 5	0.40 (0.27, 0.60)***	0.39 (0.16, 0.92)*	
Birthweight *z*-score	0.64 (0.56, 0.72)***	0.57 (0.45, 0.73)***	0.64 (0.50, 0.82)**

Males: Pseudo R^2 = 0.0936, p = 0.000; *Females:* Pseudo R^2 = 0.1342, p = 0.000

Adjusted for gestational age, maternal height, overcrowding, duration of infant breastfeeding, maternal age and marital status

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

4.4 Discussion

The study established that more than one in five children was stunted at age 2 years, with males being more susceptible. Higher birthweight was protective against stunting for both sexes. Beyond biological determinants of stunting, social factors mattered for both males and females within the first 2 years of life. Higher maternal education was protective for females, while poorer household socio-economic status was a risk for males.

Although, increased male susceptibility to stunting has been reported previously, mostly from studies conducted in sub-Saharan Africa, the underlying mechanisms for these differences have remain largely unexplored.[362] Most of the evidence suggest that stunting differences between males and females are relatively small when

compared to other stratifiers, particularly among children under 5 years; with gender disparities becoming more apparent as children get older.[217,361] However, we found that male children had 38% higher odds of being stunted as compared to females in our analysis indicating that males experienced significant vulnerability to stunting early in life in this cohort.

Several possible explanations have been offered for observed sex differences. A popular hypothesis centres on societal behavioural patterns with studies reporting greater social preference of sons to the disadvantage of daughters,[363] including dietary discrimination.[364] We did not examine dietary patterns in this study but are, however, unaware of any South African studies that indicate preferential feeding of children based on gender. A possible explanation lies in the developmental origins of sex differences in health outcomes. While poor fetal growth enhances the risk for both sexes, males and females tend to respond differently.[365] Male fetuses have been described as investing greater resources in growth, and as a consequence, have limited ability to respond to subsequent stressors placing them at greater risk for poor health and development outcomes. In contrast, female fetuses are believed to conserve resources and are able to adjust to maternal conditions in various ways (gene and protein changes), resulting in an increased probability of survival.[278,365]

Males also tend to grow faster than females from an early stage of gestation and, by growing more rapidly, the male fetus invests more in brain growth rather than placental growth.[366] At any placental weight, males tend to be longer than females, with smaller placentas. This suggests that male placentas are more efficient but have less reserve capacity, making them more vulnerable to becoming undernourished.[367]

Thus, consequences of early exposure to adversity are displayed among males early in the life cycle and persist throughout early childhood.[365] This reinforces the idea of higher environmental sensitivity among males, that is under adverse conditions, males are more at risk of negative health and growth outcomes.[368] This is further reinforced by our finding that male children growing up in the two lowest socio-economic strata were nearly three times more likely to be stunted than their peers in better off strata. The same difference in stunting prevalence was not observed among females belonging to socio-economically different groups in this cohort. This

finding is congruent with a 16-site sub-Saharan African meta-analysis,[362] that found that male children living in the poorest two quintile households were more likely to be stunted as compared to females in the same group. However, this pattern was not consistent in all studies, particularly in those conducted in higher income settings.[362]

Maternal education, often used as a proxy for socio-economic status, is independently associated with lower mortality and stunting across and within societies for both male and female children.[369,370] A possible explanation is that maternal education, through mechanisms unrelated to SES, may directly influence child health and growth through increasing female knowledge and autonomy within the household and community. This leads to appropriate and beneficial care-giving practices such as better health-seeking behaviours, and improved feeding and hygiene practices.[217] However, the benefits of maternal education only extended to females in this analysis; with female children of mothers were who more educated having a lower likelihood of stunting. Previous studies have reported that females have better survival outcomes as compared to males if their mothers are better educated, particularly in sub-Saharan Africa.[369] There is some uncertainty with regards to the underlying mechanisms for these observed differences and may be best explained in the same way that we have hypothesised socio-economic gender-responsiveness operates, i.e. that females are more adaptable to environmental stimuli in early life.[365] However, context plays a role and in societies where there are clear gender preferences (often advantaging males), this finding may be less consistent.

Higher birthweight *z*-scores reduced stunting risk for both sexes. Infant birthweight, and more specifically low birthweight (<2500g), is a well-established determinant of child stunting.[217,259] Birthweight is the product of many influences, particularly maternal health and nutrition during pregnancy (and its effects on fetal growth) and the intergenerational influences of maternal anthropometry on newborn size.[47] Therefore, although birthweight can be used to better understand modifiable processes as possible targets for intervention, any direct causal interpretations of birthweight with later outcomes should be considered with some caution.

We did not find an association between maternal depression and stunting in this study. There is some contrary evidence supporting an association between maternal depression and stunting in young children.[188-190] However, previous studies conducted in South Africa have reported similar findings to ours and thus further exploration is required to determine possible reasons for the difference.[202] Some studies have shown that children who were unwanted at conception or during pregnancy were more likely to be stunted than their counterparts.[371,372] However, this finding is not reported consistently across studies conducted in similar settings.[373] Although, a high proportion (60%) of mothers were unsure or did not want to be pregnant (when interviewed during the third trimester of pregnancy), there was no association between pregnancy wantedness and stunting in this study.

There were important determinants of stunting that were not accounted for in the analysis. The study did not include detailed data about dietary diversity, household food security and feeding practices, precluding us from examining their contribution to stunting. However, these may be important in our context as sub-optimal feeding patterns, including the early introduction of complementary foods, in this cohort has been identified previously in this cohort.[374] Other covariates we would have liked to include in the analysis, but for which data were not collected, were birth length, major or recurrent illness and micronutrient deficiencies.

The small numbers of minority race groups in the study made it difficult to conduct meaningful population group comparisons and thus, comparisons based on other stratification criteria were explored. There are obvious limitations to the conclusions that can be drawn from the findings as the underlying aetiologies and the mechanisms of the associations require more rigorous and in-depth consideration, particularly in similar contexts.

This study identified a high prevalence of stunting comparable to those in other parts of the continent.[375] Among the different regions of Africa, the decline in stunting rates since 1990 has been greatest in the northern and central parts and has barely changed in the other sub-regions (including the southern region).[375] Despite improvements in economic growth over the past three decades, significant socio-economic disparities remain, and high levels of stunting (predominantly among the

youngest children) persist in South Africa.[376] The latest South African National Health and Nutrition Survey (SANHANES) data showed that the youngest children (between 0–3 years of age) had the highest prevalence of stunting (26.5%); with more males stunted than females.[46] Thus, although the study reflects stunting prevalence in 1992, the study conclusions remain pertinent as we continue to seek effective interventions in South Africa, as do other countries with high inequity.

Government and development agency approaches to improving child survival and development have traditionally addressed proximal, largely biological and 'demand-side', determinants with less attention to distal, structural determinants since many of these lie outside the health sector. This study's findings add to the call for both a population- and individual based approach, geared to service delivery to the poor and most vulnerable in society, to minimise inequities in child health and nutrition and fundamentally address high stunting prevalence. In the case of stunting, in southern African settings, we would argue that these interventions should target male children, socio-economic inequality, mothers with lower levels of education and low birthweight infants.

Direct nutrition-specific interventions together, even when scaled up to 90% coverage rates, could reduce the burden of stunting, but only by 20%.[377] Thus, tackling the underlying structural drivers of undernutrition is essential, particularly in high prevalence settings, in order to address the further 80% reduction needed. Programmes that improve nutrition, health care and household purchasing power among the poor generally also improve growth outcomes, particularly in lower socioeconomic status children.[377] For example, an analysis of key factors contributing to the decline in stunting rates in Brazil, identified enhanced purchasing power of families, increased levels of female education, improved and expanded maternal and child health services, better water and sanitation systems and superior quality and quantity of food availability for families.[378] Although such population level interventions are more complex and take time to show impact, there is strong anecdotal evidence from health intervention programmes that even caregivers with low education and literacy levels can be empowered to provide better care to children when they are supported and equipped with the required skills.[379]

At an individual level, emphasis should be placed on improving mother's (and particularly young mother's) health literacy regarding child health and feeding practices.[380] Conditional cash transfer programs, particularly those that are linked to nutrition education and primary health care services, may aid in targeting and delivering these interventions.[377,381] Thus, approaches to stunting prevention should be comprehensive and focus on proximal and distal determinants of stunting, emphasising interventions that will have short-term individual and long-term population level impacts.

Further research is warranted to explain the stunting sex-differentials across socio-economic strata and maternal education levels. Socio-economic status is a multi-dimensional construct and more sophisticated analyses that further disaggregate the variable further into its components should be conducted in order to develop effective, targeted stunting interventions along the socio-economic spectrum in different contexts. Further exploration of the functional and long-term consequences associated with early male child vulnerability is required; both related to stunting but also for other later lifestyle diseases, such as diabetes and cardio-vascular conditions. Finally, a more sophisticated biological explanation is required as to why male children are more vulnerable and less responsive compared to female children pre- and postnatally in this context.

Stunting is a good summary indicator of growth failure, however, growth failure is cumulative and linear growth in and of itself is an important indicator of child health and well-being.[355] Therefore it would be useful to explore the processes that contribute not only to linear growth faltering but also what may affect age-appropriate growth in young children. An important extension of this research study would be to consider the associations between early life growth patterns (rates and trajectories) and subsequent stunting in order to better understand the underlying mechanisms and timing of growth faltering in this cohort.

4.5 Conclusion

Genetic and biological factors, as well as proximal maternal behaviours and caregiving practices are important determinants of infant growth and attained height,

particularly in the first 1 000 days of a child's life. This study's findings, nevertheless, support the view that interventions to address stunting require a broader approach that addresses not only the proximal causes of stunting but also its more distal drivers, such as socio-economic status and maternal education in settings with high socio-economic inequity, such as South Africa. This can be achieved through population-based structural interventions and public policies that redress equity and promote access to essential services for stunting and other forms of undernutrition, as well as activities focussed on individuals.

CHAPTER 5: CHILD DEVELOPMENT AT AGE 5 YEARS: THE EFFECTS OF MATERNAL EDUCATION, SOCIO-ECONOMIC STATUS AND EARLY LIFE GROWTH EXAMINED PROSPECTIVELY IN A LOW RESOURCE SETTING

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5.1 Introduction

Healthy brain development depends on a dynamic, bidirectional interaction between an individual's genotype and his/her environment, extending from conception into childhood and beyond.[8] Exposure to biological and psychosocial risks affects brain development and compromises the short- and long-term health and development of children, as well as their educational achievement and long-term productivity.[88] The influence of risk factors on brain structure and function depends on the timing of exposure, co-occurring or cumulative factors and differential reactivity (whether some children are more affected than others, for better or worse, by individual or environmental factors).[5,88]

Conception to age three years, when rapid growth and development takes place, is a particularly malleable period, laying the foundation for a child's ability to learn, grow and succeed.[27] There is heightened susceptibility to epigenetic changes in response to nutrition, toxins, infection, stress and other exposures.[88] Interventions during this period have maximal benefit.[27]

Most research examining the relationship between early life risks and growth and/or child development emanates from high-income settings and often examines the links in a one-dimensional or linear fashion. Children living in low socio-economic circumstances are at greater risk of poorer emotional, cognitive and social development.[18] Since risk factors are cumulative and interactive,[382] children who experience poor growth during early life, are also more likely to be exposed to suboptimal physical and psychosocial environments pre- and postnatally.[268] Clearer delineation of the relative effects of individual exposures in low and middle income settings may assist in designing better targeted interventions.

This study, using data from a longitudinal birth cohort, aimed to determine: (i) whether there were differences between males and females in relation to early life exposures, growth (between birth and 4 years) and development at age 5; (ii) the association between growth (birthweight; relative linear growth between birth and 2 years and between 2 and 4 years of age) and child development at 5 years of age; and (iii) whether relative linear growth mediated the association between household socio-economic status and maternal education and child development.

5.2 Methods

Study design and participants

Data for this study were drawn from the Birth to Twenty Plus (Bt20+) cohort study. Bt20+ is a longitudinal study of children born in 1990 in the greater Johannesburg metropolitan area, South Africa.[310] Pregnant women deemed likely to deliver within a specified period were recruited through public health antenatal facilities. Singletons born within a 7-week period (23 April – 8 June 1990), whose mothers were planning to reside in the Greater Johannesburg Metropolitan area for at least the first six months of the child's life, were enrolled (n=3 273). The study currently follows more than 2 000 children and families throughout the Gauteng province.[310] The enrolment methods, attrition, and profile of the Bt20+ cohort have been documented in detail elsewhere.[310] The cohort was demographically representative of the study area with the majority of participants being Black African and comprising roughly equal numbers of male and female participants.[310] Bt20+ is the largest and longest running study of child and adolescent health and development in Africa and tracks outcomes in several domains, i.e. physical, educational, social and psychological.[310]

Maternal and infant data collected during pregnancy, at birth, 6 months, 1, 2 and 5 years of age was extracted from the Bt20+ database. The analytical sample for this study included 636 mother-infant pairs with exposure and outcome data at all relevant time points.

Ethical approval for the study was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, South Africa (Certificate

no: M120609). Informed consent was obtained from caregivers at all data collection time points.

Child development measure at 5 years

Child development was assessed with the Revised-Denver Pre-screening Developmental Questionnaire (R-DPDQ).[329] The R-PDQ identifies preschool children at risk for delays in cognitive, motor and socio-emotional development. Thirty-two culturally-appropriate items covering the child's personal-social, fine motor, gross motor, language and cognitive abilities at age 5 are assessed (Appendix 1). During the assessment, caregivers were asked a set of questions and children were required to complete a series of simple tasks. The R-DPDQ was piloted for feasibility and appropriateness prior to inclusion in the Bt20+ study.[330] Internal consistency for the R-DPDQ measure in the Bt20+ sample was 0.72, measured by Cronbach's α. An overall developmental score was calculated by adjusting the total raw score by the child's chronological age, and replacing missing values on individual items by the series mean.[96] The study did not use externally derived age-specific norms as these may not be applicable to South African children but rather utilised within-sample variation on the scores, which were adjusted for the child's age. Mean age (months) of the analytical sample used in this study was 62.6 (SD=2.2); with a range of 58.3 to 78.5. Scores ranged from 18.1 to 54.5 with a mean of 44.1 in this study sample.

Maternal and household factors

Maternal demographic and psychosocial risk exposures were recorded using questionnaires administered verbally to mothers by trained, multilingual interviewers between the third trimester of pregnancy and the first two years of the index child's life. In addition, demographic variables such as ethnicity and sex of the child were also collected.

Ten household, maternal and child exposures were explored. Pregnancy wantedness (mother's rating of her desire to be pregnant at the time of the interview), maternal prenatal stress, tobacco use (cigarette smoking, snuff use or chewing tobacco) and alcohol use were assessed during pregnancy. Maternal age, education and marital status, as well as overcrowding in the home (classified as present if more than 3 people per room used for sleeping) and household socio-economic status (SES)

were measured in infancy. Household SES was derived from a listing of household assets (house, radio, television, car, refrigerator, washing machine and landline telephone). For analysis, principal components analysis was used to create a SES index on the basis of household assets. Using this method, study participants were categorised into one of five groups for SES; with quintile one corresponding to the lowest SES group.

Symptoms of maternal depression were assessed six months postpartum using the Pitt Depression Inventory (PDI),[322] comprising 24 items, with a range of scores from 0 to 48; a score of 20 or higher indicates a self-report consistent with postnatal depression. The measure has been used in studies locally and internationally and correlates highly with measures such as the Edinburgh Postnatal Depression Scale.[323]

Early childhood growth

Except for birthweight, all other early childhood weight and length/height (hereafter referred to as height only) measures were recorded between 3 months and 4 years of age using standard procedures.[21] Measures were converted to *z*-scores using the World Health Organization (WHO) growth standards.[21]

It is important to differentiate the effects of linear growth and weight gain because they are strongly correlated, as are repeat growth measurements of the same individual. Relative linear growth was computed as residuals obtained by regressing present length/height on previous length/height and weight measures (excluding present weight).[259] Relative weight gain was defined as present weight accounting for present length/height and all previous weight and length/height measures. These variables are expressed in standard deviation units to allow direct comparison of regression coefficients.

Potential confounders and mediators

Maternal parity, maternal height, gestational age and breastfeeding were included as covariates. Parity was defined as the number of viable prior pregnancies. Maternal height was measured using standardised techniques. Gestational age was obtained

from medical records derived from the mother's report of her last menstrual period. Information on breastfeeding included whether the infant was ever, exclusively or predominantly breastfed and duration of breastfeeding from data collected at 6 months, 1and 2 years.

Statistical analysis

Descriptive statistics were used to summarise the outcome and risk variables by sex of the child. Frequencies and percentages were used for categorical variables while means and standard deviations (SD) were used for continuous variables. A probability value of $p<0.05$ was designated for statistical significance and all analyses were conducted using Stata 13.1 (Stata Corporation, College Station, Texas, USA). Pearson's χ^2- test was used to check for differences between the analytical study sample and participants in the Bt20+ cohort who were not included in the analysis with regards to key exposure variables and the outcome (Appendix 4).

Bivariate analyses were conducted to determine the unadjusted association between individual exposures and the outcome. Thereafter, sex-stratified multiple linear regression models were used to determine the associations between early life growth and the outcome and to estimate the strength of the adjusted associations. Variables with a $p<0.10$ in bivariate analysis were included in the regression models using a stepwise approach. Individual factors, i.e. growth variables were added first (Model 1), followed by maternal (Model 2) and then household factors (Model 3).
Following regression analysis, mediation analysis was undertaken using structural equation modelling (SEM) to assess whether early life growth mediated the associations between maternal and household risk factors and child developmental outcome at age 5. Mediation assumes a temporal ordering among the relevant variables under study, supporting a causal interpretation of the links between exposures significant in regression models, mediators (birthweight, and relative linear growth between 0-2 years and 2-4 years) and development at age 5 (Figure 5.1).[332] Presentation of results decomposes the influences of one variable on another into direct, indirect and total effects. The direct effects represent the pathways from the exogenous (exposure) variables (household SES and maternal education) to the outcome (R-DPDQ) while controlling for the mediators (growth variables). The indirect effects depict the pathways from the exogenous variables to the outcome

through the mediators. The total effects equal the sum of the direct and mediation (indirect) effects of the exogenous variables on the outcome.[332]

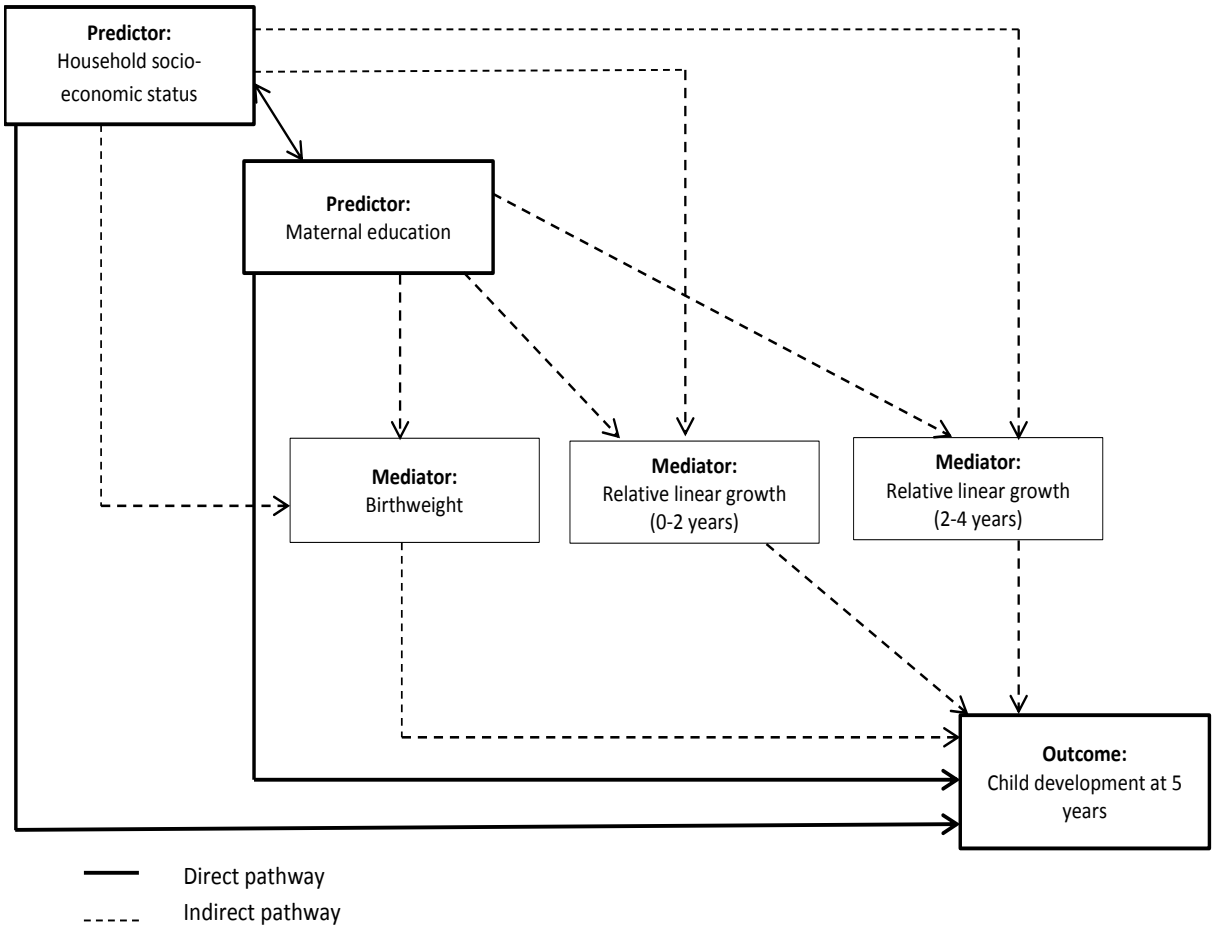

Figure 5.1 Path diagram for mediation analysis

We tested the model fit using several standardized fit statistics, to test the consistency between the predicted and observed data matrix. A good-fitting model is indicated by Comparative Fit Indices (CFI) values at or above 0.95, Root Mean Square Error of Approximation (RMSEA) of at or less than 0.05, and Standardized Root Mean Square Residual (SRMR) of less than 0.08.[332]

5.3 Results

Sample characteristics

There were 636 eligible participants of whom 53% were male. A summary of key characteristics of the study sample differentiated by sex is shown in table 5.1. Males

were significantly heavier at birth (mean difference = 110.4 g [95% CI: 35.8, 185.0]). There was no sex differences observed for relative weight gain or relative linear growth (at any time period). The mean R-DPDQ score at age 5 years was 44.1 (SD=4.8), with males scoring significantly lower than females (mean difference = -1.2 [95% CI: -1.9, -0.4]).

Table 5.1 Socio-demographic, maternal, household and growth characteristics in the study sample

Variables	Total (n=636); n (%)	Males (*n*=334); n (%)	Females (*n*=302); n (%)	$\chi^2_{(df)}$; *p*-value
Demographic variables				
Ethnicity				$\chi^2_{(3)}$= 1.02; 0.796
Black	549 (86.3)	287 (85.9)	262 (86.8)	
White	14 (2.2)	9 (2.7)	5 (1.7)	
Coloured	61 (9.6)	31 (9.3)	30 (9.9)	
Indian	12 (1.9)	7 (2.1)	5 (1.6)	
Exposure variables				
Maternal factors				
Maternal age (years)	25.2±6.2	25.2±6.2	25.2±6.2	*t* = -0.03; 0.973
Marital status				$\chi^2_{(1)}$= 4.46; 0.035*
Married/living together	203 (31.9)	119 (35.6)	84 (27.8)	
Separated/divorced/ widowed/ single	433 (68.1)	215 (64.4)	218 (72.2)	
Maternal education				$\chi^2_{(3)}$= 1.96; 0.581
≤Grade 7	66 (10.4)	37 (11.1)	29 (9.7)	
Grades 8-10	280 (44.3)	141 (42.2)	139 (46.6)	
Grades 11-12	218 (34.5)	116 (34.7)	102 (34.2)	
Post school training	68 (10.8)	40 (12.0)	28 (9.4)	
Smoking				$\chi^2_{(1)}$= 0.07; 0.794
No	347 (96.1)	186 (95.9)	161 (96.4)	
Yes	14 (3.9)	8 (4.1)	6 (3.6)	
Snuff				$\chi^2_{(1)}$= 2.85; 0.091
No	315 (92.9)	167 (90.8)	148 (95.5)	
Yes	24 (7.1)	17 (9.2)	7 (4.5)	
Chewing tobacco				$\chi^2_{(1)}$= 0.02; 0.898
No	330 (99.4)	180 (99.4)	150 (99.3)	
Yes	2 (0.6)	1 (0.6)	1 (0.7)	
Any tobacco use during pregnancy				$\chi^2_{(1)}$= 2.60; 0.107
No	325 (89.5)	169 (87.1)	156 (92.3)	
Yes	38 (10.5)	25 (12.9)	13 (7.7)	
Alcohol use during pregnancy				$\chi^2_{(1)}$= 0.79; 0.375
No	333 (93.3)	177 (92.2)	156 (94.6)	
Yes	24 (6.7)	15 (7.8)	9 (5.4)	
Pregnancy wantedness				$\chi^2_{(1)}$= 0.35; 0.556
Yes	140 (39.2)	78 (40.6)	62 (37.6)	
No/ unsure	217 (60.8)	114 (59.4)	103 (62.4)	
Maternal prenatal stress				$\chi^2_{(1)}$= 0.01;

<4	589 (92.6)	309 (92.5)	280 (92.7)	0.923
≥4	47 (7.4)	25 (7.5)	22 (7.3)	
Postnatal depression (Pitt score)				$\chi^2_{(1)}$= 0.34;
<20	482 (75.8)	250 (74.8)	232 (76.8)	0.562
≥20	154 (24.2)	84 (25.2)	70 (23.2)	
Household factors				
Overcrowding				$\chi^2_{(1)}$= 1.14;
≤3 people/ room	337 (57.3)	173 (55.3)	164 (59.6)	0.286
>3 people/ room	251 (42.7)	140 (44.7)	111 (40.4)	
Household assets				
Radio				$\chi^2_{(1)}$= 0.48;
No	71 (11.8)	40 (12.7)	31 (10.9)	0.490
Yes	529 (88.2)	275 (87.3	254 (89.1)	
Television				$\chi^2_{(1)}$= 6.54;
No	123 (20.6)	77 (24.6)	46 (16.1)	0.011*
Yes	475 (79.4)	236 (75.4)	239 (83.9)	
Car				$\chi^2_{(1)}$= 4.48;
No	397 (66.4)	220 (70.3)	177 (62.1)	0.034*
Yes	201 (33.6)	93 (29.7)	108 (37.9)	
Fridge				$\chi^2_{(1)}$= 0.74;
No	120 (20.1)	67 (21.4)	53 (18.6)	0.392
Yes	478 (79.9)	246 (78.6)	232 (81.4)	
Washing machine				$\chi^2_{(1)}$= 0.21;
No	488 (81.5)	258 (82.2)	230 (80.7)	0.645
Yes	111 (18.5)	56 (17.8)	55 (19.3)	
Telephone				$\chi^2_{(1)}$= 5.41;
No	224 (37.5)	131 (41.8)	93 (32.6)	0.020*
Yes	374 (62.5)	182 (58.2)	192 (67.4)	
Own house				$\chi^2_{(1)}$= 3.28;
No	448 (71.9)	225 (68.8)	223 (75.3)	0.070
Yes	175 (28.1)	102 (31.2)	73 (24.7)	
Growth status				
Birthweight (g)	3084.9±480.6	3137.5±485.6	3027.1±469.0	*t* = 2.91; 0.004**
Relative linear growth (0-2 years) (*z*-score)	-0.03±1.0	-0.05±0.9	-0.01±1.0	*t* = -0.52; 0.606
Relative linear growth (2-4 years) (*z*-score)	-0.02±1.0	-0.01±1.0	-0.02±1.0	*t* = 0.14; 0.892
Relative weight gain (0-2 years) (*z*-score)	0.00±1.0	0.01±1.0	-0.00±1.0	*t* = 0.13; 0.900
Relative weight gain (2-4 years) (*z*-score)	-0.06±1.03	-0.06±1.1	-0.07±1.0	*t* = 0.08; 0.934
Outcome variable				
R-DPDQ score at age 5 years	44.1±4.8	43.6±5.3	44.8±4.1	*t* = -3.12; 0.002**

†*All data are percentages except for birthweight, relative linear growth, relative weight gain and RDPDQ scores*
**p<0.05; **p<0.01; ***p<0.001*

Effects of early life growth on R-DPDQ score at 5 years

In unadjusted analyses, increased R-DPDQ scores were significantly associated with higher maternal education, height, and parity, wealthier SES, female sex, greater

birthweight, and better relative linear growth between 0-2 years and 2-4 years (Appendix 5). In sex-stratified multivariable analysis, there was an independent, positive association between growth status and child development at 5 years in both sexes (table 5.2). This association remained significant in both sexes after controlling for significant risks from bivariate analysis, i.e. maternal education, household SES, as well as maternal height and parity. Higher birthweight was the only significant predictor of better child development at 5 years among females (β = 0.55 [95% CI 0.12, 0.98]). For males, growth throughout early childhood (birth to 4 years) was associated with improved R-DPDQ scores, with better relative linear growth between 0-2 years showing the strongest association. R-DPDQ scores increased by 0.84 units for every 1 SD increase in relative linear growth between birth and 2 years (β = 0.84 [95% CI 0.30, 1.39]).

Maternal education and household SES were also independently associated with R-DPDQ scores in males and these associations remained significant, although slightly attenuated, in the fully adjusted model. Male children of mothers with post-school training scored significantly higher on the R-DPDQ (β = 2.71 [95% CI 0.37, 5.05]) as compared to children of mothers with grade 7 education or less.

Mediation analysis

Direct, indirect and total effects resulting from the SEM analysis are presented in table 5.3. Household SES showed significant direct effects on child developmental scores in both sexes, with no evidence of mediation by early life growth variables. The indirect effects of household SES on R-DPDQ scores contributed to less than 10% of the total effects for males and females. The direct path for the association between maternal education and R-DPDQ scores was significant for males only. For males, the effect of maternal education on child development was not mediated by birthweight or linear growth between birth and 2 years and between 2 and 4 years of age. The direct effect of maternal education on R-DPDQ scores accounted for 82% of the total effect along this pathway. Thus, household SES and maternal education were significant determinants of child development at age 5, independent of growth between birth and 4 years in this cohort. The model fit indices assessed indicated that the structural equation models for males and females fit the data well (table 5.3).

Table 5.2 Sex-stratified regression analysis showing β and 95% CI of the association between early life growth and R-DPDQ

Variables	MALES			FEMALES		
	MODEL 1 (n=327)	MODEL 2 (n=327)	MODEL 3 (n=303)	MODEL 1 (n=327)	MODEL 2 (n=327)	MODEL 3 (n=303)
Individual factors						
Birthweight	0.76 (0.26, 1.27)***	0.63 (0.12, 1.13)**	0.63 (0.14, 1.13)*	0.58 (0.16, 1.00)	0.51 (0.11, 0.92)*	0.55 (0.12, 0.98)*
Relative linear growth (0-2y)	0.87 (0.31, 1.44)**	0.79 (0.23, 1.35)**	0.84 (0.30, 1.39)**	0.52 (0.07, 0.97)*	0.44 (0.00, 0.88)	0.37 (-0.08, 0.82)
Relative linear growth (2-4y)	0.73 (0.21, 1.25)**	0.61 (0.10, 112)*	0.54 (0.04, 1.04)*	0.18 (-0.27, 0.63)	0.17 (-0.26, 0.61)	0.16 (-0.28, 0.60)
Maternal factors						
Maternal education						
≤Grade 7		Reference	Reference		Reference	Reference
Grade 8-10		2.26 (0.44, 4.08)*	1.42 (-0.45, 3.29)		0.56 (-1.04, 2.15)	0.38 (-1.27, 2.03)
Grade 11-12		3.70 (1.81, 5.59)***	2.44 (0.47, 4.42)*		0.77 (-0.94, 2.49)	0.51 (-1.30, 2.32)
Post school training		4.04 (1.77, 6.32)**	2.71 (0.37, 5.05)*		2.16 (0.06, 4.26)*	1.52 (-0.73, 3.77)
Household factors						
Household SES						
Quintile 1			Reference			Reference
Quintile 2			0.62 (-1.06, 2.29)			-0.81 (-2.54, 0.92)
Quintile 3			1.36 (-0.32, 3.04)			-0.58 (-2.11, 0.95)
Quintile 4			1.95 (0.17, 3.73)*			0.30 (-1.29, 1.89)
Quintile 5			2.00 (0.11, 3.89)*			1.03 (-0.68, 2.74)
R^2	0.0752	0.1425	0.1735	0.0464	0.0839	0.1168

Model 1: Adjusted for birthweight, relative linear growth (0-2 years) relative linear growth (2-4 years); *Model 2:* Adjusted for birthweight, relative linear growth (0-2 years) relative linear growth (2-4 years), maternal education, maternal height and parity; *Model 3:* Adjusted for birthweight, relative linear growth (0-2 years) relative linear growth (2-4 years), maternal education, maternal height, parity and household socio-economic status (SES); **p<0.05; **p<0.01; ***p<0.001*

Table 5.3 Effects of household SES and maternal education on R-DPDQ at age 5: influence of birthweight and relative linear growth

Variables	MALES β (95% CI)	FEMALES β (95% CI)
Direct effects		
Household SES	0.65 (0.28, 1.03)**	0.45 (0.09, 0.81)*
Maternal education	0.23 (0.03, 0.43)*	0.12 (-0.06, 0.29)
Birthweight	0.70 (0.21, 1.19)**	0.43 (0.04, 0.82)*
Relative linear growth 0-2y	0.71 (0.16, 1.26)*	0.43 (0.00, 0.87)
Relative linear growth 2-4y	0.54 (0.04, 1.05)*	0.16 (-0.27, 0.58)
Indirect effects		
Household SES	0.06 (-0.04, 0.16)	0.03 (-0.04, 0.10)
Maternal education	0.05 (0.00, 0.11)	0.05 (0.00, 0.10)
Birthweight	-0.01 (-0.08, 0.06)	0.00 (-0.04, 0.05)
Relative linear growth 0-2y	0.03 (-0.04, 0.09)	0.01 (-0.01, 0.03)
Relative linear growth 2-4y	0 (no path)	0 (no path)
Total effects		
Household SES	0.71 (0.34, 1.09)***	0.48 (0.12, 0.85)**
Maternal education	0.28 (0.08, 0.49)**	0.17 (-0.01, 0.34)
Birthweight	0.68 (0.19, 1.18)**	0.44 (0.04, 0.83)*
Relative linear growth 0-2y	0.74 (0.18, 1.29)**	0.44 (0.01, 0.88)
Relative linear growth 2-4y	0.54 (0.04, 1.05)*	0.16 (-0.27, 0.58)

† Males: n = 326; $\chi^2_{(1)} = 0.101$; p = 0.750; CFI = 1.00; RMSEA= 0.000; SRMR = 0.003
† Females: n = 285; $\chi^2_{(1)} = 0.02$; p = 0.889; CFI = 1.00; RMSEA = 0.000; SRMR = 0.002
**p<0.05; **p<0.01; ***p<0.001*

5.4 Discussion

Consistent with studies conducted in other settings, girls performed better than boys on the 5-year child development measure. Birthweight and relative linear growth throughout the early childhood period were positively associated with child development outcome, particularly among males. Beyond biological factors, social determinants, particularly SES and maternal education showed strong independent effects on child development with no mediation by linear growth between birth and 4 years of age.

Differences in cognitive abilities between males and females are widely recognised but most data originates from high-income countries and focus on older children and adults.[383] The mechanisms for the difference are largely unclear, though much of the variation is attributed to genetic or hormonal influences, biological (differences in neurological structure and function) and environmental (physical, psychosocial and socio-cultural) factors.[383,384] We postulate that all or some of these factors influence young children too.

Birthweight has often been studied as a dichotomous variable (< or > 2500g) leading to the notion that only extremes of birthweight matter when considering health and development outcomes.[385] Using birthweight as a continuous variable, we confirmed that birthweight along the continuum matters. Higher infant birthweight was associated with higher R-DPDQ scores for both sexes. Positive relationships between infant birthweight and cognitive development have been observed elsewhere, including lower resourced settings.[247,386] Thus, interventions aimed at increasing infant birthweight may be protective and lead to gains in child cognitive development, recognising that there is still some uncertainty as to the birthweight range that optimally promotes improved health, growth and development outcomes.[355] Associations between infant birthweight (used as a continuous measure) and behaviour in childhood or later life have also been reported less consistently.[244]

The effects of stunting on child development are well-described in the literature.[88] The pertinent evidence we add is that linear growth throughout the first four years of a child's life (rather than the simplistic, previously used binary classifications of stunting [present or absent]) had significant independent effects on child development, particularly among males. These effects persisted even when the influences of maternal and household factors were considered. Linear growth from 0-2 years was the strongest determinant of R-DPDQ scores in males. These findings are biologically plausible as this (conception to age two years) is a period of rapid physical growth as well as brain development, providing the foundation for cognitive, motor and socioemotional development throughout childhood and later life.[29,288] During this time, regions of the brain (such as the hippocampus) and brain processes (e.g. myelination) require sufficient quantities of different nutrients at critical periods

to ensure proper brain development. Well-nourished children will have the essential energy, protein, fatty acids and micronutrients required for brain development and will also be better able to interact with their environment and caregivers and build on their experiences in ways that promote optimal brain development.[29] There were clear associations between prenatal (using birthweight as proxy), as well as postnatal growth and child developmental outcomes. Similar findings have been reported in other studies conducted in low and middle income settings.[90,275] Compromised growth in early life, particularly during the first 1 000 days, may lead to biochemical and structural changes in the brain that can modify function and decrease learning abilities.[29] However, the positive effects of linear growth on child development persisted beyond 2 years of age in this study, emphasising the importance of growth throughout the early childhood period (0-4 years) on child developmental outcomes.

Household SES and maternal education had direct, independent effects on child development at 5 years of age. These effects were not mediated by birthweight and linear growth during the first four years of life. The findings concur with a recent Colombian study,[98] that found that height-for-age had a small effect and only mediated the effect of SES on language development; it did not mediate the effect of maternal education on cognitive development. In contrast, findings from a longitudinal study conducted in Bangladesh showed that pre- and postnatal growth significantly mediated the effects of poverty and maternal education on child cognitive outcome at 64 months of age.[90] The underlying reasons for the differences in findings could be explained by contextual factors, such as the variations in extreme/absolute poverty levels and the prevalence of malnutrition. The Bangladeshi study reported high levels of low birthweight and stunting.[90]

Longitudinal studies across income settings describe family income and poverty status as more powerful predictors of child IQ scores and behavioural development than maternal education, and associate poverty with developmental delays before one year of age, with deficits increasing at 5 years of age.[98,221] Evidence from Bangladesh and Madagascar reported significant increases in mean cognitive scores between the top and bottom wealth strata during the first five years of life.[90,221] There is some evidence to suggest that these differences in cognitive performance between SES groups are smaller in more equitable societies.[208] Typically, poorer child

outcomes in low SES settings are related to the environment with families experiencing greater stress and having fewer resources and reduced capacity to respond to, or invest in, child development.[97]

However, maternal education itself is a significant determinant of child cognitive ability, educational performance and subsequent human capital.[88] Previous studies have shown that the effect of maternal education on child cognitive and behavioural development remains strong, even after accounting for other SES effects.[18,97] We confirmed that maternal education acts as a protective factor for child development, particularly in males; with an increase of over half a SD in R-DPDQ scores for male children of mothers who had completed Grade 11 or higher. Mothers who are more educated may have increased knowledge of health issues,[93] greater awareness and knowledge of appropriate nutrition, as well as better utilisation of available services for child health and well-being.[94] Maternal education also promotes empowerment of women allowing them increased autonomy and control over household income and decision making around child care.[93] Furthermore, maternal education may impact on child development through particular parenting characteristics such as caregiver warmth toward the child, maternal sensitivity and responsiveness or the ability to provide a safe and stimulating environment for the child.[18,98]

A strength of this study is its use of prospective data from a large, longitudinal birth cohort in a low to middle income setting to test associations, including biological and environmental interactions at an individual, maternal and household level. The study extended beyond testing simple, linear cause-effect relationships to assessing causal relationships using a flexible and more powerful multivariable estimation technique. Few comparative studies have previously considered growth at different stages of development and throughout the early childhood period in their analysis of child development outcomes.

The study has a few limitations. There are strong reciprocal interactions between cognitive and socio-emotional development; with changes in one contributing to changes in the other.[286] Although the R-DPDQ included some aspects of child social and emotional development, there is a need for more in-depth exploration of how growth and nutrition could modify behavioural development. Although we were able

to account for a variety of exposures and confounding factors in the analysis, we lacked early child care quality data. This would have strengthened the study findings as these are known moderators of child development.[88] Availability of information on family/household dynamics (for example household organisation), social support systems and use of household resources would have further strengthened the study. There was considerable loss to follow up in this study due to the longitudinal nature of the analysis, which possibly compromised study power and generalisability of results.

Early life growth appears to affect child developmental outcomes differently in different settings.[90,98,244] There is a need for further research to explore the appropriate timing and approach for interventions to optimise developmental outcomes in different settings. The potential additive or mediating effects of positive environmental experiential inputs to offset the negative effects of nutritional deficits and adverse environmental conditions warrants exploration.

Our findings emphasise the importance of adopting a life course perspective to child health and development. It suggests that current global interventions focusing on improving physical growth (particularly stunting), without simultaneously addressing broader social determinants such as household SES and maternal education may fail to adequately enhance child developmental outcomes in poorer settings.

Structural interventions, such as conditional cash transfer programmes have shown positive impacts on child health outcomes, with improvement on child developmental outcomes when integrated with nurturing care interventions.[7] They extend availability of opportunities and may remove barriers to accessing protective and supportive services and have been associated with improved child health, nutrition and schooling in our and other similar settings.[7,32]

Beyond the long-term strategy of increasing maternal years of schooling, specific counselling and support to caregivers on how best to promote child's growth and development is warranted. Effective parenting programmes implemented in low and middle income settings have shown that methodologically rigorous parent support

programmes can have positive effects on the capacity of parents or caregivers to provide responsive caregiving and early learning opportunities.[7]

5.5 Conclusion

This study showed that beyond genetic and biological factors such as growth status; structural determinants, particularly household SES and maternal education, significantly affected cognitive development in young children, and more especially males, in a low resourced setting.

PART 3: DISCUSSION AND CONCLUSION

"There can be no equality of opportunity without…appropriate stimulation, nurturing, and nutrition for infants and young children. Conditions of poverty, toxic stress and conflict will have produced such damage that they may never be able to make the best of any future opportunities. If your brain won't let you learn and adapt in a fast changing world, you won't prosper and, neither will society."

Jim Yong Kim, World Bank Group President, October 1, 2015

CHAPTER 6: DISCUSSION AND CONCLUSION

This chapter synthesises and consolidates the findings from the prior chapters with regards to the key objectives of this thesis. It also identifies and discusses the main themes that emerged from the analyses. This is followed by reflections on the empirical contributions of the thesis and revisiting of the conceptual framework used. The thesis strengths and limitations are presented, followed by discussion on the implications of the findings for early childhood policy and programme development and practice, as well as recommendations for further research.

6.1 Summary of thesis findings

The aim of the thesis was to determine the effects of maternal and child environmental and psychosocial exposures during pregnancy and the first two years of a child's life ('the first 1 000 days') on growth and development outcomes in infancy and early childhood in an urban South African birth cohort. The consolidated thesis findings in line with the specified objectives are provided in Table 6.1.

Table 6.1 Consolidated study findings

Number	Objective	Key finding/s	Chapter
1.	*To determine the associations between maternal psychosocial and environmental risk factors assessed during pregnancy and subsequent infant birthweight.*	• Exposures related to maternal attitudes and behaviours during pregnancy, namely unwanted pregnancy and tobacco use during pregnancy, were significantly associated with lower infant birthweight. • Exposure to multiple relative to single factors prenatally resulted in greater reductions in infant birthweight.	3
2.	*To assess the effects of psychosocial and environmental exposures affecting the*	• Higher maternal education	4

	mother (and child) during pregnancy and the first year of the child's life on stunting at age 2 years.	was protective for female children, while poorer household socio-economic status was a risk for males. • Higher birthweight was protective against stunting for both sexes.	
3.	*To determine the associations between early life psychosocial and environmental exposures, growth (between birth and 4 years of age) and child development at 5 years of age and to assess whether relative linear growth mediates the association between key early life exposures and child development.*	• Males scored significantly lower than females on the Revised Denver Pre-screening Developmental Questionnaire (R-DPDQ) at 5 years of age. • For males, growth throughout early childhood (birth to 4 years) was associated with improved R-DPDQ scores, with better relative linear growth between 0-2 years showing the strongest association. • Beyond biological factors, socio-economic status (for both sexes) and maternal education (for males) were significant predictors of higher R-DPDQ scores. • The effects of socio-economic status (for either sex) and maternal education (for males) on developmental outcome were not mediated by relative linear growth between 0-2 years and 2-4 years.	5

6.1.1 Review of hypotheses (H0)

Hypothesis 1: **There are no associations between maternal psychosocial and environmental exposures during pregnancy and subsequent infant birthweight.**
We rejected the null hypothesis as we found that, particularly, unwanted pregnancy and tobacco use during pregnancy were significantly associated with lower infant birthweight.

Hypothesis 2: **There are no associations between maternal and child risk exposures during pregnancy and the first two years of life and stunting at 2 years of age.**
We rejected this hypothesis as the study results showed that higher maternal education was protective against stunting at age 2 years for female children, while poorer household socio-economic status was a risk for males.

Hypothesis 3: **There are no differences between males and females in relation to psychosocial and environmental exposures, growth and development at 5 years of age.**
This hypothesis is rejected as there were significant differences between males and females in this study at 5 years of age. Males were significantly heavier at birth and scored significantly lower than females on the R-DPDQ at 5 years of age. In multivariable analysis, beyond biological factors, socio-economic status (for both sexes) and maternal education (for males) were significant predictors of higher R-DPDQ scores.

Hypothesis 4: **Early childhood growth (between birth and 4 years of age) is not associated with child development at 5 years of age?**
Higher birthweight was associated with better child development at 5 years of age among females. For males, birthweight and linear growth between birth and 4 years were associated with improved R-DPDQ scores.

Hypothesis 5: **Relative linear growth does not mediate the effects of key psychosocial and environmental exposures on child development at 5 years of age.**

The effects of socio-economic status (for either sex) or maternal education (for males) on developmental outcome at age 5 years were not mediated by relative linear growth between 0-2 years and 2-4 years. Thus we fail to reject the null hypothesis.

6.2 Emerging themes from the study findings

The main themes that emerged from this thesis are:
1) Social factors are important for early child growth and development;
2) Prenatal and postnatal growth (between birth and four years of age) is important for child development;
3) Growth does not mediate the effects of socio-economic status and maternal education on child development; and
4) Sex differences in growth and development are evident in this context.

6.2.1 Social factors are important for early child growth and development

Having an unwanted pregnancy and maternal tobacco use during pregnancy had the most significant effects on subsequent infant birthweight, a proxy marker of intrauterine development. Exposure to both (relative to each individually) during the antenatal period resulted in greater reductions in infant birthweight.

Pregnancy wantedness has previously been negatively associated with infant health and development, particularly in low resource settings, and among adolescent mothers and single mothers.[116,117,343] There was a high proportion of unwanted pregnancies in this sample (57%), including ambivalence toward the pregnancy, particularly from single mothers and those living in poorer households. Most of the mothers who did not want or were ambivalent toward pregnancy were aged between 20 and 35 years, rather than adolescents. It is possible that maternal SES (or other factors related to SES) and not maternal age may be the primary driver of pregnancy intention in a context with high inequality, such as South Africa.[344] As much of the local research in this area has focused on adolescents, this study emphasises the need for further in-depth study of this age group, rather than focusing on younger women only.

While the role of cigarette-smoking on birthweight is well-documented, this thesis showed that the use of smokeless tobacco products, such as snuff, which may be more common than cigarette-smoking in some Black communities, also have negative effects on infant birthweight. It adds to the international evidence on the effects of smokeless tobacco products on subsequent infant birthweight as most of the previous studies originated from high income settings.

Household SES was associated with stunting at age 2 years and child development scores at 5 years of age, among males. Male children growing up in the two lowest SES groups were nearly three times more likely to be stunted than their peers in higher SES groups. The same difference in stunting was not observed among girls belonging to socio-economically different groups in this cohort. Longitudinal studies across income settings associate poverty with developmental delays before one year of age, with deficits increasing at 5 years of age.[98,221] Evidence from Bangladesh and Madagascar reported significant increases in mean cognitive scores in the top wealth strata compared to the lowest strata during the first 5 years of life.[90,221] There is some evidence to suggest that these differences in cognitive performance between SES groups are smaller in more equitable societies.[208] Typically, poorer child cognitive outcomes in low SES settings are related to the environment with families experiencing greater stress, having fewer resources and reduced capacity to respond to, or invest in, child development.[97]

Although often used as a proxy for SES, maternal education itself is a significant determinant of child growth, cognitive ability, educational performance and subsequent human capital.[88] Increased maternal education has been associated with decreased stunting across and within societies.[370] It is postulated that there are key causal pathways through which maternal education affects child nutrition.[91,92] One explanation is that maternal education, through mechanisms unrelated to SES, may directly influence child health and growth through increasing female knowledge and autonomy within the household and community. This leads to beneficial care-giving practices such as better health-seeking behaviours, and improved feeding and hygiene practices.[93,94,217] However, the benefits of maternal education only extended to females in the stunting analysis; with female children of mothers were who more educated having a lower likelihood of stunting. Previous studies have reported that

females have better survival outcomes as compared to males if their mothers are better educated, particularly in sub-Saharan Africa.[369]

Previous studies have shown that the effect of maternal education on child cognitive and behavioural development remains strong, even after accounting for other SES effects.[18,97] We confirmed that maternal education acts as a protective factor for child development, particularly among males; with an increase of over half a SD in R-DPDQ scores for male children of mothers who had completed Grade 11 or higher was found. Maternal education may impact on child development through particular parenting characteristics such as caregiver warmth toward the child, maternal sensitivity and responsiveness or the ability to provide a safe and stimulating environment for the child.[18,98]

These findings add to the evidence base supporting the need to address structural drivers such as SES and maternal education as key to reducing stunting and promoting development amongst young children, particularly in settings that are less resourced or have wide socio-economic disparities.

6.2.2 Prenatal and postnatal growth are important for child development

There is still some debate about the relative importance of prenatal compared with postnatal growth on cognitive and behavioural development in children. This study showed that there were clear associations between prenatal (using birthweight as proxy), as well as postnatal growth, particularly linear growth between birth and 4 years, and child developmental outcomes at age 5. Birthweight has often been studied as a dichotomous variable (< or > 2500g) leading to the notion that only extremes of birthweight matter when considering health and development outcomes.[385] Using birthweight as a continuous variable, we confirmed that birthweight along the full range matters for later child development. Higher infant birthweight was associated with higher R-DPDQ scores for both sexes. Positive relationships between infant birthweight and cognitive development have been observed elsewhere, including in low resource settings.[247,386] Thus, interventions aimed at increasing infant birthweight may be protective and lead to gains in child cognitive development, recognising that there is still some uncertainty as to the

birthweight range that optimally promotes improved health, growth and development outcomes.[355]

The effects of stunting on child development are well-described in the literature.[88] The pertinent evidence we add is that linear growth throughout the first four years of a child's life (and not only the binary classification of stunting [present or absent]) had significant independent effects on child development, particularly among males. These effects persisted even when the influences of maternal and household factors were taken into account. Linear growth from 0-2 years was the strongest determinant of R-DPDQ scores among males. Similar findings have been reported in other studies conducted in low and middle income settings.[90,275] However, the positive effects of linear growth on child development persisted beyond 2 years of life, emphasising the importance of growth throughout the early childhood period (0-4 years) on child developmental outcomes.

6.2.3 Growth as a mediating factor for child development

Two previous low-income setting studies examined the extent to which child growth, including linear growth, mediated the effects of SES and maternal education on cognitive development.[90,98] This is the first study in Africa to do so. A recent Colombian study,[98] found that height-for-age mediated the effect of SES on language development but did not mediate the effect of maternal education on cognitive development. However, this was a cross-sectional study and thus used only one set of anthropometric measures. In contrast, findings from a longitudinal study (using multiple measures of growth) conducted in rural Bangladesh showed that pre- and postnatal growth significantly mediated the effects of poverty and maternal education on child cognitive outcome at 64 months of age.[90]

In this thesis, using longitudinal data and multiple measures of growth between birth and 4 years of age, household SES and maternal education showed direct, independent effects on child development at 5 years of age. These effects were not mediated by birthweight and linear growth between 0-2 years and 2-4 years. The underlying reasons for the differences in findings could be explained by contextual factors, such as the variations in extreme/absolute poverty levels and the prevalence

of malnutrition in the samples used. The Bangladeshi study reported high levels of low birthweight (31%) and stunting by 24 months of age (52%).[90]

6.2.4 Sex differences are evident in growth and development

Males were more vulnerable to poor growth and development outcomes as compared to females in this context. Although males were significantly heavier at birth than females, male children had 38% higher odds of being stunted at 2 years as compared to females.

Although, increased male susceptibility to stunting has been reported previously, mostly from studies conducted in sub-Saharan Africa, the underlying mechanisms for these differences have remain largely unexplored.[362] Most of the evidence suggests that stunting differences between males and females are relatively small when compared to other stratifiers (such as SES), particularly among children under 5 years; with gender disparities becoming more apparent as children get older.[217,361]

Several possible explanations have been offered for observed sex differences. One possible explanation lies in the developmental origins of sex differences in health outcomes. While poor fetal growth enhances the risk for both sexes, males and females tend to respond differently.[365] Male fetuses have been described as investing greater resources in growth, resulting in a limited ability to respond to subsequent stressors, placing them at greater risk for poor outcomes. In contrast, female fetuses are believed to conserve resources and are better able to adjust to maternal conditions, resulting in increased probability of survival.[278,365]

Males also tend to grow faster than females from an early stage of gestation and, by growing more rapidly, the male fetus invests more in lean mass, including brain growth, rather than placental growth.[366] At any placental weight, males tend to be longer than females, with smaller placentas. This suggests that placentas of male foetuses are more efficient but have less reserve capacity, making them more vulnerable to becoming undernourished.[367] This reinforces the idea of higher environmental sensitivity among males, i.e. under adverse conditions, males are more at risk of negative health and growth outcomes.[368]

This hypothesis is further reinforced by our finding that male children growing up in the two lowest SES groups were nearly three times more likely to be stunted than their counterparts in wealthier strata. The same difference in stunting prevalence was not observed among girls belonging to socio-economically different groups in this cohort. Similar findings have been observed in sub-Saharan African studies; with male children living in the poorest SES groups more likely to be stunted as compared to females in the same groups.[362] However, inconsistent findings have been reported in higher income settings.[362]

Females performed better than males on the child development measure at age 5. Birthweight and relative linear growth, between birth and 4 years, were positively associated with child cognitive development outcome, particularly among males. Differences in cognitive abilities between males and females are widely recognised but most data originates from high-income countries and focuses on older children and adults.[383] The mechanisms for the differences are largely unclear, though much of the variation is attributed to genetic or hormonal influences, biological (differences in neurological structure and function) and environmental (physical, psychosocial and socio-cultural) factors.[383,384] I postulate that all or some of these factors influence young children too.

6.3 Conceptual relevance

The conceptual framework for this study (Figure 1.3 in Chapter 1) focused primarily on the immediate or proximal factors influencing child development, i.e. factors pertaining mainly to the mother and child and the immediate household environment. Socio-economic status was not considered separately but rather as one of the socio-cultural risk factors in this study and mainly in the context of the household environment. Early childhood growth was considered as both an intermediate outcome but also a possible mediator between early life exposure and child development outcomes in the preschool years. The study focused on exposures in the first 2 years of life and growth and development outcomes within the first 5 years of life as these are the most critical formative developmental years.

Based on the study findings, certain adjustments were made to the conceptual framework (Figure 6.1). The key socio-cultural factor associated with stunting at age 2 and child development at 5 years was SES at a household level. Psychosocial factors related to maternal behaviours and attitudes, namely tobacco use during pregnancy and unwanted pregnancy, were significant determinants of infant birthweight in this sample. For stunting at 2 years, higher maternal education was protective against stunting for females. Maternal education was also an independent determinant of child development outcome at age 5.

Stunting at 2 years was an intermediate outcome in this study and its effect on child development was not assessed. Instead, I investigated the relationship between growth (including linear growth) and child development using continuous growth measures between birth and 4 years of age. Growth (birthweight and relative linear growth between birth and 4 years of age) was independently associated with child development at 5 years. Growth measures did not mediate the effects of household SES and maternal education on child development. Thus, social factors and growth throughout the first four years have independent effects on child development in this context.

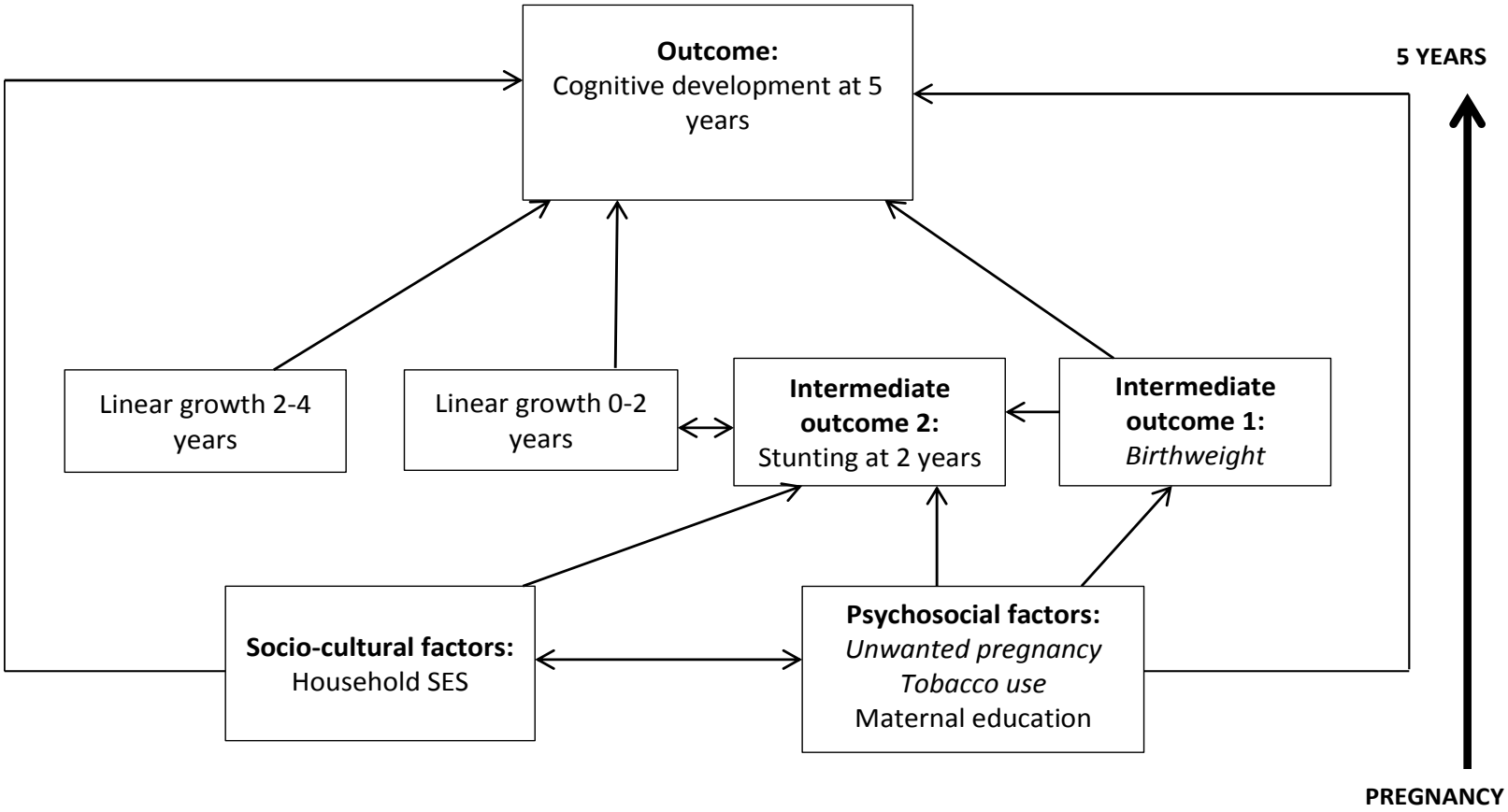

Figure 6.1 Modified conceptual framework for thesis.

6.4 Contextual relevance

6.4.1 Implications of study findings for national policies and programmes

Despite the study data being collected in the early 1990's, recent South African estimates indicate that the prevalence of unwanted pregnancy,[113] and maternal tobacco use during pregnancy,[351] remain high.

In the South African context, unwanted pregnancy is often associated with adolescent motherhood.[349,387] In this study, most mothers who had indicated unwanted pregnancy (or ambivalence) lived in low SES households and were aged between 20 and 35 years. This emphasises the need to assess for and address not only biological factors, but also psychosocial exposures, which may adversely affect pregnant mothers and their unborn children during the antenatal period. Contraception and family planning, social support and interventions to promote the autonomy and empowerment of women are also critical.

Since the enactment of tobacco control legislation in South Africa in the 1990's, there has been a steady decrease in smoking rates.[351] However, trends indicate that cigarette consumption still remains high among particular population groups, including pregnant women. National survey data report consumption rates of between 20-40% amongst Coloured/Mixed race women.[352]

Quitting smoking before or during early pregnancy will be the most beneficial. The effects of maternal smoking extend beyond pregnancy and child birth. Women who smoke are less likely to initiate breastfeeding, and those who do, are more likely to breastfeed for shorter periods.[353] Although health care workers (and society at large) are aware of the risks related to cigarette smoking during pregnancy, they are less informed about the potential risks of smokeless tobacco products on the developing fetus. Thus, it is likely that the use of smokeless tobacco products, such as snuff, is not established during health care visits and therefore not addressed.

The findings further point to the need for strengthened antenatal care as an entry point to identify and support women in addressing psychosocial exposures during pregnancy that will enable them to adopt health behaviours and attitudes that will be

beneficial to themselves and their infants. It also indicates that there is a need for primary prevention initiatives that are accessible and that start before conception. It calls for health, education and empowerment initiatives aimed at women, and adolescents, which follow them through their life course (and that of their unborn children).

This study also identified a high prevalence of stunting comparable to those in other parts of the continent.[375] Stunting rates since 1990 have barely changed in South Africa.[375] Despite improvements in economic growth over the past three decades, significant socio-economic disparities remain, and high levels of stunting (predominantly among the youngest children) persist in South Africa.[376] The latest South African National Health and Nutrition Survey (SANHANES) data showed that the youngest children (between 0–3 years of age) had the highest prevalence of stunting (26.5%); with more males stunted than females.[46] Thus, although the study reflects stunting prevalence in 1992, the study conclusions remain pertinent as we continue to seek effective interventions in South Africa, as do other countries with wide social disparities.

Genetic and biological factors, as well as proximal maternal behaviours and caregiving practices are important determinants of infant growth and attained height, particularly in the first 1 000 days of a child's life. This study's findings highlight the importance of distal drivers of child growth and development, such as socio-economic status and maternal education in less resourced settings. Government and development agency approaches to improving child survival and development have traditionally addressed proximal, largely biological and 'demand-side' determinants with less attention to distal, social determinants since many of these lie outside the health sector. Beyond the long-term aim of increasing maternal schooling, emphasis should be placed on improving mother's health literacy regarding child health and feeding practices.[380] An example of an approach that may aid in targeting and delivering these interventions is cash transfer programs, particularly those that are linked to nutrition education/counselling and primary health care services.[377,381]

Birthweight (for both sexes) and linear growth throughout the first four years of childhood (for males) were independently associated with child development at age

5. Structural determinants, particularly household SES and maternal education, significantly affected child development in young children, especially males, in this study. The effects of household SES and maternal education on child development were not mediated by linear growth (between birth and 4 years of age).

Structural interventions, such as cash transfer programmes have shown positive impacts on child health outcomes, with improvement on child developmental outcomes when integrated with nurturing care interventions.[7] They extend availability of opportunities and may remove barriers to accessing protective and supportive services and have been associated with improved child health, nutrition and schooling in our and other similar settings.[7,32] South Africa's child support grant reaches close to 12 million children and has shown impacts on child health and education.[388] However, uptake of the grant in infancy is low.[388] The significant effect of infant birthweight and linear growth between 0-2 years on later development, points to the importance of early access for vulnerable children. To positively influence optimal birthweight attainment, access to some form of cash transfer for pregnant mothers could also be justified.[389,390] Further, applications for child grants need to be processed during pregnancy so that they commence immediately after birth.

Beyond the long-term strategy of increasing maternal years of schooling, specific counselling and support to caregivers on how best to promote child's growth and development is warranted. Effective parenting programmes implemented in low and middle income settings have shown that methodologically rigorous parent support programmes can have positive effects on the capacity of parents or caregivers to provide responsive caregiving and early learning opportunities.[7] During the first two to three years of life, the public health care system reaches more children and their families than any other service. Caregiver counselling and support for child development has not yet been integrated into routine child health interactions (for well or sick care).[391] The latest Lancet series on early childhood development calls for health and nutrition services to promote and support nurturing care for young children.[27,32] Thus, this is an area that should be prioritised as part of the child health agenda as we move beyond child survival strategies and work toward improving

short- and long-term child growth and development outcomes within South Africa, in line with the UN's global 2030 "survive, thrive and transform" goals.[41]

6.4.2 International relevance

This thesis has shown that particular social risks and context matter for child growth and development. This study echoes the need to tackle social determinants of poor growth and development, particularly in LMIC and settings with high levels of inequity. Direct nutrition-specific interventions together, even when scaled up to 90% coverage rates, are estimated to reduce the burden of stunting only by about 20%.[377] Programmes that improve nutrition, health care and household purchasing power among the poor generally also improve growth outcomes, particularly in lower socioeconomic status children.[377] Although population level interventions are more complex and take time to show impact, there is strong anecdotal evidence from health intervention programmes that even caregivers with low education and literacy levels can be empowered to provide better care to children when they are supported and equipped with the required skills and knowledge.[379]

The positive effects of linear growth on child development persisted beyond 2 years of age in this study, emphasising the importance of growth throughout the early childhood period (0-4 years) on child developmental outcomes. Early life growth appears to affect child developmental outcomes differently in different settings.[90,98,244] Thus, context is important and beyond global strategies, there should be efforts to ascertain and adapt context-specific approaches to improving growth and development among young children. Current global interventions that focus on improving physical growth (particularly stunting), without simultaneously addressing broader social determinants such as household SES and maternal education, may fail to significantly enhance child developmental outcomes in poorer settings.

6.5 Strengths and limitations of the study

A strength of this study is its use of prospective data from a large, longitudinal birth cohort in a low resource setting to test associations, including biological and environmental interactions at an individual, maternal and household level. For the

birthweight analysis, data from a large prospective, urban cohort study (with data that was collected prospectively during the antenatal period and shortly after birth), was used. The use of prospective, longitudinal data reduced the risk of maternal reporting bias across the measures explored in this thesis.

The study extended beyond testing simple, linear cause-effect relationships to assessing causal relationships between maternal and household exposures, biological factors (such as growth) and later child development outcomes using a flexible and more powerful multivariable estimation technique, such as SEM. The study used repeated measures of growth during the first four years of childhood and as such measures are strongly correlated, conditional growth was used thereby removing collinearity between growth measures. Few comparative studies have previously considered growth throughout the early childhood period in their analysis of child development outcomes.

The risk factors studied were restricted to those that were measured in the Bt20+ study and thus did not include other factors that may influence infant birthweight. These include maternal access to health care and particular biological risks, such as maternal nutrition, pregnancy and birth complications, among others. Maternal tobacco use was established only on self-report. Daily consumption levels were not available and, therefore, the dose-response relationship of tobacco use on infant birthweight could not be studied.

The study of pregnancy wantedness and intention has methodological challenges, thereby limiting the interpretation of the effects of unwanted pregnancy on infant birthweight, especially as pregnancy intention was not studied. Only data on pregnancy wantedness (or ambivalence) was obtained and not whether the pregnancy was un-/intended or mistimed. Information on pregnancy intention would have provided more insight into the mothers' attitude toward the pregnancy as it may influence women's ability or compliance with seeking health care pre-, peri- and postnatally.[349]

There were important determinants of stunting that were not accounted for in the analysis. Examining the contribution to stunting of household food security and

feeding practices, including dietary diversity would have strengthened the study. These may be important in this study context as sub-optimal feeding patterns, including the early introduction of complementary foods, has been identified previously in this cohort.[374] Other covariates which would have been beneficial to include in the analysis, but for which data were not collected, were birth length, major or recurrent illness and micronutrient deficiencies.

Another limitation is the assessment of developmental status in this study, specifically the use of the R-DPDQ. The R-DPDQ is a screening tool and is usually used as a first step in the assessment process to identify children 'at risk' who need more in-depth assessment, using detailed developmental assessment measures such as the Bayley Scales of Infant Development and the Griffiths Mental Development Scales.[6,12,304] Screening tests are not diagnostic and are typically less effective in assessing milder developmental difficulties that may also have a significant impact on child development.[6,12] There are strong reciprocal interactions between cognitive and socio-emotional development; with changes in one contributing to changes in the other.[286] Although the R-DPDQ included multiple developmental domains, it included mostly aspects of cognitive and motor development and thus there is a need for more in-depth exploration of how growth and nutrition could modify behavioural development.

Although we were able to account for a variety of exposures and confounding factors in the analysis, we lacked maternal IQ and early child care quality data. This would have strengthened the study findings as these are known moderators of child development.[88] Higher maternal IQ is related to a better caregiving practices and a more stimulating home environment.[111] There may also be a genetic contribution, i.e. mothers with higher intelligence having offspring with higher cognitive functioning regardless of educational level, which may go undetected. Availability of information on family/household dynamics (for example household organisation), social support systems and use of household resources would have further strengthened the study.

Another limitation of the study was the reduction in the analytical sample size due to incomplete data at one or more time points. The analytical samples used for this study were predominantly Black African or Coloured/Mixed race, which may limit

generalisability of the findings to other population groups. There are obvious limitations to the conclusions that can be drawn from the findings as the underlying aetiologies and the mechanisms of the associations require more rigorous and in-depth consideration, particularly in similar contexts.

6.6 Research recommendations

This study emphasises the importance of psychosocial and environmental exposures in determining child growth and development outcomes and the need for more research to better understand the aetiologies of these associations. Further research is warranted to explain the stunting sex-differentials across socio-economic strata and maternal education levels. Socio-economic status is a multi-dimensional construct and more sophisticated analyses that further disaggregate the variable into its components should be conducted in order to develop effective, targeted stunting interventions along the socio-economic spectrum in different contexts. Further exploration of the functional and long-term consequences associated with early male child vulnerability is required; both related to stunting but also for other later lifestyle diseases, such as diabetes and cardio-vascular conditions. Finally, a more sophisticated biological explanation is required as to why male children are more vulnerable compared to female children pre- and postnatally in this context.

Stunting is a good summary indicator of growth failure, however, growth failure is cumulative and linear growth in and of itself is an important indicator of child health and well-being.[355] Therefore it would be useful to explore the processes that contribute not only to linear growth faltering but also what may affect age-appropriate growth in young children. An important extension of this research study would be to consider the associations between early life growth patterns (rates and trajectories) and subsequent stunting in order to better understand the underlying mechanisms and timing of growth faltering in this cohort.

The R-DPDQ is not a developmental assessment or diagnostic tool; it also does not yield scales and thus is not able to assess specifics of any particular construct (e.g. language). A useful extension of this study would be to further investigate the effects of early childhood social exposures and growth on later developmental outcomes

with more definitive assessment tools, which would allow for greater discrimination between the respective developmental domains.

Early life growth appears to affect child developmental outcomes differently in different settings.[90,98,244] There is a need for further research to explore the appropriate timing and approach for interventions to optimise developmental outcomes in different settings. The potential additive or mediating effects of positive environmental experiential inputs to offset the negative effects of nutritional deficits and adverse environmental conditions warrants exploration.

There is a need for more creative analytical strategies to ascertain the relative importance of intra-uterine versus extra-uterine influences on childhood cognitive outcomes and more generally on other health outcomes. Although this thesis focused mainly on risk factors for child growth and cognitive development, it is as, if not more, important to explore protective and promotive factors for child development. Protective factors reduce the adverse consequences of risk factors. Although risk and protective factors are theoretically distinct, many protective factors are considered to be the inverse of risk factors, e.g. secure vs insecure attachment.[88] In order to be considered as a protective factor, it should show a greater positive or mediating effect under conditions of high adversity.[280]

6.7 Conclusions

The aim of the study was to determine the effects of maternal and child environmental and psychosocial exposures during pregnancy and the first two years of the child's life ('the first 1 000 days') on growth and development outcomes in early childhood in an urban South African birth cohort.

The analyses showed that social factors related to maternal attitudes and behaviours during pregnancy, namely unwanted pregnancy and maternal tobacco use, were for determinants of early infant growth. Exposure to multiple, relative to single risks, prenatally resulted in greater reductions in infant birthweight. Social determinants, particularly household SES and maternal education, significantly affected later growth outcomes, i.e. stunting at 2 years of age, with males showing increased vulnerability. Household SES and maternal education also significantly affected child

development scores at age 5, again more especially in males. These effects were not mediated by linear growth between birth and 4 years of age in this cohort.

These findings emphasise the importance of adopting a life course perspective to child growth and development, especially as linear growth throughout the first four years of childhood (for males) were independently associated with child development. It suggests that current interventions focusing on improving physical growth (particularly stunting), without simultaneously addressing broader social determinants such as household SES and maternal education may fail to adequately enhance child developmental outcomes in poorer settings.

Study highlights

- Social factors, especially social determinants such as household SES and maternal education, were associated with early childhood growth and development in this context.

- Prenatal (using birthweight as a proxy) and postnatal growth are important for child development in the preschool years in this setting.

- Linear growth between 0-2 years and 2-4 years does not mediate the effects of household SES and maternal education on child development at age 5 years.

- Social factors and child growth, particularly linear growth *throughout* the first four years of childhood, were independently associated with child development in this setting.

- Males were particularly vulnerable to poor growth and development in this cohort.

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APPENDICES

Appendix 1: Relevant sections from the Bt20+ questionnaires used for thesis

BIRTH TO TWENTY: BABIES

ANTENATAL QUESTIONNAIRE

THIS INFORMATION WAS COLLECTED AT EVERY INTERVIEW:

DATE: **Day** ☐☐ **Month** ☐☐ **Year** ☐☐☐☐

BTT ID NUMBER: ☐☐☐☐☐☐☐

BONE ID NUMBER: ☐☐☐ **INTERVIEWER:** ☐☐☐☐☐☐

Date of birth of child:

Sex of child:

Population Group

Indian	1
Coloured	2
African	3
White	4
Other	5

2. Mother's Age: ☐☐

PREVIOUS PREGNANCIES

In this section I am going to ask you about your pregnancy now, previous pregnancies, your health and a little about the health of your close family.

1. Have you ever been pregnant before?

Yes = 1	No = 2

If **NO** go to **Q5**

If **YES** go on to **NEXT QUESTION**

2. Please give the following details for each pregnancy:

DELIVERY: Spontaneous/Vaginal=1 Assisted: Forceps = 2 Vacuum = 3 Caesarian Section = 4 Unknown = 5	SEX: Male= 1 Female= 2	BORN ALIVE BREAST FED ANY ABNORMALITY FULL TERM Yes= 1 No=2	CHILD'S HEALTH NOW Healthy= 1 Unwell= 2 Unknown= 3 Dead Now= 4

No	DOB	Delivery	Sex	Born Alive	Full Term	Child's Health	Any Abnormalities	Breast Fed
1								
2								
3								

HOME SITUATION

We would like to know a little about your home situation.

1. Are you

1 = a	2 = earning	3 = a	4 =

housewife	money	student	unemployed

2. Could you please tell me what you marital status is

1 = single	2 = divorced	3 = civil marriage	3 = common law marriage	3 = traditional marriage	4 = widow

4. Are you living with

1 = father of your child	2 = another partner	3 = with no sexual partner

LIVING CONDITIONS

The type of facilities that are provided for the area where a person lives can influence health. We are interested in what facilities are available to you. I am going to ask you some questions about your home.

1. How would you describe where you live – as a

1 = shack	2 = flat	3 = house	4 = hostel	5 – shared house with another family	6 = other

2. Is your home

1 = owned	2 = rented from another person	3 = rented from local authority	4 = provided by employer

Can you please tell me how many people live in your home?

Name (initials)	Sex M=1 F=2	Age	Contributes to family income 1=Yes 2 = No	Relationship to you

4. How many rooms in your home are used as sleeping rooms?

<u>WATER AND SANITATION SUPPLY</u>

4. Which of the following do you have in your home?

	Yes = 1	No = 2
Electricity		

Television		
Radio		
Motor vehicle		
Fridge		
Washing machine		
Telephone		
Children's toys		

EDUCATION

For various reasons people have more or less opportunity to attend school as well as getting other training or qualifications. I would like to know what schooling you and your partner had.

1. What is the highest standard you passed at school?

1 = no formal schooling	6 = grade 8
2 = grade 1 / grade 2	7 = grade 9
3 = grade 3 – 5	8 = grade 10
4 = grade 6	9 = grade 11
5 = grade 7	10 = Matric

2. Do you have any post-school training?

Yes = 1	No = 2

If **YES**, please indicate your highest training

1 = Attended courses but did not get degree / diploma
2 = In service training

3 = College diploma
4 = Technikon diploma
5 = University degree
6 = Other

If **OTHER**, please specify _____

SMOKING

We would like to know if you smoke or drink or if you are exposed to someone else's smoke.

3. Do you smoke now?

Yes = 1	No = 2

Daily (at least once per day) = 1	Occasionally (go to **Q5**)	Not at all (go to **Q7**)

7. Do you chew tobacco?

Daily = 1	Occasionally = 2	Not at all = 3

8. Do you use snuff?

Daily = 1	Occasionally = 2	Not at all = 3

ALCOHOL

1. Do you drink alcohol?

1 = Daily
2 = Several times a week

3 = Once a week
4 = Several times a month
5 = Once a month
6 = A few times a year
7 = Never

4. Do you want to be pregnant now?

Yes = 1	Unsure = 2	No = 3

STRESS

Sometimes one's life and that of one's close family goes through periods of being very stressful. I'd like to ask you some questions about any stresses you might have experienced in the last few months.

1. During the last 6 months have you or a member of your close family

   been in real danger of being killed, in one of the following ways?

1 = By criminals
2 = By police, army or other 'officials'
3 = During political activities
4 = This has not happened at all

2. During the last 6 months did you witness a violent crime (e.g. murder, robbery, assault, rape)?

Yes = 1	No = 2

3. During the last 6 months have you found that you are in so much debt that you don't know how you will repay the money?

Yes = 1	No = 2

4. During the last 6 months have you or your close family ever had too little money for basics, such as food, rent, clothes

Yes = 1	No = 2

5. Have you or one of your close family not been able to find a job for more than 6 months?

Yes = 1	No = 2

6. During the last 6 months have you or anyone in your close family been seriously ill?

Yes = 1	No = 2

7. During the last 6 months did any member of your close family die?

Yes = 1	No = 2

8. Is there anyone in your close family with a serious disability (e.g. epilepsy, mental retardation, deafness, blindness, mental illness)?

Yes = 1	No = 2

9. Is there anyone in your close family who has a problem with drugs or alcohol?

Yes = 1	No = 2

10. During the last 6 months have you had a break-up with your husband or partner?

Yes = 1	No = 2

11. During the last 6 months has your husband or partner hit or beaten you?

Yes = 1	No = 2

12. During the last 6 months have you had any serious fight or alienation from members of your family or your close neighbours?

13. During the last 6 months have you or any member of your close family been arrested, had to go to court or consulted a lawyer on a non-routine matter?

Yes = 1	No = 2

14. During the last 6 months have you given help (money, accommodation etc.) to close family or friends in need?

Yes = 1	No = 2

15. During the last 6 months have you been separated unwillingly from any of your children (excluding holidays)?

Yes = 1	No = 2

16. During the last 6 months have you experienced any problems with your other children(such as schools closing, failure at school, problem behaviour, drugs etc.)?

Yes = 1	No = 2	No other child = 3

If **YES**, specify problem _____

BIRTH TO TWENTY: DELIVERY FORM

AGE OF MOTHER

PREGNANCY HISTORY PARA

GRAVIDA

ESTIMATED PERIOD OF GESTATION IN WEEKS

BABY

WEIGHT (grams)

GESTATIONAL AGE (in weeks)

BIRTH TO TWENTY BABIES

6 MONTH CORE QUESTIONNAIRE

BIOLOGICAL MOTHER INFORMATION

2. How many times have you been pregnant?

1.	Total number of pregnancies	
2.	Total number of live births	

3.	Total number of stillbirths	
4.	Total miscarriages/abortions	

3. Have any of your children died? (i.e livebirths)

1 = Yes		**2 = No**	

If **YES**,

Age		**Cause of death/ symptoms**	**Year of death**
Years	**Months**		
1.			
2.			
3.			
4.			

FEEDING

1. Have you ever breastfed this baby?

1 = Yes		**2 = No**	

If **YES**,

a. Are you still breastfeeding this baby?

1 = Yes		**2 = No**	

If **NO**,

b. How old was your baby when breastfeeding was discontinued?

Months		Weeks	

PIT DEPRESSION SCALE

1. At the present time:

	Yes	No	Don't know
1. Do you sleep well?	0	2	1
2. Do you easily lose your temper?	2	0	1
3. Are you worried about your looks?	2	0	1
4. Have you a good appetite?	0	2	1
5. Are you as happy as you ought to be?	0	2	1
6. Do you easily forget things?	2	0	1
7. Have you as much interest in sex as ever?	0	2	1
8. Is everything a great effort?	2	0	1
9. Do you feel ashamed for any reason?	2	0	1
10. Can you relax easily?	0	2	1
11. Can you feel the baby is really yours?	0	2	1
12. Do you want someone with you all the time?	2	0	1
13. Are you easily woken up?	2	0	1
14. Do you feel calm most of the time?	0	2	1
15. Do you feel that you are in good health?	0	2	1
16. Does food interest you less than it did?	2	0	1

17. Do you cry easily?	2	0	1
18. Is your memory as good as ever?	0	2	1
19. Have you less desire for sex than usual?	2	0	1
20. Have you enough energy?	0	2	1
21. Are you satisfied with the way you are coping with things?	0	2	1
22. Do you worry a lot about the baby?	2	0	1
23. Do you feel unlike your normal self?	2	0	1

Single = 1	Civil marriage = 3	Traditional marriage = 3	Separated = 5
Divorced = 2	Common law marriage = 3	Widow = 4	Living together = 6

24. Do you have confidence in yourself?	0	2	1

BIRTH TO TWENTY : BABIES

YEAR ONE – CORE QUESTIONNAIRE

16. Present marital status of mother

18. Number of mother's previous live births ☐

19. Number of mother's previous pregnancies ☐

25. Would you describe where the child lives as

1 = Shack
2 = Flat

3 = House
4 = Hostel
5 = Shared house with another family
6 = Other

26. How many people live in this household? | | |

Adults (over 16 years old)		
Others (less than 16 years old)		

30. What is the highest standard mother has passed at school?

1 = No formal schoolin	6 = Grade 8
2 = Grade 1 / grade 2	7 = Grade 9
3 = Grade 3 - 5	8 = Grade 10
4 = Grade 6	9 = Grade 1
5 = Grade 7	10 = Matric

FEEDING

54. Have you ever breastfed this baby?

Yes = 1	No = 2

55. Are you still breastfeeding this baby?

Yes = 1	No = 2

If **NO**, how old was your baby when breastfeeding was discontinued?

Months	Weeks

BIRTH TO TWENTY

TWO YEAR QUESTIONNAIRE

Owned by family	1
Rented from another person	2
Rented from local authority	3
Provided by employer	4
Other (specify)	5

21. How many rooms in BTT child's home are used for sleeping? ☐

22a. How many -

live

Adults (**16 years and above)**	
Children (**less than 16 years)**	

in the BTT child's home?

26. Present marital status of mother –

Civil marriage only	1	Single	5
Traditional marriage only	2	Divorced	6

Both civil & traditional marriage	3	Widow	7
Living together	4	Separated	8

27. Has the marital status of the BTT mother changed since the birth of the BTT child?

Yes	No

If **YES,** what was mother's marital status at time of birth of BTT child?

Civil marriage only	1	Single	5
Traditional marriage only	2	Divorced	6
Both civil & traditional marriage	3	Widow	7
Living together	4	Separated	8

28. What is the BTT mother's highest educational qualification?

FEEDING OF THE BTT CHILD

I am going to ask a few questions about breast and bottle feeding, as well as questions about the

42. Did you ever breastfeed the BTT child?

Yes	No

If **YES,** do you still breastfeed this baby? | Yes | No |

If **NO,** how old was your baby when breastfeeding was discontinued?

or | | weeks | | | months |

ASSESSMENT OF HOME ENVIRONMENT

I'd like to ask you a few questions about your home & household activities, especially

with regard to your child

96. Is there a radio in the house? | Yes | No |

97. Does anyone in the household own a motor vehicle? | Yes | No |

98. Is there a refrigerator in the house? | Yes | No |

99. Is there a washing machine in the house? | Yes | No |

100. Is there a telephone in the house? | Yes | No |

101. Is there a television in the house? | Yes | No |

BIRTH TO TWENTY

FIVE YEAR QUESTIONNAIRE

Revised Denver Pre-screening Developmental Questionnaire (R-DPDQ)

ITEM
Instructions: *I want to ask you about how X (Child's name) is developing and also want to look at how he or she is learning to do new things.*
Asked of parent/caregiver Score the responses YES (1), NO (0), or NO OPPORTUNITY (0). NO OPPORTUNITY means that the child has not had a chance to demonstrate whether or not he or she can do the item, either because the caregiver does not allow the child to try alone or the child does not have the means, equipment, or resources to do the item.
1. Can X dress him/herself without help? *That is, choose clothes, button or zip clothes (except when fasteners are at the back), put on shoes (except for tying shoelaces)*
2. Can X play any simple board or card games? *Like Drafts or Morabaraba, the game may be homemade or bought, the child must be able to really understand and play the game*
3. Can X brush his/her teeth without help or supervision sometimes? *Including putting toothpaste on. (In case the caregiver concludes that small children should be able to brush their teeth without help — Once the caregiver has answered the question, advise them that they should brush the child's teeth occasionally to ensure proper cleaning.)*
4. Can X get him/herself a bowl of cereal, spoon, dishing it out without making too much mess, and pouring milk (or other liquid) on it?
Interviewer tests Interviewer to sit next to the child at a low table, with child comfortable, next to mother if necessary. Score the responses CORRECT/YES (1) or INCORRECT/NO (0)
5. Build tower of blocks *Put the eight blocks in front of the child, and ask the child (with demonstrations, if necessary, but not help) to stack them or build a tower or tall building. Record the highest number of blocks the child can stack before the tower topples down. Give the child three chances*
6. Count blocks (1) *Put the eight blocks in front of the child. Ask him or her to put one block on your piece of paper. Record how many blocks the child puts on the paper.*
7. Say number of blocks (1)

When child has finished, correct the number of blocks on the paper if necessary and ask the child "How many blocks are on the paper?" Record the child's answer.
8. Count blocks (5) *Ask the child to put five blocks on your piece of paper. Record the no of blocks.*
9. Say number of blocks (5) *When the child has finished, correct the number of blocks on the paper if necessary and ask the child "How many blocks are on the paper?" Record the child's answer.*
10. Imitate vertical line *Interviewer draws a vertical line in the space below. Give the child a pencil and ask him or her to draw a line just like yours. Repeat three times.*
11. Copy a circle *Show the child the first circle drawn on the questionnaire. Without naming the figure or moving your fingers or pencil to show how to draw it, ask the child to draw a picture like the one shown here. Repeat three times.*
12. Copy a cross (+) *Show the child the first cross drawn on the questionnaire. Without naming the figure or moving your fingers or pencil to show how to draw it, ask the child to draw a picture like the one shown here. Repeat three times.*
13. Copy a square *Show the child the first square drawn on the questionnaire. Without naming the figure or moving your fingers or pencil to show how to draw it, ask the child to draw a picture like the one shown here. Repeat three times.*
14. Copy a square demonstrated *If the child is unable to copy the square from the picture, show the child how to draw a square by drawing two opposite sides (rather than drawing the square with a continuous motion).* *Repeat three times.*
15. Pick a longer line *Show the child the two lines below and ask the child which line is "longer." (Don't say "bigger"—We need to know if the child understands the concepts "longer.")* *CHILD RECOGNISES: YES/NO*
16. Pick a longer line - Repeat second time *Turn the page upside down and repeat the question about which line is "longer."* *CHILD RECOGNISES: YES/NO*
17. Pick a longer line - Repeat third time *Turn the page the right way up again and repeat the question about which line is "longer."*

CHILD RECOGNISES: YES/NO

If child does not recognise the longer line, repeat three more times turning page each time

Repeat a fourth time *CHILD RECOGNISES: YES/NO*

Repeat a fifth time *CHILD RECOGNISES: YES/NO*

Repeat a sixth time *CHILD RECOGNISES: YES/NO*

18. Draw a person (3)

Put the blank sheet of paper in front of the child and ask the child to draw a picture of a person. Make sure the child has finished the drawing before moving on. Does child draw three parts? YES/NO

19. Draw a person (6)

Does child draw six parts? YES/NO

20. Knows use of objects

(a) What do you do with a cup? YES/NO

(b) What is a chair used for? YES/NO

(c) What is a pencil used for? YES/NO

21. Knows actions

Show the child the following five pictures and ask the child (tick RIGHT or WRONG):

(a) Which one flies?

(b) Which one says MEOW?

(c) Which one talks?

(d) Which one barks?

(e) Which one gallops?

22. Understands prepositions

Give the child a block and give the following instructions (Tick RIGHT or WRONG).

(a) Put the block on the table.

(b) Put the block under the table.

(c) Put the block in front of me.

(d) Put the black behind me.

23. Names colours

Put a red, blue, yellow, and a green block on the table in front of the child. Point to each block one at a time and ask "What color is this?" Scramble blocks before each question.

(a) Red RIGHT/WRONG

(b) Blue RIGHT/WRONG

(c) Yellow RIGHT/WRONG

(d) Green RIGHT/WRONG

24. Defines words

Make sure the child is listening to you and then say "I am going to say a word and I want you to tell me what it is. Say "What is a . . . . . ."Ask the child to tell you something about it. (But do not ask the child what to do with it.) Record the child's response.

Repeat the question three times if necessary to get a response from the child.

(a) Ball

(b) Lake

(c) Desk

(d) House

(e) Banana

(f) Curtain

(g) Fence

(h) Ceiling

25. Knows adjectives

Ask the child the following questions. Record the child's answers

(a) What do you do when you are cold?

b) What do you do when you are tired?

(c) What do you do when you are hungry?

26. Opposites

Say each of the following sentences slowly and distinctly and wait for the child to fill in the blank. Repeat each sentence three times if necessary.

(a) If a horse is big, a mouse is_____

(b) If fire is hot, ice is _____

(c) If the sun shine during the day, the moon shines during the_____

27. Thumb wiggle

Demonstrate with one or both hands by making a fist with thumb pointing upward. Wiggle only your thumb. Ask the child to wiggle his or her thumb (or thumbs) the same way. Do not help the child, apart from demonstrating. Record whether PASS/ FAIL if child can move the thumb of either hand without moving any other fingers

28. Balance on right foot

Have the child stand away from all support. Show the child how to balance on one foot.

Tell the child to do this and give the child three chances. Record the number of seconds the child is able to stand on RIGHT FOOT ALONE.

Right foot:

Trial 1_____seconds

Trial 2_____seconds *Trial 3_____seconds*
29. Balance on left foot *Have the child stand away from all support. Show the child how to balance on one foot.* *Tell the child to do this and give the child three chances. Record the number of seconds the child is able to stand on LEFT FOOT ALONE.* *Left Foot:* *Trial 1_____seconds* *Trial 2_____seconds* *Trial 3_____seconds*
30. Hopping on one foot *With the child away from all support, ask him or her to hop on one foot (foot of child's choice—left or right). Demonstrate. Score PASS/FAIL. Pass if the child hops on one foot two or more times in a row, either on the same place or while moving, without holding onto anything.*
31. Heel-to-toe walk *Demonstrate how to walk in a straight line, placing the heel of one foot in front of and touching the toe of the other. Walk about eight steps like this and then ask the child to do it. If necessary demonstrate again. Give the child three chances. Score PASS/FAIL. Score pass if the child can walk in a straight line at least four steps, placing the heel no more than about 2–3 cm in front of the toe, and without losing his or her balance.*
32. Interviewer rating of child's speech (all or half understandable) *Rate the child's speech as heard during the assessment. Place a tick against ALL or HALF* *UNDERSTABLE.*

Appendix 2: Differences between analytical sample and excluded sample (objective 1 analysis)

Variable	Included n (%); n=1228	Excluded n (%); n=2045	χ^2(df)/*t*; *p*-value
Demographic variables			
Child gender			$\chi^2_{(1)}$ = 9.23; *p* = 0.002**
Male	639 (52)	952 (46.6)	
Female	589 (48)	1093 (53.5)	
Ethnicity			$\chi^2_{(3)}$ = 29.03; *p* = 0.000***
Black	940 (76.6)	1628 (79.6)	
White	87 (7.1)	120 (5.9)	
Coloured	132 (10.8)	251 (12.3)	
Indian	69 (5.6)	46 (2.3)	
Explanatory variables			
Smoked during pregnancy			$\chi^2_{(1)}$ = 2.34; *p* = 0.126
No	1133 (93.0)	343 (95.3)	
Yes	85 (7.0)	17 (4.7)	
Drank alcohol during pregnancy			$\chi^2_{(1)}$ = 7.87; *p* = 0.005**
No	1066 (88.5)	328 (93.7)	
Yes	138 (11.5)	22 (6.3)	
Pregnancy wantedness			$\chi^2_{(1)}$ = 9.49; *p* = 0.002**
Yes	512 (42.8)	119 (33.6)	
No/ Unsure	685 (57.2)	235 (66.4)	
Marital status			$\chi^2_{(3)}$ = 75.66; *p* = 0.000***
Married	497 (40.5)	705 (34.9)	
Living together	22 (1.8)	191 (9.4)	
Separated/ divorced/ widowed	20 (1.6)	27 (1.3)	
Single	689 (56.1)	1100 (54.4)	
Maternal education			$\chi^2_{(4)}$ = 64.99; *p* = 0.000***
≤ Grade 7	171 (14.0)	284 (16.6)	
Grades 8 -10	478 (39.1)	778 (45.5)	
Grades 11-12	371 (30.3)	522 (30.5)	
Post school training	203 (16.6)	125 (7.3)	
Maternal age at birth			$\chi^2_{(1)}$ = 13.93; *p* = 0.000
<20 years	145 (11.8)	339 (16.6)	
≥20 years	1083 (88.2)	1704 (83.4)	
Overcrowding			$\chi^2_{(1)}$ = 0.01; *p* = 0.932
≤3 people/room	770 (62.8)	896 (63.0)	
>3 people/room	456 (37.2)	527 (37.0)	
Household assets (SES)			$\chi^2_{(4)}$ = 95.30; *p* = 0.000***
0 assets	45 (3.7)	34 (2.1)	
1 asset	100 (8.1)	75 (4.6)	
2 assets	145 (11.8)	142 (8.7)	
3 assets	198 (16.1)	258 (15.8)	
4 assets	281 (22.9)	589 (36.1)	
5 assets	212 (17.3)	321 (19.7)	
6 assets	147 (12.0)	145 (8.9)	
7 assets	100 (8.1)	68 (4.2)	
Outcome variable			
Birthweight	3138.8±486.4	3029.8±523.9	*t* = 5.91; *p* = 0.000***

t-test and chi square test conducted for continuous variables and categorical variables, respectively
**p<0·05, **p<0·01, ***p<0·001.*

Appendix 3: Differences between analytical sample and excluded sample (Objective 2 analysis)

Variable	Included n (%); n=1098	Excluded n (%); n=2175	χ^2(df)/*t*; *p*-value
Demographic variables			
Sex			$\chi^2_{(1)}$= 0.22; p = 0.643
Male	540 (49.2)	1051 (48.3)	
Female	558 (50.8)	1124 (51.7)	
Ethnicity			$\chi^2_{(3)}$= 11.73; p = 0.008**
Black	858 (78.1)	1710 (78.6)	
White	51 (4.6)	156 (7.2)	
Coloured	145 (13.2)	238 (10.9)	
Indian	44 (4.0)	71 (3.3)	
Exposure variables			
Smoking during pregnancy			$\chi^2_{(1)}$ = 0.00; p = 0.997
No	593 (93.5)	883 (93.5)	
Yes	41 (6.5)	61 (6.5)	
Snuff use during pregnancy			$\chi^2_{(1)}$= 0.07; p = 0.793
No	530 (91.5)	808 (91.8)	
Yes	49 (8.5)	120 (8.2)	
Chewing tobacco during pregnancy			$\chi^2_{(1)}$= 0.04; p = 0.850
No	567 (99.5)	874 (99.5)	
Yes	3 (0.5)	7 (0.5)	
Tobacco use during pregnancy			$\chi^2_{(1)}$= 0.01; p = 0.912
No	546 (85.9)	814 (86.1)	
Yes	90 (14.1)	132 (13.9)	
Alcohol use during pegnancy			$\chi^2_{(1)}$= 0.15; p = 0.699
No	553 (89.3)	841 (89.9)	
Yes	66 (10.7)	94 (10.1)	
Prenatal stress			$\chi^2_{(1)}$= 0.01; p = 0.907
<4	1017 (92.6)	2017 (92.7)	
≥4	81 (7.4)	158 (7.3)	
Pregnancy wantedness			$\chi^2_{(1)}$= 0.46; p = 0.498
Yes	245 (39.6)	386 (41.4)	
No/ unsure	373 (60.4)	547 (58.6)	
Marital status			$\chi^2_{(1)}$= 23.57; p = 0.000***
Married/living together	413 (37.6)	1002 (46.5)	
Separated/ divorced/ widowed/ single	685 (62.4)	1151 (53.5)	
Maternal education			$\chi^2_{(3)}$= 22.45; p = 0.000***
≤Grade 7	129 (11.8)	326 (17.7)	
Grades 8-10	466 (42.7)	790 (42.9)	
Grades 11-12	355 (32.5)	538 (29.2)	
Post school training	141 (12.9)	187 (10.2)	
Maternal age (years)	25.5±6.11	26.2±6.04	t = 3.29; p = 0.001**
Overcrowding			$\chi^2_{(1)}$= 0.24; p = 0.628
<3 people/ room	635 (62.3)	1031 (63.3)	
≥3 people/ room	384 (37.7)	599 (36.7)	

Household assets			$\chi^2_{(7)} = 57.16$; p = 0.000***
0 assets	20 (2.0)	70 (5.0)	
1 asset	84 (8.2)	211 (15.0)	
2 assets	142 (13.9)	219 (15.6)	
3 assets	163 (16.0)	238 (17.0)	
4 assets	227 (22.2)	248 (17.7)	
5 assets	175 (17.1)	197 (14.1)	
6 assets	126 (12.3)	133 (9.5)	
7 assets	85 (8.3)	86 (6.1)	
Postnatal depression (Pitt score)			$\chi^2_{(1)} = 0.17$; p = 0.677
<20	837 (76.2)	579 (75.4)	
≥20	261 (23.8)	189 (24.6)	
Ever breastfed			$\chi^2_{(1)} = 21.82.$; p = 0.000***
No	39 (3.5)	164 (7.8)	
Yes	1059 (96.5)	1942 (92.2)	
Duration of breastfeeding (months)	12.8±8.8	10.7±8.8	t = 5.44; p = 0.000***
Outcome variable			
Height-for-age at 2 years (HAZ)	-1.2±1.1	-1.1±1.2	t = -1.95; p = 0.050
Stunted at age 2 years			$\chi^2_{(1)} = 4.09$; p = 0.043*
No	856 (78.0)	579 (81.9)	
Yes	242 (22.0)	128 (18.1)	

t-test and chi square test conducted for continuous variables and categorical variable, respectively
**p<0·05, **p<0·01, ***p<0·001.*

Appendix 4: Differences on key variables between analytical sample and excluded sample (Objective 3 analysis)

Variable	Included n (%) n=636	Excluded n (%) n=2637	$\chi^2_{(df)}$/ *t*; *p*-value
Demographic variables			
Sex			$\chi^2_{(1)}$= 4.82; *p* = 0.028
Male	334 (52.52)	1257 (47.7)	
Female	302 (47.48)	1380 (52.3)	
Ethnicity			$\chi^2_{(3)}$= 36.3873; *p* = 0.000***
Black	549 (86.3)	2019 (76.6)	
White	14 (2.2)	193 (7.3)	
Coloured	61 (9.6)	322 (12.2)	
Indian	12 (1.9)	103 (3.9)	
Exposure variables			
Maternal education			$\chi^2_{(3)}$=18.22; *p* = 0.000***
≤Grade 7	66 (10.4)	389 (16.9)	
Grades 8-10	280 (44.3)	976 (42.4)	
Grades 11-12	218 (34.5)	675 (29.4)	
Post school training	68 (10.8)	260 (11.3)	
Household assets			
Radio			$\chi^2_{(1)}$= 8.03; *p* = 0.005**
No	71 (11.8)	308 (16.7)	
Yes	529 (88.2)	1542 (83.3)	
Television			$\chi^2_{(1)}$= 13.54; *p* = 0.000***
No	123 (20.6)	521 (28.2)	
Yes	475 (79.4)	1327 (71.8)	
Car			$\chi^2_{(1)}$= 0.49; *p* = 0.484
No	397 (66.4)	1256 (67.9)	
Yes	201 (33.6)	593 (32.1)	
Fridge			$\chi^2_{(1)}$= 34.35; *p* = 0.000***
No	120 (20.1)	604 (32.6)	
Yes	478 (79.9)	1246 (67.4)	
Washing machine			$\chi^2_{(1)}$= 1.21; *p* = 0.271
No	488 (81.5)	1468 (79.4)	
Yes	111 (18.5)	381 (20.6)	
Telephone			$\chi^2_{(1)}$= 26.04; *p* = 0.000***
No	224 (37.5)	914 (49.4)	
Yes	374 (62.5)	935 (50.6)	
Own house			$\chi^2_{(1)}$= 3.59; *p* = 0.058
No	448 (71.9)	1622 (75.6)	
Yes	175 (28.1)	522 (24.4)	
Birthweight (g) (mean±SD)	3084.9±480.6	3067.3±520.3	t = -0.78; *p* = 0.437
Relative linear growth (0-2 years) (*z*-score)	-0.3±1.0	0.0±1.0	t = 0.89; *p* = 0.373
Relative linear growth (2-4 years) (*z*-score)	-0.0±1.0	0.0±1.0	t = 0.54; *p* = 0.592
Relative weight gain (0-2 years) (*z*-score)	0.0±1.0	-0.0±1.0	t = -0.12; *p* = 0.903
Relative weight gain (2-4 years) (*z*-score)	-0.1±1.0	0.0±1.0	t = 2.01; *p* = 0.045
Outcome variables			
Denver score age 5y (mean ±SD)	44.1±4.8	43.4±4.7	t = -2.85; *p* = 0.005**

t-test and chi square test conducted for continuous variables and categorical variable, respectively
**p<0·05, **p<0·01, ***p<0·001.*

Appendix 5: Bivariate analysis of factors associated with child development scores at 5 years of age

Variable	Coefficient	*p*-value	95% Confidence Interval
Demographic factors			
Sex			
Male	ref		
Female	1.19	0.002**	0.44, 1.93
Ethnicity			
White	ref		
Black	-1.54	0.237	-4.09, -3.19
Coloured/Mixed race	-0.39	0.783	-3.45, 1.01
Indian	0.25	0.893	2.40, 3.96
Maternal factors			
Maternal age (years)	0.01	0.774	-0.05, 0.07
Marital status			
Married/living together	ref		
Separated/ divorced/ widowed/ single	-0.64	0.115	-1.45, 0.16
Maternal education			
≤Grade 7	ref		
Grades 8-10	1.75	0.006**	0.50, 3.00
Grades 11-12	2.92	0.000***	1.64, 4.20
Post school training	3.95	0.000***	2.37, 5.53
Pregnancy wantedness			
Yes	ref		
No/unsure	-0.54	0.276	-1.53, 0.44
Alcohol use during pregnancy			
No	ref		
Yes	0.21	0.830	-1.73, 2.15
Tobacco use during pregnancy			
No	ref		
Yes	-0.92	0.249	-2.49,0.65
Prenatal stress			
<4	ref		
≥4	0.10	0.893	-1.33, 1.53
Postnatal depression (Pitt score)			
<20	ref		
≥20	-0.58	0.196	-1.45, 0.30
Household factors			
Overcrowding			
<3 people/ room	ref		
≥3 people/ room	-0.47	0.223	-1.23, 0.29
Household assets			
Quintile 1	ref		
Quintile 2	0.73	0.251	-0.52, 1.98
Quintile 3	1.59	0.008**	0.41, 2.77
Quintile 4	2.64	0.000***	1.42, 3.86
Quintile 5	3.04	0.000***	1.76, 4.31
Growth status			
Birthweight (*z*-score)	0.64	0.000***	0.30, 0.99
Relative linear growth (0-2 yrs)	0.77	0.000***	0.39, 1.15
Relative linear growth (2-4 yrs)	0.51	0.005**	0.15, 0.87
Relative weight gain (0-2 yrs)	-0.23	0.228	-0.62, 0.15
Relative weight gain (2-4 yrs)	0.10	0.580	-0.26, 0.46

**p<0·05, **p<0·01, ***p<0·001.*

Appendix 6: Ethics clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Ms Wiedaad Slemming

CLEARANCE CERTIFICATE	**M120609**
PROJECT	Early Child Development in South Africa: Risks and Long-Term Outcomes
INVESTIGATORS	Ms Wiedaad Slemming.
DEPARTMENT	Department of Paediatrics & Child Health
DATE CONSIDERED	29/06/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/06/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Linda Richter

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 7: Change of title

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

20 June 2016
Person No: 447083
TAA

Ms W Slemming
PostNet Suite 672
Private Bag X43
Sunninghill
2157
South Africa

Dear Ms Slemming

Doctor of Philosophy: Change of title of research

I am pleased to inform you that the following change in the title of your Thesis for the degree of **Doctor of Philosophy** has been approved:

From:

To: **Early life risks and child development**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 8: Co-author agreement form

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, **Wiedaad Slemming**, student number [447083], declare that this Thesis is my own work and that I contributed adequately towards research findings published in the articles stated below which are included in my Thesis.

Signature of Student ..... **Date** 7 FEBRUARY 2017

Name of Primary Supervisor: Linda Richter

Signature of Primary Supervisor ..... **Date** 8/2/2017

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the articles by the student as part of her Thesis. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

Article 1: Title: Maternal risk exposure during pregnancy and infant birth weight

Journal name, year, volume and page numbers: *Early Human Development* 2016; 99:31-6

Authors	Name	Signature	Date
1st author	Wiedaad Slemming		7/2/17
2nd author	Braimoh Bello		22 FEB 17
3rd author	Haroon Saloojee		9 Feb 2017
4th author	Linda Richter		8/2/2017
5th author			
6th author			

Comments by primary supervisor:

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.....

Article 2: Title: Early life risk factors and stunting in urban South African two-year olds

Journal name, year, volume and page numbers: *Journal of Developmental Origins of Health and Disease* 2017 (in press)

Authors	Name	Signature	Date
1st author	Wiedaad Slemming		7/2/17
2nd author	Juliana Kagura		20 Feb 2017
3rd author	Haroon Saloojee		9 Feb 2017
4th author	Linda Richter		8/2/2017
5th author			
6th author			

Comments by primary supervisor:

.....

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1

Article 3: Title: Cognitive development at age 5 years: the effects of maternal education, socio-economic status and early life growth examined prospectively in the Birth to Twenty Plus (Bt20+) cohort

Journal name, year, volume and page numbers: *Perinatal and Paediatric Epidemiology* 2017 (submitted)

Authors	Name	Signature	Date
1st author	Wiedaad Slemming		7/2/17
2nd author	Shane Norris		20 Feb 2017
3rd author	Juliana Kagura		20 Feb 2017
4th author	Haroon Saloojee		9 Feb 2017
5th author	Linda Richter		8/2/2017
6th author			

Comments by primary supervisor:

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