IMPACT OF EARLY GROWTH ON BLOOD PRESSURE FROM CHILDHOOD TO ADULTHOOD: BIRTH-TWENTY COHORT.

BY

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A THESIS

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Declaration

I [Juliana Kagura] declare that this thesis is my own original, unaided work. It 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 any other University or institution.

Signed _____ on the

_____day of_____20_____in_____

Dedication

To my children Tinotenda and Nokutenda -you are the reason for the season!

Acknowledgements

I am deeply indebted to Professor Shane Norris for a priceless opportunity to pursue my PhD under his supervision. I appreciate his vast knowledge and skills, guidance and input in building a critical intellectual argument, hypothesis generation and writing the reports from research proposal, ethics application, publications and the whole thesis. He provided not only the platform, but also brought on board international expertise in my area of interest and sent me for statistical training required for my PhD.

Special thanks go to Professor Linda Adair for co-supervision of my work all the way from the USA! She would sacrifice some of her holiday times in South Africa just to spend time with me on building an academic argument, statistical plans and execution of hypotheses. I will be forever grateful for the on-time support from a number of experts in numerous ways: Professor John Pettifor for all the in-depth input from conceptualization to revision of all the manuscripts and Dr Elizabeth Lundeen (Emory University) for statistical training, Dr Pedro Pisa (University of Witwatersrand) and Dr Paula Griffiths (Loughborough University) for expertise in handling socioeconomic status data.

My heart-felt thanks go to my mother, Theresa, for the fervent prayers since birth, relentless emotional support and unconditionally believing in my capabilities. I am truly indebted to Felix, my husband, for being a great companion, encourager and a shoulder to lean on throughout the agonizing, but fulfilling PhD journey. Lastly, I am so grateful to my children; Tinotenda and Nokutenda who were a constant inspiration to my PhD journey.

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List of Abbreviations

BP	Blood pressure
BW	Birth weight
CO	Cardiac output
CVDs	Cardiovascular diseases
DALYs	Disability-adjusted life years
DOHaD	Developmental Origins of Health and Disease
GBTM	Group based trajectory modeling
GEE	Generalised estimating equations
GMM	Growth mixture modeling
HICs	High income countries
HIV/AIDs	Human immune-deficiency virus /Acquired Immune Deficiency syndrome.

HTN	Hypertension
IUGR	Intrauterine growth restriction
LCGA	Latent class growth analyses
LMICs	Low to Middle income countries
NCDs	Non communicable diseases
NHBPEP	National High Blood Pressure Education Program
RAS	Renin angiotensin system
RHG	Rapid height gain-linear growth
RWG	Relative weight gain-weight accrual
SBPHR/DBPHR	Systolic BP : height ration divided by Diastolic BP: height ratio
SES	Socioeconomic status
SNS	Sympathetic Nervous system

TPR	Total peripheral resistance
WHO	World Health Organisation

Theses material

Original publications

1. Kagura J, Adair LS, Musa MG, Pettifor JM, Norris SA. Blood pressure tracking in urban black South African children: birth to twenty cohort. *BMC Pediatr*. 2015;15:78

Student's contribution to publication

Student conducted a literature search, conceptualised the paper, conducted data analyses, drafted the manuscript and revised the manuscript.

2. Kagura J, Pisa P.T, Griffiths P.L, Adair L.S, Pettifor J.M, Norris S.A. Association of socioeconomic status change between infancy and adolescence and blood pressure in South African young adults: Birth to Twenty Cohort. *BMJ Open* .2016; 6:3

Student's contribution to publication

The student conceptualised the paper, drawing from a literature review, conducted data analyses and manuscript writing

3. Kagura J, Adair L.S, PhD, Munthali R.J, Pettifor J.M, Norris S A. Association Between Early Life Growth and Blood Pressure Trajectories in Black South African Children. Hypertension. 2016;68 (5):1123-31.
4.

Student's contribution to publication

The student was solely responsible for conceptualisation of the paper, data management, statistical analyses and writing of the manuscript. Statistical support for paper 3 was sought from Richard Munthali and Bobby Jones for modelling life course blood pressure.

Conference proceedings

Oral Presentation: Blood pressure tracking in urban South African children: Bt20 cohort study. **International Society of Hypertension Teaching seminar Africa region**. 17-20 April 2016 Maputo, Mozambique

Oral Presentation: Kagura J, Adair L.S., Munthali R, Norris S.A, Pettifor J.M. Early Life Growth and Life-course BP in Urban South Africa: BT20 cohort. **DOHaD congress**, 7-11 November, 2015, Cape Town South Africa

Poster Presentation: Kagura J, Adair LS, Musa MG, Pettifor JM, Norris S A. Persistent Elevated Blood Pressure in urban South African children: Birth to Twenty Cohort. Presented at the **Faculty of Health Science Research day**, University of Witwatersrand, Johannesburg, South Africa. September, 2014.

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Non-scientific publications

Check kids' blood pressure to prevent hypertension in later life. 18 August 2015.

http://www.medicalnewstoday.com/releases/298299.php

High blood pressure could go back to childhood. The Star. 20 August 2015

http://www.iol.co.za/lifestyle/family/kids/high-blood-pressure-could-go-back-to-childhood-1.1902807

Elevated blood pressure in childhood persists into adulthood. 20 August 2015

http://www.bizcommunity.com/Article/196/323/133603.html

Why we're the world's uptight people. Sunday Times. 29 November, 2015. Page 13.

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Abstract

Background

Childhood hypertension is of great concern parallel to the obesity epidemic and early manifestation of antecedents of primary hypertension like arteriosclerosis. Patterns of early growth are associated with spiraling rates of raised blood pressure (BP) in paediatric populations. However, not much is known about early growth and its effect on BP from childhood to early adulthood. This study hypothesizes early life growth is associated with BP from childhood to adulthood.

Methods

Data for this study came from a sample of black children from the Birth to Twenty cohort study of children born in Soweto, Johannesburg in 1990. Firstly, persistence of elevated BP between ages 5 and 18 was estimated from sex, anthropometry and BP measurements. Secondly, the association between socio-economic status (SES) change between infancy and adolescence computed from physical household assets and BP at 18 years of age was evaluated using multivariable analyses. Finally, longitudinal BP trajectories were identified using group-based trajectory modeling and multinomial models were used to assess the association of BW, RWG and RHG, and BP trajectories adjusted for several covariates.

Results

The prevalence of hypertension ranged between 8.4 to 24.4% and risk of maintaining the elevated BP status was almost 2-fold between ages 5 and 18 years: RRR: 1.60(95%CI: 1.29-

2.00). An upward social mobility was associated with a 5mmHg reduction in SBP (β: -4.85, 95%CI: - 8.22 - -1.48). Three distinct early patterns of BP development called trajectory groups were identified for SBP and diastolic BP (DBP) for each sex; namely: "lower", "middle" and "upper." A kilogram increase in birth weight (BW) reduced the odds of being in the middle compared to lower SBP trajectory (OR: 0.75, 95%CI: 0.58-0.96), while RWG in infancy was associated with a 4-fold increased odds of being in the upper vs lower SBP trajectory for boys (OR: 4.11, 95%CI: 1.25-13.51). In girls, relative weight gain (RWG) (OR: 1.63, 95%CI: 1.08-2.46; 1.77(1.22-2.56)) and relative height gain (RHG) (OR: 1.90, 95%CI: 1.27-2.86; 2.12(1.39-3.23)) in infancy and mid-childhood was associated with almost 2-fold increase in odds of being in the upper vs lower trajectory. The middle SBP trajectory in girls was predicted by RWG (OR: 1.33, 95%CI: 1.00-1.76) and RHG (OR: 1.58, 95%CI: 1.15-2.17) in infancy. DBP trajectories were significantly but inconsistently associated with RWG and RHG for boys and RWG in mid-childhood and infancy in girls for the middle and upper trajectories.

Conclusions

Distinct BP trajectories are established in childhood and persist into early adulthood. Improving SES throughout childhood may have a protective effect on BP. Policy recommendations around early identification of children with elevated BP accompanied by interventions targeted at optimal growth and interrupting the atypical BP trajectories may reduce the burden of disease attributed to hypertension, especially in girls.

Preface

"As obesity creeps into preschools, and hypertension and type II diabetes become pediatric problems for the very first time, the case for starting preventive health care in the cradle has become too compelling to keep ignoring."

Author: Heidi Murkoff

After an outstanding postgraduate experience as a Masters Student and research assistant in Birth to Twenty, I was very excited about the opportunity to continue my career in research through doctoral studies. This interest was prompted by the experience I had gained in data collection on anthropometry and blood pressure in the Birth to Twenty Cohort Study where I noted that there were some participants who had high blood pressure and were to be sent to the Research nurse for referrals to seek medical attention.

My professor and mentor, Shane Norris, simultaneously ignited my interest in blood pressure studies in the black South African population and challenged my quest and my capabilities into a higher level of critical thinking and encouraged me to knit my ideas into a researchable hypothesis: “blood pressure tracks in distinct manner throughout childhood and is influenced by early life growth and socioeconomic status change from birth.”

To explore this argument, I conducted an extensive literature review and worked on protocol development, ethics clearance, data collection, cleaning and analyses, dissemination of results though peer-reviewed scientific publications and media pieces. This thesis is constructed through a publication route comprising three academic papers.

The outline of the thesis is illustrated below and consists of three sections: the general introduction, empirical chapters and general discussion. The introduction section sets the scene for the thesis which includes the background of the study comprising the problem statement and conceptual framework, literature review and abbreviated methods. Then, the second section includes chapter 3 which lays a foundation by characterising blood pressure profiles of children in this cohort followed by chapter 4 exploring the social determinants of blood pressure in young adulthood then chapter 5 concludes the empirical section by presenting the relationship between early growth and life course blood pressure trajectories from childhood to adulthood.

The thesis is concluded with a general discussion evaluating the extent to which the study addressed the hypotheses, validating the conceptual framework and a reflection on the emerging themes. It also evaluates study limitations, relevance and implications of these findings and future work.

PART 1: GENERAL INTRODUCTION

- ***Chapter 1***: *Background of the study and Literature review*

- ***Chapter 2***: *Methodology*

PART 2: EMPIRICAL CHAPTERS

- ***Chapter 3***: *Blood pressure tracking in urban black south african children: birth to twenty cohort (published)*

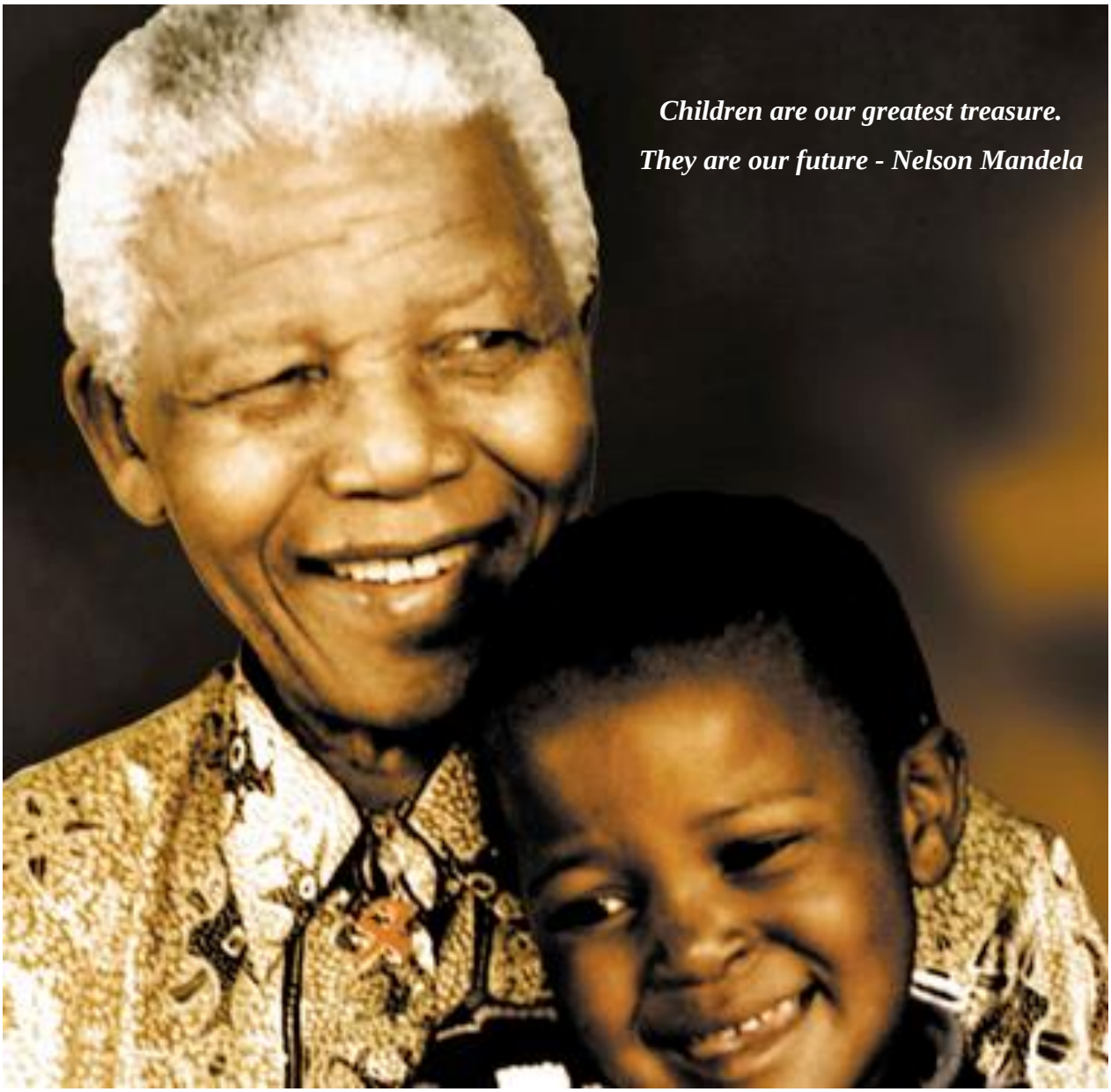
- ***Chapter 4***: *Association of socioeconomic status change between infancy and adolescence and blood pressure in South African young adults: Birth to Twenty Cohort (published)*

- ***Chapter 5***: *Early life weight gain and life course blood pressure trajectories: Birth to Twenty Cohort (published)*

PART 3: GENERAL DISCUSSION

- ***Chapter 6***: *Discussion and Conclusion*

PART 1: GENERAL INTRODUCTION



1 CHAPTER 1: INTRODUCTION

1.1 BACKGROUND

High blood pressure (BP) in children and adolescents is increasingly becoming a major health concern, especially in the face of the rising obesity epidemic over the recent decades (1). Childhood BP could be a window to adult hypertension since BP tends to track from childhood to adulthood (2). Identifying key childhood factors that influence blood pressure may be crucial for early life intervention to reduce the burden of disease attributed to hypertension in adulthood.

South Africa is going through a rapid nutrition and epidemiological transition as a result of socioeconomic changes and rapid urbanisation in the post-apartheid era. This is accompanied by a rising burden of non-communicable diseases in the midst of communicable diseases like HIV/AIDs, as well as a double burden of malnutrition. Children have also been caught up in this transition, with the co-existence of under-nutrition and over-nutrition, often in one household, leading to growth faltering (3, 4).

An emerging body of evidence has reported that an adverse early life environment influencing growth is related to high BP in childhood and adulthood. Specifically, children who are born small but gain more weight in early postnatal life are at higher risk of having raised BP in later life (5). Little is known about the impact of early life growth on longitudinal patterns of blood pressure over time, especially in South Africa where there is paucity of longitudinal data.

Therefore, this study seeks to assess longitudinal blood pressure profiles in urban South African children and examine their relationship with early life growth and socioeconomic status.

1.1.1 Extent of the problem under study

Hypertension remains a major global health threat and a modifiable risk factor for cardiovascular diseases (CVDs), strokes, dementia, renal failure, premature death and disability (6). By 2013, hypertension ranked the most expensive risk factor for disease burden across the globe with an estimated cost of all diseases attributed to hypertension at 208.1 million disability-adjusted life-years (DALYs), and raised blood pressure being responsible for 10.4 million deaths mainly due to cardiovascular diseases represented by a light blue colour in Figure 1-1(7) .

Almost a billion people worldwide are affected by hypertension with a disproportionate number of these residing in low-middle income countries (LMICs), and the under-privileged are more affected even in high income countries. (8). There is evidence suggesting that hypertension in adulthood may have its origins in childhood (9, 10). Several early life factors including socioeconomic status (SES) and growth are associated with raised BP (11). Paediatric hypertension is an emerging major health issue worldwide which is increasing in parallel to the rising obesity epidemic which is an established risk factor for elevated BP in children and adolescents (12).

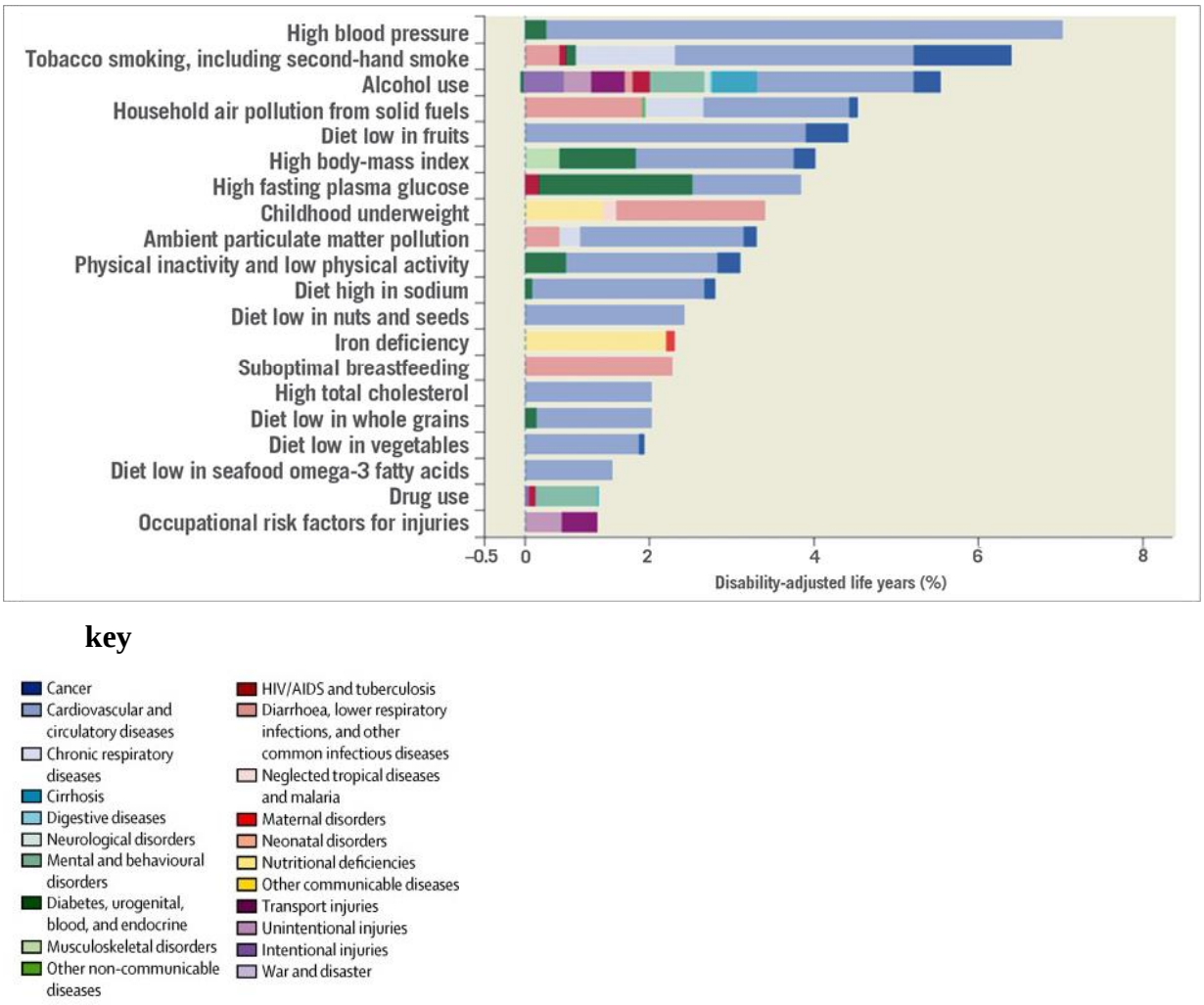


Figure 1-1 Main risk factors contributing to the Global burden of disease (% global DALYs) in 2010 (13)

Global estimates for hypertension in children and adolescents are not as well documented as in adults because of lack of regional statistics and the blood pressure measurement is often overlooked in paediatric practice. However, emerging evidence has shown that it is no longer a rare phenomenon as previously believed (14-16). Primary hypertension is defined as

hypertension with no obvious origin, while secondary hypertension can be as a result of an underlying health problem like renal or cardiovascular disease (17). Primary or essential hypertension is now being diagnosed in children and adolescents.

According to a recent review of global estimates of hypertension one in four adolescents in Africa is hypertensive (18). Children with elevated BP are at higher CVD risk compared to their normotensive counterparts and manifest physiological indicators of preclinical target organ damage, heart disease and renal failure including carotid intima media thickness (19), atherosclerosis, left ventricular hypertrophy (20), and micro albuminuria (21).

1.1.2 Study context: South Africa in transition

Urbanisation and recent socio-economic changes in South Africa since the end of apartheid in 1990 have fuelled a rapid nutritional transition and an epidemiological shift especially in the urban black population (22). The nutrition transition is characterised by a rapid shift towards high fat and sugar consumption, refined foods, acculturation and increased physical inactivity. This is accompanied by a dramatic shift in the burden of disease from communicable disease to non-communicable diseases including coronary heart disease and stroke for which high blood pressure is a key risk factor (23).

As of 2000, approximately 47 000 deaths occurring in South Africa were attributable to high blood pressure, a leading cause of death together with sexually transmitted disease (STDs) (24). South Africa still faces a multifaceted burden of disease; from the HIV pandemic to nutrition related non communicable diseases including hypertension and diabetes (25).

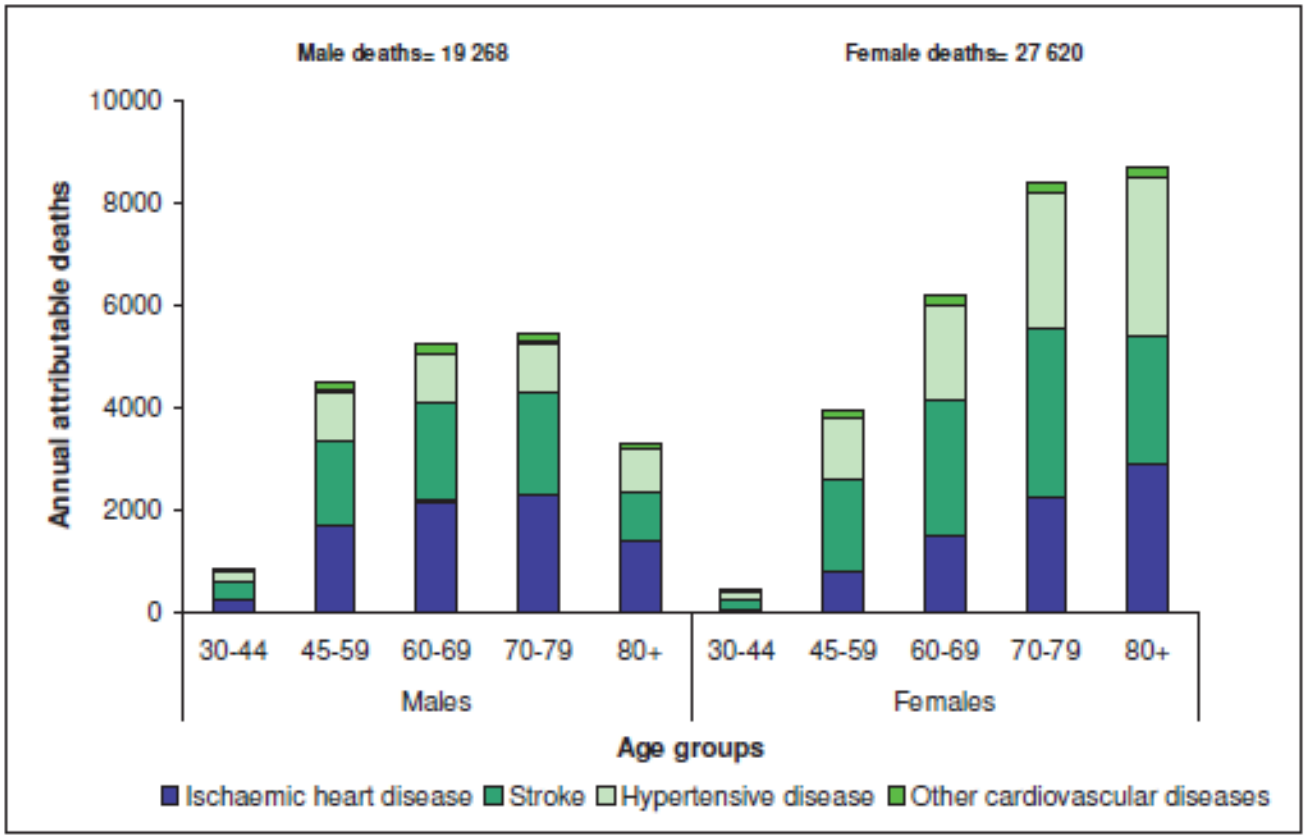


Figure 1-2 Deaths attributable to hypertension in South Africa , 2000 (24)

Children living in South Africa have been caught up in this rapid transition as evidenced by the rising prevalence of overweight and obesity, physical inactivity, high fat and salt diets and

refined foods (26). This is characterised by the co-existence of over-nutrition and under-nutrition, especially among the black population who make up the majority of the South African population. The rising trends of overweight and obesity in children as young as 2-5 years of age is of particular concern. According to the South African National Health Survey completed in 1998, the prevalence of obesity among children aged between 2 and 5 years was 20.5%, despite high levels of stunting in this age group (21.6%) (27).

1.1.3 Conceptual framework for life course approach to hypertension and other chronic disease risk

The aetiology of primary hypertension is complex and often multi-factorial with increasing evidence supporting the notion that even though hypertension is partly genetic in origin, the recent rapid progression and degree of variation in hypertension cannot be fully explained by genetics (28). Barker and colleagues proposed that adverse early life environment interacting with genes, even before birth, may set a series of physiological and metabolic changes which might change the life course 'trajectory' of an individual's health (29). There is need to understand the importance of early life factors in setting BP patterns in a growing child using the life course approach.

The WHO conceptual framework on the life course approach to the aetiology and prevention of chronic diseases in figure 1-3 illustrates how biological, behavioural, psychosocial conditions, nutrition status, and rapid or restricted growth across the life course as well as across

generations, affects the onset and progression of chronic conditions like hypertension (HT) independently, cumulatively or interactively. It states that an individual `s health trajectory is influenced by a number of societal and environmental exposures across the life span which includes foetal and infancy, childhood, adolescence, adulthood and ageing (30).

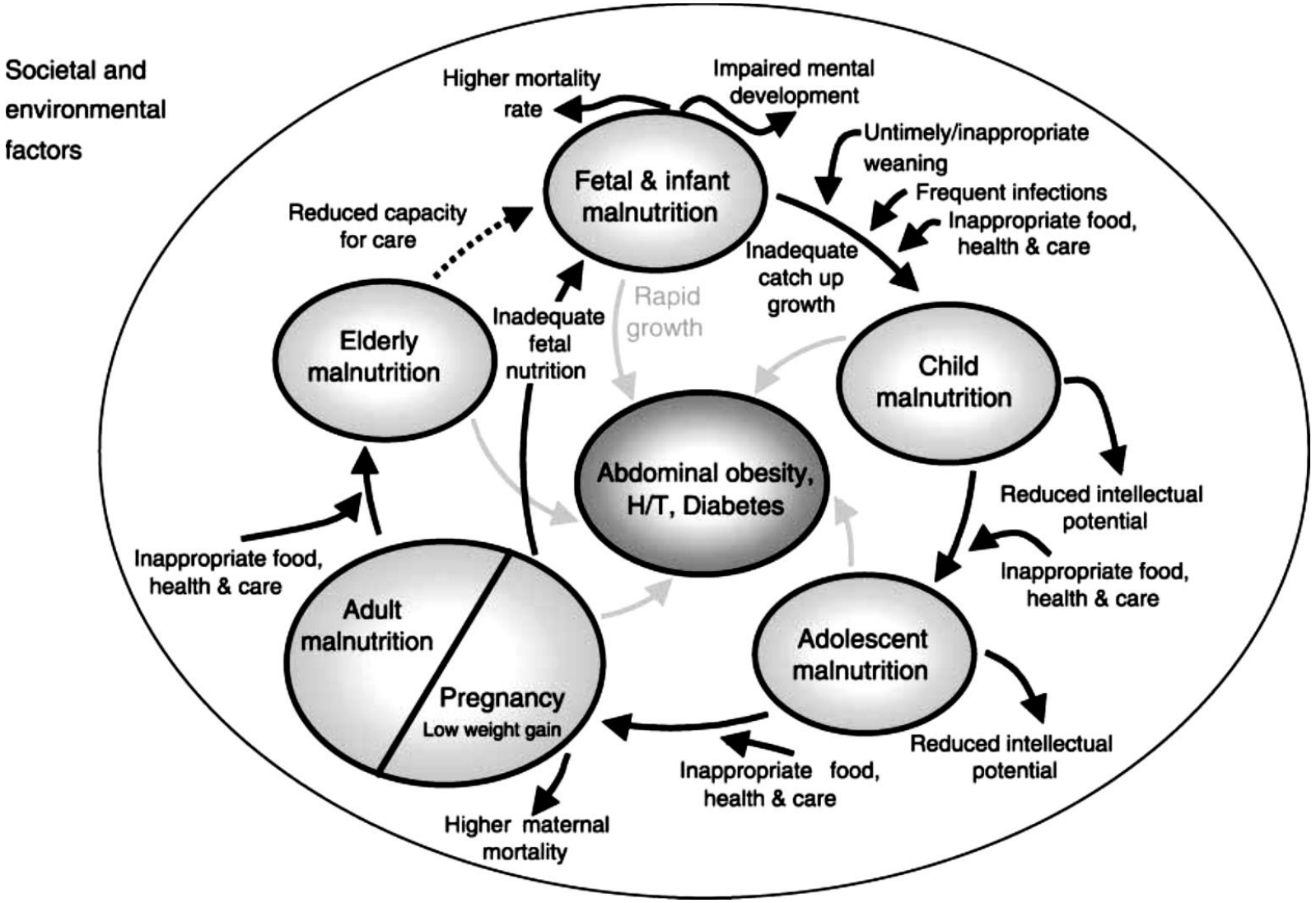


Figure 1-3 The WHO life course approach conceptual framework for prevention of non-communicable diseases (30)

The conceptual framework incorporates critical periods and the accumulation models postulated by Ben-Shlomo and Kuh (31) The critical period model suggests that any environmental (either biological or social) insult during critical periods of growth and development has an adverse long-lasting effect on later disease risk with or without modifying factors. This is based on the developmental origins of health and diseases hypothesis (DOHaD) which states that if the environmental cues coincide with the critical period of development when individuals are at high level of plasticity, they can influence short and long term adverse health outcomes like hypertension (29). The accumulation model states that exposures which are related to chronic disease risk accumulate over an individual's life span or across generations with independent insults or with a clustering of risk (32).

The conceptual framework is applicable to this current study, primarily because it realises that risk factors for chronic diseases are established earlier in life and continue over the entire life course. For instance, blood pressure profiles from birth track into adulthood and across generations predisposing individuals at any stage of life to cardiovascular disease risk and hypertension. In support of this, studies have shown that BP in early life predicts cardiovascular risk in later life, independent of current BP (33).

The framework also states that rapid growth resulting from over-nutrition is linked to hypertension development. This supports the evidence that adverse early life factors (social or biological) or across generations, resulting in foetal intrauterine growth restriction (IUGR) and/or

premature delivery followed by rapid postnatal growth is linked to high BP in later stages of life (34). Conversely, it also states that under-nutrition leading to retarded growth followed by over-nutrition and rapid growth leads to elevated BP. It also recognises the existence of over-and under-nutrition in populations in transition like South Africa, which when coupled with rapid and retarded growth in early life will both lead to the development of chronic diseases like hypertension, obesity and diabetes.

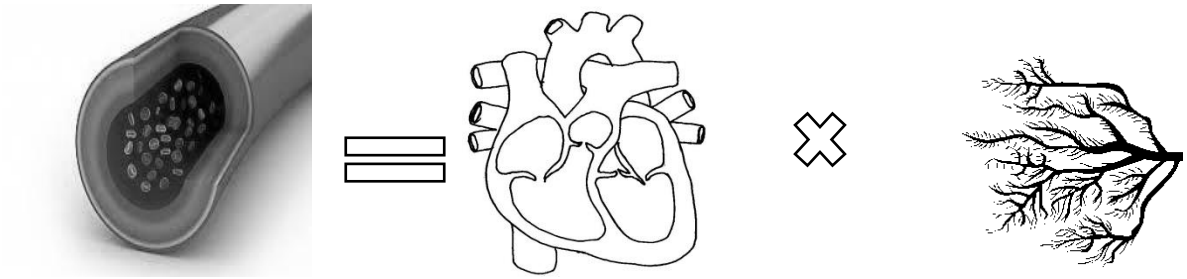
The framework also highlights that societal and environmental factors shape the life course trajectories across the life span. Socio economic transition due to industrialisation has exposed populations to deleterious infant feeding practises, dietary and physical activity patterns and a disproportionate increase in NCDs putting more pressure on the health care system. Though social gradients in BP may be different between HICs and LMICs, there is evidence reporting that low SES is related to high prevalence of hypertension in childhood and adults (35). For the purposes of this study, I focussed only on the early life portion of the framework which encompasses early rapid growth during foetal, infant period, early childhood and late adolescence and blood pressure between ages 5 and 18 years

1.2 LITERATURE REVIEW

This literature review includes hypertension epidemiology: definition, physiology, assessment, definition, prevalence and the biology of hypertension in a growing child. It also comprises evaluation of evidence on the association between socioeconomic status during the life course and blood pressure, and longitudinal BP patterns, their predictors and methodological considerations.

1.2.1 Definition and pathophysiology of raised blood pressure

Blood pressure is defined as the force exerted by circulating blood against the walls of blood vessels. It is jointly determined by the amount of blood ejected into the circulation system by the heart (cardiac output) and the force of the circulation system that impedes blood flow (total peripheral resistance), and an increase in either will result in an increase in blood pressure (36).



Blood pressure (ARTERIES) = **Cardiac output (CO) (HEART)** X **Total peripheral resistance (ARTERIOLES)**

Figure 1-4 Definition of BP (36)

1.2.1.1 Physiological control of blood pressure

The pathophysiology of primary hypertension in children and adolescents is not fully understood because it arises from interaction of a number of complex physiological processes related to the interaction of genetic and environmental factors. Some of the physiological factors linked to elevated blood pressure (increase cardiac output and/or total peripheral resistance) are over-activation of the sympathetic nervous system (37), obesity and insulin resistance (38), stress (39), reduced nephron number, renal salt retention accompanied by increased fluid volume and preload, especially in black populations(40), excess renin-angiotensin, structural and functional changes on the arterioles, and endothelial dysfunction (41).

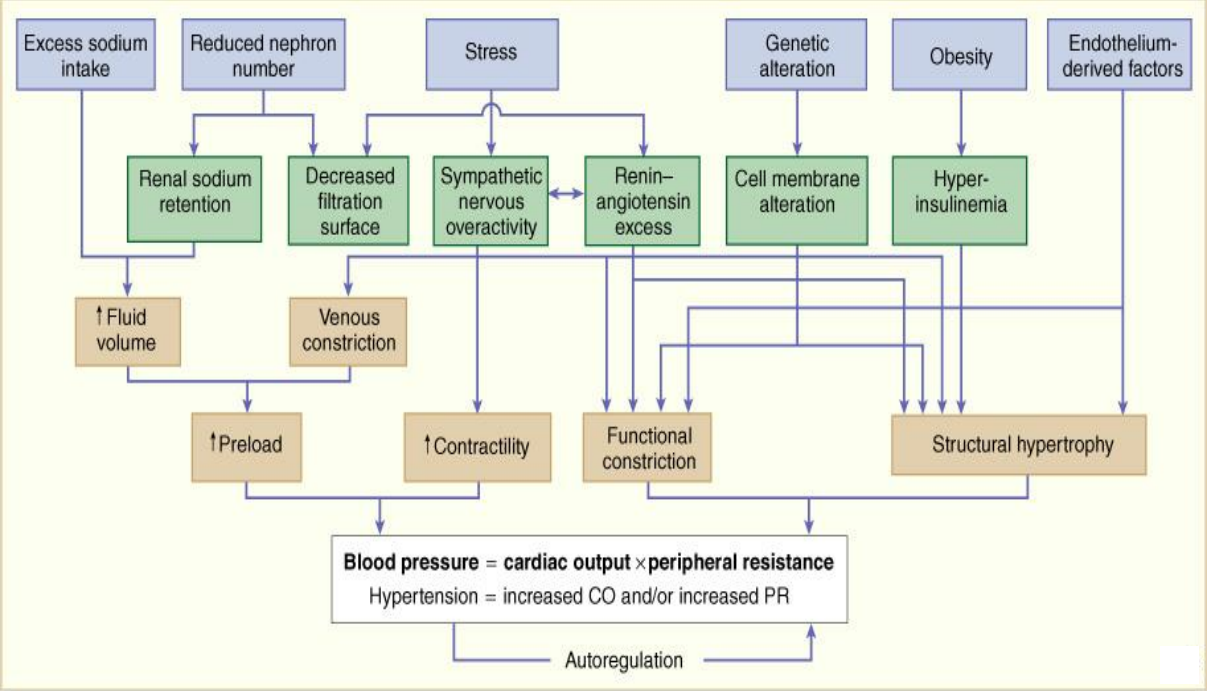


Figure 1-5 Factors involved in BP control (42)

Based on the equation defining BP illustrated in Figure 1-4 and 1-5, an increase in cardiac output is caused by an increase in heart rate and/or stroke volume. Stroke (fluid) volume is the amount of blood ejected from the heart with each contraction. Increased fluid volume may be a result of renal sodium retention due to impaired renal function in filtration, low nephron number or excess dietary sodium intake. Increased heart rate or contractility is mainly induced by over activity of the sympathetic nervous system (SNS). Prolonged stress induced contraction of blood vessels may result in hypertrophy leading to increased CO and TPR, and elevated BP (43).

On the other hand, total peripheral resistance is influenced by levels of functional vasoconstriction in small arterioles and structural changes in the peripheral arteriolar walls resulting in thickening of the blood vessel walls (structural hypertrophy). These changes may be caused by endothelial dysfunction, obesity-induced hyper-insulinemia, epigenetic effects on cell membrane transport function, or interaction between the SNS and the renin-angiotensin system. Increased secretion of renin from the kidneys may be triggered by stimulation of the SNS resulting in increased peripheral vascular resistance.

1.2.1.2 Blood pressure assessment

Over the years, a mercury sphygmanometer has been used to indirectly measure changes in arterial pressure throughout a cardiac cycle. Blood pressure is read as millimetres of mercury (mmHg) recorded as a fraction: systolic over diastolic pressure. Pulse pressure is the difference between the systolic and diastolic pressures and normally ranges between 30-50mmHg in adults.

Mean arterial blood pressure is the average pressure driving blood forward into the tissues throughout the cardiac cycle. Because it is closer to the diastolic pressure since two thirds of the cardiac cycle is spent in the resting state, the mean arterial pressure is calculated as follows: diastolic BP + 1/3 pulse pressure. For example: at 120/80mmHg, mean arterial pressure = 80 + 1/3(40) =93mmHg.

1.2.1.3 Blood pressure classification in children and adolescents

Blood pressure classification and definition of hypertension in children and adolescents are of increasing concern in the light of the importance of early life BP in the etiology of adult high blood pressure and cardiovascular diseases. However, its definition is complex and not fully understood with many methods being explored in a bid to characterize hypertension in childhood. Traditionally, before the 1970s, the cut-off for hypertension in children was classified as 140/90mmHg, similar to adults, leading to under-diagnosis of primary hypertension (44).

In 1977, a task force on blood pressure in children and adolescents prepared a first report on BP in paediatric populations and classified hypertension according to age and sex using a large nationally representative sample (45). Over the following decade, the first report was re-visited incorporating height into the age-sex-specific BP percentiles leading to the 1996 updated report on BP definition in children and adolescents (46). In 2004, the 4th report on high blood pressure in children and adolescents by the National High BP Education Program (NHBPEP) presented classifications of age, sex and height specific BP percentiles which were defined as the systolic

and/or diastolic blood pressure above 95th percentile for age, sex and height based on at least three measurements in Table 1-1(47).

The NHBPEP's age, sex and height specific percentiles have been widely used in different settings beyond the USA bringing a new era in understanding the epidemiology of paediatric hypertension. However, running these algorithmic BP classifications is cumbersome and interpretation of the percentiles is time consuming and makes it difficult to incorporate into routine paediatric practice or for use by caregivers and parents.

Table 1-1 Classification of hypertension risk in children and adolescents <18 years of age according to age, height and sex percentiles (47)

Category	Systolic pressure/ Diastolic pressure (percentiles)
Normal	<90th
Pre-hypertension	≥90th to <95th or SBP>120 mmHg and/or DBP>80mmHg
Stage 1 hypertension	≥95th to <99th
Stage 2 hypertension	≥99th

Recently, simplified tables condensed from the NHBPEP percentiles have been proposed (48). Kaelber and Pickett proposed a simplified tool for BP screening in children aged 3-18 years. They defined the abnormal BP range as (>90th percentile) for age and gender for the lower limit height that is the 5th percentile or 120/80mmHg for pre-hypertension , even if the BP is less than the 90th percentile for age and gender (Table 1-2)(48).

Table 1-2 BP values representation the minimum of abnormal BP based on age, sex and minimum height percentiles

Age, y	**Blood pressure , mmHg**			
	Male		**Female**	
	Systolic	**Diastolic**	**Systolic**	**Diastolic**
3	100	59	100	61
4	102	62	101	64
5	104	65	103	66
6	105	68	104	68
7	106	70	106	69
8	107	71	108	71
9	109	72	110	72
10	111	73	112	73
11	113	74	114	74
12	115	74	116	75
13	117	75	117	76
14	120	75	119	77
15	120	76	120	78
16	120	78	120	78
15	120	80	120	78
≥18	120	80	120	80

The second simplified method adopted from the NHBPEP by Mitchelle et al, plotted the minimum for the 95th percentile for children aged between 3 and 17, regardless of sex or height, for both SBP and DBP, separately (Table 1-3)(49).

Table 1-3 A simplified BP table for hypertension screening in children and adolescents

Source (49)

Look up blood pressure		
Age in years	**Systolic BP (mmHg)**	**Diastolic BP(mmHg)**
3 to <6	≥100	>60
6 to <9	≥105	>70
9 to <12	≥110	>75
12 to <15	≥115	>75
≥15	≥120	≥80

In 2011, another definition for paediatric hypertension was introduced using BP to height ratios (BPHR), that is: SBPHR/DBPHR of 0.75/0.48 and 0.78/0.51 for boys and girls, respectively. This method was postulated by Lu and colleagues using data from China on adolescents (50). It is a very simplified, inexpensive method that has been tested for consistency with the NHBPEP and has been replicated in diverse settings including Africa (51-53). Nonetheless, its major limitation is failure to account for the age of the child since BP increases with age hence many studies have used NHBPEP as a definition of choice.

1.2.2 Epidemiology of hypertension in children and adolescents

This section describes the prevalence of hypertension and the factors associated with primary hypertension in a growing child.

1.2.2.1 Prevalence of paediatric hypertension

There is growing concern about the increasing proportion of children and adolescents with elevated BP worldwide. Global estimates of the prevalence of hypertension (HTN) in children and adolescents are not fully understood due to lack of nationally representative data from all regions, and methodological discrepancies with respect to its measurement and definition. But over the past two decades reports have suggested that there is a dramatic increase in the prevalence of hypertension with several paediatric studies across the globe reporting prevalence of 1.0% in rural South Africa among boys aged 6-13 years (54) to 28% in Chinese children aged 7-17 years (55) (Table 1-4). Though these studies vary with regard to study design, methodology and setting, they give a clear picture that paediatric hypertension is an emerging problem, especially in the context of rising obesity levels and other health-related behaviours in this population.

All of the prevalence studies found in the literature search were cross sectional by design, conducted mainly in school settings, raising questions about the potential to establish causality

and generalizability of findings across populations. Furthermore, there is a paucity of data from urban South Africa where the nutrition transition is more evident compared to rural settings.

It is noteworthy that most of the studies done outside South Africa had three visits and three measurements on each occasion, and as a result the prevalence of hypertension was lowest at the 3rd visit. The proportion of the hypertensive children in the studies that had multiple visits decreased with each subsequent visit. This might be due to regression towards the mean or children getting familiar with the BP assessment procedure (56). For instance, a study conducted in Uganda of children aged 7-18years reported a prevalence of hypertension of 17.1%, 7,1% and 3.8% on the first, second and third visit on the same sample, respectively (57). Similarly, McNiece et al reported a prevalence of hypertension of 3,2% in the final visit in America children aged 11-17 years of age (58). Another possible reason is that childhood BP measurements are prone to the white coat effect attributed to stress response to a health measurement environment which makes it difficult to distinguish between a physiological and pathological BP value in paediatric populations. This raises the importance of ambulatory BP monitoring in children to confirm white coat and masked hypertension. However, a number of studies have shown that white coat hypertension is a significant predictor of CVD events related to target organ damage (59). Sex differences with regards to the prevalence of hypertension were also noted in some studies; with two African studies reporting a prevalence of HTN higher in boys than girls while the Iranian study found a higher prevalence in girls than boys (51, 60, 61).

The definition of hypertension and prehypertension (Pre-HTN) varies from study to study with most authors using the NHBPEP criteria. A few studies used their national representative age, height and sex specific percentiles (55, 61), while others adopted the simplified tables based on the NHBPEP (48, 49) or the BPHRs (50, 51, 53). A study on Nigerian children defined HTN based on the systolic blood pressure: height ratio over diastolic blood pressure: height ratio ((SBPHR/DBPHR) reporting 0.75/0.51 and 0.77/0.55 for boys and girls, respectively.

A variety of instruments have been used to measure paediatric BP from mercury sphygmomanometers to automated BP monitors like the Dinamap (58), Omrons (51, 62), Spacelab/Critikon(63) or InterlliVue MP50 (64). Though many studies have used the mercury sphygmomanometers, it has been under scrutiny around the safety of mercury as an environmental pollutant and its objectivity in detecting the korotkoff- sound during measurement especially in children.

Table 1-4 Global prevalence of paediatric hypertension.

Author(year)	**Location**	**Study design**	**Population**	**Method of measurement**	**Visits(n)and readings**	**BP definition /classification**	**Prevalence (%)**	
			Age(yrs)				**Pre-HTN**	**HTN**
Global								
McNiece *et al*.2007 (58)	USA	Cross sectional	11-17yrs	Oscillometric (Dinamap)	3visit	NHBPEP	15.7	3.2%
Lu,Q.2013 (50)	China	Cross sectional	7-12 yrs	Mercury sphygmomanometer	3 visits 3 measurements	NHBPEP [2]BPHR	-	1st :18.6% 2nd :4.4% 3rd: 2.7%
Urrutia-Rojas *et al.* 2006 (65)	USA							
Zhang *et al.* 2014(55)	China	Cross sectional	7-17yrs	Mercury sphygmomanometer	1 visit	Chinese reference	-	28%(B) 22.5(G)
Meng *et al.* (66)	China							
Hakim *et al*. 2014 (61)	Iran	Cross sectional	11-12yrs	Analog Barometer alpk II	1visit 2 measurement	[1]NTCPHBP	SBP:11.9(B), 7.5(G) DBP:14.5(B), 12.3(G)	SBP:18.8(B), 28.5(G) DBP:15.2(B) , 19.0(G)
Schwiebbe *et al*. 2012 (67)	Caribbean (Bonaire)	Cross sectional	5-16 yrs	Oscillometric monitor	1visit 2nd and 3rd measurement	NHBPEP		SBP:24.7% DBP:8.5%
Steinthorsdottir, *et al*. (64)	Iceland	Cross sectional	9-10 yrs	-Sphygmomanometer (2 readings) -InterlliVue MP50(2 readings)	3 visits 4 measurements	NHBPEP		3.1%
Acosta AA, 2012(63)	USA	Cross sectional		Oscillometric(Spacelab/Critikon)	3 visits 3 /4 measurements	NHBPEP	20%	4%
Mitchell,C K.2011(49)	USA	Cross sectional	3-18 yrs	Oscillometric method	1 visit 3 measurements	Simplified tables adopted from NHBPEP	17.2%	20.3%
Xi, B.2014(68)	China	Cross sectional	8-17yrs	sphygmomanometer	1 visit 2nd and 3rd measurement	[2]BPHR	8-12yrs (4.7%) 13-17yrs (14.7%)	8-12 yrs (2.6%) 13-17yrs (2.7%)
Africa								
Kidy *et al*. 2014 (57)	Uganda	Cross sectional	7-18yrs	Omron M6	3 visits 3 measurements	NHBPEP		1st : 17.1% 2nd: 7.1% 3rd:3.8%

Okoh *et al*. 2012 (69)	Nigeria	Cross sectional	6-12yrs	Mercury sphygmomanometer	3 visit 3measurements	NHBPEP		4.7%
Ellenga Mbolla *et al.* 2014 (70)	Congo	Cross sectional	5-18 yrs	Auscultator method	2 visits 3measurements	NHBPEP	20.7% (B=16.6%; G=24.3%)	1st: 10.1% 2nd:3.3%
Ejike CE, 2011(51)	Nigeria	Cross sectional	11-17 yrs	Omron	1visit 3measurements	[2]BPHR: SBPHR / DBPHR	Only thresholds for ratios	0.75/0.51(B) 0.77/0.55(G)
Agyemang C, 2005 (14)	Ghana	Cross sectional	8-16 yrs	Omron M5-1	1 visit 2 measuremets	none	-	-
Odetunde *et al.* 2014 (71)	Nigeria	Cross sectional	2-5yrs	Mercury sphygmomanometer	1 visit 3measurements	NHBPEP	1.4%	0.5%
Mehdad S et al, 2012 (72)	Morocco	Cross sectional	11-17 yrs	Mercury sphygmomanometer	1 visit 2measurements	NHBPEP	9.6%	17.4%
Ng'andu NH, 1992 (60)	Zambia	Cross sectional	7-16yrs	Mercury sphygmomanometer	1 visit 1 measurement	>95th percentile for sex	-	6.9%(B) 6.1%(G)
South Africa								
Goon *et al.* 2012 (62)	Rural	Cross sectional	10-16yrs	Omron	1 visit 2nd and 3rd measurement	NHBPEP		4.1%(B) 2.8%(G)
Monyeki *et al.* 2006(54)	Rural	Cross sectional	6-13yrs	Automated Micronta monitoring kit	1 visit 3 readings	>95th percentile for age and sex		-1.0%- 5.8%(B) -3.4% - 11.4%(G)
Mamabolo, R.L.2011 (73)	Urban	Cross sectional	12-14yrs	Mercury sphygmomanometer	1 visit 2nd and 3rd reading	NHBPEP	Elevated BP: 33.1% (B); 21.4%(G)	
Nkeh-Chungag *et al.* 2015 (74)	Peri-urban	Cross sectional	13-17 yrs	Microlife automated machine	1 visit 3 readings	NHBPEP	13.6%(B) 11.7%(G)	22.0%(B) 20.9%(G)

[1]NTCPHBP: National Training Centre program for high blood pressure

[2]BPHR Blood pressure to height ratio

1.2.2.2 Factors associated with blood pressure in a growing child

Growth and development in a child is associated with morphological and structural changes in the vasculature and the hemodynamic tree commonly known as vascular aging. Accelerated growth and development is associated with high blood pressure in children and adolescents and a major risk factor for early vascular aging which is proxy for vascular damage and cardiovascular risk (74). There is evidence to suggest that BP in childhood and adolescence is highly correlated with age, sex, growth and obesity, independent of other confounding factors. For this reason age, sex and height are included in the classification and definition of hypertension in children and adolescents (47). Other factors influencing BP in paediatric populations are ethnicity, family history of hypertension/genetics, bio-behavioral factors.

Age

Blood pressure gradually increases with age from childhood to adulthood but rises rapidly during puberty (75). Puberty has been reported to be an independent predictor of BP even in children who were born low birth weight (76). Hemodynamic factors related to age-related changes in BP from childhood to adulthood remain unclear but could be attributed to changes in vasculature in a growing child as a result of structural alterations and calcification as part of vascular remodeling (77). Primary hypertension in childhood is associated with accelerated biological maturation which causes premature aging the metabolic and vascular system termed early vascular ageing (EVA). Key features of EVA are endothelial dysfunction, vascular remodeling, increased arterial stiffness and calcification which contribute to vascular injury leading to

increased TPR in small arteries and increased arterial stiffness thereby increasing BP (78). There is evidence to show that hypertensive children compared to their normotensive counterparts have significantly higher bone age (79), advanced sexual maturation (earlier menarche)(80).

Sex

Sex is a major determinant of BP in a growing child hence its inclusion in the BP normotensive tables (81). Sex-specific differences in age-related changes in BP have been reported to emerge in puberty; with some studies reporting that the rate of change of SBP being three and two times more in puberty compared to pre-puberty and, in boys and girls, respectively (82). Furthermore, studies have shown that the incidence of hypertension is higher in boys than girls (83, 84).

The mechanisms underlying sex differences in age-related changes in BP and hypertension incidence and prevalence are not fully understood although recent reports have identified the role of sex differences in sensitivity to early life adverse environment and sex hormones in BP regulation. Furthermore, boys tend to experience more rapid 'catch up' growth compared to girls, predisposing them to higher risk of developing hypertension (85). Ojeda et al, highlighted that the renin-angiotensin system may be stimulated by testosterone leading to increased BP in boys, especially those who experienced IUGR or adverse early life environmental insults (86). On the other hand, oestrogen in girls plays a protective role by inhibiting over-activation of RAS thereby reducing BP (87).

Growth

Weight at Birth

The fetal period is characterized by rapid cell differentiation and proliferation leaving permanent changes in functional organs and physiological axes, thereby increasing disease risk. This highlights the importance of the early life environment in the physiological programming of blood pressure. Birth weight, a proxy for the prenatal environment, is inversely related to cardiovascular disease risk in later life (88). Low birth weight is defined as <2.5kg by the World Health Organization, may be a result of intrauterine growth restriction (<10^{th} percentile of birth weight for gestational age) or preterm birth or both (89, 90).

IUGR results from fetal environmental insults including maternal factors, which influence structural and functional development of key organs and physiological control of BP from as early as conception. Prenatal insults like maternal gene-environment interactions (epigenetics) may program CVD risk as a result of alterations in the key structural, functional and metabolic processes in several organs (kidney, vasculature, brain, pancreas, liver and adipose tissue) in response to insults like placental insufficiency, maternal malnutrition and high levels of glucocorticoids leading to raised BP (91).

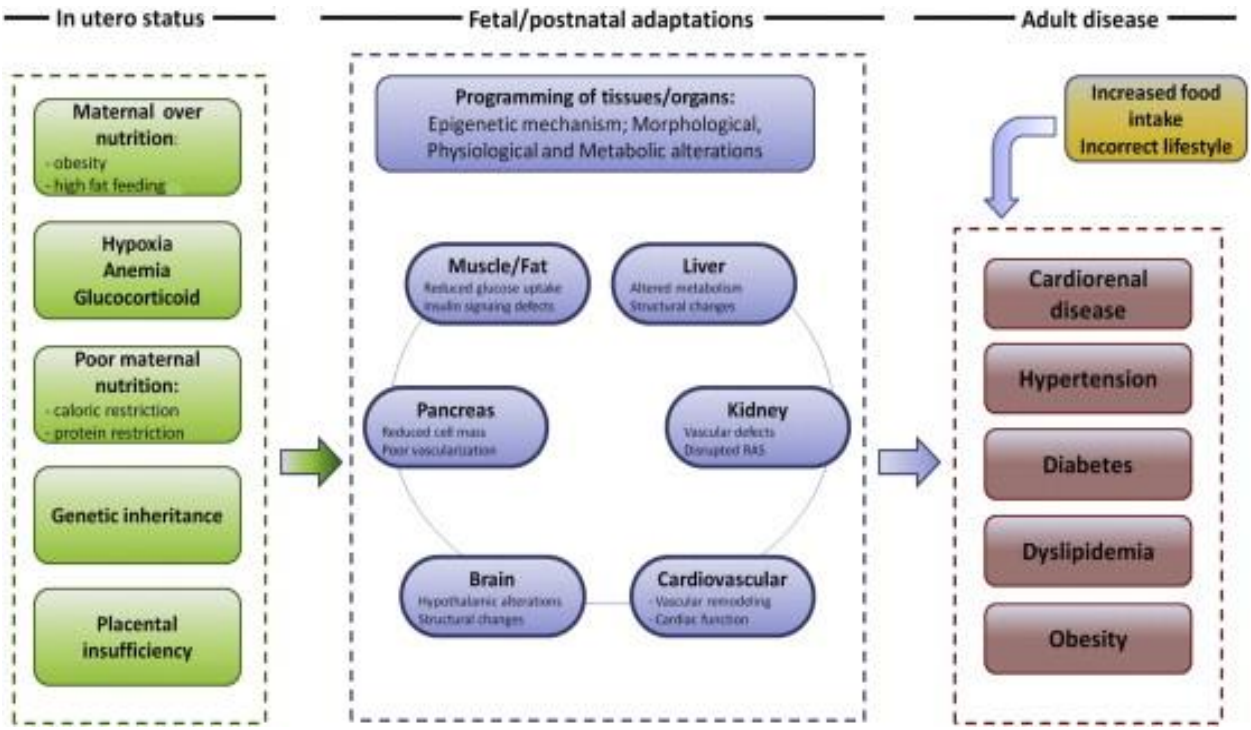


Figure 1-6 Intrauterine influences on adult chronic disease risk

Source (91)

In support of the work of Barker on the fetal origins hypothesis (92), a large body of epidemiological evidence has demonstrated that birth weight is inversely associated with hypertension in childhood and possibly amplifies with age, even after adjusting for factors like smoking, current weight and SES (93). A systematic review and meta analyses of the association between birth weight and SBP in childhood and adulthood reported that a kilogram increase in birth weight predicted a two to five mmHg reduction in SBP (34).

The mechanisms underlying the association between early life environmental cues and hypertension risk in childhood is not fully understood but there is evidence to suggest that IUGR is related to low nephron numbers (94), endothelial dysfunction, overstimulation of the RAS and the SNS leading to raised BP (95). Epidemiological studies reported endothelial dysfunction assessed by carotid stiffness in neonates, children and young adults who experienced IUGR (96-98). Intrauterine growth restriction and low birth weight is related to overstimulation of the SNS and RAS in IUGR infants and children (99). Kingdom et al;1999, reported stimulated cord blood renin activity in IUGR neonates implying that in utero insults might play a role in over-stimulation of the RAS through stress induced activation of the SNS (100).

Height

Height is a major predictor of BP and a biologically and environmentally-sensitive trait. Under-nutrition leading to retarded growth in height, called stunting, is associated with raised BP (101-103). There is considerable evidence to suggest that children born short, who became taller and gain more weight in early life are at a higher risk of having high BP. In support of this, a study in Hertfordshire reported women who were short at birth but had rapid linear growth in childhood were at higher risk of having coronary heart disease (104). With regards to men, another study reported that boys who were in the highest tertile of height velocity in childhood had higher SBP (5mmHg), DBP (3mmHg) and a 66% increased risk of having hypertension compared to those in the lowest height velocity tertile (105).

Weight

Evidence on the association between postnatal weight gain and BP is conflicting, some studies reported that weight gain in infancy is related to later BP (106, 107) while others reported no association (108), or both infancy and mid-childhood weight gain related to later BP (109). Early postnatal growth and rapid weight gain in infancy and childhood has been reported to be associated with risk of raised BP, especially in children who were small at birth (110). In line with this, most of these studies reported that high BP in individuals who had low birth weight, followed by rapid postnatal weight gain (5), even independent of linear growth (111).

A Jamaican study reported that weight gain at one year predicted SBP in 7-11 year old children, while the Barry Caerphilly Growth Study found that immediate weight gain in childhood was associated with BP at 25 years (112, 113). This illustrates the impact of weight accrual on BP which might vary with age and timing. Some reports even argue that postnatal growth might be more important for early onset of hypertension than prenatal growth (114).

The mechanisms underlying the association between weight gain and BP are not fully established but research has shown that children born small but put on more weight postnatally tend to accumulate more fat and are at higher risk of central adiposity in childhood, a major risk factor for raised BP (106, 115). Early life obesity may result from the interaction between genes and environment leading to hyperinsulinemia, endothelial dysfunction, activation of the renin-

angiotensin system and the SNS which are important factors in the pathogenesis of hypertension (116, 117).

Obesity

Obesity is a known correlate of blood pressure across the life course (118). There is evidence to suggest that BMI, marker of obesity, is positively associated with high blood pressure, with the association being stronger for boys than girls. For instance, a Brazilian study of children aged between 14-19 years of age reported that BP was associated with general and abdominal obesity in boys and not in girls, , despite that more girls were obese than boys (119). This could be attributed to the role of sex hormones and ace inhibitors in the regulation of blood pressure.

Other factors

Elevated BP is also related to low socioeconomic status, with children from low SES being at higher risk of having elevated BP compared to their wealthier counterparts (120). Blood pressure in childhood is also highly correlated with family history of BP (121, 122). In addition black children are at higher risk of having raised BP compared to white children and children of other ethnicities (123, 124). Bio-behavioral factors like physical inactivity, alcohol intake and tobacco smoking have been implicated in the association between low SES and raised BP in children and adulthood (125).

1.2.3 Tracking of blood pressure from childhood to adulthood

According to Twisk (126), tracking is the persistence of a characteristic over time or the ability of an earlier measure to predict the variable at a later time point . There is growing evidence suggesting that BP trajectory is established in early life, with childhood BP tracking into adulthood (127, 128). Chen and Wang demonstrated that tracking of BP between childhood and adulthood is positive, moderate and sex specific. They further reported that tracking coefficients were stronger with increasing baseline BP (127).

In support of the evidence on BP tracking, a 15 year longitudinal study of South Korean children aged 7-16 years who completed 12 assessments between 1989 and 2004, reported moderate tracking coefficients for both ambulatory BP (r=0.30-0.59) and office BP (SBP: r=0.54, DBP: r=0.46). They also found out that BP tracked better in boys than girls (129). Another report on Greek school children followed up over 7 years reported a high prevalence of pre-HTN (22.9%,) and HTN (24.1%,) with forty-four percent of the children who had elevated BP ($\geq 90^{th}$ percentile for age, sex, height) at age 9 years remaining in that percentile at age 16 years. Furthermore, tracking coefficients were significantly higher in boys than girls (0.38 vs 0.30) with BMI and baseline BP being the major predictors of BP tracking (10).

There is evidence to suggest that though BP tracking depends on the methodological considerations like type of instrument used to measure BP, number of BP measurements and age at baseline, it is also related to gene-environment interactions (9). The Odense Schoolchild

prospective study in Denmark reported odds ratios (OR) of remaining in the upper BP quartile ranging from 1.6-2.4 and 2.1-3.1 for DBP and SBP, respectively, and that relative weight gain or weight change predicted BP tracking over the 11 years from childhood to adulthood (130).

Biological factors, socioeconomic status and behavioral factors have also been reported to be related to BP tracking between childhood and adulthood (131). Most recent evidence has emerged that modifiable factors like diet, alcohol intake and BMI may be crucial in BP tracking. The study by Kelly et al (132), found out that Australian children who had elevated BP had 35% increased risk persisting in that status in adulthood compared to the normotensive. Furthermore, the individuals who had reverted to the normotensive BP status in adulthood from the elevated BP group had significantly dropped in BMI z-score, alcohol intake z-score, had increased their vegetable intake and had experienced an upward social mobility relative to their counterparts in the persistently elevated BP status over the follow up period.

In spite of the growing body of literature to support BP tracking from childhood through adolescence, there are conflicting studies reporting ranges from negative to positive tracking coefficients (127, 133), while others report no or conflicting sex differences (133, 134) and some suggesting that the tracking coefficients are too low to be of any clinical relevance (128). The majority of longitudinal studies on tracking of BP were conducted elsewhere and not in Africa, hence they may not be generalizable to the African context or population.

1.2.4 Life course socioeconomic status and blood pressure and hypertension risk

Socioeconomic status is an established determinant of health across the life course. According to the WHO, the environment in which children are born, raised and get older influences their health trajectory (135). There is evidence to suggest that social gradients in cardiovascular disease risk and hypertension emerge as early as in childhood (136). However, these reports assume socioeconomic status is static in nature by using a single measure of SES at one time point. Social epidemiology has now adapted a life course approach to understand the influence of socioeconomic status over time on health using three models: the social origins, social mobility and the cumulative models. We found most studies from HICs like USA, Netherlands, UK, Finland, and Sweden, one from a LMIC, Brazil and none from Africa testing these models (Table 1-5).

Most of the studies focus on the accumulation model and the social origins hypothesis and reported on the social mobility model. Despite a huge body of epidemiological evidence supporting the social origins of raised BP in later life, owing to the work by Barker and colleagues (125, 137-139), there is still conflicting findings in testing the social mobility model on BP. Murray et al highlighted that the influence of life course SES models on CVD risk factors like BP may be sex specific. They fitted all the models on CVD risk in British birth cohort of 1946 and reported that the critical period/social origins model best fitted the men and the cumulative model was pronounced in women for CVD risk at 53 years (140).

The social origins model states that early life is a critically sensitive period where adverse socioeconomic status can influence adult health, regardless of intervening changes in SES (141). A Finnish study also reported that childhood SES was related to adult BP independent of current SES (138). This may be regarded as over-adjustment or introducing co-linearity by putting two highly correlated SES variables in one model, raising questions about the precision of the estimates.

The accumulation model states that persistent poverty or low SES sets in motion a cascade of life experiences that accumulate over the life course which is detrimental to blood pressure and its associated risk factors in later life (31, 140, 142). A UK study demonstrated that SES in childhood as well as in adulthood influences BP, BMI and other metabolic disease risk factors (35).

With regards to the social mobility models, change in SES across the life course may be vital for later BP. Several studies reported that an upward mobility in SES (Low-High) is related to low BP compared to a persistent low SES profile, while a downward mobility (High-Low) has a deleterious effect on BP (140, 143), even across generations (144). In a bid to disentangle the three life course models, a case control study was conducted on a sample of men and women who has events of myocardial infarction and they established eight SES trajectories. Their findings highlighted the importance of upward/downward social mobility and the social origins and the cumulative burden of SES (143).

Table 1-5 Summary of major findings on the association between life course SES and BP

First author. Year	Study characteristics			Main findings and life course SES model supported
	Location	**Study design**	**Variables and Age (years)**	
Hogberg, L.2012. **(144)**	Sweden	Twin cohort study	Parental SES BP at ≥80yrs	Upward SES change related to lower odds of hypertension and downward SES mobility associated with higher odds of hypertension in adulthood [social mobility model]
van den Berg, G. 2013 **(125)**	Netherlands	Birth cohort study	Parental SES BP at 5/6yrs	Children from a low parental SES have higher BP levels compared to richer children [social origins hypothesis]
Poulton, R. 2002. **(141)**	New Zealand	Birth cohort study	SES at7time points Adult health at 26yrs	Childhood SES has long lasting adverse influence on health including BP regardless of current SES[cumulative model]
Schreier, H. M.2010. **(139)**	Canada	Retrospective cohort study	Grandparent SES Offspring BP at 13yrs	Low parental SES associated with their child's offspring raised BP [intergenerational social origins model]
Kivimaki, M. 2004. **(138)**	Finland	Cohort study	Baseline at 8yrs BP at 42yrs	Early life SES influences later BP independent of current SES through its effect on BMI [social origins hypothesis]
Power, C. 2007 **(35)**	UK	Birth cohort study	SES in childhood and adulthood BP at 45 yrs	Early life and current SES is related to CVD risk factors including BP [accumulation model]
Chen, E. 2007. **(145)**	USA		10/11 and 14/15yrs	Low SES in early life is associated with later health outcomes independent of the current SES [Social origins

				hypothesis]
Marin, T. J. 2008. **(142)**	USA		Recall life course SES BP at 14-18yrs	Early life SES which persists into adolescence is associated with highest adolescent BP [accumulation / social origins models]
Murray, E. T. 2011. **(140)**	UK		53yrs	Supported the life course SES cumulative model in women and social origins model in men
Hallal, P. C. 2012.**(146)**	Brazil	Birth cohort study	SES:0 and 11yrs NCD:15yrs	SES trajectories not associated with BP at 15yrs Current SES major predictor of NCD risk
James, S. A. 2006**.(147)**	USA	African American Cohort study	Childhood and adulthood SES BP at	Compared to the stable high SES, the odds of being hypertensive were almost 7 times more for the persistent low SES and the high-low SES, 4 times more for the low-high SES. [accumulation model-but inconsistent social mobility model]
Matthews, K. A. 2002. **(148)**	USA (black/white)	Cohort study	SES at 0, 2,5, 7,10yrs BP at 18-30 yrs	Decline in SES trajectory related to incident hypertension[social mobility model]

1.2.5 Early life growth and life course blood pressure

A large body of epidemiological evidence on the developmental origins of health and disease (DOHaD) hypothesis has confirmed that the early life environment may be crucial in setting pathophysiological processes that determine BP in later life (149, 150). The DOHaD hypothesis recognizes that both prenatal and early postnatal life may be critical periods for the development of high BP. However, it is not clear whether these findings hold for life course longitudinal BP patterns. The purpose of this review was to identify key studies on longitudinal BP trajectories from childhood to adulthood, and assess their relationship with early life factors such as growth and SES (Table 1-6).

Blood pressure trajectories-overview and summary of studies

In the summary table of studies on predictors of life course BP , the majority of the longitudinal studies are from the USA (151-157), UK (158-161), the Caribbean(162), Australia (163), Italy (164), and none from Africa. Most of the studies reported longitudinal BP from childhood (153, 154, 156, 158, 162, 165) but some of these explored the influence of early life factors on longitudinal BP (152, 154, 155, 159, 163). The studies highlighted that longitudinal BP patterns vary according to family history of high BP , SES, physical inactivity and dietary intake (154), as well as maternal gestational hypertension (159).

The Bogalusa heart study reported that low birth weight was associated not only with later BP but also with its rate of change and variability over approximately 25 years, suggesting that over-activation of the sympathetic nervous system in utero due growth faltering may be an underlying mechanism linking birth weight to life course BP. In addition, this study also found black children had higher BP variability over time compared to white children (152). This was also supported by Daniel and colleagues, who reported that the rate of BP change in black girls was significantly higher than that of white girls. They also highlighted that BMI as an independent predictor of the change in SBP over time especially in children who were obese, tall and had entered puberty earlier (153)

There is evidence that weight gain in infancy is related to life course BP. An Australian birth cohort study of children followed up from birth until age 17 years also reported that accelerated infant weight gain predicted hypertension at 17 years independent of size at birth. This cohort study in Western Australia following up children from birth to 17 years of age on eight occasions used fractional polynomials based on linear mixed models to model longitudinal patterns of BP (163).

A USA study of children of Black (n=1213) and White (n=1166) girls aged 9/10 years at baseline who were followed up to age 14 years reported that BP increased with age, greater in Black girls compared to White girls over the course of 4 years. It also reported that height was an independent predictor of age-related changes in BP, even after adjusting for puberty and BMI.

Changes in BP were higher in black girls who were obese and tall, and had sexually matured earlier (153). The major strength of this study was that it had low attrition rates (<20%), but it only focused on girls limiting its ability to extend the findings to boys who have being reported to be at higher risk of having raised BP.

The Coronary Artery Risk Development in Young Adults study (CARDIA) from young adulthood (18-30 years) in 1998/1999 through to 2010/2011 in Black and White individuals reported 5 trajectories of BP classified as: low-stable, moderate-stable, moderate-increasing, elevated-stable and elevated-increasing. Participants who were women, White, highly educated and those who had fewer con-current risk factors were in the low-stable group. The individuals in the rapid increasing compared to stable groups were more likely to be African-Americans, having higher BMI and were smokers (166).

Another study by a UK birth cohort born in 1946 was followed up for 53 years, over 20 time points, to characterise BP in midlife. This study reported two latent classes for BP in men and three classes for women DBP, and three classes for pulse pressure for both sexes. They found out that participants in the normal SBP trajectories had higher birth weight, were taller at age 7 years and had a low BMI at 36 years. The "increaser"-group for SBP but not DBP, was associated with a persistent low life course SES and physical inactivity was associated with the "increaser" group in SBP and DBP (161).

Another cohort study (Project HeartBeat!) of childhood BP in which almost 700 children aged 8, 11 or 14 years at baseline were followed up every four months for four years to describe longitudinal patterns of BP noted that SBP rapidly increased between ages 8 and 16 years before levelling off, with the slope being steeper for boys compared to girls without clear ethnic differences. On the other hand, clear ethnic differences were noted in the DBP curve with black children having higher means at all ages and the mean DBP was higher in boys than girls but there were no sex and ethnic differences in the rate of change (slope) of DBP. The SBP and DBP trajectories were significantly predicted by central and overall adiposity; in addition, fat-free mass was associated with SBP (157).

Methodological considerations in modeling longitudinal BP

Longitudinal analyses of BP compared to cross sectional analyses harness the change of BP over time or age. To determine the changes in BP over time requires repeated measures on the same individuals on at least two occasions. The main rationale of these longitudinal studies is to establish the changes of BP over time (at individual and/or intra-individual levels) and analyses of the determinants of these changes (ref. Some of the methods used to analyse longitudinal BP were highlighted in Table 1.5; namely: latent class growth mixture modeling (153, 164, 167), generalised estimating equations (GEE) (159, 165) and multilevel modeling (151, 155-158, 162).

The majority of the studies have used multilevel modelling which is sometimes referred to as mixed effect models with at least two levels; first level being occasion or time point and the

second level being the individual participant. Growth curve modeling is used to fit an unconditional model that estimates a curve of the development of BP over time using the mean (average growth for a population) and covariance structure (variance of growth). However, this method assumes all children follow a uniform pattern of BP changes with time (168).

Another method used in these studies, is finite mixture modelling using either latent class growth mixture modeling (GMM) in Mplus (169, 170) or group-based trajectory modeling(GBTM) using SAS Proc traj (171). These two methods identify clusters of individuals following a similar developmental pattern of a variable of interest called trajectories. A major difference between GMM and GBTM is that GMM assumes that a population distribution has two or more trajectories where each represents a mean growth curve and allows the intercept and slope to vary at individual level but in GBTM the level and change of BP is set at zero just like in Latent class growth analyses (LCGA) (172).

Given the dynamic nature of BP within any paediatric population characterised by different percentiles for age, sex and height, we would also expect to find heterogeneity in longitudinal BP and clusters of individuals within certain age, sex and height-related changes in BP. Growth mixture modelling relaxes the assumption of one growth curve by allowing free parameter estimates across unobserved values thereby assigning individuals to subgroup latent classes. However, when running complex models like adding classes, covariates may add computational time and convergence issues with improper solution and overall model instability hence it is not

uncommon to resort to estimate the level of change rather than the rate of change or export the latent classes to other software packages such as STATA, SAS, SPSS or excel for further analyses (173).

Statistical packages like Mplus and SAS proc traj use maximum likelihood estimations provided data is missing at random (MAR) (174). In addition, the models have to take into account key factors that influence the age-related changes in BP in a growing child, for example height. Adding all these variables into a model tends to introduce complexity and model specification becomes arbitrary especially in finite mixture modeling.

The choice of number of latent classes or trajectory groups may be informed by research questions, model parsimony, proportions in each class and tests for model fit like the Bayesian information criteria (BIC) class posterior probability and proportions (173). The BIC is a good indicator of number of classes for model fit; the smaller the BIC the better the model fit. It takes into consideration the likelihood of the test and the number of parameters in the model hence the more complex the model becomes the lower the BIC. In addition, the best model fit will have a high entropy, posterior probabilities and mode than 1% of total counts in each latent class(175).

Table 1-6 Early life predictors of life course BP trajectories.

Author(reference)	Study location	Age range (yrs)	Longitudinal analyses	Main findings
Bonati, M. T.2014 (164)	Italy	≥5yrs followed up for 25 years 3 time points	Mplus: GMM	Two distinct trajectories
Chen,W. 2012 (152)	USA Bogalusa heart study (all ethnicities)	4-17yrs followed up over 25yrs 6-15 measurements	Growth curve modelling(GCM)	SBP fits cubic terms. Low birth weight inversely associated with SBP variability, rate of change over time
Hlaing, W. M. 2006 (154)	USA(African American(AA) and caucasian	6-9yrs followed up for 12 years , 5 time points	Non-linear mixed models(NLME)	SBP growth velocity is greater in: boys than girls, AA vs non-AA. BP trajectory vary by SES, diet, physical activity and family history of HTN
Howe, L. D.2013 (158)	UK Avon longitudinal study(ALSPAC)	followed up from 6 to 17 yrs	Multilevel modelling	No association of BMI SNPs and changes in SBP
Huang, R. C.2015(163)	Australia	0 to17yrs	Linear mixed modelling	Decelerating adiposity from birth is related to a declining life course BP towards the normative range
Kerner, B. 2009.(176)	Framingham	25yrs at baseline	Mplus :GMM	3 latent classes identified

	Heart Study	over 30 year follow up at 4 time points		(entropy~0.66) and cubic terms for SBP
Nichols, S.2012.(162)	Carribean: Trinidad and Tobago	11 yrs at baseline followed up until 18years	multilevel mixed regression	BMI, body fatness and weight are the main predictors of sex-specific BP changes
Staley, J. R.2015.(159)	UK	7-18yrs	Linear spline random-effects models.	Maternal gestational HTN predicted high offspring BP trajectories independent of birth weight
Strand, B. H.2012. (160)	UK	36,43,53 yrs	Mixed Models	Childhood SES important for rate of change of adiposity and SBP
Su, S.2015. (155)	USA	5 to 38 yrs (13 time points)	Individual growth curve modeling (GCM)	Adverse experiences associated with higher BP trajectories
Tielemans, S. M.2015. (167)	Men from Minnesota study (USA) & Zutphen study (Netherlands)	Minesota study (45-55yrs) Zutphen study (40-60), followed over 10yr period with annual BP measurements	Group-based Trajectories modeling(GBTM): SAS proc traj	Identified four distinct trajectories for SBP and DBP
Wang, X.2006.(156)	USA	7-30 yrs	Multilevel growth models	BP trajectories are sex and ethnic group specific
McGavock, J. M.2007(165)	Canada	5-19 yrs	Generalized linear models	Children with higher BMI gained greater SBP change and grater stroke volume
Briollais, L.2003 (151)	USA Framingham	Analyses restricted to 25-75 yrs at 4	Multilevel modelling	The SBP intercept and slope were significantly

	heart study	time points		predicted by BMI and several specific regions on chromosomes 1,8,17.
Daniels S.R. 1998 (153)	USA AA and White American girls	9/10yrs at baseline, followed up annually until 14 yrs	Generalised linear models (GEE)	BMI an independent predictor of SBP and DBP over time especially in girls who are tall and obese and reached sexual maturity earlier.
Wills A.K. 2012. (161)	UK birth cohort	Started in 1945 up to 53yrs with over 20 time points	GMM: Mplus	Entropy>0.78. 2 classes for men BP, while 3 classes for women. SES key determinant in the 'increaser' SBP class
Labarthe D.R 2009. (157)	USA: Project heartbeat!	Aged 8/11/14 at baseline followed up for 4 years with measurements every 4months	Multilevel modelling : MLwiN	SBP (cubic terms), DBP4(quadratic terms).BP rate of change higher in boys than girls and related to central and overall adiposity

1.2.6 Summary of the literature review

This literature review has highlighted a number of issues with respect to BP in children and adolescents. The prevalence of elevated BP in children and adolescents seems to be rising and tracks into adulthood. Age, sex, height and early life growth and environmental factors are the major determinants of BP in paediatric population. Global estimates are still unknown due to a number of factors like differences in definition and classification of hypertension in childhood, methodological issues in measurement and assessment, and lack of routine inclusion in paediatric visits.

Research also shows that upward SES mobility has a protective effect while a downward SES mobility has a deleterious effect on BP, particularly in adulthood and persistent low SES is associated with high BP. There are various methods of evaluating the change of BP over time, and birth weight, sex, socioeconomic status, weight gain or BMI are related to the level and change of BP over time.

1.2.7 Gaps in the literature

This review has highlighted that BP tracks from childhood to adulthood and despite a large body of evidence on BP tracking, the research findings from various parts of the world remain inconclusive about tracking of BP, possibly because of varying methodological issues in BP

assessment in paediatric populations, or varying geographical or environmental background of studies.

Some of the studies evaluating BP tracking from childhood overlooked children at high risk at baseline (those with BP≥90th percentile for their age, sex and height) (128). This limits the generalizability of their findings to at risk population who have been reported to be at higher risk of developing hypertension and early-onset of cardiovascular injury. A few studies reported the independent influence of BMI on BP tracking. In light of the growing obesity epidemic amongst South African children and adolescents, there is need to evaluate whether BP tracking is mediated by BMI.

Social determinants of raised BP are well established, however the evidence for the influence of life course SES on BP is still scarce worldwide, especially reports on the influence of SES mobility/change on BP in adolescents. A number of life course SES models have been tested but there is inconclusive evidence on the impact of SES mobility/change and BP. Most of the studies were limited to the HICs and may not be generalized to LMICs where socio-economic transitions are more prominent. Understanding the impact of socio-economic status change within a South African context is important for understanding the impact of post-apartheid policies tailor made to improve to the social wellbeing of previously disadvantaged populations.

A number of studies assessed BP trajectories and a few of them focused on paediatric groups (childhood and adolescence). However, most of these studies overlooked the impact of height on age-related changes in BP in a growing child. Furthermore, the majority of the studies evaluated the impact of obesity on the age-related BP changes over time. The problem when using BMI as a marker for obesity does not disentangle the effect of height from early life weight gain which is related to BP via activation of the SNS and RAS (117).

Most studies establishing BP trajectories were based on longitudinal cohort studies and all the studies done in South Africa were cross sectional in nature, making it difficult to assess the BP profiles over time in paediatric populations and the impact of related factors. To our knowledge there is no study in South Arica that has explored the association between life course SES and BP, in spite of the socioeconomic transition underway in this setting. This study is crucial for exploring life course aetiology of high blood pressure from childhood which is an important window of opportunity for interventions since the early life period is a period where humans is capable of adapting to environmental cues.

1.2.8 Relevance and justification

LMICs are experiencing a rapid nutrition and epidemiological transition characterised by a rapid increase in NCDs (177). These countries are expected to be home to most hypertensive adults in the near future unless interventions are implemented to interrupt this development. CVD is most

prevalent in midlife (35-64 years of age) especially in LMICs (178), implying that the main risk factors may track from early life and manifest in adulthood (179).

Owing to the increasing epidemic of obesity in childhood, a risk factor for hypertension, evaluation of blood pressure in children has become a major public health concern. Therefore, it is vital to assess the early life biological (growth) and socio-economic interactions that are associated with blood pressure profiles in order to have a better understanding of the aetiology of hypertension for primary prevention. However, there is paucity of longitudinal paediatric data in Subsaharan Africa due to lack of funding and prioritisation of paediatric hypertension.

The detection of BP patterns (trajectories) from childhood to young adulthood and evaluating the impact of early life growth in An African context may add to the body of evidence from high income countries (HICs) which can inform policy around early life interventions targeting BP. This has been proven not only to be cost-effective, but also may leave a profound mark on reduction in hypertension risk and CVD burden in later life (180). The importance of understanding BP trajectories in early life may shed more light in understanding the etiology of early-onset of hypertension in Sub-Saharan Africa

1.3 Overall aim

To assess the prevalence and tracking of elevated BP from age 5 to 18 years, investigate the relationship of SES change and BP at 18 years, and evaluate the impact of early growth on BP changes over time independent of height.

1.3.1 Specific Objectives

1. To evaluate the prevalence and tracking of elevated BP between ages 5 and 18 years
2. To assess the association between SES change between infancy and adolescence, and BP and hypertension risk at 18 years
3. To assess the impact of weight gain and linear growth in infancy and mid-childhood on distinct BP trajectories for boys and girls between ages 5 and 18 years, independent of height

1.3.2 Research questions and hypotheses

Research question 1: Does elevated BP track from childhood to adulthood?

Hypothesis (H0): Elevated BP does not track from childhood to adulthood

Research question 2: Is SES change/mobility related to BP and hypertension risk at age 18 years

Hypothesis (HO): There is no relationship between SES change and later BP

Research question 3: Are there any distinct sex specific-BP trajectories between ages 5 and 18 years?

Hypothesis (HO): There are no distinct sex specific BP trajectories between 5 and 18 years of age

Research question 4: Is there an association between early growth and BP trajectories independent of height?

Hypothesis (H0): Early growth in infancy and mid-childhood is not related to BP trajectories independent of height

2 CHAPTER 2: METHODOLOGY

This chapter comprises the study setting and design, data management and analyses plan, and ethical considerations. Data for this study was obtained from the Birth to Twenty cohort which is the longest running birth cohort in Africa following up children born in the Soweto-Johannesburg metropole in 1990.

2.1 Study setting

This study was conducted in Soweto in the Gauteng province of South Africa, only 15km from Johannesburg. Soweto is an abbreviation for South West Townships, which developed over time since 1904 to accommodate black gold miners and black people who were displaced from their homes in Johannesburg which were designated for whites following the passing of the Group Areas Act of 1950 which imposed racial segregation on residential areas.

Soweto comprised of thirty-four suburbs and covered approximately 200km^2 and as of 1990, the population was estimated to be 3 to 4 million people when the cohort commenced (181). The population growth was fuelled by rapid, unplanned urbanization resulting in an ethnically and socioeconomically diverse community. This period was characterized by dramatic political, socioeconomic changes in South Africa which had an impact on child health. The study commenced in the midst of the racial inequality gap inherited from the apartheid regime especially with regards to access to health services, child health and socioeconomic status (182).

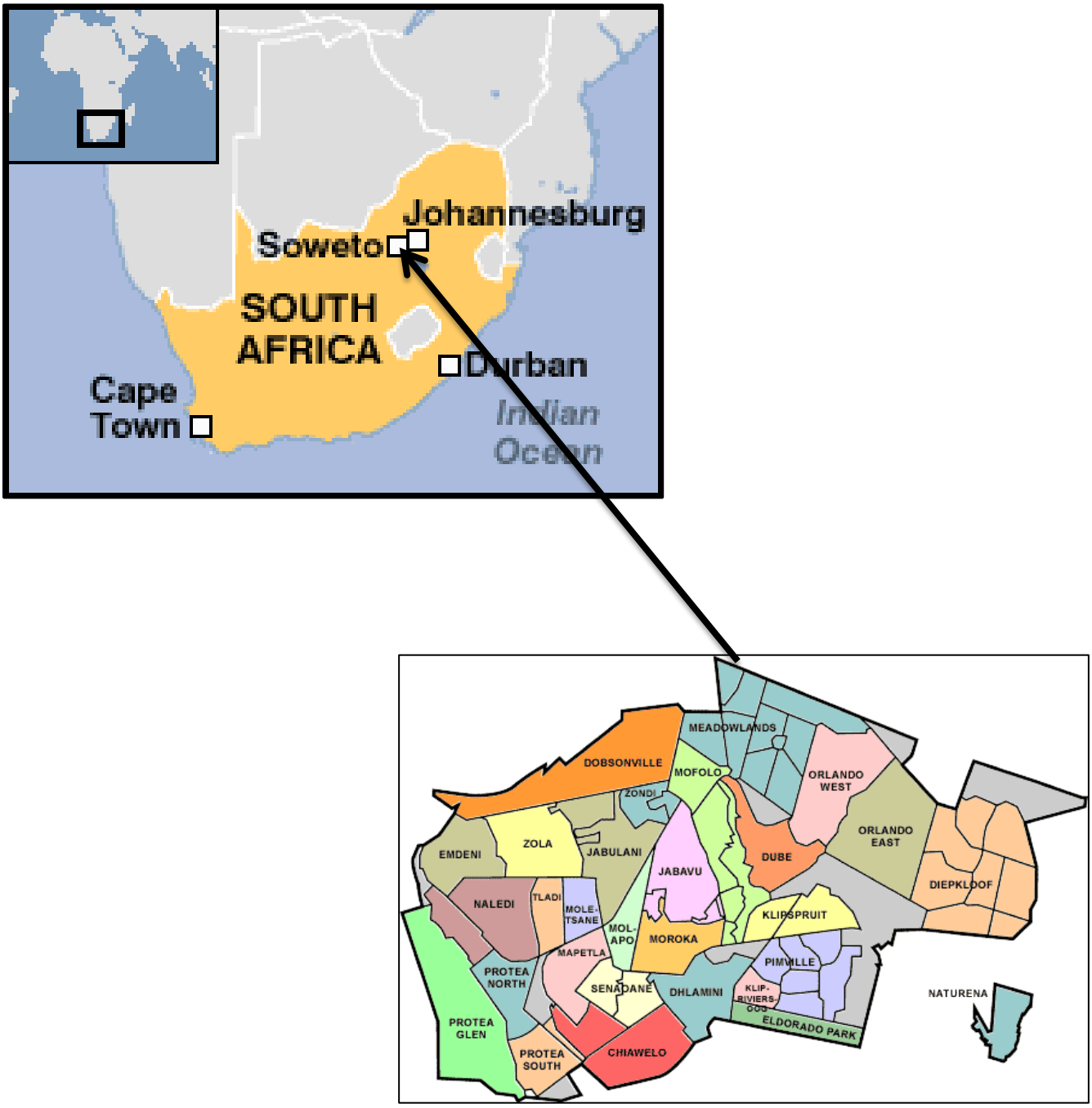


Figure 2-1 The Map of Soweto, Johannesburg-South Africa

2.2 Study design: Birth to Twenty cohort

Data for this study came from the Birth to Twenty longitudinal cohort study (BT20) which is a prospective longitudinal study of singleton children born in a seven week period between April and May 1990 in the Soweto/Johannesburg metropole. Its initial aim was to explore biological socioeconomic environment, psychosocial factors and physical measures associated with growth and development of urban children, but after age 10 years the study began to explore biochemistry, bone health and factors related to metabolic disease risk.

All mothers within the study area who expected to deliver two weeks prior to 23rd of April 1990 and a week after the 10th of May 1990, and who were resident in the study area 6 weeks after delivery were invited to participate. The study was piloted in 1989 on mothers in their second or third trimester of their pregnancy and revealed that approximately 20% of the mothers who delivered in the study area were not permanent residents in the study area and 3273 children met the inclusion criteria for the BT20 study (181).

2.3 Data collection and management

A baseline data collection questionnaire was used to gather information on pregnant women attending antenatal clinics in the study between March and May 1990 by trained interviewers. After delivery, children were followed up at local public health authority baby clinic to collect data from hospital birth notification records on delivery which included mothers demographic

details(name, contact details, parity, age, marital status and employment), details of the infant (e.g. time, infant sex, ethnicity, birth weight, gestational age).

Data were collected on environmental exposures, nutrition, growth and development, access to health care and early life risk factors and from age 10 years, body composition, physiological measures, risk factors for metabolic diseases like insulin resistance and lipids were measured (183). Attrition rates per annum were on average less than 3% per annum for the cohort (184). Data cleaning was conducted by first using the summary statistics to identify outliers and also random selection of IDs to cross check with the filed questionnaires. Analyses were conducted using appropriate statistical software depending on the research question.

2.3.1 Data collection instruments

Standard, general questionnaires were used at each data collection point and were piloted and validated before commencing each data collection wave. The questionnaires were administered in English by a trained research assistant since most participants understood English. However, in rare cases where the participant could only speak their own language, an interviewer whose first language matched that particular participant would administer the questionnaire. The socioeconomic status and anthropometry questionnaire section used in this study are presented in Appendix 1

2.3.2 Measures and procedures

Anthropometry measures

Weight, height and blood pressure were part of the general questionnaire administered by two research assistants trained on anthropometric measurements; female and male observer for girls and boys, respectively. Weight and height were measured using standard procedures (185). Blood pressure was measured by a trained research assistant in triplicates and the details of the procedures are presented in the methods section in Chapters 3, 4 and 5.

Socioeconomic status and demographic variables

Maternal factors such as height, parity, gravidity, marital status and age were collected using a socio-demographic questionnaire at recruitment. Socioeconomic status was based on the number of household assets owned by mother of caregiver for example car, fridge, and television. The list of household consumer durables was based on a validated demographic health survey questionnaire used in LMICs. Details of the measures and procedures used in this study are all outlined in the methods section of chapters 3, 4 and 5. Gestational age for the child was estimated based on the maternal report of last menstrual period. Sex, ethnicity and other demographic factors of the child were recorded at birth.

2.3.3 Analytical strategy for the study

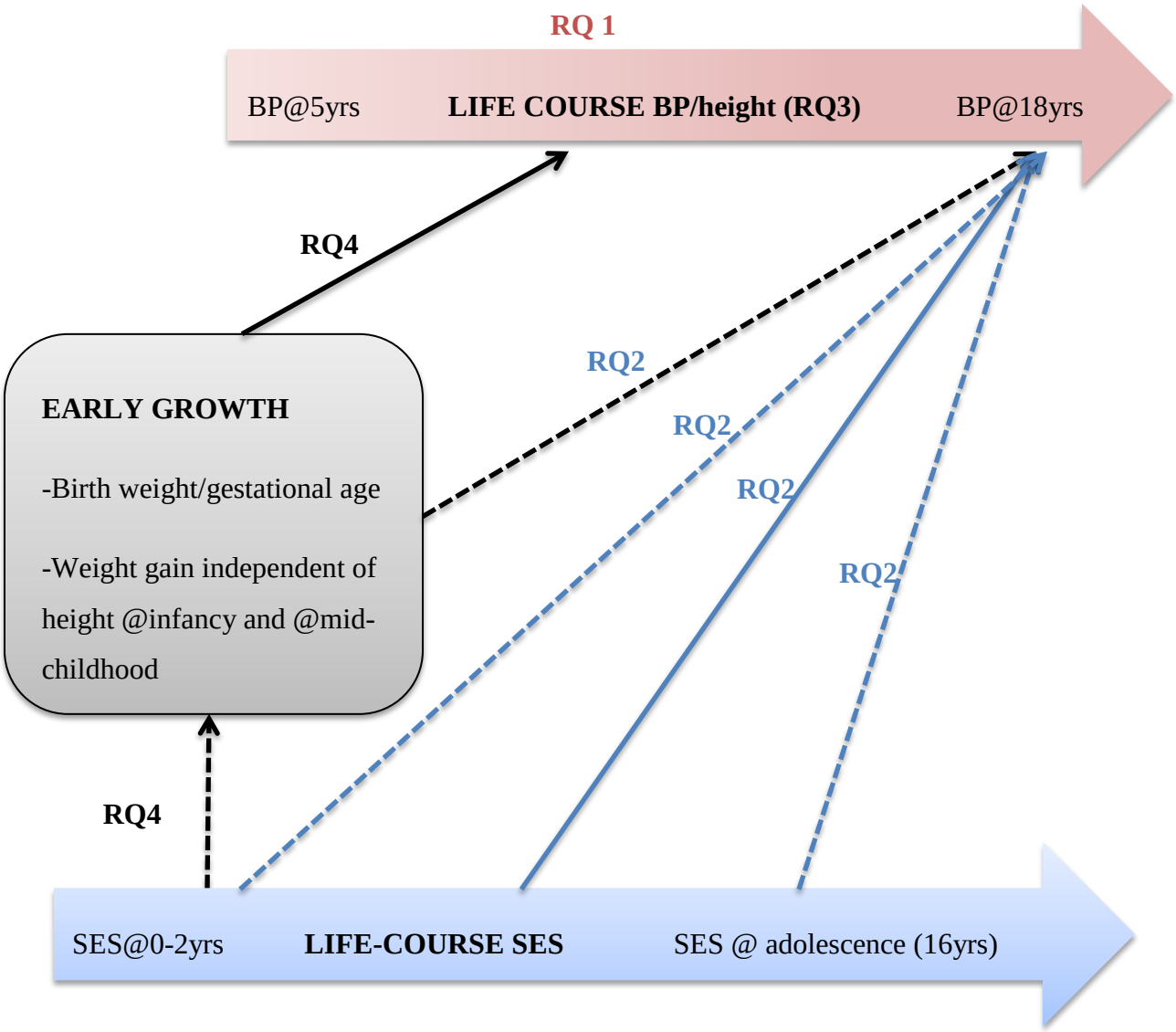


Figure 2-2 Data analysis strategy for the current study

Research Question 1 (RQ1): Does BP track from age 5 to 18 years?

After data cleaning of BP data at every time point, summary statistics were conducted to determine the age-, sex- and height-specific prevalence of prehypertension and hypertension (elevated BP) using the NHBPEP criteria. Comparisons between using CDC- and the WHO-standardized height z scores to define hypertension risk showed no significant differences. Children who had reached eighteen years had their BP classified using adult cut-offs from the Seventh report of the Joint National committee on prevention, detection, evaluation and treatment of high blood pressure (JNC7) : prehypertension (SBP: 120-139mmHg and /or DBP: 80-89mmHg) and hypertension (SBP: ≥140mmHg and /or DBP≥90mmHg) (186).

Research question 2 (RQ2): Is SES change between infancy (0-2yrs) and adolescence (16yrs) associated with BP and hypertension risk at 18 years independent of growth?

Socioeconomic status in infancy and adolescence was based on household assets ownership and a matrix was used to define SES change using the three tertiles of SES at these two time points. The persistent low SES group was designated the reference group. The independent influence of growth (birth weight, gestational age, relative weight and height gain at 2, 4, 18 years of age) on the relationship of SES change and BP and hypertension was explored using multivariate analyses.

Research question 3 (RQ3): Are there sex- and height-specific BP trajectories between ages 5 and 18 years?

To address RQ3 which sought to determine the BP trajectories, finite mixture modelling techniques in Mplus and SAS proc traj in STATA were explored. The main objective was to identify meaningful subgroups of individuals following similar age-related level (intercept) and change (slope) of BP from age 5 to 18 years.

The first step was to export data in compatible format to Mplus, and basic exploratory analyses were run to give summary statistics and correlation matrices and to check for any atypical trends of missing data and outliers. The second step was to fit the appropriate model. We used the intercept, slope, quadratic and cubic terms for black children in the sample for boys and girls, and SBP and DBP, separately using LCGA and GMM to reach the optimal solution in Mplus. I found that three classes for each sex and for SBP and DBP fit this data well using the model fit criteria of high posterior probabilities, and meaningful distinct classes from graphical displays and low BIC. However, I encountered convergence issues when running multinomial logistic regressions with height as a time varying covariate so I ended up using group based trajectory modeling (GBTM) with a STATA plug-in macro developed by Jones and Nagin (187).

For this study , we explored 2, 3, 4, and 5 class models for both SBP and DBP by sex with and without time varying covariates (height between ages 5 and 18 years) to identify the best model fit based on low BIC, posterior probabilities (>0.7) and the nature of the trajectories.

Research question 4 (RQ4): What is the impact of early growth on BP trajectories independent of height between ages 5 and 18 years?

GBTM can be used to run models with both time varying(height between ages 5 and 18 years) and time constant covariates(SES, maternal factors like parity) resulting in trajectories showing probability of group membership over time. The output has an estimated intercept, regression coefficient, a Wald test for statistical significance and BIC. Details of the analyses are found in chapter 5 statistical analyses section.

2.4 Ethical considerations

Informed consent was sought on behalf of the participant when they were minors, from the primary caregivers or parents prior to data collection at each data collection visit. At age 18 years, the participant consented to participate in the study. Ethics clearance for this particular study was obtained from the University of Witwatersrand Human Research Ethics Committee (Certificate no: M130556 –Appendix 2).

PART 2: EMPIRICAL CHAPTERS

3 CHAPTER 3: BLOOD PRESSURE TRACKING IN URBAN BLACK SOUTH AFRICAN CHILDREN: BIRTH TO TWENTY COHORT

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(Published: BMC Pediatrics. 2015; 15:78) (188)

3.1 Background

The increasing prevalence of childhood and adolescent hypertension is rapidly emerging as a global public health concern (189, 190). Although the condition was rarely diagnosed in children due to the lack of its inclusion during routine screening, there is now growing evidence to suggest that essential hypertension in adulthood has its roots in childhood and adolescence (191, 192). Epidemiological evidence from longitudinal cohorts such as the Young Finns study (193), Bogalusa Heart study (194), Muscatine study (134) and the Kangwha study (129) showed that BP tracks from childhood to adulthood. In line with this, a systematic review and meta-regression analysis of a various paediatric cohorts by Chen and Wang (127) reported moderate BP tracking from childhood to adulthood, with overall tracking coefficients stronger for systolic blood pressure compared (SBP=0.38) to diastolic blood pressure (DBP=0.28) with marginal sex discrepancies.

The majority of longitudinal studies following blood pressure patterns from childhood to adulthood comes from high income countries (HICs), there being a paucity of similar studies from low-middle income countries (LMICs) like South Africa where epidemiology of hypertension appears to be unique. The most recent global report from the WHO-SAGE study ranked South Africa highest in prevalence of hypertension in people aged 50 or older (78%) (195). The Heart of Soweto study reported a hypertension prevalence of 55% among adults aged 52.8 years (196). A few studies in South Africa have assessed blood pressure profiles in children and adolescents and have reported a prevalence of hypertension in black children ranging from 1% to 25.9% (54, 62, 197, 198). However, these studies were cross sectional, mostly conducted in rural settings and were not designed to establish tracking of elevated blood pressure into late adolescence.

The longitudinal tracking of BP may provide insight into the aetiology of essential hypertension in adult Black South Africans. Until now, no studies have adequately addressed this because of the lack of longitudinal data on BP in children and adolescents in the same setting. The present study aims to (1) describe the prevalence of elevated BP in a population of urban black South African children and adolescents aged between 5 to 18 years, (2) assess tracking of BP from childhood to at 18 years of age.

3.2 Methods

3.2.1 Study Sample

Data for this study are from the Birth-Twenty cohort, which is following singleton infants, born in the Soweto-Johannesburg Metropolis (N=3273) in 1990. Mothers of these children were residents of Soweto recruited from antenatal clinics who were expected to deliver within the seven-week period between 23 April and 8 June 1990. Follow up was done telephonically or through field visits and contact with parents/caregivers and participants were maintained between data collection time points by newsletters and birthday cards. The details of recruitment and cohort attrition have been described elsewhere (183). For this study, only black participants were selected who had anthropometric measurements and BP assessments in 1995 (n=1026), 1998(n=1024), 2002(n=1351), 2003(n=1391), 2005(n=1624), 2008(n=1587).

3.2.2 Measures

Anthropometry

Trained research assistants carried out anthropometric measurements. Weight was measured on a digital scale to the nearest 0.1kg with participants in light clothes without shoes. Standing height was measured by means of a wall-mounted stadiometer (Holtain, UK) to the nearest 0.1cm. Body Mass Index (BMI) was computed using the formula: weight (kg) divided by height squared (m^2) and converted to WHO BMI z scores for age in STATA.

Blood Pressure assessment

Blood pressure was measured using an Omron 6 automated machine (Kyoto, Japan) from the age 10 years onwards; while a Dinamap Vital Signs monitor 1846SX (Critikon, USA) was used at age 5 years. Three individual measurements were taken at intervals of 2 minutes with participants in a seated position and using an appropriate cuff size after 5 minutes of sitting in a resting position. The first BP reading was discarded and the second and third BP measurements were averaged for all the analyses. We used age, sex and height standardized percentile tables for BP classification in children and adolescents in the analysis where BP status was classified for each gender and CDC-standardised height percentile as either normotensive ($<90^{th}$ percentile), prehypertensive ($\geq 90^{th}$ to $< 95^{th}$ percentile or >120/80 mmHg if $<90^{th}$ percentile) or hypertensive ($\geq 95^{th}$ percentile) using the fourth report from the National High Blood Pressure Education Program working group on high blood pressure in children and adolescents (NHBPEP) (47) as a guideline.

3.2.3 Statistical Analyses

We used descriptive statistics to assess sex differences in variables, for comparison of participants followed up between baseline and age 18 years and to compute proportions of BP status at each time point using student t-test for continuous variables and chi square test for categorical variables. Pearson correlations were used to assess the tracking of BP from baseline at 5 years to the end of follow-up at 18 years. We used multinomial logistic regression models to compute relative risk ratios (RR) to assess the risk of having elevated BP at 18 years of age given

an elevated BP status in childhood or adolescence with normotensive status as a reference group (RR=1). The probability value for statistical significance was $p<0.05$ unless indicated and all the analyses were done using STATA 11.

Ethical considerations

Prior to the study, ethical approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (M130556). Informed consent was sought from parents/caregivers when the participants were minor at the beginning of each data collection session. Data on this study is available to researchers on request from the Developmental Pathways for Health Research Unit data management.

3.3 Results

Study characteristics

Age and sex-stratified mean systolic (SBP), diastolic blood pressures (DBP) and BMI are presented in

Table 3-1. Boys had a marginally higher SBP compared to girls at mean ages 16 and 18 years of age ($p<0.001$). Girls tended to have slightly higher DBP compared to boys but the differences were only significant at mean ages 13 and 14 years ($p<0.001$). Sex differences emerged from age 13 years to 18 years with girls having markedly higher BMI compared to boys ($p<0.001$).

No differences were noted between those who did and did not have information on anthropometry and BP measurements at ages 5 and 18 years, except that those who had measurements at both 5 and 18 years of age had marginally lower BMI (Appendix 3) hence BMI was adjusted in all the models.

Table 3-1 Sex differences in BP and BMI in urban black South African children by mean age

Sex	**Mean age(years)**	**N**	**SBP(mmHg)**	**DBP(mmHg)**	**BMI(Kg/m^2)**
Males	5	503	108(13)	63(8)	16(1)
	8	506	109(10)	69(8)	16(1)
	13	643	106(10)	65(8)	18(3)
	14	659	108(11)	68(9)	19(3)
	16	779	117(12)	68(10)	20(3)
	18	766	121(11)	71(9)	20(3)
Females	5	523	108(12)	64(9)	16(1)
	8	523	109(11)	70(9)	16(2)
	13	708	106(10)	67(8)	19(4)
	14	732	107(10)	70(9)	21(4)
	16	845	110(12)	68(9)	22(4)
	18	821	115(10)	72(9)	23(5)

A student's t-test was used for all analyses and results presented as mean (standard deviations) and level of significance set at:*P<0.05; ***p<0.001

Prevalence of prehypertension and hypertension

Table 3-2 shows the prevalence of pre-hypertension and hypertension at the various time points in childhood and adolescence. The prevalence of prehypertension remained fairly constant across the ages, ranging from 9.2% at age 8 years to 16.4% at age 16 years in the sexes combined. The prevalence of hypertension in boys and girls combined ranged from 22.4% at age 5 years to 15.7% at age 18 years, with the prevalence falling in the intervening years. Sex differences in BP status only emerged at age 16 years, with the proportions of boys having elevated BP being higher than girls ($p<001$).

Table 3-2 Sex-specific BP status in urban black South African children aged 5 to 18 years

Age(years)	**Sex**	**BP status**		
		Normotensive N (%)	**Pre hypertensive N (%)**	**Hypertensive N (%)**
5	M	353(70.2)	52(10.3)	98(19.5)
	F	342(65.4)	49(9.4)	132(25.2)
	Total	695(67.8)	101(9.8)	230(22.4)
8	M	334(66.3)	44(8.7)	126(25.0)
	F	348(66.4)	51(9.7)	125(23.9)
	Total	682(66.3)	95(9.2)	251(24.4)
13	M	490(82.9)	63(10.7)	38(6.4)

	F	522(79.6)	67(10.2)	67(10.2)
	Total	1015(81.3)	130(10.4)	105(8.4)
14	M	502(76.1)	75(11.4)	83(12.6)
	F	548(74.9)	92(12.6)	92(12.6)
	Total	1050(75.4)	167(12.0)	175(12.6)
16	M	466(59.7)	172(22.1)	142(18.2)***
	F	653(77.2)	94(11.1)	99(11.7)
	Total	1119(68.8)	266(16.4)	241(14.8)
18	M	552(72.0)	96(12.5)	119(15.5)
	F	595(72.2)	98(11.9)	131(15.9)
	Total	1147(72.1)	194(12.2)	250(15.7)

A chi square test was conducted to describe the gender differences in blood pressure status at each age category and significance:*$p<0.05$; ***$p<0.001$. Some proportions do not add up to 100% because of rounding off to the nearest 0.1 percentage.

Tracking of blood pressure

Tracking coefficients are presented in Table 3-3 with the average BMI-adjusted correlation coefficients between ages 5 and 18 years for SBP and DBP ranging from 0.20 to 0.57 and 0.17 to 0.51, respectively. It is noteworthy that all the tracking coefficients remained significant even after adjusting for BMI. Overall, the mean tracking coefficients for SBP were marginally higher than those for DBP with inconsistent sex differences in the multivariate models.

Table 3-3 Sex specific tracking correlation coefficients for blood pressure from 5 to 18 years of age

Correlation between two mean age categories	**Systolic BP**				**Diastolic BP**			
	Boys		**Girls**		**Boys**		**Girls**	
	Crude	**Adjusted**	**Crude**	**Adjusted**	**Crude**	**Adjusted**	**Crude**	**Adjusted**
5-8	0.26 ***	0.22***	0.39 ***	0.33***	0.19 ***	0.18***	0.21***	0.17***
5-13	0.28 ***	0.20***	0.27 ***	0.20***	0.24 ***	0.21***	0.20***	0.17***
5-14	0.25 ***	0.20***	0.16 ***	0.16***	0.22 ***	0.22***	0.15***	0.13***
5-16	0.22 ***	0.20***	0.25 ***	0.23***	0.23 ***	0.26***	0.26***	0.25***
5-18	0.23 ***	0.19***	0.18 ***	0.13**	0.23 ***	0.25***	0.15***	0.14**
Average	**0.25**	**0.20**	**0.30**	**0.21**	**0.22**	**0.22**	**0.19**	**0.17**
8-13	0.42***	0.38***	0.43***	0.38***	0.25***	0.20***	0.32***	0.26***
8-14	0.42***	0.41***	0.43***	0.39***	0.28***	0.31***	0.36***	0.36***
8-16	0.27***	0.30***	0.40***	0.44***	0.18***	0.17***	0.31***	0.30***
8-18	0.29***	0.29***	0.34***	0.29***	0.22***	0.22***	0.27***	0.28***
Average	**0.35**	**0.35**	**0.40**	**0.38**	**0.23**	**0.23**	**0.32**	**0.30**

13-14	0.53***	0.61***	0.60***	0.61***	0.53***	0.55***	0.58***	0.62***
13-16	0.50***	0.57***	0.42***	0.49***	0.39***	0.43***	0.41***	0.44***
13-18	0.50***	0.53***	0.41***	0.40***	0.36***	0.39***	0.47***	0.49***
Average	**0.51**	**0.57**	**0.47**	**0.50**	**0.42**	**0.46**	**0.49**	**0.51**
14-16	0.53***	0.57***	0.47***	0.54***	0.48***	0.51***	0.46***	0.49***
14-18	0.47***	0.45***	0.54***	0.44***	0.39***	0.39***	0.48***	0.48***
Average	**0.50**	**0.51**	**0.51**	**0.49**	**0.43**	**0.45**	**0.47**	**0.49**
16-18	0.46***	0.36***	0.44***	0.34***	0.37***	0.34***	0.45***	0.42***

Simple and multiple linear regressions adjusted for BMI-age z score. Significant at **p<0.01 ***p<0.001

Relative Risk of having Elevated BP status at age 18 years

Table 3-4 provides the relative risk ratios at each age category for having elevated BP in late adolescence. BP status was classified as normotensive (<90th percentile) or elevated BP (combining prehypertension and hypertension groups). There is a consistent, significant relationship between BP status at each of the ages 5, 8, 13, 14, 16 years and that in late adolescence ($p<0.001$). Between a third and a half of children who had elevated BP at ages 5, 8, 13, 14 and 16 years, remained with elevated BP status at 18 years, while approximately 20% of children who were normotensive at each age group had elevated BP at age 18 years. The majority of the participants remained normotensive between an earlier time point and age 18 years (range: 77-80%) while 43.8% (age 5 years) to 63.9% (age 13 years) of those who had elevated BP became normotensive at age 18 years.

The relative risk of having an elevated BP at age 18 years for children or adolescents with BP above the 90th percentile for their age, sex and height is presented in Table 3-4. Children who had an elevated BP at each of the age categories had risk of between 1.60 (95%CI: 1.29 to 2.00) and 2.71 (95%CI: 2.32 to 3.17) of having an elevated BP at 18 years of age compared to their normotensive peers ($p<0.001$ in all adjusted models). Adjusting for BMI only reduced the risk slightly.

Table 3-4 Relative risk of elevated BP in urban black South African children between childhood and adolescence

Mean Age(years)	**BP Status**	**BP status at 18 years**			**Relative Risk (95%CI)**	
		Normotensive	**Elevated BP**	**Total**	**Crude**	**BMI-adjusted**
5	**Normotensive**	461(77.3)	135(22.7)	596(69.4) ***	1(ref)	1(ref)
	Elevated BP	168(63.9)	95(36.1)	263(30.6)	1.60(1.28-2.00)	1.60(1.29-2.00)
	Total	629(73.2)	230(26.8)	859(100.0)		
8	**Normotensive**	454(77.2)	134(22.8)	588(66.7) ***	1(ref)	1(ref)
	Elevated BP	184(62.8)	109(37.2)	293(33.3)	1.75(1.43-2.14)	1.69(1.39-2.06)
	Total	638(72.4)	243(27.6)	881(100.0)		
13	**Normotensive**	719(78.4)	198(21.6)	917(81.5) ***	I(ref)	1(ref)
	Elevated BP	91(43.8)	117(56.3)	208(18.5)	2.70(2.28-3.20)	2.56(2.16-3.04)
	Total	810(72.0)	315(28.0)	1125(100.0)		
14	**Normotensive**	770(80.1)	191(19.9)	961(75.2)***	1(ref)	1(ref)

	Elevated BP	147(46.5)	169(53.5)	316(24.8)	2.84(2.43-3.32)	2.71(2.32-3.17)
	Total	917(71.8)	360(28.2)	1277(100.0)		
16	**Normotensive**	830(80.0)	207(20.0)	1037(69.4)***	1(ref)	1(ref)
	Elevated BP	246(53.7)	212(46.3)	458(30.6)	2.34(2.01-2.72)	2.28(2.00-2.65)
	Total	1076(72.0)	419(28.0)	1495(100.0)		

Chi square test was used to assess the difference in BP status at a given two time points and results presented as proportions: n (%). Some proportions do not add up to 100% because of rounding off to the nearest percentage and level of significance set at ***P<0.001

3.4 Discussion

The present study reports a high prevalence of elevated BP, which persists into late adolescence, in a longitudinal cohort of urban black South African children and adolescents. Approximately one-third to a half of children who were hypertensive at some time during childhood and adolescence were hypertensive at age 18 years. The risk of having elevated BP at 18 years of age was lowest at age 5 years and highest at age 14 years.

We reported an overall prevalence of hypertension (>95th percentile) of 22.4% and 24.4% at ages 5 and 8 years, respectively. The prevalence of hypertension in children and adolescents reported in other studies varied considerably from 0% to as high as 25.9% in children aged 6 to 15years of age (62, 65, 199). A study from the North-West province of South Africa reported a prevalence of hypertension of 25.9% in Grade one learners aged 6 years based on one visit and an average of three BP measurements classified according to NHBPEP (198). Studies from other countries in the Sub Saharan Africa have reported a lower prevalence of hypertension in children than the current study; Zambia (6.9% in boys and 6.1% in girls) (60), Congo (10.1%) (70), Nigeria (4.7%) (69). This could possibly be attributed to the epidemiological transition taking place in South Africa and which is characterized by a shift from under-nutrition to overnutrition, and by refined foods and high salt intake in children and adolescents which are risk factors for elevated BP in children, but this needs to be tested within our population (200). It is noteworthy that though many studies from HICs have reported a prevalence of hypertension in children as low as 3% (63, 201), it is reported that the prevalence of hypertension is high in Hispanic (23.6%) and

African-American (17,2%) populations aged between 8 and 13 years (65) which is comparable to our study.

Our results suggest that there is a positive weak-to-moderate tracking of BP in this cohort which is comparable to other studies; with adolescent baseline BP tracking better compared to childhood BP (202, 203). Similar to our findings, Bao and colleagues (203) reported tracking coefficients varying from 0.36 to 0.50 for SBP and 0.20 to 0.42 for DBP in children ages 5 to 14 years after a 15 year-follow-up period, with BMI having no effect on the degree of tracking. Similarly, Toschke et al (128) reported a pooled tracking coefficient of 0.37 from 29 cohort studies of children aged 10 to 20 years. Consistent with other studies, we found out that SBP tracked better than DBP (133, 204). Clarke et al (204) reported tracking coefficients in SBP and DBP of 0.30 and 0.18, respectively.

Existing evidence on sex differences in BP tracking is conflicting; some studies have shown no major differences (133, 205) whereas others have reported that SBP track better in boys (0.38) compared to girls (0.30) but girls (0.22) have higher tracking coefficients compared to boys (0.20) for DBP (10). A previous review on blood pressure tracking from childhood to adulthood found little sex differences in BP tracking with men having stronger tracking for SBP and DBP (127). We have shown that sex differences in BP tracking become more pronounced in adolescent baseline ages compared to childhood; with SBP tracking better in boys than girls and DBP tracking better in girls than in boys. The mechanism underlying these sex discrepancies in

BP tracking before or during adolescence are not fully understood and require further research though some authors have suggested that pubertal development might influence BP tracking especially in adolescence (206).

We found that about 36% of the children who had elevated BP at ages 5 or 8 years retained the elevated BP status at age 18 years of age. These findings are consistent with a recent report from a Germany study of 13 261 both sick and healthy children aged between 3 and 21 years, attending an outpatient clinic, in which the persistence of elevated blood pressure was as high as 35.6% in a six-year follow-up study(207). Similar results have been reported from the USA on data from the National Childhood Blood Pressure database (208). The Bogalusa Heart Study of children initially aged 5-14 years found that of those who were clinically diagnosed with hypertension after 26 years, 48% and 41% had elevated SBP and DBP at baseline, respectively (202).

Some longitudinal studies used odds and hazard ratios (HR) to assess the association between an earlier BP status and the end of follow up BP status (>90th percentile). For instance, the Fels Longitudinal study reported that the odds of having elevated BP as an adult aged 30 years or above given a childhood elevated BP status (5 to 7, 8 to 13 or 14 to 18 years of age) ranged from 1.8 to 4.4 (209). A school-based screening program from Texas, USA reported that the likelihood of having hypertension after a 2-year follow up in children aged 10 to 19 years was almost 5-fold; HR:4.89(95%CI:1.48-16.19) (210).

Consistent with previous studies, girls had significantly higher mean DBP than boys at ages 8, 13, 14 and 18 years; but boys had higher SBP than girls between ages 14 and 18 years and these sex differences became more apparent as the adolescents grew older. BMI was considered as a covariate in tracking of blood pressure. Sex differences emerged in BMI in adolescence with girls having higher BMI compared to boys.

A positive feature of this study is its longitudinal design which has confirmed in a LMIC setting results similar to those reported in HICs. We also made use of automated BP monitors, which reduce observer bias compared to the sphygmomanometer that has been reported to be prone to subjectivity in detecting the Korotkoff sounds in children (211). Furthermore, we classified BP status by sex, height and age of the child, which are the main confounders of BP status in growing individuals. We acknowledge that our study had a limitation in that BP classification was different to the NHBPEP recommendations that children and adolescents should only be classified as pre-hypertensive or hypertensive based on an average BP from three measurements on three different occasions in the same year.

3.5 Conclusions

This longitudinal study of BP in urban black South African children confirms the existence of elevated BP in a significant proportion of children and adolescents. We also reported that the majority of children (77 to 80%) who were designated normotensive remained in that status showing that in as much as it is vital to identify the children at risk of having persistent elevated

BP, it is also important to fully assess the profiles of the children who remain normotensive or who had elevated BP initially but reverted to the normotensive status at 18 years of age to inform early life intervention programs. The implications of these findings are that early identification of children with elevated BP and associated risk factors through pediatric screening programs and timely interventions could be vital to reduce the risk of elevated BP in adulthood. In addition, more research is required to assess the feasibility and the cost effectiveness of the screening and intervention programs in LMICs such as South Africa.

4 CHAPTER 4: ASSOCIATION OF SOCIOECONOMIC STATUS CHANGE BETWEEN INFANCY AND ADOLESCENCE AND BLOOD PRESSURE IN SOUTH AFRICAN YOUNG ADULTS: BIRTH TO TWENTY COHORT

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4.1 Background

Hypertension is a major public health problem and an independent modifiable risk factor for cardiovascular diseases, which is increasingly becoming a problem in low-to-middle income countries (LMICs)(8). Research has documented that socioeconomic status (SES) influences blood pressure (BP) with low SES being predictive of elevated blood pressure in children (213) and adulthood (214, 215). In addition, early life factors like birth weight and weight gain may influence the SES change-BP relationship since children from low SES families are likely to be born small and at higher risk of excessive weight gain and high blood pressure (216, 217).

Most of the evidence on social inequalities in blood pressure comes from longitudinal and cross sectional studies and assumes SES is quite stable over time. However, SES across an individual's lifespan is dynamic in nature especially in societies experiencing socio-political

transitions like South Africa (218), hence the SES-BP relationship might change even within short periods of time in the early life-course (219).

There has been growing interest in a life course approach to social inequalities in hypertension epidemiology, owing to the evidence that high blood pressure in adulthood evolves from early life; hence the importance of early life environment as a factor influencing the development of hypertension. Life course approaches assume that an individual's health is influenced by dynamic biological and social exposures throughout a life span and that the exposures may not be static over the entire life course (31). There are three major conceptual models proposed in life course social epidemiology: social origins (critical periods/latent effect) model, accumulation model and the social mobility model (141, 143).

The social origins hypothesis states that early life is a critical period for biological programming where low SES plays a preeminent role in programming health, with children growing up in a low SES environment having raised BP (138), independent of their SES in intervening years (142). We have previously reported finding no relationship between SES in infancy and blood pressure in this cohort of South African adolescents in contrast to the social origins hypothesis (220). The accumulation model proposes that persisting low SES is detrimental to health. Research on cardiovascular disease risk indicates that low SES in early life has an additive effect on risk factors like blood pressure (32, 140). The social mobility model suggests that upward social mobility has a protective effect on hypertension risk while a downward SES change is

deleterious to cardiovascular disease risk in adulthood (147, 148). Hogberg and colleagues reported that intergenerational upward social mobility from low SES was associated with 18% reduction in hypertension risk in a Swedish Twin study of 12 030 adults (144).

The social mobility model has been widely used in life course social epidemiology. However, there is limited literature on social mobility and hypertension, especially among children and adolescents, and most of the studies have concentrated on the intergenerational effect of social mobility on blood pressure using parental and participants' occupation or education to determine life course SES or have used later adulthood BP as an outcome. None of the studies adjusted for initial SES and weight gain, making it difficult to disentangle early life SES environmental effects and weight gain from social mobility effects (141, 144, 147, 221).

Adolescence is a crucial developmental stage characterized by environmental and social changes, and the onset of hormonal and physiological factors that influence physical health outcomes like blood pressure.(222) The studies to date have focused on social mobility in high income countries, where less variability in experiences of SES over the early life-course exist compared to the dynamic SES environments of low and middle income countries (223).

Post-apartheid South Africa has been undergoing a rapid social and political transition. The volatility of social environment in the post-apartheid era which has seen improvements in SES in previously disadvantaged black populations makes the Birth to Twenty prospective longitudinal

cohort a unique and valuable resource to explore the social mobility hypothesis using blood pressure as an outcome which is highly sensitive to changing environments.

This study seeks to test the hypothesis that an upward SES change during childhood and adolescence would be associated with lower blood pressure in early adulthood. Therefore, this study aims to (1) examine the association between SES change and BP and hypertension risk at 18 years of age, and (2) explore whether the SES change-BP relationship is explained by birth outcomes and weight gain between birth and adolescence.

4.2 Methods

4.2.1 Study design and participants

Data for this study came from the Birth to Twenty birth cohort (BT20) - a prospective longitudinal study of children born in Soweto, Johannesburg, South Africa in 1990. Details of recruitment and enrollment into the cohort study are outlined elsewhere.(183) Data for this study were collected at birth, and at ages 2, 4, 16 and 18 years. For the purpose of this study, only black children who had data on blood pressure during late adolescence (18 years), SES data in infancy and during adolescence, birth weight and gestational age, weight gain in infancy, mid-childhood and from mid-childhood to adolescence were included in the analysis (n=838). We only selected black children since they comprise the majority of the BT20 study (Figure 4-1). Ethics approval was obtained from University of Witwatersrand Human Research Ethics Committee (M130556). Informed consent was obtained from caregivers and participants gave

their assent at all data collection time points before the participants turned 18 and their consent once they had turned 18 years of age.

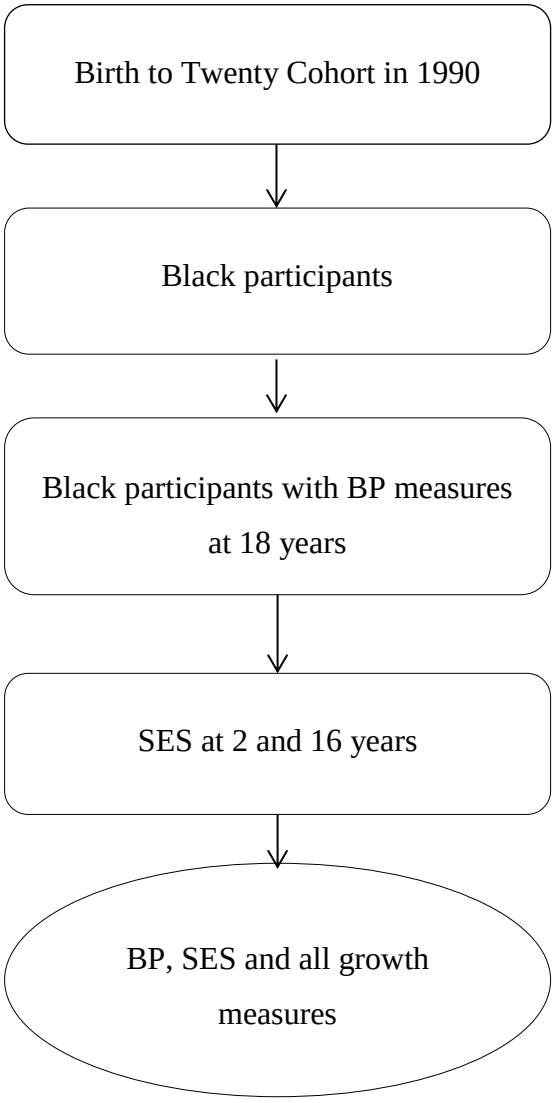

Figure 4-1 Flow chart of the study population with SES, growth and blood pressure at age 18 years

4.2.2 Measures

Blood pressure assessment

Blood pressure was measured in triplicate using the Omron M6 (Kyoto, Japan) and an appropriate cuff size with participants in a seated position after an initial five minute rest, and a two minutes rest between each of the three measurements. An average of the second and third measurements was used for the analyses of systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate. The mean SBP and DBP were used to calculate mean arterial pressure (MAP) using the traditional formula: MAP = [(2 x diastolic) + systolic] / 3. (224) Hypertension risk was classified using the age, sex and height specific percentiles from the National High Blood Pressure Education Program Working Group on Hypertension control in Children and Adolescence, with hypertension being defined as $\geq 95^{th}$ percentile and non-hypertension as $<95^{th}$ percentile.(47)

Socioeconomic status change

We used physical asset-based household SES measures tool in infancy and at 16 years of age which utilized a validated standardised questionnaire based on the Demographic and Health survey for developing countries (available at: http://www.dhsprogram.com/). The selection of an asset-based household SES was inspired by the notion that assets are more dynamic and sensitive than other measures, like education and occupation, especially in previously disadvantaged populations undergoing rapid economic and social transition. The physical assets SES measures (for example television, car and refrigerator) were assessed by asking the

caregiver or participant whether they had the asset in question (Yes/No). The physical asset scores were computed from all the 'YES' answers and were categorized into tertiles: low (1), medium (2) and high (3) for each of the two time points. Thereafter, nine categories of the social mobility model were generated according to the literature and were defined as: low-low(11), low-medium(12), low-high(13), medium-low(21), medium-medium(22), medium-high(23), high-low(31), high-medium(32) and high-high(33). (225)

Potential confounders and mediators

Sex, gestational age and birth weight were included from data collected at birth. Weight and height at 2, 4 and 18 years were measured using standard procedures. Relative weight gain was defined as weight gain independent of height during infancy, at mid-childhood (2-4 years) and at adolescence to adulthood (4-18 years) and was computed as residuals obtained by regressing current weight on current height and previous weight and height to deal with the potential multi co-linearity between weight and height (226). We also used SES in infancy as a covariate since it was a proxy for early life environment so that the SES change variable represents a true measure of social mobility. Because BP in children is age, sex and height specific, we adjusted for these three factors in all the models which included SBP, DBP and MAP. To assess alcohol and tobacco use during adolescence, participants at age 17 years were asked whether they had taken alcohol or smoked tobacco in the last month/ intake (No/Yes).

4.2.3 Statistical analyses

Chi square tests and t-tests were used to describe the study characteristics by sex and hypertension risk for categorical and continuous variables, respectively. Multiple linear regressions were used to assess the association between SES change SBP, DBP and MAP adjusting for SES in infancy, birth weight and weight gain in infancy, mid-childhood and from mid-childhood to adulthood. We further adjusted the multivariate models for alcohol intake and baseline BP. Additional exploratory models were run for boys and girls separately (results not shown). We also computed the crude and adjusted odds ratios (and 95% confidence intervals) from logistic regressions for the association between SES change and hypertension risk. The statistical analysis were performed in STATA 13 with level of significance set at $p<0.05$ (two-tailed).

4.3 Results

Descriptive statistics

Table 4-1 shows the study population characteristics by sex and hypertension risk (N=838; 48.0% boys). Boys were heavier at birth and at ages 2 and 4 years and taller at 2, 4 and 18 years than girls. Systolic blood pressure was significantly higher by 6 mmHg in boys than girls; on the contrary, girls had significantly higher DBP than boys at age 18 years. There were no sex differences with respect to all SES measures, gestational age, being born small for gestational age, weight at age 18 years and MAP.

Overall, 14.8% of the participants in the study sample were hypertensive (n=124) and 49.1% of these were boys. Participants who were hypertensive were significantly 5.5kg heavier at age 18 years compared to their normotensive counterparts. No major differences in hypertension risk with respect to SES change between infancy and adolescence, birth measures, weight and height in childhood and height at 18 years were observed.

Table 4-1 Study characteristics in infancy and adolescence by sex and blood pressure status at age 18 years (n=838)

Variables	**All**	**Boys N (%)**	**Girls N (%)**	**P value**	**Non-Hypertensive N (%)**	**Hypertensive N (%)**	**P value**
Socio economic status (Exposure)							
Household SES change between infancy and adolescence,%							
Low-low(ref)	255(30.4)	133(33.1)	122(28.0)	0.522	211(29.6)	44(17.3)	0.541
Low-medium	97(11.6)	45(11.2)	52(11.9)		81(11.3)	16(12.9)	
Low-high	35(4.2)	17(4.2)	18(4.1)		34(4.8)	1(0.81)	
Medium-low	99(11.8)	41(10.2)	58(13.3)		85(11.9)	14(11.3)	
Medium-Medium	71(8.5)	32(8.0)	39(8.9)		61(8.5)	10(8.1)	
Medium-high	43(5.1)	25(6.2)	18(4.1)		38(5.3)	5(4.0)	
High-low	78(9.3)	39(9.7)	39(8.9)		67(9.4)	11(8.9)	
High-Medium	81(9.7)	37(9.2)	44(10.1)		67(9.4)	14(12.0)	
High-high	79(9.4)	33(8.2)	46(10.6)		70(9.8)	9(7.3)	
Total	838	402(48.0)	436(52.0)		714(85.2)	124(14.8)	
Participant characteristics							
In childhood							

Gestational age, weeks (SD)	838	38(1.7)	38(1.8)	0.3736	38(1.7)	38(1.8)	0.8009
Birth weight ,g (SD)	838	3.1(0.5)	3.0(0.5)	**<0.01**	3.1(0.5)	3.1(0.5)	
Small-for-Gestational age(SGA),%							
No	743	348(86.6)	395(90.6)	0.066	639(89.5)	104(83.9)	0.068
Yes	95	54(13.4)	41(9.4)		75(10.5)	20(16.1)	
Weight at age 2,kg (SD)	838	11.6(1.5)	11.3(1.4)	**0.0177**	11.4(1.4)	11.5(1.5)	0.5112
Weight at age 4,kg(SD)	838	15.6(1.9)	15.2(2.0)	**<0.01**	15.3(2.0)	15.6(2.0)	0.0884
Height at age 2, cm(SD)	838	83.4(3.5)	82.5(3.2)	**<0.001**	83.0(3.3)	82.8(3.5)	0.4768
Height at age 4, cm(SD)	838	99.1(3.9)	98.6(3.8)	**0.0309**	98.8(3.9)	98.8(4.0)	0.854
In Adolescence							
Age, years(SD)	838	17.8(0.4)	17.8(0.4)	0.4521	17.8(0.4)	17.8(0.4)	0.2287
Weight at age 18, kg(SD)	838	59.8(10.2)	59.3(12.4)	0.6017	58.7(10.2)	64.2(15.5)	**<0.001**
Height at age 18,cm(SD)	838	170.6(8.2)	159.6(6.0)	**<0.001**	165.1(8.8)	163.5(9.9)	0.0685
Blood pressure measures at 18 years							
SBP, mmHg(SD)	838	121(10.6)	115(9.5)	**<0.001**	115(8.5)	131(11.2)	**<0.001**
DBP, mmHg(SD)	838	71(8.5)	72(8.5)	**0.0410**	70(6.9)	81(11.0)	**<0.001**
MAP, mmHg(SD)	838	87(8.2)	87(8.4)	0.1525	85(6.3)	99(8.3)	**<0.001**

Values are presented as mean (standard deviation) computed from a t-test for continuous variables or as N (%) for categorical variables obtained from a chi square test and Fischer's exact for N<5.

Determinants of blood pressure and hypertension status

In unadjusted analyses, SBP was significantly associated with change from low-to high SES between infancy and adolescence, sex, age, weight and height at 18 years, and relative weight gain independent of height at 0-2 and 4-18 years (Appendix 4). DBP was significantly associated with sex (higher in males), age and weight at age 18 years and weight gain from age 4 to 18 years. MAP was predicted by weight and height at 18 years, and weight gain from age 4 to 18 years. Hypertension risk was significantly associated with weight at 18 years and weight gain at ages 2-4 and 4 to 18 years.

Association between SES change and blood pressure and hypertension status

Multiple linear regression analyses of SES change characterized by nine subgroups and age-, sex- and height-adjusted SBP, DBP and MAP are presented in Table 4-2. SES change from low to high tertile was significantly associated with 4.8 mm Hg lower SBP compared to those who maintained a low SES profile between infancy and adolescence, adjusted for SES in infancy, SGA and weight gain between infancy and adulthood. The associations between DBP and MAP, and SES change were statistically insignificant in all the models.

Table 4-2Multiple regression models for the relationship between SES change and SBP, DBP and MAP at 18 years of age in Urban Black South Africans

Blood pressure measure	**SBP**						**DBP**						**MAP**					
	Model 1(n=838)			**Model 2(n=838)**			**Model 1(n=838)**			**Model 2(n=838)**			**Model 1(n=838)**			**Model 2(n=838)**		
Covariates	**B**	**95%CI**	**P value**	**β**	**95%CI**	**P value**	**β**	**95%CI**	**P value**	**β**	**95%CI**	**P value**	**β**	**95%CI**	**P value**	**β**	**95%CI**	**P value**
SES change																		
Low-low(ref)																		
Low-medium	-0.74	-3.08 to1.60	0.532	-0.38	-2.63 to 1.86	0.737	-0.52	-2.52 to 1.48	0.608	-0.33	-2.32 to 1.66	0.743	-0.62	-2.56 to1.33	0.532	-0.34	-2.24 to 1.55	0.723
Low-high	-5.10	-8.61 to-1.58	**<0.01**	-4.85	-8.22 to -1.48	**<0.01**	-2.41	-5.42 to 0.60	0.117	-2.27	-5.25 to 0.71	0.136	-2.99	-5.91 to 0.07	**0.045**	-2.81	-5.66 to 0.03	0.053
Medium-low	-0.52	-3.52 to 2.48	0.735	-0.69	-3.57 to 2.19	0.639	1.20	-1.37 to 3.77	0.358	1.09	-1.45 to 3.64	0.398	0.44	-2.05 to 2.94	0.725	0.34	-2.09 to 2.77	0.782
Medium-Medium	-1.77	-5.01 to1.48	0.285	-2.23	-5.35 to 0.89	0.16	-0.13	-2.91 to 2.64	0.925	-0.34	-3.10 to 2.42	0.811	-1.19	-3.88 to 1.51	0.388	-1.44	-4.07 to 1.19	0.282
Medium-high	-0.90	-4.64 to 2.83	0.634	-1.07	-4.66 to 2.51	0.557	-0.02	-3.22 to 3.18	0.99	-0.15	-3.33 to 3.02	0.925	-0.51	-3.61 to 2.60	0.749	-0.60	-3.63 to 2.43	0.696
High-low	-3.65	-7.79 to 0.48	0.083	-3.93	-7.90 to 0.04	0.062	-1.20	-4.74 to 2.34	0.505	-1.39	-4.90 to 2.13	0.439	-1.81	-5.24 to 1.62	0.302	-1.98	-5.33 to 1.37	0.247
High-Medium	-1.38	-5.50 to 2.73	0.51	-2.03	-5.98 to 1.91	0.312	1.36	-2.16 to 4.88	0.448	1.03	-2.45 to 4.53	0.56	0.39	-3.02 to 3.81	0.821	-0.60	-3.39 to 3.27	0.972
High-high	-3.47	-7.84 to 0.90	0.12	-3.41	-7.60 to 0.78	0.34	0.03	-3.71 to 3.77	0.989	0.00	-3.71 to 3.71	1.000	-1.41	-5.04 to 2.23	0.448	-1.35	-4.89 to 2.19	0.456
Sex	-4.03	-5.86 to -2.20	**<0.001**	-4.2	-5.98 to -2.42	**<0.001**	1.94	0.38 to 3.51	**0.015**	1.78	0.21 to 3.37	**0.026**	0.54	-0.98 to 2.06	0.486	0.47	-1.04 to 1.97	0.544
Participant age, years	2.49	0.69 to 4.30	**<0.01**	2.42	0.69 to 4.14	**<0.01**	-1.30	-2.84 to 0.25	0.1	-1.32	-2.85 to 0.21	0.092	-0.08	-1.58 to 1.43	0.921	-0.14	-1.60 to 1.32	0.853
Participant height, cm	0.17	0.06 to 0.28	**<0.01**	0.18	0.08 to 0.29	**<0.01**	0.07	-0.02 to 0.16	0.132	0.07	-0.02 to 0.16	0.131	0.12	0.02 to 0.21	**<0.01**	0.13	0.04 to 0.22	**<0.01**
Household SES in infancy	0.55	-0.46 to 1.55	0.285	0.64	-0.32 to 1.60	0.192	-0.15	-1.01 to 0.70	0.726	-0.10	-0.95 to 0.75	0.818	0.10	-0.73 to 0.93	0.821	0.17	-0.64 to 0.98	0.683
Small-for-Gestational age				0.87	-1.22 to 2.96	0.415				-0.16	-2.01 to 1.69	0.866				0.51	-1.25 to 2.28	0.571
Relative weight gain (0-2years)				1.06	0.38 to 1.74	**<0.01**				0.49	-0.12 to 1.09	0.114				0.65	0.07 to 1.22	**0.028**
Relative weight gain (2-4years)				0.65	0.02 to 1.27	**0.044**				0.29	-0.26 to 0.85	0.300				0.62	0.08 to 1.15	**0.023**
Relative weight gain (4-18years)				2.79	2.12 to 3.47	**<0.001**				1.28	0.68 to 1.87	**<0.001**				1.85	1.28 to 2.42	**<0.001**

Adjusted R^2 value	0.1053	0.1804	0.0064	0.0260	0.0076	0.0605

[1]Model 1: adjusted for sex, current height, age, and household SES in infancy.

[2]Model 2: Model 1 + growth (SGA, relative weight gain in infancy and mid-childhood)[3]Baseline BP : SBP at 5 for SBP, DBP at 5 for the DBP and MAP at 5 for the MAP models, accordingly

Adjusted logistic regression models (Table 4-3) show no significant association between SES change from the low-high category and hypertension risk. Relative weight gain at 2-4 and 4-18 years predicted 30% and 66% increased odds of hypertension independent of SES change, SES in infancy, SGA and relative weight gain in infancy.

Table 4-3 Adjusted odds ratios of being hypertensive at 18 years in urban black South African children (n=838)

	Model 1			**Model 2**		
Covariates	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P Value**
SES change between infancy and adolescence						
Low-low(ref)	1			1		
Low-medium	0.92	0.48 to 1.72	0.787	0.99	0.51 to 1.88	0.968
Low-high	0.14	0.02 to 1.04	0.055	0.14	0.02 to 1.04	0.055
Medium-low	0.61	0.27 to 1.42	0.255	0.57	0.24 to 1.34	0.197
Medium-Medium	0.61	0.25 to 1.52	0.290	0.53	0.21 to 1.36	0.186
Medium-high	0.49	0.16 to 1.50	0.213	0.47	0.15 to 1.48	0.198
High-low	0.51	0.16 to 1.64	0.259	0.46	0.14 to 1.56	0.214
High-Medium	0.65	0.21 to 2.02	0.455	0.51	0.16 to 1.65	0.262
High-high	0.38	0.11 to 1.37	0.140	0.36	0.10 to 1.33	0.125
Household SES in infancy	1.14	0.86 to 1.52	0.359	1.20	0.89 to 1.61	0.237
Small-for-Gestational age(SGA),%				1.33	0.75 to 2.33	0.328
Relative weight gain (0-2years)				1.18	0.96 to 1.45	0.119
Relative weight gain (2-4years)				1.31	1.08 to 1.58	**<0.01**
Relative weight gain (4 to18years)				1.65	1.35 to 2.04	**<0.001**
Pseudo R^2 value	0.0135			0.0630		

Model 1 adjusted for SES at baseline,

Model 2 model 1 +growth (SGA, relative weight gain in infancy and mi-childhood)

Furthermore, additional multivariate analyses of factors associated with blood pressure and hypertension risk in urban South African black participants aged 18 years are presented in Appendix 5. In these associations adjusting for alcohol intake and baseline blood pressure did not significantly alter the variance explained by the models.

4.4 Discussion

Main findings

We found that an upward mobility in SES was strongly associated with lower SBP at 18 years of age in contrast to remaining in a low SES profile between infancy and adolescence. This study highlights that the association between an upward social mobility and reduced SBP is not fully explained by growth trajectories in relative weight since the association remained significant even after controlling for growth. There was no association between SES change and DBP, MAP and hypertension risk.

Comparison with other studies

Our results are consistent with previous studies which reported that upward social mobility is related to reduced blood pressure. The Pitt county study of African American men aged 25 to 50 years at baseline in 1988 by James et al (147) reported that compared to the stable low SES group between childhood and adulthood, upward SES mobility between childhood and adulthood was associated with 47% reduction in hypertension risk using education, occupation and

employment status to compute life course SES. Childhood SES data were collected retrospectively in this study thereby compromising internal validity of the findings. The Swedish study of twins born between 1926 and 1958 reported 16% lower odds in the upwardly mobile SES group compared to the stable low SES group independent of familial factors.(144) This study used intergenerational SES measures based on parental and the offspring occupation as a measure for life course SES and self-reported hypertension status which is prone to information bias.

Contrary to our findings, a USA study conducted between 2002 and 2003 reported that children who experience an upward mobility trajectory in SES between 14 to 18 years of age had higher SBP compared to those who remained in the low SES profile. However, the results might have been influenced by the under-representation of low SES children in their study. (142) Hallal et al, (146) found no association between socioeconomic trajectories from birth to 11 years of age and SBP and DBP in 15 year old Brazilian adolescents born in 1993 using household income as an indicator of SES.

Possible explanation of the findings

Being small for gestational age had no independent effect on the association between SES change and SBP at 18 years implying that postnatal growth might be more important for programming of social gradients in blood pressure than prenatal growth. Social mobility effects on SBP are not fully explained by growth implying that a dynamic SES environment may

influence blood pressure through additional mechanisms. Potential mechanisms through which an upward mobility in SES reduces blood pressure have been evaluated; including bio-behavioral factors and chronic stress. (227) An upward mobility in social class might imply that adolescents are protected from negative health behavior associated with poor households such as poor diet, lower levels of physical activity, and higher prevalence of tobacco smoking or alcohol intake. However, in this study, adding alcohol use to the models did not alter the associations.

Association between SES change and blood pressure was significant for SBP but not DBP, implying that SBP might be more sensitive to environmental factors compared to DBP. Persistent low SES is a chronic stressor which is related to an increase in sympathetic nervous system reactivity and changes in vasculature which raises SBP.(228) High SBP may be an indicator of vascular dysfunction as a result of progressive stiffening of arterial walls or changes in the vasculature and it has been reported to be a stronger predictor of hypertension and cardiovascular diseases than DBP.(229)

Sex had a distinct independent relationship with SBP, DBP and hypertension risk. However, when the analyses were stratified by sex, the associations remained significant for boys only in the SES change-SBP models only, implying that the protective effect of upward social mobility may be apparent in boys and not girls but this needs to be further explored with a larger sample size (Appendix 6).

Strengths and limitations

These findings were based on a prospective birth cohort, thereby minimizing recall bias and having the potential to establish a causal relationship between life course SES and blood pressure. Asset based-SES measures are more sensitive measures for SES compared to education and employment in LMICs since using schooling years for education might not take into account repeated years (230), employment can be informal and transitory, and income and expenditure are notoriously difficult to assess without extensive validation from secondary sources (231).

In contrast to previous studies on social mobility and hypertension which used self-reported measures of hypertension, we employed an objective measurement of blood pressure by trained research assistants. Furthermore, the study used both sexes in black urban South African adolescents from a rapidly transitioning urban environment which can be generalized to other African societies in transition. Sex, age and height adjusted blood pressure measures were used in the multivariate models since blood pressure in children and adolescents varies according to age, height and sex (232). Unlike other studies, we adjusted for covariates to disentangle the effect of early life SES and weight gain on the SES change-BP relationship hence increasing the potential to infer causality.

There are a number of considerations that may pose as limitations. Firstly, we could not include other ethnic groups due to under-representation in the low SES group at the two time points; hence our findings may not be generalizable to the entire South African population. The

proportion of hypertensive participants who were in the low-high SES change category was low and this might have resulted in underestimation of the upward social mobility-hypertension risk association resulting in marginal associations. Alcohol intake and tobacco use were self-reported hence we do not rule out reporting bias. There was potential for selection bias in the analytical sample, however, there were no significant differences between the black participants included and those excluded from the study with regards to the key study variables thereby increasing the potential to generalize these findings.

4.5 Conclusions

Our study adds to a limited body of evidence concerning the protective effect of upward social mobility on blood pressure and shows an association between SES change in the early life-course from birth to adolescence and SBP in early adulthood. There is a need for replication of this study to assess its generalizability in other geographical settings and other ethnic groups. These study findings imply that national social and economic policies introduced in the post-apartheid era which seek to improve quality of life among previously disadvantaged black populations have the potential to reduce cardiovascular disease burden attributed to high blood pressure.

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5 CHAPTER 5: ASSOCIATION BETWEEN EARLY LIFE GROWTH AND BLOOD PRESSURE TRAJECTORIES IN BLACK SOUTH AFRICAN CHILDREN

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5.1 Introduction

Hypertension remains a major cause of morbidity and premature mortality, and a leading risk factor for the global burden disease worldwide (234). High blood pressure (BP) in adulthood will affect three quarters of the population in low and middle income countries (LMICs) by 2025 (8). Of great concern is the emergence of hypertension in pediatric populations concomitant with the rising epidemic of obesity(116). We recently showed that BP tracks from early childhood to late adolescence in a black South African population; one in three children with elevated BP at age 5 years (>90th percentile for age, height and sex) remain so at age 18 years (188), Since children with elevated BP may show early signs of cardiovascular damage, renal injury and are likely to have high BP in adulthood (130, 235), identifying children with atypical BP patterns and risk factors may be crucial for early life intervention to modify progression to hypertension in adulthood.

Substantial evidence suggests that early life growth predicts elevated BP, particularly in children who are small at birth but experience accelerated growth in childhood (5, 34, 236). Conventional growth modelling techniques have been used to explore how early life growth relates to mean levels or changes in BP in children and adolescents. Those studies use a single mean growth curve to describe BP trajectories in a given population and assume that covariates influence the growth curve in a similar way (237). Yet BP is a highly variable physiological characteristic, hence describing a population using a single estimated trajectory oversimplifies the complexity of BP tracking patterns that characterize children and adolescents. In addition, height is a known marker of early life environment and a major correlate of BP in childhood and adolescence (238), and thus should be incorporated in longitudinal modelling of BP.

Recently, investigators have begun to use finite mixture models to identify distinct clusters of individuals following similar patterns of BP change over time (176, 239). One recent study identified four SBP trajectory groups between ages 7 and 38 years using group-based trajectory modeling (GBTM) on data from the Dunedin longitudinal birth cohort. That study reported that low birth weight was associated with higher odds of being in the hypertensive trajectory group (240). In support of those findings, a UK birth cohort reported two to three BP trajectory groups in midlife (36 to 53 years) and confirmed that individuals with higher birth weight were likely to be in the normative BP group than in the 'BP increaser' groups (161). Trajectories of BP in black children and adolescents in South Africa have not been identified, and are complicated by more ambiguous definitions of elevated BP in children than in adults. GBTM may be useful in identifying children with atypical patterns of SBP and DBP and their associated risk factors.

To our knowledge, no study in Africa within a LMIC scenario has explored the association between early life growth and trajectories of BP in children and adolescents, which is likely to be important because of the increasing burden of hypertension on this continent. We hypothesized that early growth, in particular lower birth weight and rapid postnatal weight gain is associated with a higher height-adjusted BP trajectory in a Black South African pediatric population. The aim of this study was to use Birth to Twenty longitudinal birth cohort data (Bt20) to (1) identify distinct trajectory groups for BP between 5 and 18 years of birth, (2) examine the association between early growth and BP trajectories and (3) assess the influence of height on the association between early growth and BP trajectories.

5.2 Methods

5.2.1 Study population

The data analyzed here are from the Bt20 cohort study of singleton children born within a 7-week period in Soweto, Johannesburg in 1990 (n=3273). Details of recruitment and selection criteria for the cohost study are described elsewhere (183). All parents and caregivers of the children provided written informed consent, and the University of Witwatersrand Committee granted ethical approval for Research on Human Subjects (certificate number: M130556). The study sample was restricted to black participants (approximately 78% of the cohort), who had not been pregnant during adolescence and had anthropometric measurements, SBP and DBP measurements at two or more of the following mean ages: 5years (n=1046;49.0% boys), 8years (1175;48.8%), 10years (n=695;48.6%), 13years (n=1355;47.5%), 14years (n=1392;47.4%),

16years (n=1657;48.1%) and 18years (n=1592;48.2%) . The overall sample size was n=1937 (1005 girls and 932 boys).

5.2.2 Assessment of blood pressure

BP was measured in a seated position in triplicate: after a five minute rest and a two minute interval between measurements, using Dinamap Signs monitor 1846SX (Critikon, USA) at 5years and an Omron M6 (Omron, Kyoto, Japan) at 8 to 18years. All the measurements were taken by a trained research assistant using an appropriate cuff size. Hypertension status at age 5 years was classified as greater than 95th percentile for age, sex and height using the Fourth report on National High Blood pressure program in children and adolescence (47).

5.2.3 Assessment of growth

Birth weight and gestational age were obtained from birth notification records entered at birth. Subsequently, weight was measured using a digital scale to the nearest 0.1kg and height was measured using a calibrated stadiometer. Birth weight, weight-for-age and height-for-age z-scores were computed using WHO growth standards (241). To deal with high correlation of repeated weight and height measures in longitudinal data, conditional weight independent of height (relative weight gain) and relative height gain independent of weight (relative linear growth) were computed as standardized residuals derived from sex-specific linear regressions of a current growth measure on a prior one in infancy (0-2years) and mid-childhood (2-5 years) (226, 242).

5.2.4 Assessment of covariates

Maternal and infant characteristics at birth were identified using standard questionnaires. Socio-economic status (SES) in infancy was represented as a count of household assets reported by the mother or caregiver.

5.2.5 Statistical analysis

Group based trajectory modeling (GBTM) was performed using a STATA plug in program of SAS Proc Traj to estimate model parameters using maximum likelihood estimation in STATA 11(243). We used a censored normal model for continuous variables, firstly without covariates, then including height as a time varying covariate (preliminary analyses). To identify the groups, two-class models were specified for SBP and DBP for each sex, then classes were added sequentially until parsimony was attained for linear, quadratic and cubic terms (Table S1). To test the model with the best fit we used the following criteria: low Bayesian Information Criterion (BIC), high posterior probabilities (above 0.7), not less than 1% of total sample in a trajectory group and prior knowledge from the literature (174). Thereafter, the groups defined from the best-fitting models were used as categorical outcome variables in multinomial logistic regression models with covariates (time varying and time invariant) yielding the log-odds estimates, standard errors and p values, from which odd ratios and 95% confidence intervals (95% CI) were computed.

Not all participants had measures at all occasions; hence we compared those who were included in the sample and those with missing BP measures with respect to key variables to inform whether missingness was random (Table S2). Descriptive statistics were conducted to characterize average BP per occasion by BP class membership. ANOVA was used to describe continuous study sample characteristics for each BP trajectory and to validate the trajectory groups using BP status at age 5 years of age and $\varkappa^2$ test was used for categorical study variables. Multinomial logistic regressions were conducted in traj and the estimates and standard errors converted to odds ratios and 95% confidence intervals

5.3 Results

1005 girls and 932 boys had BP measurements on at least two occasions. There were no significant differences between the analyzed sample and those not included (n=631) with regards to birth weight, weight in infancy and mid-childhood, height in infancy and childhood, but the two samples differed with regards to SES in infancy. Those in the included sample had lower number of household assets compared to those excluded ($p<0.0001$).

In each sex, the best-fitting models included three distinct trajectories for SBP and DBP with cubic terms (Table S1). For descriptive purposes, the BP trajectories were labelled as 'lower', 'middle' or 'upper'. The lower trajectory was considered as the reference group in all regression analyses (Figure 1 and 2). The BP trajectories represent mean BP based on the posterior probabilities of being assigned to a particular class. In boys (Figure 1 A-D), the upper SBP

trajectory group (16.4%) started at 125.0mmHg at age 5 years and increased to 132.4mmHg by age 18 years. The middle SBP trajectory group (55.3%) started at 107.3mmHg and increased to 122.9mmHg. The lower SBP trajectory group (28.2%) started at 101.9mmHg and increased to 115.2 mmHg. In girls (figure 2A-D), the upper SBP trajectory group (13.6%) started at 120.5 mmHg and increased to 125.7mmHg, the middle SBP group (53.2%) started at 110.4mmHg and increased to 116.9mmHg; and the lower SBP group (33.2%) started at 99.0mmHg and increased to 107.5mmHg (Table 1).

Adding child's height between 5 and 18 years as a time varying covariate reduced by half the proportion of individuals in the upper SBP trajectory in both boys (7.1%) and girls (7.5%) (Figure 1B and 2 B) but made no major differences for DBP (Figure 1D and 2D). Table S3 describes the association of age terms and height, and BP trajectories for the time varying models. Height between ages 5 and 18 was positively associated with all BP trajectories in boys and girls, except an apparent protective effect on the upper SBP trajectory in girls (est:-0.25, SE: 0.10, p=0.0125). The DBP trajectory for girls was not associated with height between ages 5 and 18.

Hypertension status at age 5 years was highly predictive of height-adjusted BP trajectory (Table S4). The relative risk of being in the upper and middle SBP trajectory given a BP status above the 95^{th} percentile for age sex and height was 3.85 and 21.80 times higher compared to the lower trajectory in boys. In girls, the relative risk ratios were almost six and seven fold greater for the

middle and upper relative to the lower SBP trajectory for a BP measure above the 95th percentile for age, height and sex. With respect to DBP trajectories, BP status at age 5 years was highly predictive of the BP trajectory groups with higher risk for the upper and middle trajectory groups compared to the lower one in both sexes.

SBP trajectory group membership in boys was associated with relative linear growth in infancy and childhood, and SES in infancy, while in girls it was associated with relative weight and relative height gain in infancy and childhood, parity, maternal age and household assets in infancy and SBP at age 5 years. With respect to DBP, rapid relative weight gain in infancy, rapid linear growth in mid-childhood, DBP at age 5 years and SES in infancy was significantly associated with the girls' trajectory group membership (Table 2). For the height-adjusted BP trajectories, weight gain in infancy and childhood, parity, BP at 5 years of age and SES between 0-2 years of age remained as determinants of class membership for the girls, while in boys, relative linear growth in mid-childhood and BP at age 5 years were associated with BP trajectory groups.

Relative weight gain in infancy and rapid linear growth between birth and mid-childhood was associated with SBP trajectory group membership in boys after adjusting for time invariant covariates (Table 3). However, in height-adjusted models, a unit increase in birth weight reduced the risk of being in the middle trajectory by 25% (OR: 0.75; 95%CI 0.58-0.96, p=0.0223) while rapid weight gain in infancy was associated with almost a 4-fold higher risk (OR: 4.11; 1.25-

13.51; p=0.0202) of being in the upper trajectory. In girls, relative weight gain and linear growth in infancy were associated with higher odds of being in the middle and upper relative to the lower SBP trajectory in height-adjusted models.

Rapid weight gain in infancy and mid-childhood and linear growth were associated with higher odds of being in the middle versus lower DBP trajectory (Table 4). However, in height-adjusted models, an association only remained for relative weight gain in infancy (OR: 1.43; 1.06-1.95; p=0.0214). The upper versus lower DBP trajectory group in boys was positively associated with relative weight gain in infancy and linear growth in mid-childhood, but these associations were diminished or reversed in height-adjusted models, leaving linear growth in infancy as the only significant predictor of upper versus lower DBP trajectory (OR: 0.47; 0.29-0.76; p=0.0021). In girls, relative weight gain and linear growth in mid-childhood were positively associated with being in the middle versus lower DBP trajectory, while weight gain in infancy was a predictor of upper vs lower DBP trajectory (OR: 2.53; 1.14-5.57; p=0.0219).

5.4 Discussion

Using GBTM, we identified three sex-specific trajectories for SBP and DBP; each showing gradual increases in BP with age in Black South African children. In boys, upper and middle BP height-adjusted trajectory membership was inversely associated with birth weight and positively associated with relative weight gain and linear growth in infancy. Girls who experienced accelerated growth (both in weight and height) in infancy and childhood tended to be in the

upper vs lower SBP trajectory, while rapid growth in infancy positively predicted being in the middle vs lower class. With regard to DBP in girls, rapid relative weight gain in infancy and mid-childhood were predictors for the upper and middle trajectories (in comparison to the lower trajectory). These findings support the hypothesis that accelerated relative weight gain in early life may program higher long-term disease risks (244).

A major feature of our study is that we confirmed heterogeneity in BP over time in children and adolescents by reporting three latent classes for SBP and DBP for each sex. Previous longitudinal cohort data analyses of BP trajectories focused on adult populations (245, 246) or growth curve modelling using one BP trajectory (154). Consistent with the findings from the Framingham Heart study of 1060 males aged 25+ with longitudinal BP measurements at four time points, we identified three trajectory classes for SBP and DBP(176). However, other studies found different numbers of classes, including a UK study which reported 2 classes each for SBP and DBP in midlife in men (161). The CARDIA cohort in USA examined adults aged 18 to 30 years at baseline and reported five distinct trajectories of mid-BP (mean of SBP and DBP). However, this study did not disentangle the age-related changes in SBP and DBP, which are physiologically distinct measures (166).

In the present study, height between 5 and 18 years of age was closely associated with trajectory groups, except for the girls' upper SBP and DBP trajectories. These findings might imply that stature may have a greater impact on BP in boys than girls. With regards to sex differences, a

study of BP trajectories in a Caribbean adolescent population aged 11 to 18 years reported that rate of change of both SBP and DBP was greater in boys than in girls (162). Sex discrepancies in BP trajectories and their associations with early growth might be attributed to influence of androgens on the regulation of long term BP in response to early environmental factors (247). Although the specific mechanisms underpinning sex differences in the programming of life course BP are not fully known, testosterone is reportedly positively associated with renin angiotensin activation and oxidative stress, which in turn contribute to elevated BP differently in males (86) and females (87).

This study confirms that BP increases with age and height between ages 5 and 18 years, except in the upper BP trajectories for girls. Unlike in adults, height is a recognized major determinant of childhood BP and is routinely considered to evaluate childhood BP centiles and hypertension status (46). Childhood height is an indicator of growth of the arterial tree, which influences hemodynamic BP control mechanisms especially vasculature structure and function (248). These findings are consistent with a number of cross sectional studies(249) and confirm the importance of inclusion of age and height in the definition of elevated BP in children and adolescents. Since there are physiologic increases in childhood BP with height, it is important to consider the effect of height as a covariate when identifying trajectory groups, so as to avoid simply categorizing tall children with normal BP for their height.

For height-adjusted BP trajectories, the association between infant and mid-childhood linear growth and BP, especially for boys and for DBP, implies that change in BP may be more susceptible to later stature in boys than girls. In support of the fetal origins hypothesis, we reported that higher birth weight was associated with lower odds of being in the middle versus the lower boys' SBP trajectory in the final models. This finding may indicate that children who are born low weight but who go on to increase their stature after mid-childhood may be at risk of having moderately increasing BP.

In support of the growing evidence on BP tracking in childhood (128), we have shown that hypertensive status at age 5 years was highly predictive of BP trajectory between 5-18 years. This finding validates the importance of early detection through routine BP screening in childhood to identify children who are most likely to follow elevated BP trajectories over their life course. Early onset of elevated BP may indicate that physiological mechanisms influencing variation in BP and risk of elevated BP might start in early life and may amplify with age in response to genetic and environmental factors.

A major strength of this study is its prospective nature. In addition, there were no major differences between those children excluded from the study and the analytical sample with regards to key study characteristics and any differences were adjusted in the multivariate models. We employed GBTM to identify sex-specific BP trajectories. This is an extension of traditional growth modelling which takes into account time varying and invariant covariates in

characterizing the change in BP over time and heterogeneity within BP data. GBTM is suitable for examining physiological traits like BP which are highly variable in children and adolescents and provides better model fit and parsimony compared to linear mixed models (174). However, inferences regarding latent class membership and their association with relative weight gain in early life might not extend to the entire South African population since the analyses were confined to the black ethnic sample. Use of ambulatory blood pressure monitoring measure may provide more insight into BP trajectories compared to an average BP measurement on one occasion. Future research studies need to replicate group based trajectory modeling in other cohort studies using other time varying covariates like physical activity and dietary patterns.

In the context of an emerging epidemic of hypertension in black LMIC populations, this study suggests that BP trajectories may be set early in childhood, with BP in early childhood BP highly predictive of BP trajectories. Early life growth, in particular high relative weight gain, may be a crucial target for interventions to interrupt elevated BP trajectories and to prevent the early onset of raised BP. Further research needs to identify individuals in the middle and upper trajectories, to assess other cardiovascular disease indicators such as left ventricular hypertrophy, arterial stiffness, and to consider appropriate interventions in early life to interrupt the trajectories and benefit long-term health.

5.4.1 Perspectives

In summary, this study highlights the potential for early interventions aimed at optimizing growth in early life may play an important role in prevention of elevated BP progression in

children and adolescents. This calls for a concerted effort among global healthcare practitioners, researchers, and other related organizations to prioritize pediatric hypertension on the global health agenda especially in Low to Middle Income countries (LMICs) where the burden of disease attributed to hypertension is already high in midlife and exerting pressure on the health care system. Future research needs to explore the clinical relevance of the elevated BP trajectories, the key risk factors and progression to and hypertension and cardiovascular disease in adulthood.

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Novelty and Significance

What is new?

- This is the first study to show distinct BP trajectories from early childhood to late adolescence in African children
- Rapid early growth predicts higher longitudinal BP trajectories in childhood

What is relevant?

- Age related changes in SBP in children and adolescents are height dependent hence longitudinal profiles of paediatric BP should account for stature.

Summary

- Distinct trajectories of age-, sex- and height- dependent BP are detectable in children from 5 years of age. Rapid growth (both in weight and linear) in infancy and mid-childhood predict the progression of BP between mid-childhood and late adolescence

Figures

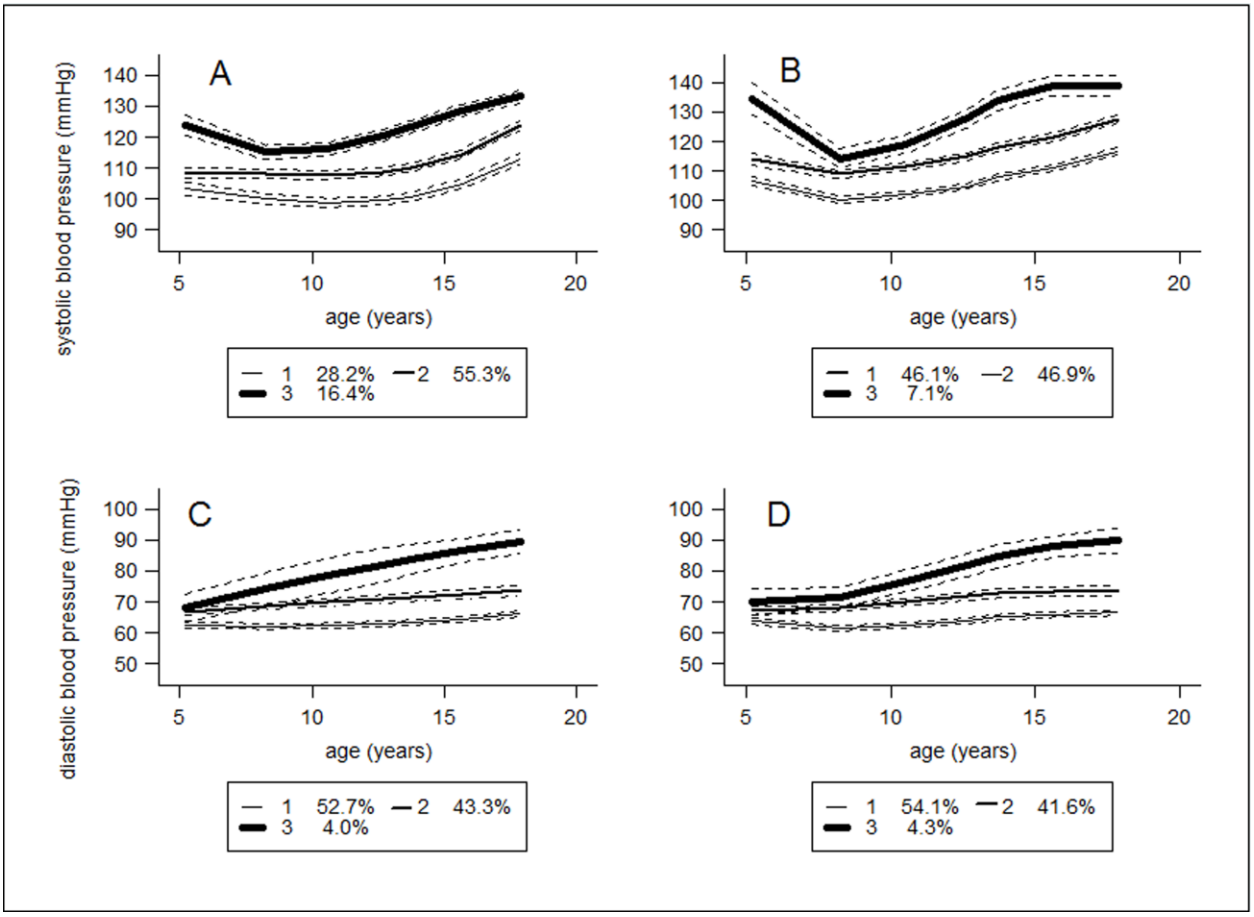

Figure 5-1 Trajectories of blood pressure for boys between 5 and 18 years of age.

A. Systolic blood pressure over time. **B**. Systolic blood pressure over time adjusted for height as a time varying covariate. **C**. Diastolic blood pressure over time. **D**. Diastolic blood pressure over time accounting for height per time point

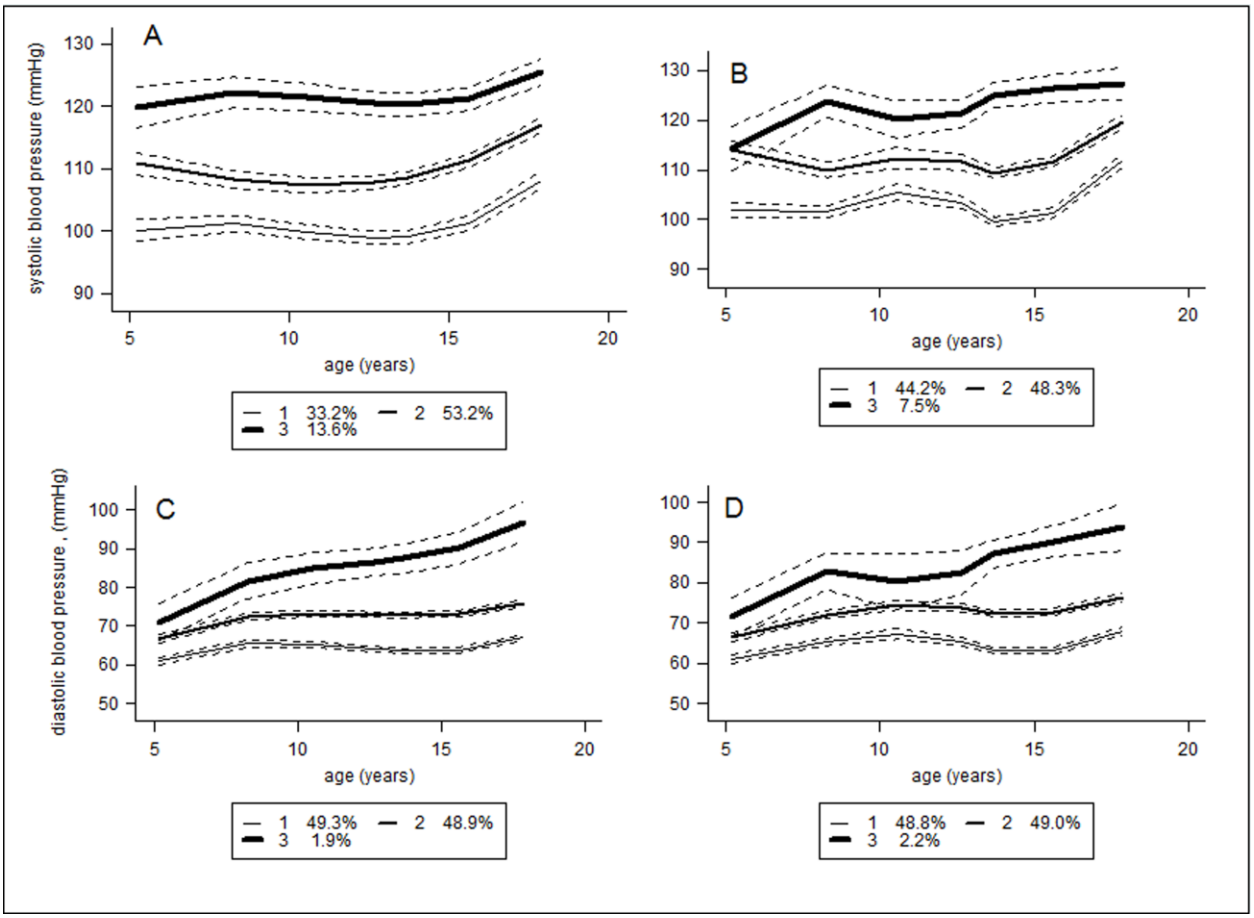

Figure 5-2 Girls trajectories of blood pressure between 5 and 18 years of age

A. Systolic blood pressure changes with age. **B**. Systolic blood pressure over time adjusted for height at each time point. **C**. Diastolic blood pressure over time. **D**. Diastolic blood pressure over time accounting for height per time point.

Table 1 Sex -specific Mean BP by trajectory group membership

Mean Age(years)	SBP trajectory group membership						DBP trajectory group membership					
	Boys			Girls			Boys			Girls		
	Low	Middle	Upper	Low	Middle	Upper	Low	Middle	Upper	Low	Middle	Upper
5	101.9(10.8)	107.3(10.4)	125.0(12.0)	99.0(8.6)	110.4(9.9)	120.5(13.3)	60.5(7.5)	65.8(7.8)	69.9(8.3)	60.5(6.9)	67.2(8.7)	70.0(8.6)
8	101.7(7.5)	110.8(8.6)	119.0(10.9)	101.7(7.0)	110.3(8.4)	125.5(10.0)	65.9(7.0)	73.1(7.5)	75.1(6.8)	66.1(7.0)	73.8(7.5)	85.6(12.0)
10	98.5(9.1)	106.8(9.4)	117.9(14.7)	99.1(8.5)	107.0(9.6)	119.2(13.2)	63.8(7.4)	69.7(7.8)	76.4(12.0)	64.2(7.5)	71.0(7.5)	80.3(12.8)
13	96.9(6.7)	107.2(6.6)	119.1(9.2)	98.0(6.6)	107.5(6.9)	119.3(8.8)	61.0(5.9)	69.7(6.4)	80.6(11.5)	62.8(5.7)	72.3(6.6)	83.3(7.4)
14	98.6(6.9)	109.1(7.3)	122.6(9.9)	99.0(6.8)	108.5(7.5)	120.3(9.7)	63.0(5.9)	72.7(6.7)	86.7(8.5)	65.1(5.9)	75.1(6.9)	91.0(7.2)
16	105.3(8.0)	117.3(9.0)	132.3(11.3)	100.0(8.3)	112.7(9.1)	124.1(10.6)	62.8(6.4)	72.3(1.1)	90.9(13.1)	62.9(6.7)	73.2(7.3)	93.4(12.6)
18	111.4(7.6)	122.9(8.2)	132.4(10.4)	107.5(7.0)	116.9(8.1)	125.7(9.2)	66.8(6.4)	75.3(7.2)	88.1(7.8)	67.2(6.2)	76.6(6.9)	97.5(12.2)
	SBP trajectory group membership-height adjusted						DBP trajectory group membership-height adjusted					
5	103.7(10.4)	110.7(12.0)	130.9(10.4)	100.6(9.1)	113.6(10.9)	113.1(13.6)	61.4(7.8)	64.9(8.1)	76.7(9.8)	60.4(7.0)	70.0(8.2)	70.0(8.2)
8	104.7(8.3)	113.7(9.5)	118.0(10.3)	102.9(7.4)	113.2(9.2)	126.9(11.0)	66.7(7.2)	73.6(7.8)	73.9(5.1)	66.1(6.9)	85.3(11.0)	85.3(11.0)
10	101.4(9.8)	109.6(10.9)	117.8(15.3)	100.0(8.4)	110.0(10.2)	118.9(17.3)	64.2(7.5)	70.3(8.1)	76.1(10.6)	63.8(7.4)	80.4(11.3)	80.4(11.3)
13	100.6(7.8)	110.0(7.9)	121.0(10.9)	100.0(7.0)	109.1(7.4)	122.8(9.9)	61.6(6.0)	70.6(6.9)	80.8(13.4)	62.7(5.7)	84.0(7.1)	84.0(7.1)

14	102.2(7.9)	112.2(8.5)	128.2(10.4)	100.3(7.2)	110.3(7.3)	124.9(9.9)	63.6(6.2)	73.5(7.0)	86.8(9.7)	65.0(5.9)	89.5(7.4)	89.5(7.4)
16	109.1(9.1)	121.2(9.9)	137.2(12.5)	102.0(8.8)	114.7(9.1)	128.0(11.6)	63.5(6.7)	72.9(7.9)	96.3(11.9)	62.6(6.5)	91.2(12.2)	91.2(12.2)
18	115.2(8.9)	125.7(8.3)	134.0(13.5)	109.2(7.4)	118.3(7.7)	130.4(11.9)	67.2(6.4)	76.5(7.7)	87.4(7.9)	67.0(6.1)	96.0(11.8)	96.0(11.8)

*****Summary statistics showing mean blood pressure and standard deviations across the trajectory group memberships of blood pressure between ages 5 and 18 on seven time points depicted by mean ages.

Table 2 Study sample characteristics by sex and BP trajectory groups

Study characteristics	SBP trajectory group						DBP trajectory group					
	Boys			Girls			Boys			Girls		
	Lower	Middle	Upper	Lower	Middle	Upper	Lower	Middle	Upper	Lower	Middle	Upper
Gestational age(weeks)	38.0(1.5)	37.9(1.9)	38.0(2.0)	37.9(1.8)	38.0(1.8)	37.8(1.9)	37.9(1.9)	38.0(1.6)	37.8(2.9)	37.9(1.9)	37.9(1.6)	38.1(2.2)
Birth weight(g)	3110.4(0.5)	3132.2(0.5)	3116.1(0.5)	3023.8(0.5)	3027.7(0.5)	3061.3(0.4)	3125.2(0.5)	3132.4(0.5)	3078.6(0.6)	3025.4(0.5)	3034.7(0.5)	3121.4(0.4)
Relative weight gain infancy	-0.05(0.9)	0.14(1.0)	0.17(1.0)	-02(1.0)	0.20(1.0)	0.30(1.0)**	0.05(1.0)	0.17(1.0)	0.01(1.1)	0.07(1.0)	0.20(0.9)	0.78(0.8)*
Relative weight gain mid-childhood	-0.14(1.0)	0.02(1.0)	0.07(1.2)	-0.16(1.0)	-0.08(1.0)	0.32(1.0)**	-0.06(1.0)	0.04(1.1)	0-0.13(1.5)	-0.14(1.1)	0.001(1.0)	0.44(1.0)
Relative linear growth infancy	-0.31(0.8)	-0.05(1.0)	0.19(0.9)***	-0.31(0.9)	0.01(1.0)	0.14(1.0)***	-0.13(1.0)	-0.03(1.0)	0.16(1.0)	-0.12(1.0)	-0.01(1.0)	-0.31(1.2)
Relative linear growth mid-childhood	-0.20(1.1)	0.04(1.0)	0.04(0.9)*	-0.19(1.0)	0.03(1.0)	0.40(0.9)***	-0.13(1.0)	0.11(1.0)	0.30(1.1)*	-0.07(1.0)	0.07(1.0)	0.64(1.0)*
SBP at 5 years of age/mmHg	103.1(11.9)	108.4(11.1)	124.7(14.0)***	104.0(1.4)	115.6(11.4)	118.7(16.0)***	-			-		
DBP at 5 years of age/mmHg	-			-			60.2(7.7)	63.8(7.9)	71.7(7.9)***	60.4(6.8)	66.7(8.7)	69.4(10.7)***
Parity: ≤2	92(41.4)	298(33.8)	51(35.7)	149(48.5)	301(33.6)	40(33.6)	278(33.8)	156(39.5)	7(25.0)	304(36.7)	182(38.0)	4(28.6)
>2	130(58.6)	583(66.1)	92(64.3)	158(51.5)	595(66.4)	79(66.4)***	545(66.2)	239(60.5)	21(75.0)	525(63.3)	297(62.0)	10(71.4)
SES in infancy(household assets)	4(2)	3(2)	3(2)**	4(2)	3(2)	3(2)*	3(2)	3(2)	3(1)	3(2)	3(2)	3(1)**
	SBP trajectory groups-height adjusted						DBP trajectory groups-height adjusted					

Gestational age	38.0(1.7)	37.9(2.0)	37.9(2.0)	37.9(1.8)	37.9(1.9)	37.9(1.5)	37.9(1.8)	38.0(1.7)	37.6(3.1)	37.8(2.0)	38.0(1.7)	38.0(2.1)
Birth weight	3160.0(0.5)	3077.2(0.5)	3070.0(0.5)	3031.1(0.5)	3026.1(0.5)	3074.1(0.4)	3140.0(0.5)	3090.7(0.5)	3133.3(0.5)	3009.6(0.5)	3040.0(0.5)	3111.8(0.4)
Relative weight gain infancy	0.11(1.0)	0.10(1.0)	0-0.02(1.1)	-02(0.9)	0.25(1.0)	0.26(0.9)**	0.08(1.0)	0.15(1.0)	0-0.19(1.0)	0.02(1.0)	0.23(1.0)	0.81(0.8)***
Relative weight gain mid-childhood	0.01(1.1)	0-0.07(1.0)	0.03(1.2)	-0.19(1.0)	-0.02(1.0)	0.19(1.0)*	-0.06(1.0)	0.07(1.1)	0-0.03(1.0)	-0.17(1.1)	0.02(1.0)	0.44(1.0)*
Relative linear growth infancy	-0.09(0.9)	-0.06(1.0)	0-0.33(0.9)	-0.15(1.0)	0.01(1.0)	0-0.09(1.0)	-0.04(1.0)	-0.18(0.9)	0-0.04(1.0)	-0.06(1.0)	0-0.06(1.0)	-0.51(1.2)
Relative linear growth mid-childhood	-0.09(1.0)	0.05(1.1)	0.24(0.8)*	-0.07(1.0)	0.04(1.0)	0.24(0.8)	-0.04(1.0)	0.005(1.0)	0.12(0.9)*	-0.06(1.0)	0.05(1.0)	0.40(0.9)
SBP at 5 years of age/mmHg	110(12.0)	103.7(8.1)	130.9(10.4)***	100.6(9.1)	113.6(10.9)	113.1(13.7)***	-			-		
DBP at 5 years of age/mmHg	-			-			61.4(7.8)	64.9(8.1)	76.7(9.8)***	60.4(7.0)	67.0(8.6)	69.6(8.2)***
Parity : ≤2	162(36.8)	262(35.1)	17(28.3)	206(47.8)	265(31.8)	19(32.8)***	305(34.2)	130(38.8)	6(28.6)	207(43.1)	278(33.7)	5(29.4)**
>2	278(63.2)	484(64.9)	43(71.7)	225(52.2)	568(68.2)	39(67.2)	585(65.7)	205(61.2)	15(71.4)	273(56.9)	547(66.3)	12(70.6)
SES in infancy	3(2)	3(2)	3(2)	3(2)	3(2)	3(2)	3(2)	3(2)	3(1)	3(2)	3(2)	3(1)*

*Model showing the summary statistics of factors associated with the BP trajectories with level of significance: ***p<0.001, **p<0.01, *p<0.05

†Analysis of variance for continuous exposures (gestational age, birth weight, weight and linear growth between 0-2yrs, 2-5yrs, BP at 5yrs and asset-based SES score) and chi square test for categorical variable, parity, associated with the BP trajectories

Table 3 Association of birth weight relative weight gain and linear growth in infancy and mid-childhood, and SBP trajectory groups between 5 and 18 years (OR, 95%CI, p value)

A. BOYS	**Model 1**			**Model 2**			**Model 3**			**Model 4**		
Middle vs Lower trajectory group	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**
Birth weight(z score)	1.02	0.76-1.38	0.8736	0.99	0.73-1.35	0.9738	0.77	0.6-0.98	0.0307	0.75	0.58-0.96	0.0223
Relative weight gain in infancy	1.54	1.14-2.09	0.0050	1.65	1.2-2.26	0.0021	1.21	0.95-1.55	0.1237	1.23	0.96-1.59	0.1046
Relative weight gain in mid-childhood	1.20	0.94-1.54	0.1522	1.28	0.96-1.7	0.0918	1.25	0.99-1.57	0.0653	1.26	0.98-1.62	0.0712
Relative linear growth in infancy	1.76	1.28-2.43	0.0005	1.72	1.26-2.35	0.0007	0.84	0.64-1.11	0.2157	0.84	0.64-1.11	0.2299
Relative linear growth in mid-childhood	1.65	1.24-2.18	0.0005	1.58	1.19-2.11	0.0018	0.85	0.67-1.09	0.2021	0.89	0.7-1.15	0.3774
Upper vs Lower trajectory group												
Birth weight(z score)	1.03	0.7-1.51	0.8705	1.02	0.66-1.56	0.9453	0.69	0.31-1.55	0.3652	0.67	0.28-1.61	0.3685
Relative weight gain in infancy	1.58	1.08-2.33	0.0190	1.67	1.09-2.56	0.0196	3.74	1.43-9.83	0.0074	4.11	1.25-13.51	0.0202
Relative weight gain in mid-childhood	1.34	0.95-1.89	0.0950	1.36	0.92-2.02	0.1221	1.21	0.59-2.48	0.6088	1.20	0.54-2.65	0.6604
Relative linear growth in infancy	2.15	1.41-3.28	0.0004	2.18	1.39-3.43	0.0007	1.62	0.67-3.93	0.2847	1.98	0.71-5.48	0.1912
Relative linear growth in mid-childhood	1.44	1-2.09	0.0513	1.53	1.02-2.3	0.0400	1.02	0.44-2.34	0.9645	1.12	0.39-3.2	0.8392
B.GIRLS												

Middle vs Lower trajectory group												
Birth weight(z score)	1.23	0.93-1.63	0.1490	1.12	0.85-1.48	0.4309	1.09	0.84-1.42	0.5190	0.97	0.73-1.28	0.8223
Relative weight gain in infancy	1.39	1.04-1.86	0.0276	1.37	1.02-1.85	0.0350	1.33	1.02-1.75	0.0378	1.33	1-1.76	0.0492
Relative weight gain in mid-childhood	1.00	0.75-1.32	0.9802	1.09	0.81-1.46	0.5669	1.11	0.85-1.44	0.4507	1.22	0.93-1.59	0.1546
Relative linear growth in infancy	2.11	1.51-2.94	0.0000	2.07	1.48-2.91	0.0000	1.60	1.15-2.21	0.0053	1.58	1.15-2.17	0.0046
Relative linear growth in mid-childhood	1.14	0.87-1.49	0.3394	1.12	0.85-1.48	0.4209	1.03	0.79-1.36	0.8098	1.01	0.75-1.35	0.9578
Upper vs Lower trajectory group												
Birth weight(z score)	1.34	0.93-1.94	0.1123	1.31	0.89-1.92	0.1682	1.35	0.94-1.94	0.1043	1.27	0.86-1.88	0.2246
Relative weight gain in infancy	1.67	1.14-2.44	0.0085	1.59	1.06-2.37	0.0236	1.69	1.14-2.5	0.0084	1.63	1.08-2.46	0.0211
Relative weight gain in mid-childhood	1.65	1.18-2.31	0.0038	1.76	1.22-2.55	0.0026	1.69	1.2-2.38	0.0026	1.77	1.22-2.56	0.0025
Relative linear growth in infancy	2.35	1.59-3.48	0.0000	2.23	1.48-3.35	0.0001	1.98	1.33-2.96	0.0008	1.90	1.27-2.86	0.0019
Relative linear growth in mid-childhood	1.95	1.37-2.78	0.0002	1.99	1.36-2.91	0.0004	2.03	1.38-2.99	0.0003	2.12	1.39-3.23	0.0005

*The multinomial logistic regression showing odds ratios, 95% confidence intervals and the p values from GBTM showing:

†Model 1: Multinomial logistic regression of growth variables and SBP trajectory classes adjusted for gestational age (time-invariant covariate-a proxy for intrauterine environment).

Model 2: Multinomial logistic regression of growth variables and SBP trajectory classes adjusted for gestational age, parity, SES in infancy, maternal age (time-invariant covariates-intrauterine environment and maternal factors).

Model 3: Multinomial logistic regression of growth variables and SBP trajectory classes with height as time-varying covariate (a marker of childhood environment) and gestational age as a time-invariant covariate.

Model 4: Multinomial logistic regression of growth variables and SBP trajectory classes with height as time varying covariate and gestational age, parity, SES in infancy, and maternal age as a time-invariant covariates.

Table 4 Association of birth weight relative weight gain and linear growth in infancy and mid-childhood, and DBP trajectory groups between 5 and 18 years (OR, 95%CI, p value)*

A. BOYS	Model 1			Model 2			Model 3			Model 4		
Middle vs Lower trajectory group	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**	**OR**	**95%CI**	**P value**
Birth weight(z score)	0.97	0.72-1.33	0.8688	0.99	0.71-1.38	0.9371	0.82	0.64-1.06	0.1359	0.83	0.63-1.10	0.2019
Relative weight gain in infancy	1.73	1.23-2.42	0.0015	1.76	1.22-2.56	0.0028	1.37	1.04-1.8	0.0251	1.43	1.06-1.95	0.0214
Relative weight gain in mid-childhood	1.37	1.01-1.85	0.0447	1.44	1.03-2.01	0.0351	1.22	0.96-1.56	0.1029	1.26	0.96-1.64	0.0926
Relative linear growth in infancy	1.02	0.71-1.46	0.9100	1.13	0.76-1.67	0.5598	0.72	0.55-0.94	0.0171	0.78	0.58-1.05	0.1001
Relative linear growth in mid-childhood	1.51	1.06-2.15	0.0228	1.68	1.19-2.38	0.0034	0.97	0.75-1.24	0.8032	1.14	0.86-1.52	0.3633
Upper vs Lower trajectory group												
Birth weight(z score)	0.93	0.65-1.34	0.7133	0.93	0.63-1.36	0.7017	0.81	0.46-1.42	0.4609	0.68	0.45-1.03	0.0658
Relative weight gain in infancy	1.57	0.98-2.52	0.0614	1.77	1.16-2.72	0.0087	1.03	0.55-1.90	0.9359	1.38	0.89-2.15	0.1519
Relative weight gain in mid-childhood	1.12	0.72-1.72	0.6190	1.40	0.94-2.08	0.0976	0.93	0.56-1.54	0.7739	1.37	0.88-2.13	0.1627
Relative linear growth in infancy	1.21	0.81-1.81	0.3535	1.17	0.76-1.78	0.4787	0.75	0.36-1.56	0.4392	0.47	0.29-0.76	0.0021
Relative linear growth in mid-childhood	1.75	1.20-2.54	0.0036	1.83	1.23-2.71	0.0028	1.05	0.63-1.76	0.8473	0.80	0.53-1.21	0.2848
B.GIRLS												

Middle vs Lower trajectory group												
Birth weight(z score)	1.07	0.86-1.35	0.5310	1.02	0.80-1.30	0.8553	1.03	0.82-1.30	0.7790	0.99	0.78-1.26	0.9339
Relative weight gain in infancy	1.36	1.07-1.73	0.0108	1.27	0.99-1.63	0.0611	1.31	1.03-1.67	0.0265	1.27	0.98-1.63	0.0677
Relative weight gain in mid-childhood	1.23	1.00-1.51	0.0511	1.30	1.04-1.63	0.0234	1.20	0.97-1.47	0.0956	1.28	1.02-1.61	0.0317
Relative linear growth in infancy	1.27	1.01-1.59	0.0392	1.24	0.97-1.58	0.0809	1.15	0.89-1.47	0.2858	1.08	0.83-1.42	0.5544
Relative linear growth in mid-childhood	1.28	1.03-1.58	0.0234	1.27	1.00-1.60	0.0460	1.18	0.94-1.48	0.1502	1.17	0.91-1.49	0.2205
Upper vs Lower trajectory group												
Birth weight(z score)	1.16	0.44-3.06	0.7615	1.47	0.73-2.97	0.2830	1.46	0.72-2.95	0.2944	1.44	0.68-3.03	0.3379
Relative weight gain in infancy	4.25	1.51-11.94	0.0061	2.90	1.36-6.18	0.0057	2.65	1.25-5.58	0.0106	2.53	1.14-5.57	0.0219
Relative weight gain in mid-childhood	1.08	0.47-2.48	0.8640	1.58	0.81-3.10	0.1835	1.47	0.77-2.82	0.2468	1.52	0.80-2.90	0.2047
Relative linear growth in infancy	0.88	0.37-2.14	0.7856	1.07	0.55-2.10	0.8396	0.88	0.44-1.74	0.7039	1.00	0.49-2.02	0.9942
Relative linear growth in mid-childhood	2.20	0.90-5.36	0.0840	1.56	0.80-3.04	0.1950	1.52	0.80-2.90	0.1996	1.48	0.74-2.96	0.2715

*Multinomial logistic regression models showing the odds ratios, 95% confidence intervals and p values of the association between growth and BP trajectories:

†Model 1: Multinomial logistic regression of growth variables and DBP trajectory classes adjusted for gestational age (time-invariant covariate).

Model 2: Multinomial logistic regression of growth variables and DBP trajectory classes adjusted for gestational age, parity, SES in infancy, maternal age (time-invariant covariates).

Model 3: Multinomial logistic regression of growth variables and DBP trajectory classes with height as time-varying covariate and gestational age as a time-invariant covariate.

Model 4: Multinomial logistic regression of growth variables and DBP trajectory classes with height as time varying covariate and gestational age, parity, SES in infancy and maternal age as a time-invariant covariates.

PART 3: GENERAL DISCUSSION

"It is easier to build strong children than repair broken men…"

Frederick Douglass (1818-1895)

6 CHAPTER 6: GENERAL DISCUSSION

This chapter is the synthesis of consolidated findings with regards to key objectives of this thesis. It also comprises of reflections on the emerging themes, conceptual and contextual relevance, the strengths and limitations, future research and the conclusion.

6.1 Summary of study findings

The overarching objective of this study was to describe the BP profiles in BT20 between ages 5 and 18 years and to examine the impact of early growth on the longitudinal BP trajectories. The consolidated findings in line with the objectives of the study are outlined in table 6-1

Table 6-1 Consolidated study findings

Chapter	Objective	Key findings
3	**Assess the prevalence of elevated BP**	High prevalence of hypertension at as early as age 5 years (22.4%).

	between 5 to 18 years	
3	**Examine BP tracking between ages 5 and 18 years**	Low to moderate tracking of BP between 5 and 18 years of age and 36.1% of children above the 90th percentile for age, sex and height at 5 years of age maintained the elevated BP status at mean age 18 years. The relative risk of remaining in the elevated BP status compared to remaining in the normative range between 5 and 18 years of age was 60%: (OR1.60: 95%CI:1.29-2.00).
4	**Examine the association between SES change in childhood, and BP at 18 years of age**	Upward social mobility compared to a persistent low SES between infancy and adolescence was significantly associated with a 5mmHg lower SBP (β= -4.85 : 95% CI:-8.22 to -1.48, p<0.01)
5	**Identify distinct BP trajectories**	Three distinct sex-specific trajectory group memberships for BP were identified using group based trajectory modeling: “lower”, “middle” and “upper.” Height between ages 5 and 18 years and cubic age terms

		were positively associated with BP trajectories except for girls upper SBP and DBP.
5	**Assess the association of early-life growth and BP trajectories between ages 5 and 18 years,**	Accelerated weight accrual and linear growth were associated with the upper compared to the lower SBP trajectory in girls In boys, increased birth weight and faster relative weight gain in infancy were major predictors of the middle and the upper trajectories compared to the lower one. The associations between early growth and DBP trajectory group membership were inconsistent.

6.1.1 Hypotheses re-visited

In the context of the consolidated findings, I revisited the hypotheses for this thesis.

Hypothesis 1: Elevated BP does not track from childhood to adulthood

We reject the hypothesis that stated that BP does not track from childhood to adulthood in this theses and suggest that there is a low-to-moderate degree of tracking with regards to tracking

coefficients and almost one in three children maintain an elevated BP status between 5 and 18 years of age.

Hypothesis 2: There is no relationship between SES change and later BP

There is an association between an upward SES change between infancy and adolescence and SBP hence we reject the hypothesis that a change in SES does not predict BP. However, this hypothesis held for DBP, MAP and hypertension status.

Hypothesis 3: There are no distinct BP trajectories between 5 and 18 years of age

We have also rejected the assumption of homogeneity in longitudinal BP throughout childhood and concluded that there are distinct patterns of BP change over time.

Hypothesis 4: Early growth in infancy and mid-childhood is not related to BP trajectories independent of height

Trajectories of BP change over time are associated with some patterns of early life growth hence the assumption that early growth is not associated with BP between childhood and adulthood fails to hold in this present study.

6.2 Emerging research themes from the findings

Based on the consolidated findings of this thesis and the relevant literature, the emerging themes are: (1) early emergence of high BP which is sustained to early adulthood; (2) Sub-groups of individuals can be identified as having distinct patterns of BP over time, and (3) early growth and increases in stature predict age-related BP changes over time.

6.2.1 Early establishment and persistence of elevated BP

This thesis has helped me reflect back to my cardiovascular physiology classes as an undergraduate student. We were taught that BP increases with age along with height and weight in a growing child. However, strikingly new perspectives to high BP in this study are the early onset in children as long as 5 years of age and the persistence of elevated BP into early adulthood in one in three children. Though this was based on BP readings on one occasion, the current paediatric high BP estimates tend to reflect the current state of adult hypertension in South Africa which is home to the most hypertensive population worldwide, with prevalence of 30 to 40 % over the recent years, and in a younger individuals compared to other regions of the world (250).

Childhood hypertension often goes unnoticed with its subtle ripple effects often manifesting only in adulthood with complications may not be reversed. This implies that by the time hypertension

is detected in adulthood, considerable damage may have occurred to the arterial system, heart, and other organs related to BP control. These physiological and metabolic markers may be detected in children using non-invasive to assess the extent of vascular injury or end organ damage in childhood (20, 251).

6.2.2 The dynamics of SES and SBP

Children are born into socially and economically diverse environments which may set in motion a cascade of delicate biological and metabolic responses upon which trajectories of BP are set for life. Socioeconomic disparities in South Africa are an intense aftermath of the apartheid regime which left black South Africans in poor housing conditions, low income and education levels compared to their white counterparts. At the dawn of the post -apartheid era, still inequalities among black people exists with the majority still falling short of key socioeconomic indicators like employment and education (252).

This study provided a new dimension in social epidemiology in the South African context by highlighting that BP was lower among black children whose SES improved between infancy and compared to those who had persistent low SES. It is not clear whether these findings will hold as the wave of transition continues to sweep across this South African black population. There is strong evidence to confirm social patterning of BP in both HICs and LMICs, though the

gradients differ from setting to setting. HTN is more prevalent in urban versus rural areas due to the nutrition transition (253), and in urban areas high BP disproportionately affect the poor compared to the rich (254).

6.2.3 Stature and childhood BP trajectories

Many key organs responsible for BP control are developed and set by birth for example the number of nephrons are set at birth. This implies that environment prior and during gestation may set a child in a particular course of BP development over time. In response to growth and development of a child, variations in BP could be identified in this study as early as at 5 years of age. We found out that early rapid growth along with stature were significant drivers of the BP trajectories, especially in the upper trajectories of SBP. These findings confirm the importance of height in paediatric BP.

The role of height in BP in children and adolescents has been reported elsewhere , with a unit increase in height significantly predicted almost a 2mmHg increase in SBP and a 1mmHg in DBP in Indian (199) and American children (255). However, most studies modelling longitudinal blood pressure in children and teenagers often overlook the influence of height on BP of a growing child mainly because of the complexities related to its inclusion in the models.

The challenge with modeling height as a time varying covariate in Mplus was convergence issues leading to the use of GBTM in a STATA plug in program developed by Jones and Nagin (243, 256). Both GMM and GBTM are useful in establishing distinct patterns of BP change over time which might be of conceptual and empirical relevance for policy and clinical practice as they provide a non-parametric presentation of a continuous variable like BP. These trajectory groups may be useful in identifying children with anomalous BP patterns and their key characteristics and possible underlying biological mechanisms.

The advantage of GBTM over GMM in MPlus is that GBTM does not assume a normal distribution of the variable in a population, but uses statistical algorithms to estimate the unknown distribution of the trajectories across a given population. On the other hand, GMM works on assumption that the population comprises at least two subgroups, each of which follows a growth curve model with random effects. GBTM produces a visual summary of the trajectory groups with confidence intervals depicting the level and change of the trajectory group. However, there is an assumption of no individual variation around the mean group trajectory since it is constrained to zero hence there is no detail on variation within trajectory group with regards to level and rate of change (257).

My recommendation is that choice of use of either GMM or GBTM should be based on the research question, conceptual framework and the intended use of information on BP trajectories.

For instance if the research question focusses on understanding individual variation in a particular trajectory group, then GMM should be a preferred option but if there objective is to assess factors associated with group membership, then the need for individual variation within a group may be relaxed.

6.3 Conceptual relevance

The conceptual framework for this thesis was selected based on its life course approach to chronic diseases and how growth and societal factors across the life span influences hypertension risk. Based on the relevant literature, overall research objective, key findings and emerging themes of this thesis, major modification to the conceptual framework are: (1) persistence of BP status along with increasing stature and early establishment of sub-groups of individuals with distinct patterns of BP over time, (2) improving socioeconomic status between childhood and adolescence reduces SBP and (3) use of conditional relative weight and height gain as proxies for rapid growth may be useful in dealing with multicolinearity in life course models. These major modifications are highlighted in red in Figure 6-2

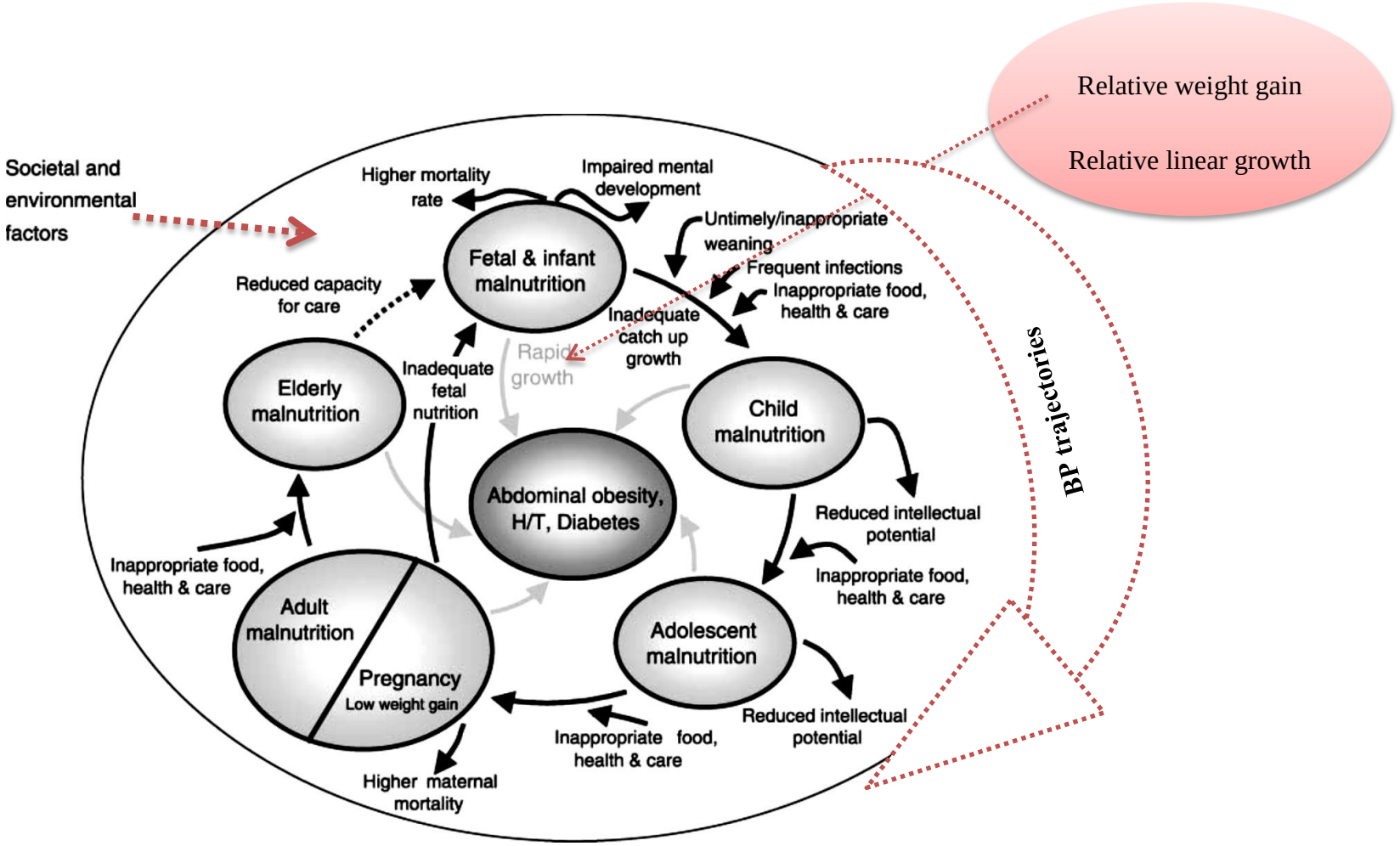

Figure 6-2 A modified conceptual framework on life course approach to chronic diseases prevention

6.4 Study relevance-locally and internationally

Early establishment of elevated BP is relevant for policy, practice and research for several reasons. Firstly, detection and prevention of elevated BP should start earlier in life before emergence of complications related to high BP which could be more costly to eradicate or manage. Secondly, interventions should target optimal growth in early life though maternal nutrition before or during pregnancy, promotion of exclusive breastfeeding, appropriate weaning practices and low-calorie in childhood. This body of work has highlighted that elevated BP may be established earlier in life. Thirdly, since poor household condition in early life is a critical puzzle in BP etiology, there is need to address social disparities to improve child health by addressing household needs, health services and improving maternal education and empowerment and ownership.

These findings have theoretical relevance for policy, practice and research and call for a multi-stakeholder approach to early detection, public health awareness, prevention and control of high blood pressure in children and adolescents by global health bodies, civil society groups, health practitioners, researchers, community and parents or caregivers. There is need for policy formulation and action around reducing the burden attributable to hypertension beginning in early life. Against increasing evidence to suggest that hypertension is established in early life, there is need to raise public awareness and engagement on paediatric HTN, its risk factors, complications and prevention strategies.

Early detection may pose long term benefits hence there is need to advocate for inclusion of routine BP checks along with growth monitoring in children. Currently, there is no consensus on BP classification criteria hence researchers and paediatric practice need to develop valid, reliable and universally easy-to use BP normative charts to make detection of hypertension in children and adolescents as easy as in adults. Emulating the Chinese BP reference charts, South Africa should establish national BP normative charts to which are representative of the local population.

There is need for policies that safeguard paediatric population against risk factors for elevated BP in childhood, for example, marketing of high salt, empty calorie foods to children and controlled food vending around schools, sedentary lifestyles by engaging parents, schools and government to promote healthy lifestyles and physical education. In South Africa, there is need for the Ministries of Education, Social development and Health to reinforce policies which promote healthy lifestyles from as early as preschool like compulsory physical education in schools and curriculum on healthy lifestyles.

6.5 Strengths and limitations

This study has potential to infer causality by virtue of its prospective cohort design with long term follow up from birth to 18 years. The study sample was large, increasing external validity. The excluded sample was also comparable to the analytical sample. Data for this study were

collected prospectively and the validated questionnaires for SES and anthropometry were consistent over time minimizing information bias.

The cohort had repeated measures of BP over seven occasions, measured by trained research assistants. The use of automated BP machines minimized observer bias compared to the sphygmomanometer where the observer's ability to detect the Korotkoff sound for DBP measurement is highly subjective. Furthermore three measurements of BP were obtained at each occasion and the second and third measurements were averaged to represent the BP at a given time point thereby minimizing white coat effect. Potential confounders were measured during data collection and adjusted accordingly in all the multivariate analyses increasing the potential of this study to establish causality.

Despite a number of the strengths, some issues have to be acknowledged as potential shortcomings. Firstly, loss due to follow up in this cohort study (less than 25% overall) was inevitable due to deaths and migrations and other reasons. Comparisons on key variables for those who were retained in the analyses and those who were excluded for each research objective enhanced external validity. For longitudinal analyses, after exploratory analyses, we made an assumption that BP data were missing at random (MAR). The GBTM technique employed maximum likelihood estimation to deal with potential bias related to missing data.

Measurement of BP using two different automated machines (the Dinamap at age 5, and Omron from 8 years onwards) may have introduced differential misclassification in BP in childhood time points. However, there is evidence to suggest that there are no major differences with regards to BP measurements in pediatrics using the two automated machines (258).

We also noted that the proportions of individuals in the downward mobility group were very small hence this might have affected statistical power in the multivariate analyses. The problem of repeated measures of early life growth is that they were strongly correlated. To account for this we computed conditional variables to reduce multi-collinearity. The associations between early growth and the upper DBP trajectory membership were inconsistent, probably because of low statistical power due to low proportions in those groups.

6.6 Future research

Based on the findings from this thesis, we postulate that it is possible to identify children with persistent elevated BP in childhood and that there could be underlying bio-physiological mechanisms driving BP in children. Future research has to:

1. Confirm the estimates of elevated BP in children starting from age 5 years in the Soweto, Johannesburg to reinforce the rationale to prioritise hypertension screening in children.

2. Evaluate the feasibility of screening children for primary hypertension by assessing absolute risk and intention to treat.

3. Establish the clinical hypertension status in this cohort study and to assess the biochemistry, cardiovascular physiology (arterial stiffness, early cardiovascular aging) and kidney function to understand the underlying mechanisms in relation to the BP trajectories identified in this current thesis.

4. Prioritise development of valid, easy to implement and simplified paediatric BP measurement protocols and normative definitions that can be used in diverse settings to establish global and regional trends in paediatric hypertension

6.7 Conclusions

In conclusion, this thesis demonstrated the importance of examining childhood BP because elevated BP tracks into adulthood independent of the biological effect of height. It also highlighted the importance of optimizing growth and socioeconomic environment in the early life period upon which key foundations for BP variations are created. This can be achieved

through promoting breastfeeding in infancy and appropriate weaning diet, physical activity in childhood and reducing the social inequality inherited from the apartheid era

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APPENDICES

Appendix 1 Birth to Twenty Questionnaire Anthropometry and SES sections

University of the Witwatersrand
Department of Paediatrics and Child Health

BIRTH TO TWENTY BARA SITE: 18TH YEAR
ADOLESCENT ROUTINE QUESTIONNAIRE

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

BTT ID NUMBER: ☐☐☐☐☐☐☐

BONE ID NUMBER: ☐☐☐

Consent Table (Initial the appropriate column)

Components	Yes	No
Core Questionnaire		
Anthropometric Measurements		

Contact details of a relative or a friend who will **always** know where you live (different to information on contact sheet):

Name: _____ Relationship: _____

Landline number: _____ Cell number: _____

Work number: _____ Other: _____

PARTICIPATION IN BIRTH TO TWENTY CONSENT

I agree to myself being a participant in Birth to Twenty study

The goals and methods of the study are clear to me.

I understand that the study will involve interviews. All the details and purposes of this study have been explained to me. I understand that I have the right to refuse to participate in the study.

I agree to participation in Birth to Twenty study on condition that:

1. I can withdraw from the study at any time voluntarily and that no adverse consequences will follow on withdrawal from the study.

2. I have the right not to answer any or all questions posed in the interviews and not to participate in any or all of the procedures / assessments.

3. The University of the Witwatersrand Human Ethics committee has approved the study protocol and procedures.

4. All results will be treated with the strictest confidentiality.

5. Only group results, and not my individual results, will be published in scientific journals and in the media.

6. The study scientific team are committed to treating participants with respect and privacy through interviews conducted in private and follow-up counselling available on request.

7. I will receive a referral note to a health service if any result is out of the normal range or a problem is detected in the course of the study.

PARTICIPANT:

Printed Name	**Signature / Mark or Thumbprint**	**Date and Time**

RESEARCH ASSISTANT:

Printed Name	Signature	Date and Time

SURVEY CONSENT

I agree to myself being a participant in the study

The goals and methods of the study are clear to me.

I understand that the study will involve interviews. All the details and purposes of this study have been explained to me. I understand that I have the right to refuse to participate in the study.

I agree to participation in the study on the condition that:

1. I can withdraw from the study at any time voluntarily and that no adverse consequences will follow on withdrawal from the study.

2. I have the right not to answer any or all questions posed in the interviews and not to participate in any or all of the procedures / assessments.

3. The University of the Witwatersrand Human Ethics committee has approved the study protocol and procedures.

4. All results will be treated with the strictest confidentiality.

5. Only group results, and not my individual results, will be published in scientific journals and in the media.

6. The study scientific team are committed to treating participants with respect and privacy through interviews conducted in private and follow-up counselling available on request.

7. I will receive a referral note to a health service if any result is out of the normal range or a problem is detected in the course of the study.

PARTICIPANT

Printed Name	**Signature / Mark or Thumbprint**	**Date and Time**

RESEARCH ASSISTANT:

Printed Name	**Signature**	**Date and Time**

Research Assistant: **Date:**

SECTION 3 HOUSEHOLD SES

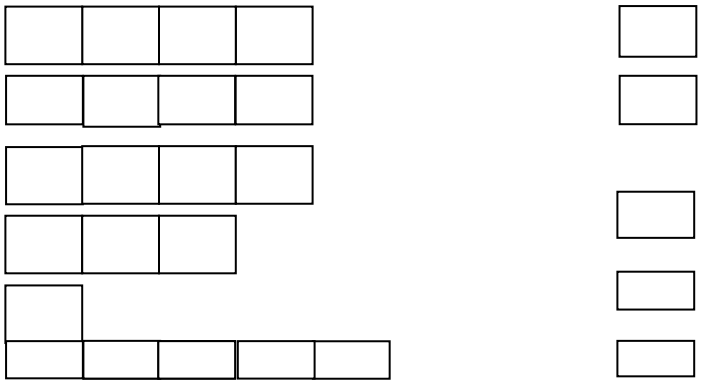
2. Which of the following do you have in your household at the **present** time? (please tick one box for each **item**)

Item	No [0]	Yes [1]
a) Electricity		
b) Motor vehicle		
c) Fridge		
d) Microwave		
e) Washing machine		
f) Landline telephone		
g) Cell phone		
h) Television		
i) Radio		
j) Video machine/DVD		
k) MNet		
l) DSTV/Satellite		
m) Computer		
n) Internet access		

SECTION 7: MEASUREMENTS

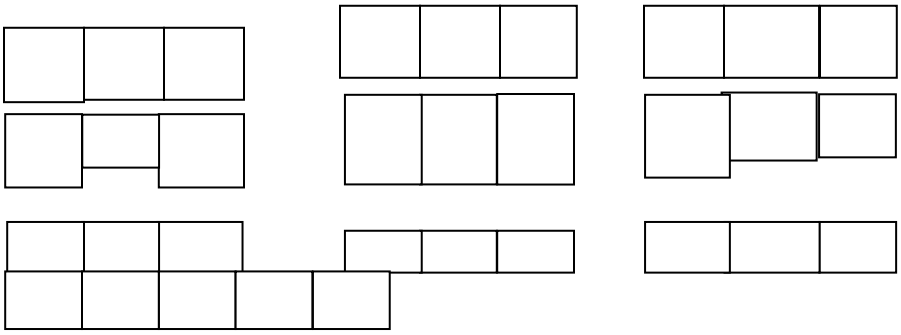
ANTHROPOMETRY

- STANDING HEIGHT: (mm)
- SITTING HEIGHT: (mm)
- WEIGHT: (kg)
- WAIST CIRCUMFERENCE: (mm)
- HIP CIRCUMFERENCE: (mm)



BLOOD PRESSURE

- SYSTOLIC BP
- DIASTOLIC BP
- PULSE
- TIME OF BP



Research Assistant: **Date:**

SELF COMPLETE Q: Y N **RA:** **Date:**

QUALITY CHECKED BY: **DATE:**

Notes:

Appendix 2 The ethics clearance certificate

R14/49 Ms Juliana Kagura M130556

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130556

NAME: (Principal Investigator) Ms Juliana Kagura

DEPARTMENT: Division of Paediatrics & Child Health/DPHRU
CH Baragwanath Academic Hospital

PROJECT TITLE: Impact of Early Growth on Blood Pressure from Early Childhood to Adulthood: Birth -Twenty Cohort

DATE CONSIDERED: 31/05/2013

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Shane Norris

APPROVED BY:

Professor PE Cleaton-Jones, Chairperson, HREC (Medical)

DATE OF APPROVAL: 24/06/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date 24/06/2013

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3 Comparison of the Study Sample that had BP status measured at ages 5 and 18 years and those who did not.

Baseline variables (5years)	**N**	**BP status at both ages 5 and 18 years**	**N**	**No BP status at both ages 5 and 18 years**	**P value**
SBP(mmHg)	895	108±13	7	109±15	0.8524
DBP(mmHg)	859	63±8	7	(64±8)	0.6664
Height(cm)	859	107.8±4.5	80	(106.9±3.2)	0.0722
Weight(kg)	859	18.3±2.3	210	(18.2±2.0)	0.6855
BMI	859	15.6±1.3	80	(16.1±1.6)	0.0012
Sex: Males (%)	429	50.0	406	50.0	0.981
Females (%)	430	50.1	406	50.0	

t-test and chi square test conducted for continuous variables and categorical variable, respectively.

Appendix 4 Bivariate analysis of factors associated with blood pressure and hypertension risk in urban South African black participants aged 18 years (n=838)

	SBP			DBP			MAP			Hypertension risk		
Exposure variables	**β**	**95% CI**	**p value**	**β**	**95% CI**	**p value**	**β**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
SES change												
Low-low (ref)										1		
Low-medium	-0.89	-3.34-to 1.56	0.474	-0.39	-2.38 to 1.60	0.702	-0.54	-2.47 to 1.40	0.586	0.95	0.51 to 1.77	0.865
Low-high	-4.94	-8.64-to -1.23	**<0.01**	-2.24	-5.26 to 0.77	0.144	-2.78	-5.71 to 0.14	0.062	0.14	0.02 to 1.06	0.057
Medium-low	-0.13	-2.56 to 2.30	0.916	1.12	-0.86 to 3.10	0.266	0.61	-1.31 to 2.53	0.534	0.79	0.41 to 1.52	0.478
Medium-Medium	-1.39	-4.15 to 1.36	0.321	-0.34	-2.58 to 1.90	0.765	-1.15	-3.33 to 1.03	0.301	0.79	0.37 to 1.65	0.526
Medium-high	0.50	-2.88 to 3.89	0.771	-0.23	-2.99 to 2.52	0.869	-1.16	-2.83 to 2.52	0.909	0.63	0.24 to 1.69	0.361
High-low	-2.29	-4.95 to 0.36	0.091	-1.69	-3.85 to 0.47	0.125	-1.63	-3.73 to 0.47	0.128	0.79	0.38 to 1.61	0.512
High-Medium	-0.23	-2.85 to 2.39	0.865	1.02	-1.11 to 3.15	0.348	0.63	-1.44 to 2.70	0.548	1.00	0.52 to 1.94	0.995
High-high	-2.31	-4.95 to 0.34	0.087	-0.41	-2.56 to 1.74	0.711	-1.21	-3.30 to 0.88	0.256	0.62	0.29t o 1.33	0.216
Participant characteristics												
Childhood												
Gestational age, weeks	0.01	-0.37 to 0.41	0.943	0.03	-0.28 to 0.35	0.836	0.03	-0.27 to 0.34	0.826	0.97	0.88 to 1.07	0.559
Birth weight, kg	0.40	-0.98 to 1.78	0.568	-0.12	-1.24 to 1.01	0.836	0.00	-1.09 to 1.09	0.999	0.96	0.67 to 1.40	0.861
Small-for-Gestational age(SGA),%												
No(ref)										1		
Yes	2.02	-0.16 to 4.19	0.069	-0.05	-1.83 to 1.74	0.96	0.76	-0.95 to 2.48	0.383	1.56	0.92 to 2.66	0.099
Adolescence												

Age, years	2.81	0.98 to 4.65	**<0.001**	-1.1	-2.61 to 0.40	0.15	0.11	-1.35 to 1.56	0.887	1.41	0.86 to 2.30	0.172
Sex												
Boys(ref)										1		
Girls	-6.10	-7.41 to -4.77	**<0.001**	1.19	0.07 to 2.31	**0.04**	-0.81	-1.90 to 0.27	0.142	1.00	0.69 to 1.45	0.99
Alcohol intake												
No										1		
Yes	-1.05	-2.40 to 0.31	0.131	-0.23	-1.38 to 0.93	0.701	-0.50	-1.61 to 0.61	0.378	0.81	0.57 to 1.16	0.259
Smoking												
No										1		
Yes	-1.29	-2.69 to 0.11	0.071	0.93	2.41 to 0.55	0.217	-1.06	-2.69 to 0.57	0.201	0.72	0.44 to 1.19	0.203
Weight at age 18yrs, kg	0.25	0.19 to 0.30	**<0.001**	0.12	0.07 to 0.17	**<0.001**	0.17	0.13 to 0.22	**<0.001**	1.04	1.02 to 1.06[3]	**<0.001**
Height at age 18yrs,cm	0.35	0.27 to 0.42	**<0.001**	0.00	-0.07 to 0.06	0.888	0.10	0.04 to 0.17	**<0.01**	0.99	0.97 to 1.01	0.236
Relative weight gain (0-2years)	0.87	0.15 to 1.59	**0.02**	0.45	-0.14 to 1.04	0.135	0.56	0.00 to 1.13	0.051	1.13	0.94 to 1.38	0.194
Relative weight gain (2-4years)	0.64	-0.02 to 1.30	0.058	0.12	-0.42 to 0.66	0.652	0.48	-0.04 to 1.00	0.068	1.28	1.07 to 1.55	**<0.01**
Relative weight gain (4-18years)	2.56	1.86 to 3.26	**<0.001**	1.29	0.71 to 1.87	**<0.001**	1.77	1.22 to 2.32	**<0.001**	1.59	1.30 to 1.93	**<0.001**

Appendix 5 Additional multivariate analyses of factors associated with blood pressure and hypertension risk in urban South African black participants aged 18 years.

	SBP[1](n=655)				DBP[1](n=655)				MAP[1](n=655)				Hypertension risk[2](n=653)			
	β	95% (CI)		p value	β	95% (CI)		p value	β	95% (CI)		p value	Odds Ratio	95% (CI)		P value
SES change																
Low-low(ref)																
Low-medium	-1.35	-4.19	1.49	0.350	-0.60	-3.12	1.92	0.639	-0.86	-3.27	1.55	0.482	0.61	0.28	1.34	0.215
Low-high	-4.78	-8.92	-0.65	**0.024**	-0.34	-4.02	3.33	0.855	-1.77	-5.28	1.73	0.321	0.27	0.06	1.23	0.091
Medium-low	-0.85	-4.38	2.67	0.634	0.98	-2.16	4.11	0.540	0.35	-2.64	3.34	0.820	0.56	0.22	1.45	0.232
Medium-Medium	-3.64	-7.59	0.32	0.071	-1.69	-5.21	1.82	0.344	-2.37	-5.72	0.99	0.166	0.45	0.15	1.35	0.153
Medium-high	1.07	-3.14	5.28	0.619	1.19	-2.56	4.93	0.533	1.15	-2.43	4.72	0.528	0.64	0.20	2.05	0.458
High-low	-4.28	-9.26	0.71	0.093	-1.06	-5.49	3.38	0.640	-2.15	-6.38	2.08	0.319	0.43	0.10	1.77	0.243
High-Medium	-0.99	-5.89	3.90	0.691	2.81	-1.54	7.16	0.204	1.53	-2.62	5.69	0.469	0.46	0.12	1.75	0.254
High-high	-3.54	-8.76	1.68	0.184	0.99	-3.66	5.63	0.676	-0.52	-4.95	3.91	0.818	0.50	0.12	2.13	0.351
Current participant age, yrs	2.45	0.26	4.64	**0.028**	-1.03	-2.98	0.91	0.298	0.14	-1.71	2.00	0.879				
Current participant height, cm	0.08	-0.05	0.21	0.227	-0.02	-0.13	0.10	0.761	0.01	-0.09	0.12	0.808				
Baseline BP at 5 yrs	0.13	0.07	0.19	**0.000**	0.18	0.09	0.27	**0.000**	0.16	0.08	0.24	**0.000**	1.38	0.84	2.29	0.204
Household SES in infancy	0.29	-0.95	1.53	0.650	-0.39	-1.49	0.71	0.489	-0.16	-1.21	0.89	0.770	1.05	0.74	1.48	0.782
Current alcohol intake	-0.71	-2.31	0.90	0.386	0.13	-1.29	1.56	0.854	-0.16	-1.52	1.20	0.822	0.84	0.54	1.32	0.454
Sex	-4.98	-7.17	-2.78	**0.000**	1.26	-0.71	3.22	0.210	-0.82	-2.69	1.05	0.390				
small for gestational age(SGA)	2.00	-0.45	4.45	0.109	0.45	-1.73	2.63	0.687	0.93	-1.15	3.01	0.379	1.87	1.05	3.32	**0.033**

Relative weight gain (0-2years)	1.19	0.35	2.03	**0.005**	0.53	-0.22	1.27	0.166	0.75	0.04	1.46	**0.039**	1.13	0.90	1.43	0.301
Relative weight gain (2-4years)	0.35	-0.38	1.09	0.348	0.32	-0.33	0.97	0.340	0.32	-0.31	0.94	0.319	1.21	0.98	1.48	0.072
Relative weight gain (4-18years)	3.43	2.62	4.24	**0.000**	1.38	0.65	2.10	**0.000**	2.06	1.37	2.75	**0.000**	1.61	1.28	2.03	**0.000**
	R^2=0.2014				R^2=0.0544				R^2=0.0823				Pseudo R^2=0.0631			

[1]Model adjusted for BP measures and SES at baseline, alcohol intake, height and age at 18yrs, sex, growth (SGA, relative weight gain in infancy and mi-childhood)

[2]Model adjusted for BP measures and SES at baseline, alcohol intake at 18yrs, growth (SGA, relative weight gain in infancy and mi-childhood)

Appendix 6 Sex differences association between SES change and systolic blood pressure (SBP) at 18 years of age

Covariates	**SBP at 18 years of age**							
SES change	**BOYS(n=332)**				**GIRLS(n=324)**			
Low-low(ref)	**β**	**95%CI**		**p value**	**β**	**95%CI**		**p value**
Low-medium	-3.86	-7.4	-0.33	0.032	3.4	-0.89	7.69	0.120
Low-high	-9.11	-14.59	-3.62	0.001	-0.22	-6.15	5.71	0.940
Medium-low	-1.25	-5.88	3.37	0.594	1.4	-3.86	6.67	0.600
Medium-Medium	-4.03	-8.93	0.86	0.106	0.02	-6	6.05	0.990
Medium-high	-1.58	-6.5	3.33	0.527	3.1	-3.74	9.95	0.370
High-low	-6.05	-12.21	0.11	0.054	-1.43	-9.17	6.3	0.720
High-Medium	-3.4	-9.5	2.7	0.273	1.05	-6.49	8.58	0.780
High-high	-3.8	-10.07	2.46	0.233	-1.79	-10.19	6.61	0.680

Current participant age, yrs	4.01	1.15	6.87	0.006	1	-2.13	4.14	0.530
Current participant height, cm	0.17	0.01	0.33	0.038	0.02	-0.17	0.21	0.840
Baseline BP at 5 yrs	0.2	0.12	0.28	0	0.06	-0.03	0.15	0.210
Household SES in infancy	0.08	-1.38	1.55	0.91	0.76	-1.23	2.75	0.450
Current alcohol intake	2.85	-0.02	5.72	0.051	1.41	-2.62	5.44	0.490
Small for gestational age(SGA)	1.1	0.07	2.13	0.036	1.32	0	2.65	0.050
Relative weight gain (0-2years)	0.59	-0.4	1.58	0.24	0.05	-0.98	1.09	0.920
Relative weight gain (2-4years)	4.1	3.03	5.17	0	2.39	1.23	3.55	0.000
Relative weight gain (4-18years)	1.48	-0.61	3.57	0.166	0.44	-1.88	2.75	0.710
		R^2=0.2921				R^2=0.0970		

Appendix 7 Bayesian information criteria for different number of classes to identify the best model fit using group based trajectory modeling·

SBP trajectory group membership											
class number	**-BIC**	**Posterior probabilities (%)**					**Class proportions (%)**				
2	15320.94	0.82	0.87				66.6	33.4			
3	15263.21	0.83	0.71	0.82			28.2	55.3	16.4		
4	15245.94	0.81	0.71	0.77	0.82		25.6	54.5	3.3	16.6	
5	15227.72	0.80	0.70	0.81	0.81	0.82	23.5	53.7	3.4	17.8	1.6
DBP trajectory group membership											
2	14314.34	0.85	0.83				72.1	27.9			
3	14278.86	0.83	0.70	0.87			52.7	43.3	4.0		
4	14257.14	0.77	0.82	0.72	100.00		21.4	18.1	59.6	0.8	
5	14249.51	0.80	0.80	0.68	0.75	0.99	4.2	6.0	50.4	38.7	0.8
B:GIRLS											
SBP trajectory group membership											
class number	**BIC**	**Posterior probabilities**					**Class proportions**				
2	16094.31	0.81	0.86				62.8	37.2			
3	16029.43	0.83	0.71	0.82			33.2	53.2	13.6		
4	16001.34	0.84	0.67	0.78	0.79		30.5	50.2	10.6	8.7	
5	15986.83	0.84	0.76	0.66	0.80	0.88	27.9	11.9	49.4	10.1	0.7
DBP trajectory group membership											
2	15196.43	0.78	0.85				58.2	47.8			

3	15133.37	0.71	0.86	0.93			49.3	48.9	1.9		
4	15126.8	0.70	0.79	0.73	0.90		48.1	39.6	10.4	1.9	
5	15105.95	0.82	0.80	0.63	100.00	0.71	32.8	13.0	46.9	0.2	7.0

*Model fit criterion included a BIC, posterior probabilities and class proportions starting from a two-class to a seven-class model

†the graphical presentation was also taken into account for model fit criteria (see figure1 and 2)

Appendix 8 Characteristics of black children enrolled in Birth to Twenty cohort (BT20) and the analytical sample

Characteristics	**Analytical (n=1937)**	**Excluded(n=631)**	**Test statistic**
Sex: n (%)			
Male	932(48·1)	314(49·8)	χ^2=0·5167; p=0·472
Female	1005(51·9)	317(50·2)	
Gestational age (weeks)	37·9(1·8)	38·0(1·9)	0·3328
Birth weight (g)	3070·7(0·5)	3094·9(0·5)	0·2951
Participant weight at 2 years	11·4(1·4)	11·7(1·2)	0·0132
Participant weight at 5 years	18·2(2·1)	18·1(1·5)	0·9783
Participant height at 2 years	83·1(3·3)	82·8(4·0)	0·3646
Participant height at 5years	107·5(4·5)	106·4(2·9)	0·1267
SES in infancy (household physical assets)	2(2)	3(2)	0·0000
Maternal age(years)	25·8(6·2)	26·1(5·9)	0·1843
Maternal parity	2(1)	2(1)	0·0545

*Comparison between the analytical and enrolled samples were conducted using a t-test for continuous variables and the chi square test for sex differences

Appendix 9 Association of age terms and height between 5 and 18 years, and BP trajectories in boys (A) and girls (B): [est(SE), p value]·

A: BOYS							
BP trajectory membership		**SBP**			**DBP**		
		estimate	**SE**	**P value**	**Estimate**	**SE**	**P value**
Lower	**Intercept**	54·96657	8·4521	0·0000	13·19449	4·8031	0·0060
	age	2·76482	2·06446	0·1806	9·2305	1·26746	0·0000
	age²	–0·69844	0·18491	0·0002	–0·99558	0·11292	0·0000
	age³	0·02714	0·00512	0·0000	0·02978	0·00313	0·0000
	height	0·52719	0·03988	0·0000	0·21631	0·02545	0·0000
Middle	**Intercept**	61·75927	9·3720	0·0000	2·48097	7·14448	0·7284
	age	0·20566	1·73997	0·9059	13·5148	1·79941	0·0000
	age²	–0·47453	0·1554	0·0023	–1·27737	0·16354	0·0000
	age³	0·02108	0·00433	0·0000	0·03612	0·00457	0·0000
	height	0·47579	0·03402	0·0000	0·19771	0·03542	0·0000
Upper	**Intercept**	147·7969	6·4370	0·0000	128·2765	31·42626	0·0000
	age	–27·0923	5·87834	0·0000	–27·5346	8·72308	0·0016
	age²	1·80292	0·53049	0·0007	2·52555	0·81421	0·0019
	age³	–0·04032	0·0149	0·0068	–0·0709	0·02319	0·0022
	height	0·74727	0·11617	0·0000	0·28869	0·15986	0·0710

B: GIRLS

BP trajectory membership	**SBP**			**DBP**		
	Estimate	**SE**	**P value**	**Estimate**	**SE**	**P value**

Lower	**Intercept**	57·5533	6·87806	0·0000	16·21327	5·54732	0·0035
	age	7·03695	1·75165	0·0001	10·87849	1·36305	0·0000
	age²	–0·97357	0·15972	0·0000	–1·07238	0·12508	0·0000
	age³	0·03399	0·00453	0·0000	0·03151	0·00355	0·0000
	height	0·27137	0·03922	0·0000	0·12002	0·03241	0·0002
Middle	**Intercept**	102·3708	7·39317	0·0000	26·8031	5·57144	0·0000
	age	–0·85209	1·80256	0·6364	9·91387	1·40324	0·0000
	age²	–0·23534	0·16528	0·1545	–0·88626	0·12771	0·0000
	age³	0·0133	0·0047	0·0046	0·02489	0·00361	0·0000
	height	0·19018	0·04367	0·0000	0·08041	0·03052	0·0085
Upper	**Intercept**	90·07066	18·16137	0·0000	43·50199	29·40977	0·1392
	age	14·54482	4·65254	0·0018	15·92225	7·38911	0·0312
	age²	–1·02141	0·41636	0·0142	–1·11563	0·67744	0·0997
	age³	0·02562	0·01174	0·0291	0·0292	0·01919	0·1283
	height	–0·25451	0·10182	0·0125	–0·26558	0·15897	0·0949

*The level (intercept) and change (age-linear, age²-quadratic and age³-cubic terms) of blood pressure, standard errors and level of significance of the three height-adjusted blood pressure trajectories

Appendix 10 Association between BP status(>95th percentile for age, sex and height) at age 5 years and being in the middle and upper BP compared to the lower trajectories in urban black South African children aged 5-18 years*

	SBP trajectory		DBP trajectory	
	RRR(95%CI)	**P value**	**RRR(95%CI)**	**P value**
A. BOYS				
Lower trajectory group(ref)				
Middle trajectory group	3.85(2.25-6.59)	0.000	3.09(1.94-4.92)	0.000
Upper trajectory group	21.80(8.72-54.50)	0.000	14.15(3.40-58.83)	0.000
B.GIRLS				
Lower trajectory group(ref)				
Middle trajectory group	5.69(3.41-9.52)	0.000	4.62(2.92-7.34)	0.000
Upper trajectory group	7.05(3.03-16.38)	0.000	9.27(2.66-32.30)	0.000

*****The relative risk ratios and the 95% confidence intervals of being in the middle or upper trajectory compared to the lower trajectory given blood pressure status at age 5(reference: **0**: $\leq 95^{th}$ percentile;**1**: >95th percentile for age, height and sex)