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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 atherosclerosis. 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 life course BP. This study hypothesizes that birth weight (BW), rapid relative weight gain (RWG) and relative height gain (RHG) in childhood may be important for setting life course BP trajectories.

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 early trajectory groups were identified for SBP and diastolic BP (DBP) for each sex; namely: "lower", "middle" and "upper." A kilogram increase in BW reduced the odds of being in the middle vs 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, RWG (OR: 1.63, 95%CI: 1.08-2.46; 1.77(1.22-2.56)) and RLG (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 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 went through 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 (submitted)*

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).

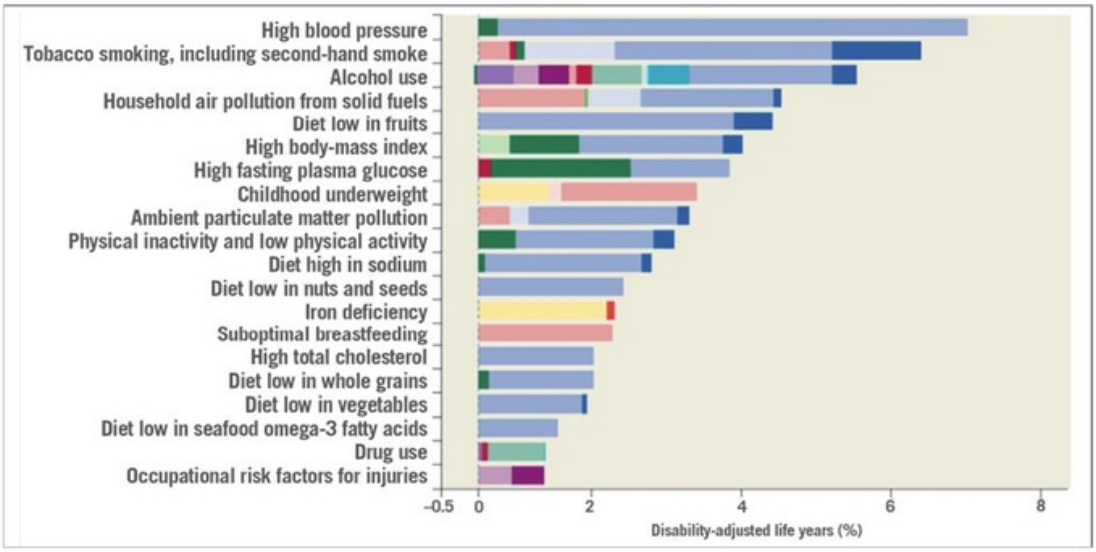


Figure 1-1 Main risk factors contributing to the Global burden of disease (%global DALYs) in 2010 (8)

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. (9). There is evidence suggesting that hypertension in adulthood may have its origins in childhood (10, 11). Several early life factors including socioeconomic status (SES) and growth are associated with raised BP (12). 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 (13).

Global estimates for hypertension in children and adolescence 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).

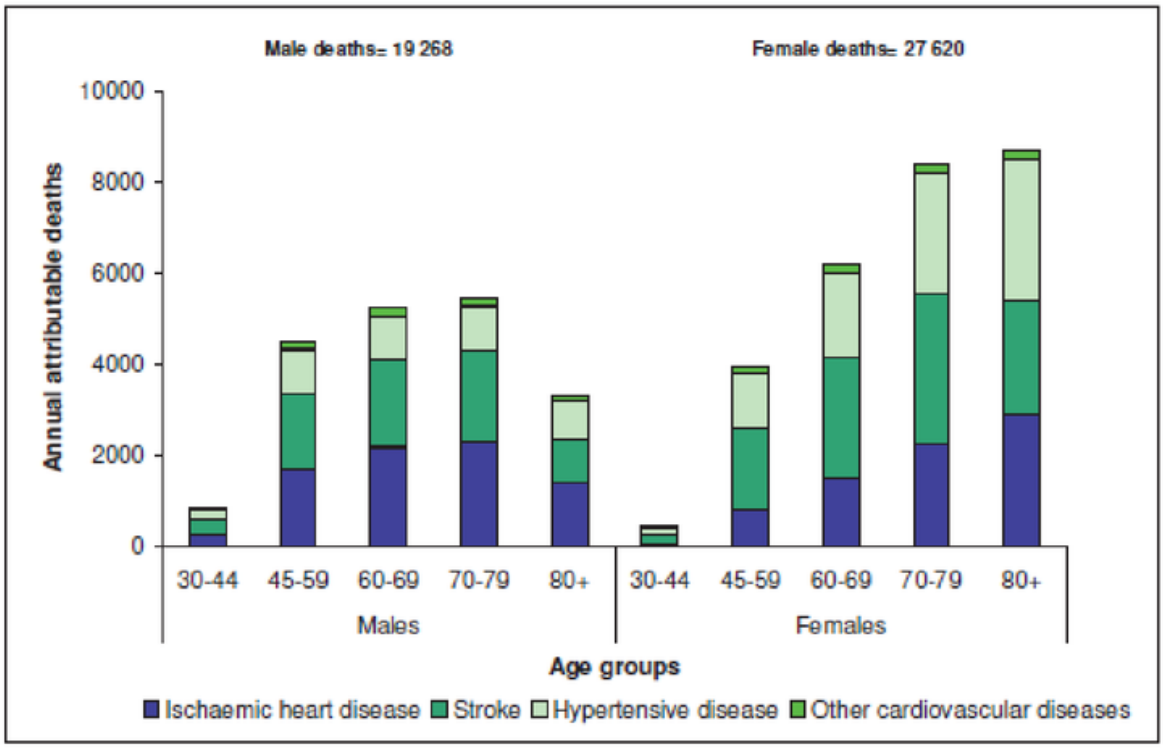


Figure 1-2 Deaths attributable to hypertension in South Africa , 2000 (24)

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 (H/T) 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).

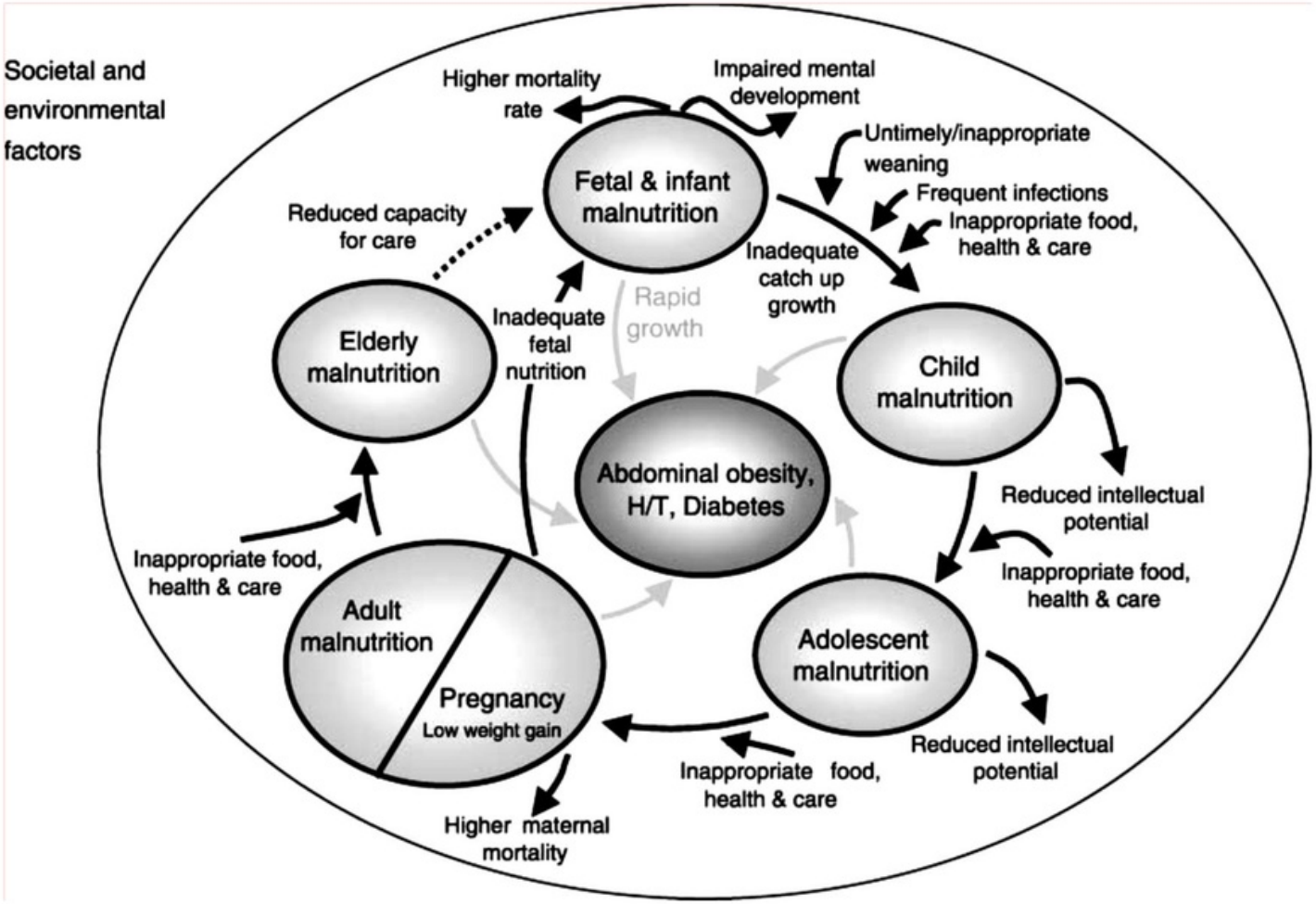


Figure 1-3 The WHO life course approach conceptual framework for prevention of non-communicable diseases (30)

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.

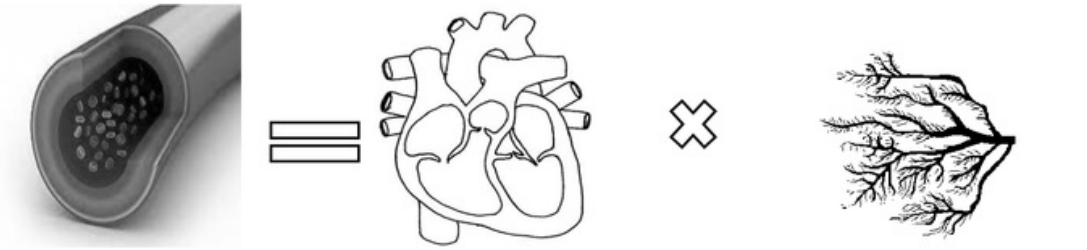
The framework also highlights that societal and environmental factors shape the life course trajectories across the life span. Socio economic transition due to industrialisation has exposed populations to deleterious infant feeding practises, dietary and physical activity patterns and a disproportionate 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(40), excess renin-angiotensin, structural and functional changes on the arterioles, and endothelial dysfunction (41).

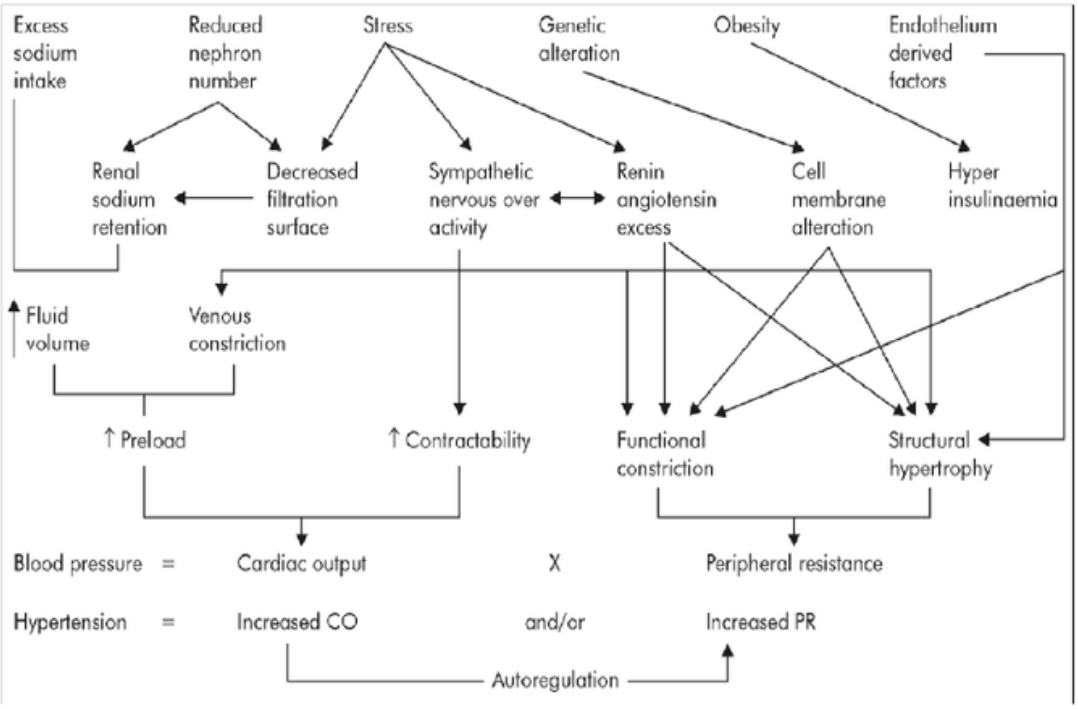


Figure 1-5 Factors involved in BP control (42)

Based on the equation defining BP illustrated in Figure 1-4 , 1-5 and 1-6, 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 on the peripheral arteriolar walls resulting 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 (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

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 if ……..		
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). 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, 59, 60).

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, 60), 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, 61), Spacelab/Critikon(62) or InterlliVue MP50 (63). 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 (64)	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.* (65)	China							
Hakim *et al.* 2014 (60)	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 (66)	Caribbean (Bonaire)	Cross sectional	5-16 yrs	Oscillometric monitor	1visit 2nd and 3rd measurement	NHBPEP		SBP:24.7% DBP:8.5%
Steinthorsdottir, *et al.* (63)	Iceland	Cross sectional	9-10 yrs	-Sphygmomanometer (2 readings) -InterlliVue MP50(2 readings)	3 visits 4 measurements	NHBPEP		3.1%
Acosta AA, 2012(62)	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(67)	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 (68)	Nigeria	Cross sectional	6-12yrs	Mercury sphygmomanometer	3 visit 3measurements	NHBPEP		4.7%
Ellenga Mbolla *et al.* 2014 (69)	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 (70)	Nigeria	Cross sectional	2-5yrs	Mercury sphygmomanometer	1 visit 3measurements	NHBPEP	1.4%	0.5%
Mehdad S et al, 2012 (71)	Morocco	Cross sectional	11-17 yrs	Mercury sphygmomanometer	1 visit 2measurements	NHBPEP	9.6%	17.4%
Ng'andu NH, 1992 (59)	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 (61)	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 (72)	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 (73)	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 adolescence 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 and growth, 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 (74). Puberty has been reported to be an independent predictor of BP even in children who were born low birth weight (75). 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 (76).

Sex

Sex is a major determinant of BP in a growing child hence its inclusion in the BP normotensive tables (77). 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 ((78). Furthermore, studies have shown that the incidence of hypertension is higher in boys than girls (79, 80).

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 (81). 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 (82). On the other hand, oestrogen in girls plays a protective role by inhibiting over-activation of RAS thereby reducing BP (83).

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 related to cardiovascular disease risk in later life (84). 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 (85, 86).

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 (87).

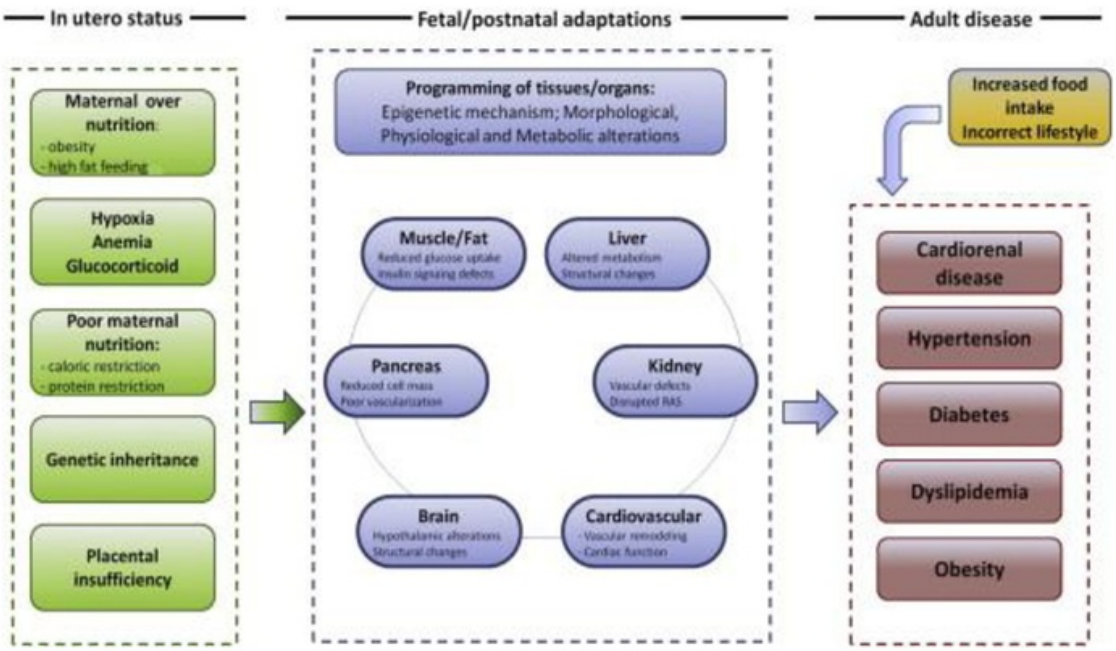


Figure 1-6 Intrauterine influences on adult chronic disease risk

Source (87)

In support of the work of Barker on the fetal origins hypothesis (88), 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 (89). 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 (90), endothelial dysfunction, overstimulation of the RAS and the SNS leading to raised BP (91). Epidemiological studies reported endothelial dysfunction assessed by carotid stiffness on neonates, children and young adults who experienced IUGR (92-94). Intrauterine growth restriction and low birth weight is related to overstimulation of the SNS and RAS in IUGR infants and children (95). Kingdom et al 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 (96).

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 (97-99). There is considerable evidence to suggest that children born short, but became taller and gain more weight have 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 (100). 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 a lowest height velocity tertile (101).

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 (102, 103) while others reported no association (104), or both infancy and mid-childhood weight gain related to later BP (105). 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 (106). 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 (107), even independent of linear growth (108). 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 (109, 110). 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 (111).

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 (102, 112). 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 (113, 114).

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 (115). Blood pressure in childhood is also highly correlated with family history of BP (116, 117). In addition black children are at higher risk of having raised BP compared to white children and children of other ethnicities (118, 119). Bio-behavioral factors like physical activity, alcohol intake and tobacco smoking have been implicated in the association between low SES and raised BP in children and adulthood (120).

1.2.3 Tracking of blood pressure from childhood to adulthood

According to Twisk (121), 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 (122, 123). 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 (122).

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 (124). 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 remained 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 (11).

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 (10). The Odense Schoolchild prospective study in Denmark reported odds ratios (OR) of remaining in the upper BP quartile ranged 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 (125).

Biological factors, socioeconomic status and behavioral factors have also been reported to be related to BP tracking between childhood and adulthood (126). 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 (127), 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 (122, 128), while others report no or conflicting sex differences (128, 129) and some suggesting that the tracking coefficients are too low to be of any clinical relevance (123). 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 (130). There is evidence to suggest that social gradients in cardiovascular disease risk and hypertension emerge as early as in childhood (131). 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 (120, 132-134), 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 (135).

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 (136). A Finnish study also reported that childhood SES was related to adult BP independent of current SES (133). 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, 135, 137). 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 (135, 138), even across generations (139). 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 (138).

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. **(139)**	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 **(120)**	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. **(136)**	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. **(134)**	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. **(133)**	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. **(140)**	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. **(137)**	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. **(135)**	UK		53yrs	Supported the life course SES cumulative model in women and social origins model in men
Hallal, P. C. 2012.**(141)**	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.**(142)**	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. **(143)**	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 (144, 145). 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 (146-152), UK (153-156), the Caribbean(157), Australia (158), Italy (159), and none from Africa. Most of the studies reported longitudinal BP from childhood (148, 149, 151, 153, 157, 160) but some of these explored the influence of early life factors on longitudinal BP (147, 149, 150, 154, 158). The studies highlighted that longitudinal BP patterns vary according to family history of high BP , SES, physical activity and dietary intake (149), as well as maternal gestational hypertension (154).

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 (147). 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 (148)

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 (158).

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 (148). 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: 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 smokers (161).

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 (156).

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 (152).

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 (148, 159, 162), generalised estimating equations (GEE) (154, 160) and multilevel modeling (146, 150-153, 157).

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 (163).

Another method used in these studies, is finite mixture modelling using either latent class growth mixture modeling (GMM) in Mplus (164, 165) or group-based trajectory modeling(GBTM) using SAS Proc traj (166). 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) (167).

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 parkages such as STATA, SAS, SPSS or excel for further analyses (168).

Statistical packages like Mplus and SAS proc traj use maximum likelihood estimations provided data is missing at random (MAR) (169). 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 (168). 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(170).

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 (159)	Italy	≥5yrs followed up for 25 years 3 time points	Mplus: GMM	Two distinct trajectories
Chen,W. 2012 (147)	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 (149)	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 (153)	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(158)	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.(171)	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.(157)	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.(154)	UK	7-18yrs	Linear spline random-effects models.	Maternal gestational HTN predicted high offspring BP trajectories independent of birth weight
Strand, B. H.2012. (155)	UK	36,43,53 yrs	Mixed Models	Childhood SES important for rate of change of adiposity and SBP
Su, S.2015. (150)	USA	5 to 38 yrs (13 time points)	Individual growth curve modeling (GCM)	Adverse experiences associated with higher BP trajectories
Tielemans, S. M.2015. (162)	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.(151)	USA	7-30 yrs	Multilevel growth models	BP trajectories are sex and ethnic group specific
McGavock, J. M.2007(160)	Canada	5-19 yrs	Generalized linear models	Children with higher BMI gained greater SBP change and grater stroke volume
Briollais, L.2003 (146)	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 (148)	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. (156)	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. (152)	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 adolescence. 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) (123). 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 children and adolescence, 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.

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 (114).

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 (172). 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 (173), implying that the main risk factors may track from early life and manifest in adulthood (174).

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.

The detection of BP patterns (trajectories) from childhood to young adulthood and evaluating the impact of early life growth 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 (175).

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 relative weight gain on BP changes over time independent of linear growth.

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 BP trajectories between 5 and 18 years of age

Research question 4: What is the impact of early growth on 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 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 200km² and as of 1990, the population was estimated to be 3 to 4 million people when the cohort commenced (176). 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 (177).

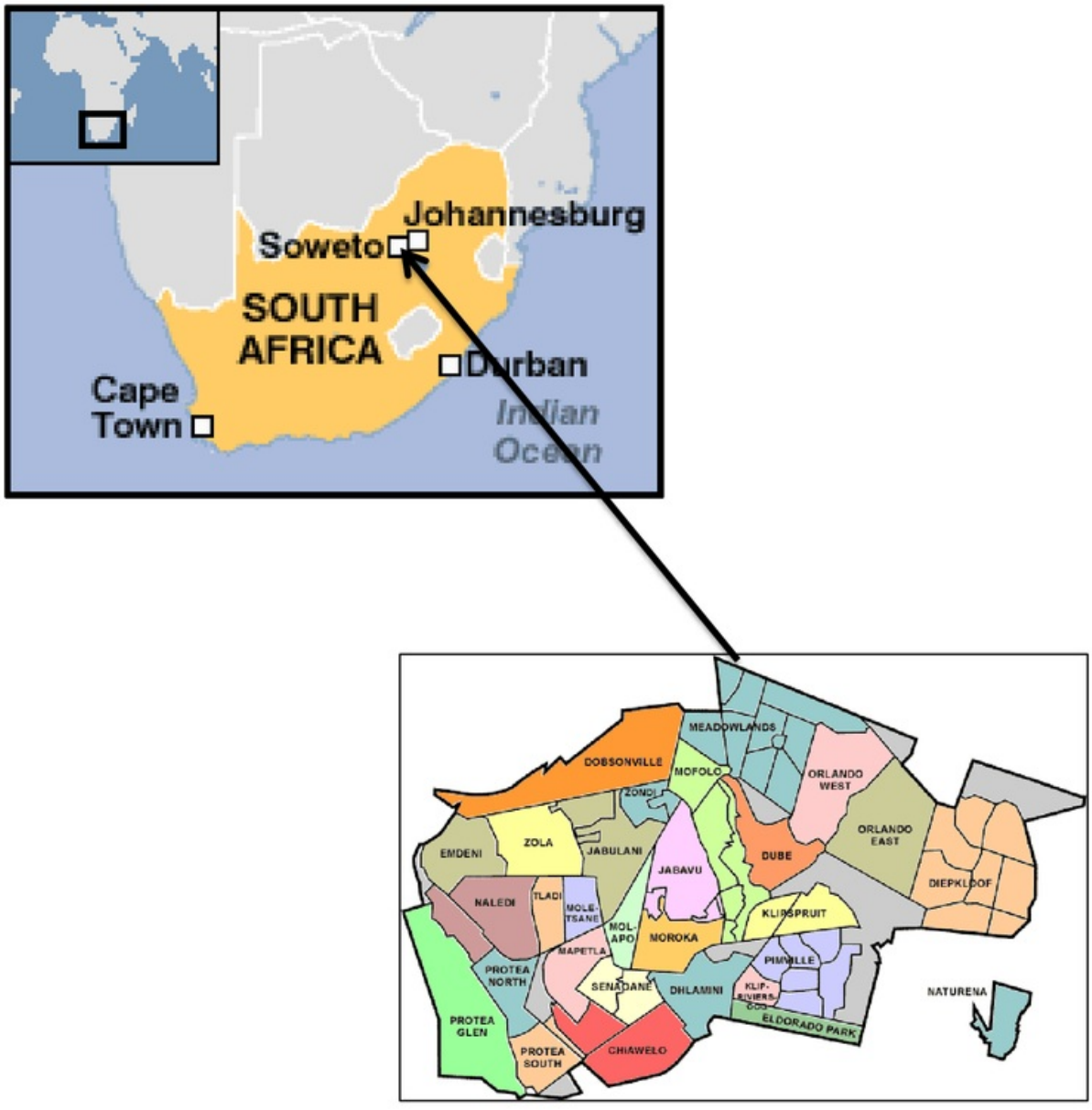


Figure 2-1 The Map of Soweto, Johannesburg-South Africa

2.2 Study design: Birth to Twenty cohort

Data for this study came from the Birth to Twenty longitudinal cohort (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 (176).

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 (178). Attrition rates per annum were on average less than 3% per annum for the cohort (179). 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 **Error! Reference source not found.**

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 (180). 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 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

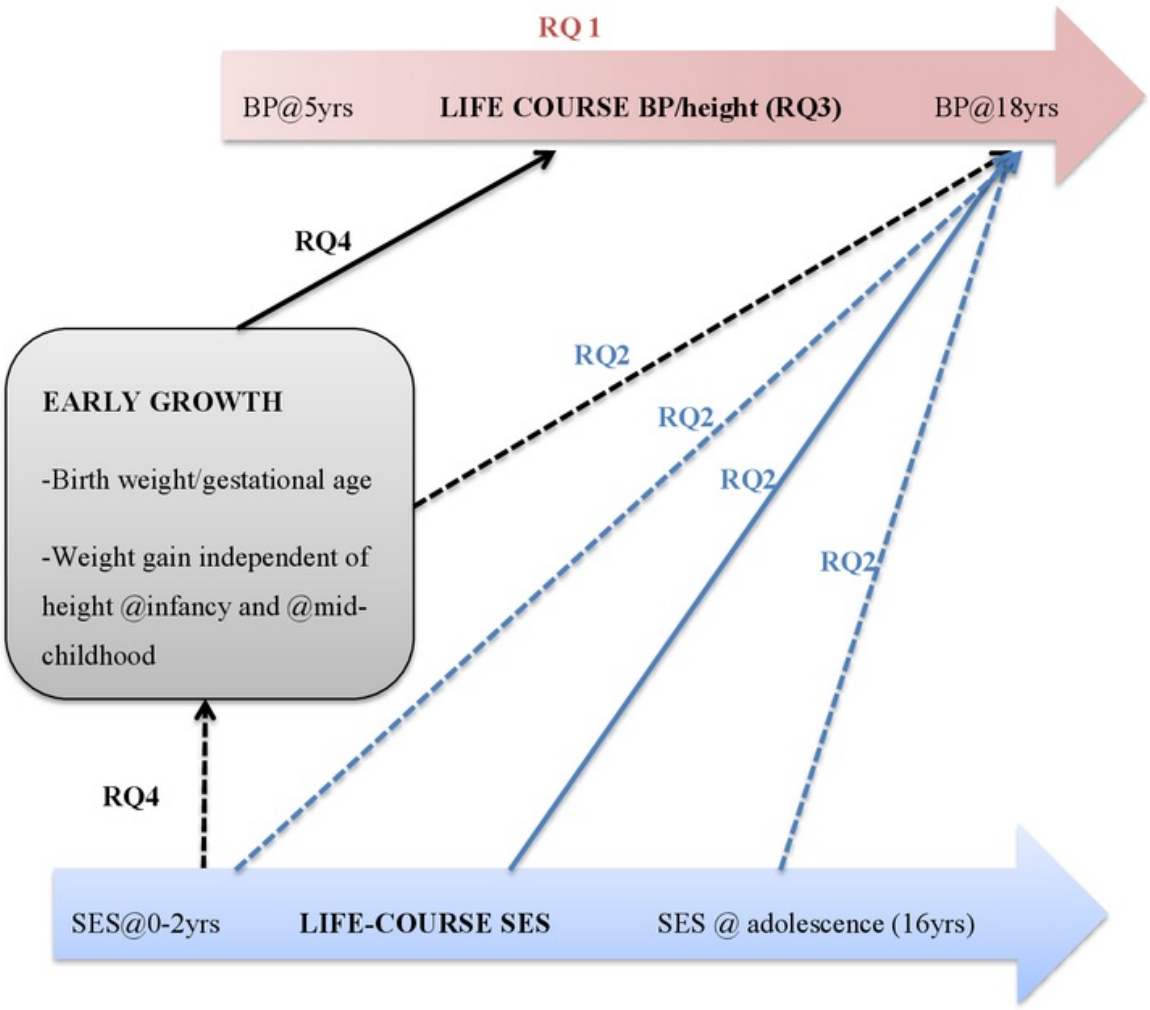


Figure 2-2 Data analysis strategy for the current study

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, DBP: 80-89mmHg) and hypertension (SBP: ≥140mmHg, DBP≥90mmHg) (181).

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 (182).

GBTM can be used to run models with both time varying and time constant covariates 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. 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. 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 –**Error! Reference source not found.**).

PART 2: EMPIRICAL CHAPTERS

PART 3: GENERAL DISCUSSION

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

Frederick Douglass (1818-1895)

3 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.

3.1 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 3-1 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, 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.

3.1.1 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.

3.2 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.

3.2.1 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. owever, 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 (183).

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, 184).

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3.2.2 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 (185).

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 (186), and in urban areas high BP disproportionately affect the poor compared to the rich (187).

3.2.3 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. Though variation in BP is thought to be genetic in origin, we also 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 (188) and American children (189). 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 (190, 191). 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 (192).

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.

3.3 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

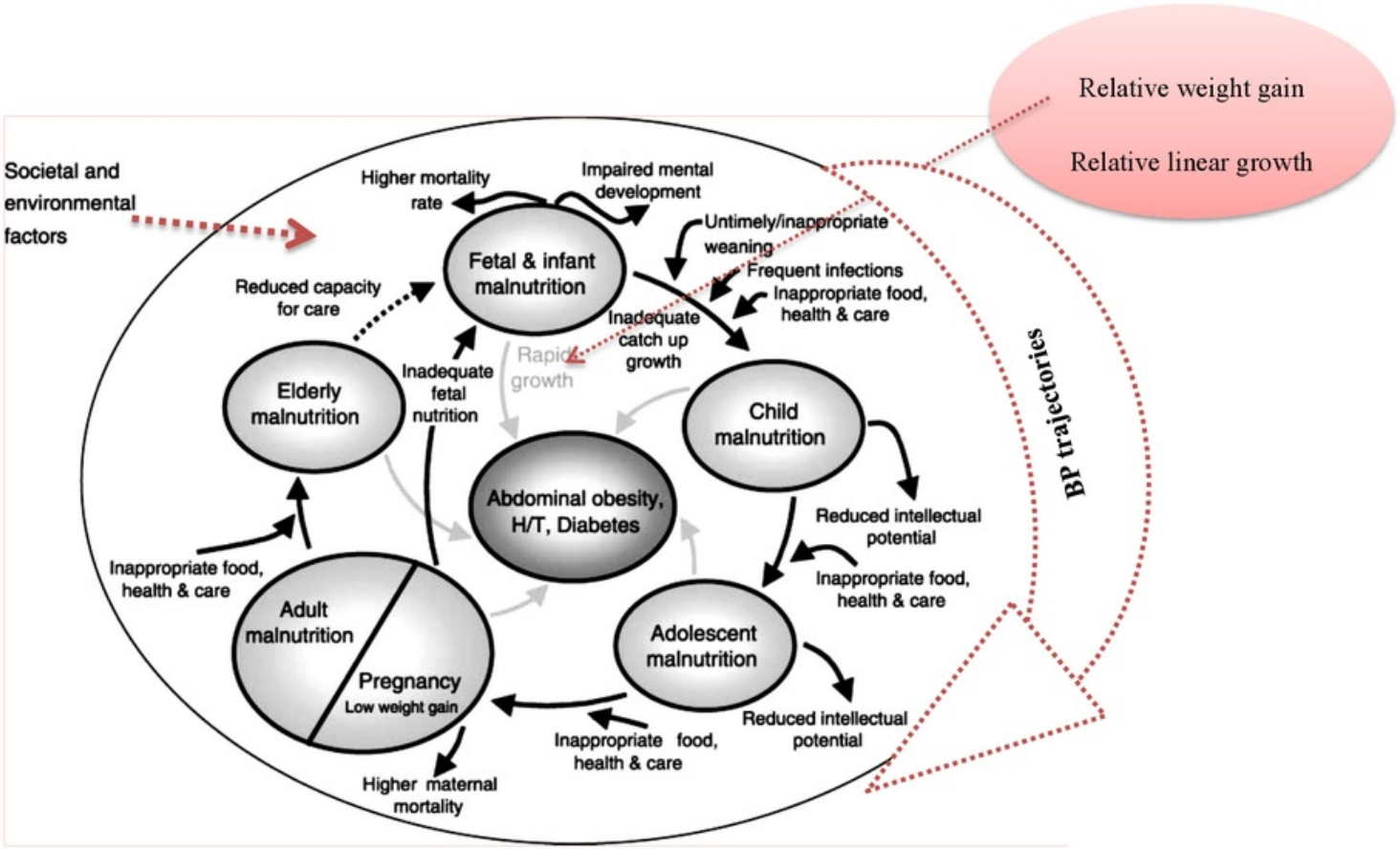

Figure 6-2 A modified conceptual framework on life course approach to chronic diseases prevention

3.4 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 adolescence 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.

3.5 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 ages 5 and 8, and Omron from 10 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 (193).

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.

3.6 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

3.7 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.

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