BLOOD PRESSURE CHANGES FROM CHILDHOOD TO ADOLESCENCE

BLOOD PRESSURE CHANGES BY AGE FROM CHILDHOOD TO ADOLESCENCE IN SOUTH ASIAN CHILDREN

By

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Blood pressure changes by age from childhood to adolescence in South Asian children

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ABSTRACT

Research statement: To investigate the age specific blood pressure change in South Asian children from childhood to adolescence over a six year period and to determine whether this change of blood pressure varies by baseline characteristics.

Rationale: Children exhibit age related incremental changes in blood pressure from birth onwards which reach adult levels during late adolescence. The best way to measure age-related changes in blood pressure from childhood to adolescence is through prospective longitudinal studies.

Objectives: to investigate the changes in blood pressure among South Asian children aged 6 to 11 years who were followed for a period of six years.

Methods: Blood pressure and anthropometric data were collected from 703 children who were 5 to 11 years of age in 2005 and were re-examined after six years (age range of 11 to 17 years in 2011). Average difference between baseline and follow-up blood pressure measurements was evaluated using the paired t-test. A linear regression model with follow up blood pressure and blood pressure change as outcomes and sex, weight, and height as regressors were fitted to assess whether these predictor variables were associated with the dependent variables.

Summary of results: Systolic and diastolic blood pressure increases from childhood to adolescence. Baseline blood pressure appears to be the strongest predictor of follow up blood pressure. Change in body mass index influences blood pressure more than baseline body mass index. Boys showed higher levels of change in systolic blood pressure compared to girls. Age showed an interaction with sex for change in systolic blood pressure. Boys exhibited higher change in systolic blood pressure than girls in older age groups compared to younger age groups.

Potential implications: The study findings will increase awareness about high blood pressure in children and lead to preventive strategies to contain the burden of hypertension in future.

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LIST OF ABBREVIATIONS

ANCOVA	**Analysis of covariance**
ANOVA	**Analysis of variance**
BMI	**Body mass index**
BP	**Blood pressure**
CI	**Confidence interval**
cm	**Centimeter**
CVD	**Cardiovascular diseases**
DBP	**Diastolic blood pressure**
DBP4	**Diastolic blood pressure based on Korotkoff phase 4**
DBP5	**Diastolic blood pressure based on Korotkoff phase 5**
HBP	**High blood pressure**
HDL-C	**High density lipoprotein cholesterol**
K4	**Korotkoff phase 4**
K5	**Korotkoff phase 5**
Kg	**Kilogram**
Kg/m^2	**Kilogram per meter squared**
LDL-C	**Low density lipoprotein cholesterol**
LOWESS	**Locally weighted scatterplot smoothing**
Mlbm	**Measures of insulin resistance adjusted for lean body mass**
mm Hg	**Millimeters of mercury**
ns	**Non significant**
PHV	**Peak height velocity**
PWW	**Peak weight velocity**
SBP	**Systolic blood pressure**
SD	**Standard deviation**
SE	**Standard error**

DECLARATION OF ACADEMIC ACHIEVEMENT

I hereby declare that the research study presented in the form of my master's thesis was conceptualized and implemented by myself in full with academic inputs and suggestions from members of my thesis committee.

I also assume full responsibility for all omissions and errors that may have happened in spite of my scrutiny to the best of my efforts.

s/d

MANU RAJ

OVERVIEW OF THE STUDY

Title: Age related changes in blood pressure from childhood to adolescence in a South Asian cohort of children

Research statement - *To investigate the age specific blood pressure change in South Asian children from childhood to adolescence over a six year period and to determine whether this change of blood pressure varies by different baseline characteristics.*

Type of Thesis: Analytical study using a prospective cohort design.

Overview and Rationale

Children exhibit age related incremental changes in systolic and diastolic blood pressure from birth onwards which reach adult levels of blood pressure during late adolescence. [1] The age related change in blood pressure during childhood has future health implications. Children and adolescents with blood pressure greater than the 90thpercentile for a given age have roughly a threefold greater likelihood of becoming adults with hypertension compared to those whose blood pressure is at or below the 50th percentile.[1]

The evolution of blood pressure levels from birth to adult levels is believed to be completed during late adolescence. Classical descriptions of age-related changes in blood pressure during childhood and adolescence are mainly based on cross-sectional studies which measured blood pressure at a single point of time. These studies do not capture within-individual changes in blood pressure that may occur at this phase of life. The best way to

measure age-related changes in blood pressure from childhood to adolescence is through longitudinal studies in which BP is repeatedly measured at timed intervals in the same cohort. In a pooled analysis of population cohorts from UK, Wills et al reported phases for systolic blood pressure (SBP) which included a rapid increase coinciding with peak adolescent growth.[2]

In a six year follow up study of a cohort of Chinese children (n=2946) aged 4-14 years at baseline, Li et al reported that the rate of increase in systolic blood pressure was 1.9 mm Hg per year in boys and 1.37 mmHg per year in girls.[3] The same for diastolic blood pressure was 0.5 mm Hg per year in boys and 0.4 mmHg per year in girls. Similar cohort studies are not available from South Asia necessitating the need for such studies in this population.

In addition to age, gender, height, weight and body mass index are also known to influence blood pressure levels in childhood and adulthood.[4-7] The reported correlations of anthropometric measurements with blood pressure are based on a single time point and so it is still unclear whether the same factors influence the rate at which blood pressure progresses from childhood to adolescence.

Quantification of the factors which influences age related changes in blood pressure from childhood to adolescence is relevant. Such information would enable us to understand the evolution of blood pressure in this phase of life and help to potentially mitigate the burden of high blood pressure early in life.

Study Hypothesis

Systolic and diastolic blood pressure exhibits age related changes from childhood to adolescence.

Objectives of the proposed study

Primary Objective: To investigate the changes in systolic and diastolic blood pressure among South Asian children aged 6 to 11 years who were followed for a period of six years.

Secondary Objectives:

(a) To examine the influence of changes in body mass index on age related changes in systolic and diastolic blood pressure from childhood to adolescence.

(b) To examine the influence of gender on age related changes in systolic and diastolic blood pressure from childhood to adolescence.

Methods and statistical analysis plan

One urban school from the district of Ernakulam, Kerala, India was selected for this study. The school was selected as there was an ongoing annual school health program. Blood pressure and anthropometric data (weight and height) were collected from students, 5–16 years of age, during the two screening years for the study (1560 children in 2005 and 1654 children in 2011). Combined, the two screenings provided a cohort of 703 children who were 5 to 11 years of age in 2005 and were re-examined six years (age range of 11 to 17 years in 2011). During both surveys, blood pressure was measured at a single visit (two readings by the same observer, separated by two minutes) using a mercury sphygmomanometer utilizing the methodology recommended by The Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents (2004).[4]

For analysis, the children will be divided into 7 age categories; 5, 6, 7, 8, 9, 10 and 11 years. The analysis of variance (ANOVA) will be performed to assess whether on average, the within individual blood pressure trends vary across age categories. In case the trends are heterogeneous across age groups, then in each category, the average difference between baseline and follow-up blood pressure measurements will be evaluated using the paired t-test at 0.05 alpha-level (adjusting for multiple comparisons). However, if the trends are homogenous across groups, to increase the study power, all age categories will be collapsed together and a single paired t-test (alpha 0.05) will be performed.

In addition, a general linear regression model with follow up blood pressure and blood pressure change as outcomes (dependent variables) and sex, weight, and height as regressors (independent or predictor variables) will be fitted to assess whether these predictor variables are associated with the dependent variables.

As a secondary analysis, the role of change in body mass index on age related progression of blood pressure will be analyzed by comparing mean change in blood pressure (δ BP) across various categories of children based on change in body mass index (δ BMI). The statistical approach used here will be ANCOVA (analysis of covariance) which will allow us to adjust for covariates like baseline body mass index, age and gender. A p value for linear trend will be reported as significant if it is less than 0.05.

Similarly the role of gender in age related progression of blood pressure will also be analyzed by comparing mean δ BP between boys and girls across individual age groups using ANCOVA (adjusting for covariates like change in body mass index and baseline blood pressure). In the event of identifying a gender based difference for δ BP, a test for interaction

(between age and gender for δ BP) will be done and this will be considered to be significant if a p value of <0.05 is observed.

Selection of the topic

The school health program was initiated by the candidate, who is a pediatrician, in 2005. The follow up evaluations were conducted in 2011 as part of the thesis project for the candidate's MSc study program. Previous studies from the same population suggest the possibility of a different distribution of blood pressure in this pediatric population.[6,7] This observation has also prompted me to examine the age related changes of blood pressure in this population from childhood to adolescence by means of a prospective cohort design and to study the role of factors in influencing this change of blood pressure.

Potential implications of this study

The findings of the study will inform us about the rate of progression of blood pressure with age from childhood to adolescence. The observation will also inform us of the role of change in body mass index and gender in modifying this age related progression of blood pressure. The results may also help us predict the subset of children (by means of simple cross sectional school based blood pressure surveys) who are more probable to exhibit higher blood pressures in adolescence and later life. Documentation of such findings will increase the awareness and lead to preventive strategies to contain the morbidity and mortality burden of hypertension in low resource countries like India.

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REVIEW OF LITERATURE

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide.[1]It is projected that the annual number of deaths due to cardiovascular diseases (CVD) will increase from 17 million in 2008 to 25 million in 2030.[1] High blood pressure is a lead contributor to the global burden of cardiovascular diseases. Globally, two-thirds of all strokes and half of all coronary disease can be attributed to high blood pressure.[2]

The global prevalence of hypertension is increasing as per a recent analysis of worldwide data.[3] Hypertension is a greater population burden in economically developing countries than in developed countries despite the fact that prevalence is more common in the latter.[3] The larger population of developing countries results in a considerably larger absolute number of individuals affected by hypertension from developing economies.[3] Hypertension is showing an increasing trend in developing countries like India.[4] In India, prevalence of hypertension has increased by 30 times in urban populations over 25 years, and by 10 times in rural populations over 36 years.[4]

2. Scenario of hypertension in South Asia

The scenario of hypertension related burden is passing through a critical phase in South Asia.[1] The WHO World Health Statistics 2012 report points out that the age-standardized prevalence of raised blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) among adults (aged 25 years or more) from South Asia increased from 23% in 1980 to 25% in 2008.[1] This is in contrast to the declining trend for raised blood pressure seen in Americas, Europe and Western pacific regions during the same period.[1] Thus the secular trend data from South Asian countries suggest that if current trends continue there is a greater likelihood of a further increasing burden of high blood pressure (BP) related diseases in these countries.

3. Hypertension in children

There is evidence that hypertension in adults may originate in childhood. Blood pressure is well known to increase from birth to adulthood.[5] Normal BP distribution show lowest levels in the early days of life. Blood pressure gradually increases from very low levels at birth and reaches comparable levels to that of an adult by late adolescence.[5] High BP can be seen in any age from birth onwards and the prevalence of high BP increases with age.[5]

The public health significance of high BP in childhood and adolescence is based on observations that confirm a strong association of BP levels during childhood to those during adulthood.[6] In spite of the fact that the prevalence of clinical hypertension is of a far lesser magnitude in children than in adults, evidence exists to support the concept that hypertension may originate in childhood.

Although high BP in children doesn't usually result in mortality or cardiovascular disability, intermediate markers of target organ damage, such as left ventricular hypertrophy, thickening of the carotid vessel wall, retinal vascular changes, and cognitive changes, are detectable in children and adolescents with high BP.[7-11]

Cardiac structural changes in children with high BP may persist in certain subsets even with appropriate control of BP.[12] Familial patterns for BP have been established from early infancy and children with high BP are more likely to come from families with a history of hypertension.[13-16] Children and young adolescents with BP greater than the 90th percentile for age have roughly threefold greater likelihood of becoming adults with hypertension compared to those with BP at the 50th percentile.[5]

4. Blood pressure studies in children and adolescents

Blood pressure studies in children and adolescents have focused on various aspects of age related BP changes during this phase of life. These aspects include age related changes of BP, influence of growth trajectories on age related changes of BP and tracking of BP with age. In addition, studies have also examined the impact of measurement protocols on longitudinal follow up of BP during childhood and adolescence. Several studies have attempted prediction of future BP levels and cardiovascular risk from BP and anthropometric measurements made during infancy, childhood and adolescence. Researchers have also examined the association of secular trends in adiposity and BP during childhood and adolescence. Studies have also reported BP variations by ethnicity during childhood and adolescence. The review of literature will focus on summarizing the evidence available for each of these themes and attempt to identify un-answered questions related to these themes. The themes in the following section are presented in **Table 1** below.

Table 1. Themes covered in the Review of Literature	
4.A	***Age related changes in BP from early childhood to adolescence***
4.B	***Childhood growth trajectories and BP status in later life***
4.C	***Tracking of BP in children and adolescents***
4.D	***Measurement protocols and variations in BP measurement***
4.E	***Predicting future BP levels from childhood measurements***
4.F	***Childhood BP and its relation to future cardiovascular risk***
4.G	***Secular trends in adiposity and its association with BP trends in children***
4.H	***High blood pressure in South Asian children***

4. A. *Age related changes in blood pressure from early childhood to adolescence*

Pooled analysis of blood pressure studies in children

Several studies have reviewed the results of population-based, cross-sectional surveys and compared the reported levels of BP among these surveys.[17-19] A pooled analysis was done by Brotons et al in 1989 that included 79 eligible studies (1966 to 1984).[19] The studies were from Europe (28 studies), North & South Americas (27 studies), Western Pacific (16 studies), Africa (5 studies), and South East Asia (3 studies).

Blood pressure methods varied in many aspects among the studies and were described insufficiently in many instances. The setting of the study was mostly in schools (when stated) and the participation rate was described only in 18% of studies. Most studies were cross sectional in nature (67 cross sectional studies, 12 longitudinal studies) with the main objective of describing normative blood pressure data in healthy children.

In 15% of studies, observer training was described in the published paper. The criterion for diastolic BP was stated to be Korotkoff Phase 4 in 32% of the surveys, Korotkoff Phase 5 in 25% and was inconsistent or unstated in the remainder. Resting time before measurement was noted in 38% of the reports, position of the subject in 69%, and the arm used in only 12%.

In 53% of the surveys, multiple cuffs of different sizes were used, but this aspect was not addressed in 32% of the reports. In 43% of the surveys, multiple readings were taken, but in 47% of reports the number of readings was not indicated. The instrument used was the mercury sphygmomanometer in 70% of studies, while the random-zero device was used in 12% and an automated device in 5%; the choice of instrument was not stated in 9% of reports. The 79 eligible studies included children and adolescents from ages 6 to 18 years.[19]

The results of the study indicated increasing values for systolic BP among boys and girls from age 6 to 16 years although the patterns were different for both genders from age 14 onwards. Beyond 14 years of age, systolic BP values for boys continued to increase to age 17 but did not increase further between 17 and 18. For girls, the increase to age 16 was very slight, and the mean values at ages 17 and 18 were actually lower than at 16. The greatest slopes of systolic BP by year of age were 3.2 mmHg per year from 12 to 15 or 16 for boys and 2.1 mmHg per year for girls from 9 to 13. For diastolic BP, increasing values with age were generally observed from 6 to 18 for both boys and girls, unlike the patterns for systolic BP. The slopes were approximately 1.0 mm Hg per year throughout this age range for girls, and a very slight differentiation appeared between slopes for boys between the intervals from 6 to 13 years and from 13 to 18 years. Thus, for DBP, there was an apparent, though very slight, separation of the age patterns for boys and girls after age 11, whereas this occurred at age 14 for SBP.[19] The values for age specific (pooled) BP means are presented as **Table 2** below.

Table.2. Pooled values for systolic and diastolic blood pressure from 79 studies[19]

Age	Males		Females	
	Systolic BP (mm Hg)	**Diastolic BP (mm Hg)**	**Systolic BP (mm Hg)**	**Diastolic BP (mm Hg)**
6	100.6	59.2	100.3	59.5
7	101.8	61.0	101.8	61.8
8	103.3	60.2	103.8	62.0
9	104.8	63.1	104.8	63.2
10	105.8	63.5	106.7	63.6
11	107.5	64.6	109.0	64.2
12	108.6	64.7	110.4	65.5
13	111.9	64.5	113.3	67.7
14	114.8	65.4	113.9	67.5
15	118.3	67.3	114.7	68.4
16	121.1	68.8	115.7	70.6
17	122.8	70.3	114.7	71.7
18	122.6	71.5	111.3	72.5

SBP – systolic blood pressure, DBP diastolic blood pressure.

The overall pattern of change in systolic BP with age, seen in the pooled data for all qualifying studies suggested that a marked increase in systolic BP with age was nearly universal during childhood and adolescence and was especially steep in the early to middle years of the second decade of life. The departure of the male and female patterns for systolic BP also appeared consistent, with mean values for girls actually decreasing with age after 16 years compared to boys.[19]

Comparison of pooled analysis with studies from South Asia

Studies were published from South Asian countries recently that looked at BP distribution in children.[20, 21] A recent survey (2005) of 24,842 school children (5 to 16 years) from India reported BP data for 20,263 children.[20] A comparison of age categorized mean BP levels between this study and the pooled analysis from Brotons et al discussed above is presented as **Table 3** below.

Table.3. Age related changes in BP during childhood and adolescence – Brotons et al vs Raj et al.[19, 20]

	Boys				Girls			
Age	**SBP (Brotons)**	**SBP (Raj)**	**DBP (Brotons)**	**DBP (Raj)**	**SBP (Brotons)**	**SBP (Raj)**	**DBP (Brotons)**	**DBP (Raj)**
6	100.6	96.5	59.2	60.9	100.3	95.9	59.5	61.7
7	101.8	97.7	61.0	62.9	101.8	97.9	61.8	63.3
8	103.3	99.5	60.2	64.3	103.8	98.8	62.0	63.7
9	104.8	100.5	63.1	66.0	104.8	101.5	63.2	66.5
10	105.8	102.1	63.5	67.3	106.7	104.4	63.6	68.5
11	107.5	103.5	64.6	68.3	109.0	107.3	64.2	70.0
12	108.6	105.3	64.7	68.6	110.4	109.8	65.5	71.7
13	111.9	108.0	64.5	69.1	113.3	112.3	67.7	72.6
14	114.8	111.0	65.4	71.2	113.9	113.2	67.5	73.3
15	118.3	113.8	67.3	72.8	114.7	114.4	68.4	74.2
16	121.1	115.1	68.8	73.2	115.7	114.7	70.6	74.5

Age in completed years. SBP and DBP values are from Brotons et al[19] & Raj et al.[20] DBP values are based on korotkoff Phase V in both sources. SBP – systolic blood pressure, DBP – diastolic blood pressure. Blood pressure units in mm Hg

The comparison of these data sets (unadjusted for weight or height) sheds light into some interesting findings. Overall, systolic BP among boys appears to be higher in the pooled data set compared to the Indian data for all ages. The comparison for systolic BP among girls differed from that in boys. Indian girls exhibited much lower values (approximately 4 mm Hg) at lower ages in comparison to the pooled data set but the gap narrowed to 1 mm Hg at the highest (16 years) age group. The mean diastolic BP levels were higher for Indian children (both boys and girls) compared to the pooled data set consistently across all age groups. The gap in diastolic BP was approximately 4 mm Hg at the highest (16 years) age group.

Even though the comparisons for age related mean BP levels showed differences between the two data sets, the gender relationship of systolic BP and diastolic BP for both sets remained similar. Girls exhibited higher diastolic BP levels than boys for both data sets across all age groups except for one year (age 11 for the pooled data set, age 8 for Indian data set). In the case of systolic BP, girls initially started with lower values in both datasets and exhibited higher values for a period compared to boys (10-13 years in pooled dataset, 9-15 years in the Indian dataset). After this period, boys exhibited higher values for both datasets.[19, 20]

Role of body mass index in age related changes of blood pressure in children

The age related changes of BP in children appears to be clearly influenced by categories of body mass index.[22] These separations by body mass index levels appear similar in both genders and for both systolic and diastolic BP.

Zhang et al recently published a cross sectional study of 8568 Asian children (4333 boys, 4235 girls) in the age group 7-18 years from China.[22] The study underlines the important role of body mass index in influencing the BP levels during childhood and adolescence. The mean BP levels were lowest in the lowest quartile for body mass index in all age groups (both boys and girls) and increased across higher body mass index quartiles. The highest mean BP

levels were seen among children in the highest quartile of body mass index. This increasing pattern of mean BP across higher quartiles of body mass index was similar for systolic and diastolic BP.

The data from the study are summarized as **Table 4** below.

Table. 4. Mean systolic & diastolic blood pressure across body mass index categories in children.[22]

Systolic blood pressure (mm Hg)				
Age (years)	**BMI <25th P**	**BMI 25th-49thP**	**BMI 50th -74th P**	**BMI ≥75th P**
Boys				
7-9	93.74	95.64	97.67	105.92
10-12	99.05	101.58	106.58	111.94
13-15	108.61	112.61	114.54	119.53
16-18	117.05	117.88	120.95	124.97
Girls				
7-9	92.53	94.72	96.90	102.65
10-12	98.12	100.87	105.52	109.42
13-15	104.48	105.85	107.87	112.45
16-18	105.96	106.62	108.15	112.89
Diastolic blood pressure (mm Hg)				
Boys				
7-9	57.68	58.03	59.91	65.65
10-12	61.95	62.89	64.99	69.09
13-15	67.83	68.00	69.34	71.62
16-18	71.28	71.81	72.22	74.14
Girls				
7-9	57.11	57.34	60.50	63.39
10-12	61.17	62.58	65.25	68.00
13-15	66.16	66.78	67.86	69.58
16-18	67.13	67.59	68.12	70.44

BMI - Body mass index. Systolic and Diastolic blood pressure values are in mm Hg.

Association of height and weight with blood pressure during childhood

In addition to adiposity, height also plays a role in the age related changes in BP seen during childhood. Regression models that have examined the role of height and age on changes of BP with age confirm the role of height in childhood BP distribution.[23, 24]

Rosner et al recently published a study that examined the role of height in progression of BP during childhood.[23] The authors pooled data from 11 blood pressure studies during childhood and constructed a data set of 49,967 normal weight children (age 1 to 17 years). They constructed a polynomial regression model using age in years and height in SD (standard deviation) units. Each SD of height predicted a change in systolic BP of 2.29 mm Hg in boys and 1.75 mm Hg in girls. The corresponding change for diastolic BP was 1.42 mm Hg for boys and 1.39 mm Hg for girls.

A similar model was published by Raj et al using data from 20, 263 normal weight children (age 5 to 16 years) from India.[24] The change in systolic BP per SD of height was 2.3 mm Hg for boys and 1.36 mm Hg for girls. The corresponding values for diastolic BP were 1.18 mm Hg for boys and 0.89 mm Hg for girls respectively.[24]

The independent role of weight and height in influencing BP was explored in a recent study by Ma et al from china.[25] The authors collected data from a nationally representative sample of 231,227 children aged 7-18 years. The relationships between body size and BP measurements were assessed using linear regression analysis. The researchers reported that body size measurements were significantly associated with BP levels. The study reported that systolic BP increased 4.14, 3.70 and 2.88 mm Hg in boys and 2.98, 2.63 and 1.87 mmHg in girls, corresponding to 1 SD increase in weight, BMI and height, respectively. Diastolic BP increased 2.37, 2.02 and 1.87 mm Hg for boys and 1.92, 1.61 and 1.36 mmHg for girls, corresponding to 1 SD increase in weight, BMI and height respectively.[25]

The authors reported that after adjustment for height, weight was still substantially associated with BP.[25] The authors reported an increase of 3.96 mm Hg for systolic BP and 2.00 mm Hg for diastolic BP in boys, and 2.92 mm Hg for systolic BP and 1.73 mm Hg for diastolic BP in girls, corresponding to 1 SD increase in weight with the adjustment for height. On the contrary, after adjustment for weight, systolic BP only increased 0.27 mm Hg in boys and 0.10 mm Hg in girls, and diastolic BP increased 0.55 mm Hg for boys and 0.31 mm Hg in girls, corresponding to 1 SD increase in height.[25]

The details of the regression analysis (adjusted) are presented in **Table 5** below.

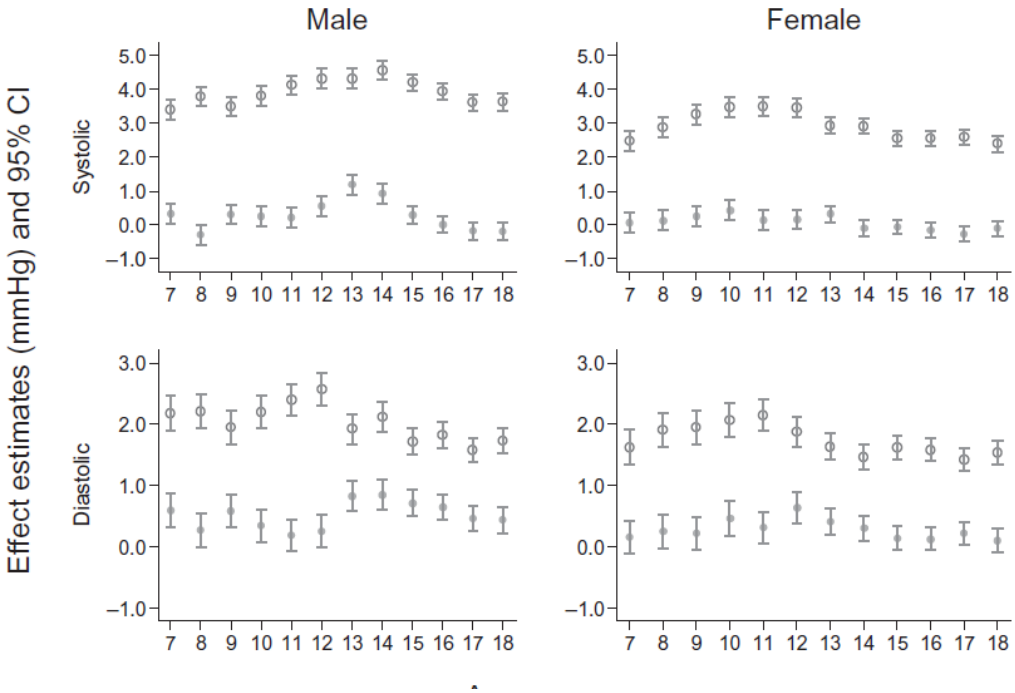
Table.5. Changes in blood pressure with changes in weight and height.[25]

	Systolic BP		**Diastolic BP**	
	Change in BP (mm Hg)	95% CI	Change in BP (mm Hg)	95% CI
Males				
Weight*	3.96	3.88, 4.04	2.00	1.93, 2.07
Height#	0.27	0.19, 0.35	0.55	0.48, 0.62
Females				
Weight*	2.92	2.84, 2.99	1.73	1.66, 1.80
Height#	0.10	0.03, 0.17	0.31	0.24, 0.37

Blood pressure change (mmHg) corresponding to 1 standard deviation increase in weight and height.
**Adjusted for age and height. # Adjusted for age and weight.*

The authors also examined changes in BP with change in weight and height in each age category to see if there was any difference in the impact of weight and height on BP across age groups.

The details are presented as **Figure. 1** below.



Blood pressure increases corresponding to 1 SD increase in weight (upper line) and height (lower line). Adjusted for height when calculating the effect of weight and vice versa. CI, confidence interval.

Figure 1. Changes in blood pressure with changes in weight and height.[25]

The study findings suggest that weight has a bigger influence on both systolic and diastolic BP across all age groups compared to height and the pattern is similar in boys and girls.[25]

Section Summary – Age related changes in BP from early childhood to adolescence
Pooled data analysis of 79 studies suggests that the overall trend of age related changes of BP in children and adolescents across various populations is similar. ***Height, weight and body mass index influences BP in children and adolescents. An increase in the levels of these variables increases BP levels during childhood.*** ***Weight appears to have a stronger positive association on BP during childhood when compared to height.***

4.B. *Childhood growth trajectories and blood pressure status in later life*

Childhood growth parameters (weight for age, height for age, weight for height and body mass index for age) and their trajectories are well known to influence BP levels at various ages.[26-33] The period of growth that influences BP during childhood and adulthood is unclear. In general, pediatric and adolescent cohort studies that focused on this theme have suggested that growth during antenatal, infancy, early childhood, late childhood and adolescence has the potential to modify BP in later life.

Previous research has suggested an inverse association between birth weight and BP in adulthood.[26,27] In a recent critical review of the developmental determinants of BP, Adair et al concluded that the majority of human epidemiologic studies demonstrate an inverse association of birth weight with adult BP.[34] The authors also reported that current evidence suggests higher risk of hypertension among individuals with lower weight at birth. As per the authors, the most adverse BP outcomes occur among subjects who were small at birth but relatively large when they reached adulthood.[34] The pathophysiology of this relationship between birth weight and BP is unclear. Adaptive physiological or endocrinological responses during critical periods of fetal life or infancy that persist into later life are the suggested reasons for this inverse relationship between birth weight and BP as per currently available evidence.[34]

Early Childhood growth and blood pressure in children

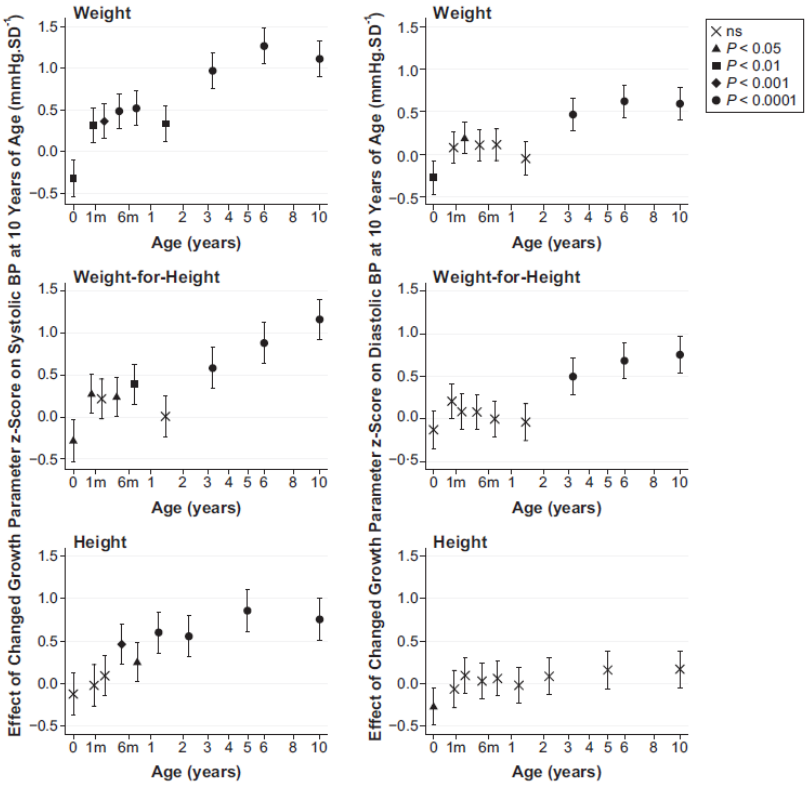
Avon Longitudinal Study

The Avon Longitudinal Study of Parents and Children that was published recently, looked at the association of BP with childhood growth parameters (weight, weight for height and height) in 3230 boys and 3346 girls (mean age 10.6 years) who were enrolled at birth for the study.[28] The authors reported that at 10 years, 1 standard deviation (SD) greater weight (7.1 kg

in boys and 7.8 kg in girls) was associated with 1.93 mm Hg (95% CI, 1.72-2.15 mm Hg) greater systolic BP and 0.82 mm Hg (95% CI, 0.63–1.02 mm Hg) greater diastolic BP.[28] Systolic BP was also associated with weight for height and height in a similar pattern as per the study. Systolic BP increased by 1.50 mm Hg (95% CI, 1.27–1.72 mm Hg) per SD of weight for height and by 1.22 mm Hg (95% CI, 1.00–1.44 mm Hg) per SD of height.

The authors reported that Diastolic BP was associated with weight-for-height but not with height. In the study, diastolic BP increased by 1.13 mm Hg (95% CI, 0.93–1.33 mm Hg) per SD of weight for height and by 0.01 mm Hg (95% CI, -0.19 to 0.20 mm Hg) per SD of height.[28] There were no sex based differences for these associations as per the study.

The independent associations of separate growth intervals with BP at age 10 as per the study are shown in **Figure 2** below.



Each point shows the strength of association (+/- 95% CI) for the period of growth from the preceding point or throughout gestation for the measure at birth and represents a difference from normal population growth over that period. Symbol shape (key) in the legend represents the statistical significance level for the null hypothesis where P values are calculated for the difference of each measurement from its previous measurement. Age is plotted on a square-root transformed axis.

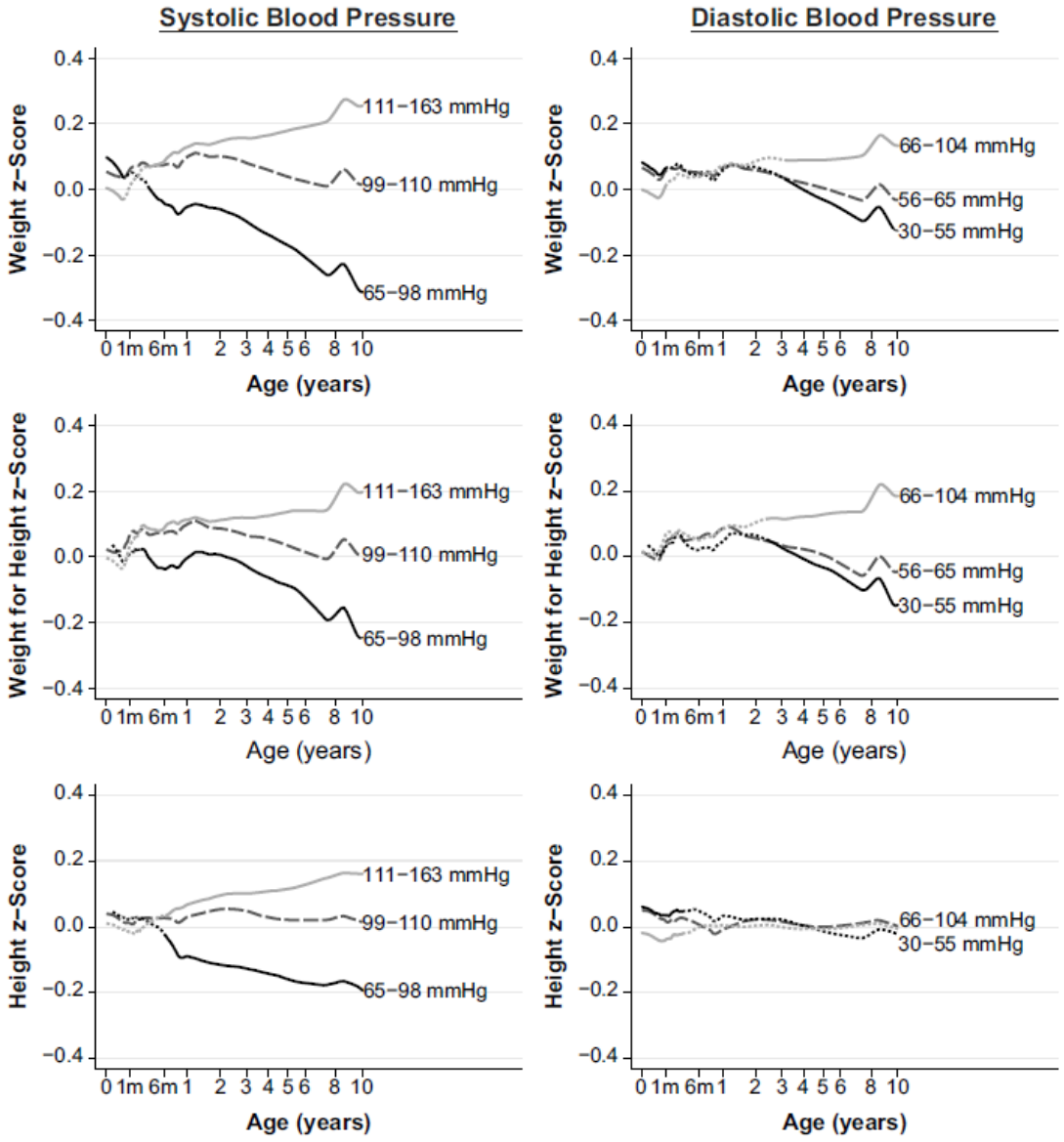
Figure. 2. Conditional growth models for weight, weight for height, and height in relation to blood pressure at 10 years.[28]

In this study, greater systolic BP at 10 years was associated with lower prenatal growth of weight and with greater growth in any measure at any stage after birth.[28] Weight for height showed a relationship with systolic BP that was similar to that shown by weight. Greater diastolic BP at 10 years was associated with lower prenatal growth of weight and length and with post-infancy growth in weight and weight for height. Interestingly, infancy growth in any measure had minimal effect on diastolic BP.[28]

As per the study, children with higher systolic BP at age 10 years started life with lower weight, no difference in length, and no difference in weight for height compared with children with a lower systolic BP.[28] These children steadily gained height, weight, and weight for height at a greater rate in first 10 years, while those with lower BP (at age 10 years) grew at a comparatively lower rate. The strongest association was reported between BP and weight.

The reported patterns of associations of weight and weight for height with diastolic BP were similar to that for systolic BP, but the effects were generally smaller in comparison. The study reported that children with higher diastolic BP at age 10 years were shorter at birth, whereas those with lower diastolic BP at age 10 years were longer at birth. In spite of this finding, there was only a minimal difference in height growth after this between these two groups of children who differed by diastolic BP levels at 10 years as per the study results.[28]

Growth patterns based on weight, weight for height and height, according to categories of systolic and diastolic BP as reported by the study are shown in Figure 3 below.



The middle half of the population (dashed line) is shown for comparison. Where the other lines are dotted, P< 0.05 for a 2-way t test of the null hypothesis that the growth parameters are the same. Age is plotted on a square-root transformed axis.

Figure.3 . Mean growth trajectories for the upper (pale line) and lower (dark line) quartiles of blood pressure at 10 years.[28]

LISAPLUS Study

A recently published study based on data from the prospective German birth cohort (LISAplus) examined the influence of weight and height velocities during infancy on systolic and diastolic BP during late childhood.[29] The study included 1127 children who had a birth weight of at least 2500 grams. All were followed up to 10 years of age. Growth was modeled using nonlinear mixed-effect models. Associations between peak growth velocities and BP levels at 10 years were calculated with linear regression models.

The authors reported that higher peak height velocity (PHV) and peak weight velocity (PWV) in infancy were associated with significant increase in systolic BP and diastolic BP in children at 10 years. They reported that for every 2 standard deviation increase in PHV (10.2 cm per year), systolic BP increased by 2.94 mm Hg after adjustment for potential confounders. In addition, for every 2 standard deviation increase in PWV (5.1 Kg per year), systolic BP increased by 2.13 mm Hg and diastolic blood pressure by 1.91 mm Hg in the study.[29]

Based on their study results from this prospective birth cohort, the authors concluded that children who grew quickly during infancy exhibited higher systolic and diastolic BP irrespective of their weight status at school age.

The details are presented in **Table. 6 below**

Table. 6. Associations between systolic and diastolic blood pressure at age 10 years and peak weight and height velocities in infancy.[29]

	Beta coefficient	CI	P value
Systolic blood pressure			
Peak Weight Velocity	2.13	0.51, 3.74	0.010
Peak Height Velocity	2.94	1.34, 4.54	<0.001
Diastolic blood pressure			
Peak Weight Velocity	1.91	0.52, 3.30	0.007
Peak Height Velocity	1.05	-0.34, 2.43	0.140

Adjusted for parental education, maternal age, maternal height and weight before pregnancy, smoking during pregnancy, gestational age at birth, paternal height and weight, parental diabetes and hypertension, birth weight, breastfeeding and current body mass index levels.

The Collaborative Perinatal Project

The US Collaborative Perinatal Project (CPP) studied 55,908 pregnancies in an observational cohort at 12 medical centers in the United States and followed the offspring through 7 years of age.[30] By the end of the study, 29 973 children (born between 37 and 42 weeks of gestation) completed the 7-year follow-up and were included in the analysis. The cohort was biracial (Caucasian & African American). Childhood weight was recorded 5 times during the CPP study follow-up: birth, 4 months, 1 year, 4 years, and 7 years. Weight for age measured at all the above time points were converted to Z scores using study means and SDs. These Z score changes were used to assess body size in relation to the previously recorded size, thereby quantifying increase or decrease in relative size. Multivariable logistic regression models that included birth weight and race were used in the study to predict high systolic and diastolic BP at 7 years of age.[30]

The authors reported that each 1 kilogram in birth weight increased the odds for high systolic BP by 2.19 (95%CI 1.92, 2.49, p< 0.001) and high diastolic BP by 1.82 (95% CI 1.59, 2.08, p <0.001) when race and change in weight *z* scores were also included in the regression model. The authors also reported that an increase in weight *z* score of 1 SD above the previous weight *z* score increased the odds for high systolic BP at 7 years by 1.65 (birth to 4 months), 1.79 (4 months to 1 year), 1.71 (1–4 years), and 1.94 (4–7 years). In addition, the study reported that Caucasian race increased the odds for high systolic BP by 1.51 mm Hg (95% CI 1.36, 1.66, p<0.001).[30]

The details of the prediction model are presented as **Table 7** below.

Table. 7. Prediction models for high blood pressure at age 7 years.[30]

Risk Variable	Odds Ratio*	95% CI	*P value*
High systolic blood pressure (7 years)[#]			
Birth weight, kg	2.19	1.92–2.49	<0.001
White race	1.51	1.36–1.66	<0.001
Weight gain, birth to 4 m	1.65	1.54–1.75	<0.001
Weight gain, 4 m to 1 y	1.79	1.66–1.93	<0.001
Weight gain, 1 to 4 y	1.71	1.61–1.80	<0.001
Weight gain, 4 to 7 y	1.94	1.81–2.08	<0.001
High diastolic blood pressure (7 years)[#]			
Birth weight, kg	1.82	1.59–2.08	<0.001
White race	1.28	1.16–1.42	<0.001
Weight gain, birth to 4 m	1.43	1.34–1.52	<0.001
Weight gain, 4 m to 1 y	1.44	1.34–1.56	<0.001
Weight gain, 1 to 4 y	1.45	1.37–1.53	<0.001
Weight gain, 4 to 7 y	1.56	1.45–1.67	<0.001

**Odds Ratios reflect risk adjusted for other variables in model: birth weight, race, and 4 change points in z score intervals. All Odds Ratios are for 1 unit change in weight z scores during interval. # Defined as blood pressure > 90th percentile of distributions within the CPP population blood pressure distributions by gender and age. Kg - kilogram, m - months, y - years.*

Late childhood growth and blood pressure in children

The COMPASS study from Sweden and PELOTAS study from Brazil clearly identifies the role of late childhood as well as adolescent growth in modifying BP.[31, 32]

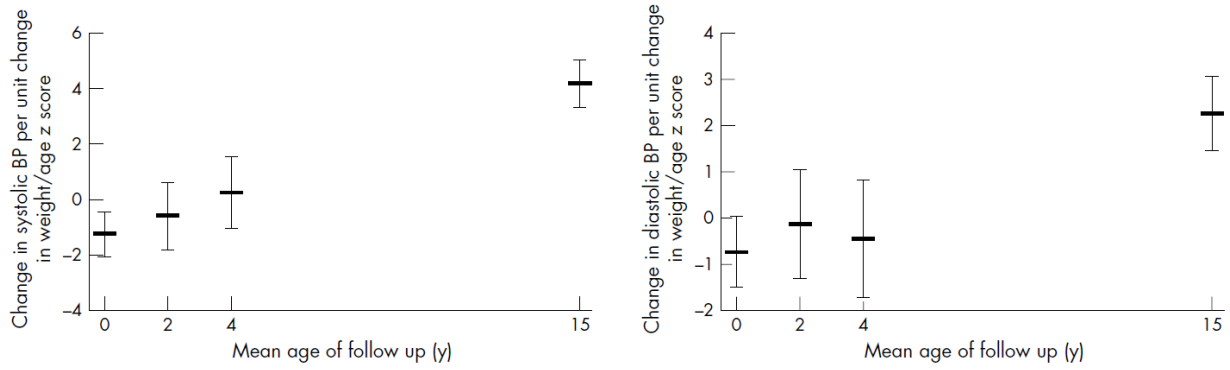
The PELOTAS Study

The PELOTAS cohort was initiated in 1982 and repeat surveys were done in 1984, 1986 and 1997.[32] Anthropometric measurements were done for all subjects included in the cohort during all the screens. BP was measured twice in the final screen, at the beginning and in the end of the interview, in the sitting position with a calibrated aneroid sphygmomanometer. The mean values of the two measures were used in the analyses. The final analysis included data from 749 adolescents.

The authors reported that after controlling for possible confounding variables, birth weight was negatively associated with systolic BP. As per the study results, one unit increase in standard deviation score of birth weight for gestational age was associated with a decrease of 1.23 mm Hg (95% CI -2.03 to -0.43) in systolic BP.[32] The authors also reported that weight for age z score at the age of 15 years was positively associated with systolic BP. As per the study results, each unit increase in standard deviation score of weight for age (at 15 years) was associated with an increase of 4.4 mm Hg (95% CI 3.50 to 5.3) of systolic BP.

On the contrary, diastolic BP was not reported to be associated with birth weight as per the study results.

The multiple linear regression modeling of systolic and diastolic BP on all adolescents using birth weight and weight Z scores (20 months, 40 months and 15 years) as well as separately for those who were having normal birth weight and low birth weight are presented as **Figure 4**.



Changes in systolic and diastolic blood pressures (mm Hg) associated with a 1 z score increase in birth weight and weight for age z scores at the mean ages of 20 months, 42 month, and 15 years. Adjusted for family income, duration of breast feeding, gender, maternal height, and maternal smoking during pregnancy.

Figure. 4. Changes in systolic and diastolic blood pressure associated with birth weight and weight for age.[32]

The data from PELOTAS cohort suggests that the contribution of birth weight in the progression of systolic BP with age is minimal in higher ages.[32] The contribution of birth weight for diastolic BP progression with age is virtually nonexistent. The most important contributor to systolic and diastolic BP was the most recent weight change status.[32]

COMPASS Study

The COMPASS study (community-based study of physical activity, lifestyle and self-esteem in Swedish school children) was initiated in the year 2000 in Stockholm County, Sweden.[31] All children, born between 1985 and 1987 in the selected county were invited to

participate in the study which included a health examination at approximately 15 years of age. In total, data from 2438 adolescents (1189 girls and1249 boys) were available for analysis.

Information on height and weight during childhood was collected and height and weight growth curves fitted for each child. Weight and height at age 1 and 10 years were derived from growth curves constructed from study data but weight and height at 15 years of age were obtained from the health examination. Weight Z-scores at birth, 1, 10 and 15 years of age were used as predictor variables in the analyses. In addition, change in weight z-scores from birth to age 1 year, from 1 to 10 years and from 10 to 15 years were also used as predictor variables.[31]

The authors reported that systolic BP increased 0.99 mmHg (95% CI, 0.27, 1.71) in girls and 1.02 mmHg (95% CI, 0.31, 1.73) in boys per 1 SD increase in weight during infancy. The study also reported that effect of weight change from 10 to 15 years on systolic BP among boys was much higher when compared to girls. Boys exhibited an increase of 3.70 mm Hg (95% CI, 2.67, 4.73) of systolic BP per 1 SD increase in weight. The corresponding value for systolic BP increase per SD of weight in girls was only 1.30 mmHg (95% CI 0.38, 2.22)

The details of the predictor model are presented as **Table 8** below.[31]

Table. 8. Linear regression models of systolic blood pressure based on weight z-score at birth, and 1, 10 and 15 years of age.[31]

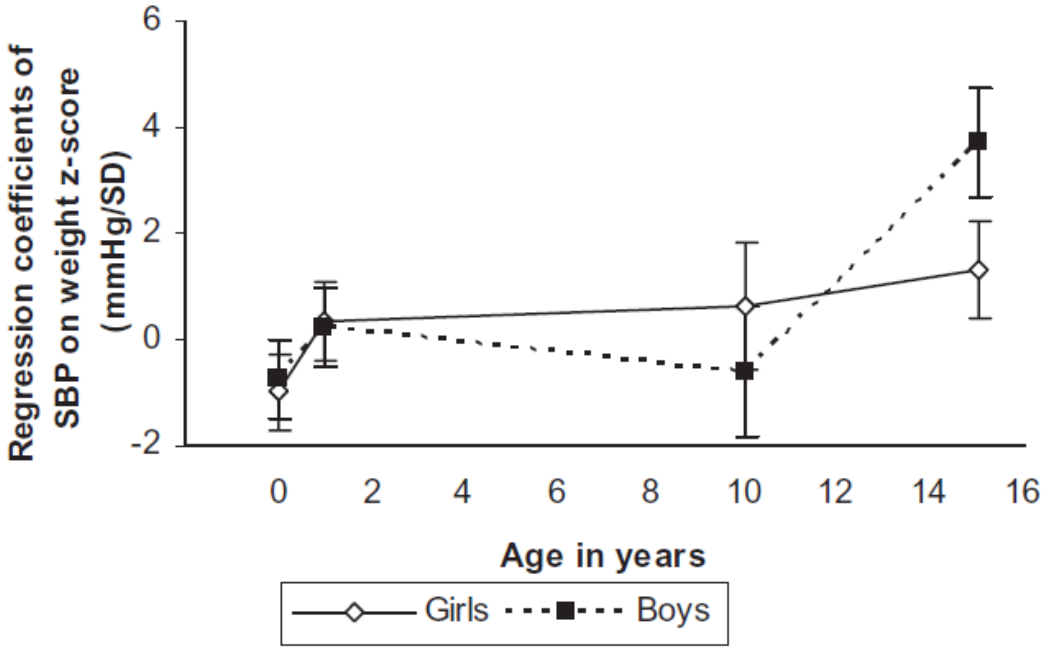
Age	Model A#		Model B*		Model C$	
	Girls (95% CI)	Boys (95% CI)	Girls (95% CI)	Boys (95% CI)	Girls (95% CI)	Boys (95% CI)
Birth	**-0.20** (-0.76, 0.35)	**-0.14** (-0.69, 0.40)	**-0.47** (-1.17, 0.22)	**-0.15** (-0.90, 0.60)	**-0.99** (-1.69, -0.28)	**-0.76** (-1.50, -0.02)
1 year	**0.98** (0.48, 1.48)	**0.92** (0.40, 1.43)	**0.85** (0.16, 1.55)	**0.84** (0.15, 1.53)	**0.35** (-0.39, 1.10)	**0.24** (-0.49, 0.96)
10 years	**1.94** (1.41, 2.46)	**2.30** (1.76, 2.84)	**1.45** (0.72, 2.18)	**2.09** (1.36, 2.81)	**0.63** (-0.57, 1.82)	**-0.61** (-1.83, 0.61)
15 years	**2.11** (1.61, 2.61)	**3.12** (2.59, 3.64)	**1.78** (1.22, 2.34)	**2.89** (2.28, 3.50)	**1.30** (0.38, 2.22)d	**3.70** (2.67, 4.73)^

Values are regression coefficients with 95% confidence intervals. Models A and B = Regression of Systolic blood pressure on weight z-scores one at a time. Model C = Regression of Systolic blood pressure on weight z-scores mutually adjusted from birth to age 15 years. #Adjusted for age at health examination. ***** *Adjusted as in # above and additionally for length/height at the age under consideration from birth to 15 years.* **$** *Adjusted as in * above and additionally for maternal age at birth, birth order, parental education, maternal country of birth and maternal pregnancy-induced hypertension or hypertension before pregnancy. ^Equivalent to weight change between 10 and 15 years of age.*

The authors concluded that weight gain in infancy and later childhood was positively associated with systolic BP at age 15 years, while birth weight showed a weaker inverse association with systolic BP.[31] The degree of weight change in infancy appeared to be equally important for systolic BP in both girls and boys. The contribution of weight gain during pubertal years (10-15 years) appeared to exhibit a differential pattern between both sexes as per study

results. Pubertal growth spurt resulted in a bigger change in systolic BP among boys compared to girls (3.70 mm Hg v/s 1.30 mm Hg).[31]

The sex based difference of weight change related BP in pubertal period is clearly visible in the **Figure 5** presented below.



Regression models of Systolic blood pressure (mmHg) on weight z-score at birth, 1, 10 and 15 years, mutually adjusted. The models are adjusted for exact age at measurement of systolic blood pressure and length/height at the respective ages from birth to age 15 years and additionally adjusted for confounding factors. (Maternal age at birth, birth order, parental educational level, maternal country of birth and maternal pregnancy-induced hypertension or hypertension before pregnancy) Estimated regression coefficients with 95% confidence intervals.

Figure.5. Regression models of systolic blood pressure based on weight status at birth, 1, 10 and 15 years.[31]

Section Summary - Childhood growth trajectories and BP status in later life
All three cohorts i.e., AVON, LISAPLUS and CPP confirm the role played by early childhood growth (weight, height or BMI) in modifying BP later in childhood. ***Among these, weight and weight gain appear to play a dominant role compared to other growth measures. The cohorts also suggest that the role of birth weight is smaller compared to that of weight gain later in infancy and early childhood. Diastolic BP doesn't appear to be modified by birth weight.*** ***Both the PELOTAS cohort and the COMPASS cohort suggest that weight gain during adolescence is an important factor that has the potential to modify systolic and diastolic BP. In addition, the COMPASS study suggests that pubertal growth spurt results in a bigger change in systolic BP among boys compared to girls.***

4.C. *Tracking of blood pressure in children and adolescents.*

Longitudinal studies of BP provide more information on the age related changes of BP as well as the tracking of BP from childhood to adolescence and adulthood. Such information is required for a better understanding of the evolution of hypertension. Tracking has been defined as the maintenance of the relative ranking of an individual with respect to his peers.[35] Tracking in pediatric BP studies is usually described as correlation coefficients between absolute values, percentile categories, ranks or Z scores obtained from the same population at two or more time points.

Landmark studies like the Muscatine study, Bogalusa Heart study and the Dormont High School Study showed that BP tracking correlations during childhood were positive but were substantially lower than those in adulthood.[36-39] Studies also reported that BP tracking was stronger for shorter follow-up periods and in older children.[40-43]

Meta-analysis of childhood BP studies that reported tracking of BP

Chen et al recently performed a systematic review of studies that examined BP tracking and conducted a meta–regression analysis to examine the predictors of BP tracking degree by summarizing findings from different studies published over the past 4 decades (1970-2006).[6] Of the 50 studies included in the systematic review, the length of follow-up ranged from 6 months to 47 years. The reported BP tracking correlation coefficients varied from -0.12 to 0.80 for systolic BP and from -0.16 to 0.70 for diastolic BP, with a mean of 0.38 for systolic BP (SD 0.16) and 0.28 for diastolic BP (SD 0.15). In men, the mean (SD) of the systolic and diastolic BP tracking correlation coefficients were 0.39 (0.15) and 0.29 (0.16) respectively. In women, the corresponding figures were 0.38 (0.15) and 0.26 (0.15).[6]

Six out of the 50 included studies were from Asia. The details of the studies from Asia are presented as **Table 9** below.

Table.9 Tracking of blood pressure in Asian children - meta regression analysis.

Chen et al[6]

Study	n	Age*	Follow up*	Tracking Correlations	
				SBP	DBP
Wada et al[44]	280	14-15 y	5 y	0.35 boys 0.32 girls	0.33 boys 0.33 girls
Suh et al[45]	304	6 y	4 y	0.43 boys 0.35 girls	0.24 boys 0.27 girls
Li et al[46#]	2598	4 –14y	4 y	0.19 – 0.56 boys 0.06 - 0.52 girls	0.02 – 0.36 boys 0.02 – 0.38 girls
Suh et al[42]	219	6 y	11 y	0.41 boys 0.44 girls	0.28 boys 0.14 girls
Murata et al[47]	334	13 y	10 y	0.45 (all)	0.36 (all)
Tan et al[48]	507	8 y	4 y	0.53 boys 0.37 girls	0.30 boys 0.25 girls

**Age & follow up in years. SBP systolic blood pressure, DBP diastolic blood pressure. # Li et al[46] reported tracking separately for each age group and the range across age groups is presented in the table.*

In general, systolic BP appeared to track with the increase in baseline age better than diastolic BP as per the meta-analysis. In cohorts with baseline ages of 8 years or younger, the strength of systolic BP tracking increased sharply with baseline age; among those with baseline age of 8 to 15 years, systolic BP tracking remained stable at 0.40; and for those older than 15 years, tracking increased again with age. The baseline age difference in diastolic BP tracking differed slightly from that of systolic BP. The predicted 5-year follow-up tracking correlation coefficient was 0.42 for systolic BP and 0.32 for diastolic BP.[6]

According to the study, the wide range of tracking correlations reported by individual studies could be due to differences in factors like baseline age, length of follow up, number of follow up visits and number of measurements per visit.[6] In general, higher age at baseline,

shorter follow up periods, more follow up visits and more measurements per visit increased the tracking correlation of both systolic and diastolic BP.[6]

The meta-analysis reinforces the fact that BP tracks from childhood to adulthood and that an elevated BP in childhood is likely to help predict adult hypertension.

Accuracy of childhood BP tracking correlations

Childhood BP tracking correlations, although positive, have been considered too low to make accurate predictions for an individual. The reasons for this low accuracy of predictions for adult BP based on childhood BP levels could be due to three factors i.e., variability in BP measurement, within subject variability of BP during childhood and emergence of factors that modify BP later (after the childhood BP screen) in life.

These correlations, however, can be improved substantially by tackling two modifiable factors i.e., by minimizing variability due to measurement error and by capturing within person variability of BP. One such method is to average BP over multiple visits in succession, which partially accounts for within-person variability. This useful method was demonstrated by Gillman et al in a previously published study.[49]

In a cohort of 333 school children, the researchers measured BP 3 times on each of 4 successive weekly visits, in each of 4 consecutive years, using a random-zero sphygmomanometer. With a model that allows estimation of correlations and that uses all available longitudinal data, the authors calculated tracking correlations corrected for within-person variability. Age and sex adjusted tracking correlations for 3 years of follow-up based on the means from 1,2,3,4, and infinity visits for systolic BP according to the model were 0.43, 0.56, 0.62, 0.66, and 0.73, respectively. For diastolic BP, these tracking correlations were 0.20, 0.37, 0.46, 0.50, and 0.70, respectively.[49]

The study suggests that by using multiple sets of follow up visits (and visits within each follow up set in close succession), the tracking correlations for both systolic and diastolic BP can be improved substantially.[49] The use of corrected tracking correlations so obtained, would allow determination of the maximal extent to which childhood blood pressure can predict adult levels. Such adjustments in tracking correlation will improve the accuracy of the prediction model and therefore the usefulness of screening to identify children at high risk of developing hypertension.

Even though this methodology is more accurate, this is relatively impractical in most school health screenings for children. School health screenings are usually done with minimum personnel and limited time allotted from working hours in school schedule. This methodologically superior technique should be limited to studies where the emphasis is on the accuracy of a prediction equation for future risk of hypertension from childhood data.

Section Summary - Tracking of blood pressure in children and adolescents
Systolic and diastolic blood pressure tracks from childhood and adolescence to adulthood. The tracking of systolic BP is better than diastolic BP. Shorter periods of follow up, higher age at baseline and repeated measures during follow up can increase the correlation of baseline BP to follow up BP.

4.D. *Measurement protocols and variations in blood pressure measurement*

The best approach for BP measurement in children for longitudinal follow up studies remains controversial till date. The items still debated are the number of measurements for each visit, type of BP measuring device and the cut point for diastolic BP (Korotkoff phase 4 or 5).

Choice of instrument and measurement of blood pressure in children

Compared with direct intra-arterial BP measurement, the manual auscultatory technique using Korotkoff sounds tends to give systolic BP values slightly lower and diastolic BP values slightly higher.[50, 51] While oscillometric monitors rely on pressure oscillations to reproduce BP levels accurately, mercury sphygmomanometers rely on Korotkoff sounds to measure BP levels.[52]

In mercury manometers, the accuracy of measurement of BP is determined primarily by the observer technique.[52] On the contrary, the accuracy of oscillometric monitors is determined by the validity of the algorithms used in these monitors to derive the systolic and diastolic BP values.[52] Studies that examined the reliability of oscillometric measurement of BP in the past have reported mixed findings. Studies in children have reported overestimation of systolic BP by oscillometric instruments (4 to 5 mm Hg) while one study among adults reported that these machines are reliable.[53, 54, 55]

Classification of diastolic blood pressure in children

The optimal approach to measurement of diastolic BP in childhood is an area of debate. It is still unclear whether the choice of Korotkoff phase 4 (K4; the muffling of the sound) or Korotkoff phase 5 (K5; the disappearance of sound) is the best representation of diastolic BP when using the mercury manometer.[56, 57] K5 has been recommended and universally used to measure diastolic BP in adults, but published recommendations for children's diastolic BP

assessment have varied considerably, from abandoning the measurement of diastolic BP in children to measuring either K4 or K5 or a combination of both.[58]

Impact of measurement protocols on diastolic blood pressure in children

Chen et al conducted a meta-analysis of 50 studies (published between 1970 and 2006) to examine the impacts of different BP measurement protocols on BP tracking correlations from childhood into adulthood.[58] The explanatory variables included the use of Korotkoff phase 4/Korotkoff phase 5, BP device, and number of BP measurements per visit.[58]

Of these studies, for diastolic BP, 64.6% used mercury manometer, 6.3% used random-zero manometer, 6.3% used ultrasound device, and 4.2% used an automated device. Regarding the number of diastolic BP readings at each survey time point, 8.3% of studies recorded diastolic BP once, 25.0% recorded twice, 47.9% recorded > 3 times, and 18.8% did not provide detailed information. The patterns were similar for systolic BP. Regarding diastolic BP measurement, 50% used K4 and 30% used K5; 6% recorded K4 and K5 but did not specify which one was used; 4% used an automated device; and 8% did not provide the details.[58]

Tracking correlation coefficients for diastolic BP measured using Korotkoff phase 4 was higher than that of Korotkoff phase 5. Diastolic BP tracking assessed by automated device was higher than that of Korotkoff phase 5 and higher than the mercury manometer. Diastolic BP tracking was slightly higher with multiple BP measurements per visit, but measurements of 3 times did not improve the tracking further compared with 2 measurements.[58]

The details of the comparisons are presented as **Table 10** below.

Table. 10. Impact of blood pressure measurement protocol items on diastolic blood pressure tracking.[58]

	Variable	β	SE	P
1	**BP measurement (mercury manometer as reference)**			
	Random-zero manometer	0.013	0.063	0.841
	Ultrasound device	−0.065	0.063	0.304
	Automated device	0.223	0.080	0.005
	Unknown*	0.032	0.053	0.546
2	**No. of BP measurements per visit (1 as reference)**			
	2	0.122	0.069	0.078
	≥3	0.082	0.059	0.169
	Unknown	−0.007	0.074	0.928
3	**Korotkoff Phases (K4 v/s K5, automated v/s K4, automated v/s K5)**			
	K4 v/s K5	0.035	0.030	0.243
	Automated devices vs K4	0.112	0.072	0.118
	Automated devices vs K5	0.152	0.067	0.024

The outcome variable was blood pressure tracking correlation coefficients. The models were controlled for sex, baseline age, length of follow-up, publication year, and race/population for variables 1 & 2. Model was adjusted for sex, baseline age, length of follow-up, number of blood pressure measurements per visit, publication year, and race/population for variable 3. β regression coefficient. SE standard error.

Section Summary - Measurement protocols and variations in BP measurement
Measurement protocols can influence BP measurement. Mercury sphygmomanometers appear to have low systematic error when compared to other BP (indirect measurement) instruments. Automated BP instruments report better tracking for diastolic BP compared to mercury manometer. Diastolic BP defined by K4 (DBP4) tracks better than levels defined by K5 (DBP5).

4.E. *Predicting future blood pressure levels from childhood measurements.*

Researchers working in the area of BP have attempted various statistical models to predict future BP from data collected during childhood and adolescence. Most of these attempts at predicting future BP were done using models that included baseline measurements of BP, height, weight and adiposity as well as changes in height, weight or adiposity levels from baseline to follow up.[38, 59-61]

The BOGALUSA Heart Study Cohort

The Bogalusa heart study cohort examined the predictors of follow up systolic and diastolic BP.[61] This longitudinal cohort was constructed from two cross-sectional surveys approximately 15 years apart which covered 1505 subjects aged 5 to 14 years at initial study. At the time of follow up these subjects were 20 to 31 years of age. Variables that were used for predicting follow up BP included age, race, and sex, baseline systolic & diastolic BP, weight, height and body mass index (BMI), and changes from baseline to follow-up in weight, height, and BMI. The BP levels reported were the mean of six replicate readings taken by two randomly assigned trained nurses using mercury sphygmomanometer.

Of the childhood characteristics, baseline BP level was most predictive of the follow-up level, followed by change in BMI.[61] Each mm Hg of systolic BP difference at baseline predicted a change in 0.46 mm Hg at follow up. For diastolic BP the corresponding figure was 0.33 mm Hg. Together baseline BP and change in body mass index from baseline to follow up predicted the major share of variation of follow up BP (systolic and diastolic) explained by the model. The details of the predictors for follow up systolic and diastolic blood pressure are presented in **Tables 11 & 12** below.

Table. 11. Predictors of follow up systolic blood pressure – BOGALUSA Cohort[61]

Independent Variable#	Regression Coefficients	P Value
Baseline SBP (mm Hg)	0.46 (0.42)	<0.001
Change in BMI (kg/m 2)	0.33 (0.14)	<0.01
Change in Weight (kg)	0.08 (0.14)	<0.001
Black v white	2.17 (0.10)	<0.001
Male v female	4.73 (0.22)	<0.001

Values are regression coefficients (standardized regression coefficients).
 # independent variables included age, race, and sex, baseline systolic blood pressure (SBP), weight (Wt), height and body mass index (BMI), and changes from baseline to follow-up in weight, height, and body mass index.

Table. 12. Predictors of follow up diastolic blood pressure BOGALUSA Cohort[61]

Independent Variable#	Regression Coefficients	P Value
Baseline DBP (mm Hg)	0.33 (0.31)	<0.001
Change in BMI (kg/m 2)	0.39 (0.21)	<0.001
Baseline height (cm)	0.06 (0.13)	<0.001
Male v female	3.66 (0.21)	<0.001

Values are regression coefficients (standardized regression coefficients).
#independent variables included age, race, and sex, baseline diastolic blood pressure (DBP), weight (Wt), height (Ht), and body mass index (BMI), as well as changes from baseline to follow-up in weight, height, and body mass index.

The BOSTON Study Cohort

Cook et al reported a similar study from Boston where childhood BP values were used to predict adult blood pressure values.[60] Children aged 8-12 years were examined at school, for four weeks, at one-week intervals in 1978. The cohort was seen for three consecutive years. At each of the four visits each year, a series of three seated BP measurements were taken with a random-zero sphygmomanometer.

The children in this cohort were followed up in 1989-1990, when they were aged 18-26 years. To evaluate whether measures of height, weight, or body mass index (BMI) would add to the predictive model in addition to baseline BP levels, the authors used multiple combinations of these variables to identify the best predictor combination. They reported three multivariate linear regression models using baseline values and five multivariate linear regression models using change (from baseline to follow up levels) of these variables separately for systolic and diastolic blood pressure. All models had baseline BP as the common variable.[60]

The details of the models are presented as **Tables 13 & 14** below.

TABLE.13. Prediction of young adult blood pressure from baseline variables – BOSTON Cohort[60]

	Model			
Systolic blood pressure		**Beta**	**SE**	**P value**
1	SBP at 10 years	0.418	0.064	<0.0001
	Height	0.018	0.191	0.924
2	SBP at 10 years	0.455	0.073	<0.0001
	Weight	- 0.024	0.026	0.362
3	SBP at 10 years	0.453	0.071	<0.0001
	BMI	- 0.134	0.147	0.362
Diastolic blood pressure				
1	DBP at 10 years	0.222	0.057	0.0001
	Height	0.095	0.184	0.607
2	DBP at 10 years	0.221	0.059	0.0002
	Weight	0.009	0.023	0.708
3	DBP at 10 years	0.222	0.059	0.0001
	BMI	0.043	0.134	0.748

SBP systolic blood pressure, DBP diastolic blood pressure (both in mm Hg) BMI - body mass index (Kg per m^2). Height in inches, weight in pounds.

TABLE. 14. Prediction of young adult blood pressure from baseline variables. BOSTON Cohort[60]

Model				
Systolic blood pressure		**Beta**	**SE**	**P value**
1	SBP at 10 years	0.410	0.063	<0.0001
	Change in height	0.947	0.260	0.0003
2	SBP at 10 years	0.454	0.072	<0.0001
	Change in weight	0.073	0.024	0.002
3	SBP at 10 years	0.447	0.072	<0.0001
	Change in BMI	0.257	0.167	0.124
4	SBP at 10 years	0.444	0.071	<0.0001
	Change in height	0.729	0.283	0.010
	Change in weight	0.046	0.025	0.071
5	SBP at 10 years	0.434	0.071	<0.0001
	Change in height	0.951	0.259	0.0002
	Change in BMI	0.269	0.163	0.098
Diastolic blood pressure				
1	DBP at 10 years	0.220	0.058	0.0001
	Change in height	0.130	0.281	0.642
2	DBP at 10 years	0.217	0.059	0.0003
	Change in weight	0.031	0.025	0.202
3	DBP at 10 years	0.221	0.059	0.0002
	Change in BMI	0.232	0.171	0.175
4	DBP at 10 years	0.217	0.059	0.0003
	Change in height	-0.004	0.308	0.989
	Change in weight	0.031	0.027	0.248
5	DBP at 10 years	0.216	0.059	0.0003
	Change in height	0.149	0.282	0.597
	Change in BMI	0.228	0.172	0.185

SBP systolic blood pressure, DBP diastolic blood pressure (both in mm Hg) BMI - body mass index (Kg per m2) Height in inches, weight in pounds.

The authors concluded that while childhood height and weight were predictive of future BP when used in models without baseline BP, both were no longer predictive when BP was in the model, and the coefficients for weight and body mass index reversed direction in the presence of baseline BP. They also suggested that additional measures of adult height and weight, or projected changes from childhood could potentially improve prediction models of BP.[60]

Section Summary - Predicting future BP levels from childhood measurements
The findings from the two cohort studies (BOGALUSA & BOSTON) suggests that precise estimates of baseline BP and baseline anthropometric indices will help to predict future BP values with reasonable accuracy. ***Both cohorts suggest that baseline BP is the best predictor of future BP.***

4.F. *Childhood blood pressure and its relation to future cardiovascular risk*

In addition to predicting adult BP, childhood BP is also known to predict other factors that are related to cardiovascular risk in later life. Adulthood studies that looked at childhood BP and its relationship with future cardiovascular risk have also examined the relationship of childhood body mass index with future cardiovascular risk. Surprisingly, these studies have provided conflicting results.[38, 62-65]

Data from Bogalusa study showed that childhood body mass index but not systolic BP predicted adult clustering of body mass index, fasting insulin, BP, cholesterol/ high density lipoprotein (HDL) ratio and triglyceride/HDL ratio.[64] The NHLBI Growth and Health Study showed that body mass index but not systolic BP in girls at age 10 years predicted development of the metabolic syndrome at age 19 years.[65] On the contrary, in The Fels Longitudinal Study, body mass index did not predict the metabolic syndrome independent of childhood systolic BP.[63]

A recently published longitudinal study examined the independent influence of body mass index and systolic BP or diastolic BP at mean age 13 years on factors associated with cardiovascular risk like systolic BP, body mass index, cholesterol, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides in adulthood.[66] In addition, the study also measured insulin resistance (fasting insulin, fasting glucose and insulin clamp measure of insulin resistance) among the subjects. All the adult measures were done at mean age 24 years. The authors reported that in a multivariable model (baseline and change from baseline for body mass index and systolic BP), baseline systolic BP predicted adult systolic BP, cholesterol, triglycerides and fasting glucose; baseline body mass index predicted all the adult risk factors except systolic BP and fasting glucose; change in body mass index predicted systolic BP, total cholesterol, HDL-C, LDL-C, triglycerides, insulin sensitivity, fasting

insulin and fasting glucose; whereas change in systolic BP predicted only body mass index.[66] The details are presented in **Table 15** below.

Table. 15. Prediction of future cardiovascular risk from childhood systolic blood pressure and body mass index[66]

	beta coefficient +/- SE			
	Baseline SBP	**Baseline BMI**	**DSBP**	**DBMI**
SBP	0.45 ± 0.05*	0.04±0.12	N/A	0.45 ± 0.12*
BMI	0.03±0.03	1.23 ± 0.05*	0.1 ± 0.02*	N/A
Cholesterol	0.43± 0.20*	0.83 ± 0.38*	0.16±0.18	1.96 ± 0.39*
HDL-C	-0.08±0.07	-0.56 ± 0.13*	0.05±0.06	-0.52 ± 0.13*
LDL-C	0.29±0.18	0.83 ± 0.34*	-0.04±0.16	1.61 ± 0.35*
Triglycerides	0.01± 0.003*	0.03 ± 0.01*	0.004±0.003	0.04 ± 0.01*
Insulin	-0.04±0.08	0.78 ± 0.15*	0.09±0.07	0.73 ± 0.15*
Glucose	0.19 ± 0.07*	0.11±0.14	0.12±0.06	0.77± 0.14*
***M*lbm**	-0.03±0.03	-0.12 ± 0.05*	-0.01±0.02	-0.37 ± 0.06*

*Models adjusted for age, sex and race. DBMI, BMI at follow-up minus BMI at baseline; BMI body mass index. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DSBP, change in systolic blood pressure from baseline to follow up; Mlbm, insulin sensitivity. * P<0.05. SE standard error.*

The details of the multi variable model using diastolic BP and body mass index from the study are presented in **Table 16** below.

Table. 16. Prediction of future cardiovascular risk from childhood diastolic blood pressure and body mass index[66]

	beta coefficient +/- SE			
	Baseline DBP	**Baseline BMI**	**DDBP**	**DBMI**
DBP	0.32 ± 0.04*	0.14±0.13	N/A	0.31 ± 0.13*
BMI	0.07 ± 0.02*	1.22 ± 0.05*	0.05 ± 0.02*	N/A
Cholesterol	0.39 ± 0.17*	1.0 ± 0.37*	0.28±0.16	1.84 ± 0.38*
HDL-C	-0.01±0.06	-0.59 ± 0.13*	-0.09±0.05	-0.46 ± 0.13*
LDL-C	0.16±0.15	0.96 ± 0.34*	0.19±0.14	1.49 ± 0.35*
Triglycerides	0.01 ± 0.003*	0.03 ± 0.01*	0.01± 0*	0.04 ± 0.01*
Insulin	0.15 ± 0.07*	0.75 ± 0.14*	0.09±0.06	0.73 ± 0.15*
Glucose	0.09±0.06	0.20±0.14	0.01±0.06	0.79±0.14*
***M*lbm**	-0.04±0.02	-0.13 ± 0.05*	-0.02±0.02	-0.36 ± 0.06*

*Models adjusted for age, sex, and race. DBMI, BMI at follow-up minus BMI at baseline; DBP, diastolic blood pressure; DDBP, change in diastolic blood pressure from baseline to follow up; HDLC, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Mlbm, insulin sensitivity. * P<0.05.SE standard error.*

Even though the overall results from the study suggests that baseline BP and body mass index measured during childhood and adolescence can predict future cardiovascular risk, we cannot be sure about this conclusion. The independent role played by baseline BP and body mass index in these models can only be explored by constructing models where BP is adjusted for body mass index and vice versa which was not done in the above mentioned study.[66]

Section Summary - Childhood BP and its relation to future cardiovascular risk
Childhood BP levels appear to predict future cardiovascular risk similar to BMI during childhood. The overall heterogeneity across the above mentioned studies and methodological issues prevents us from concluding which of these simple measurements (body mass index or BP) during childhood or adolescence best predicts future cardiovascular risk in adulthood.

4.G. *Secular trends in adiposity and its association with blood pressure trends in children*

Globally adiposity levels among all age groups are showing an increasing trend. The scenario is no different in the pediatric age group.[67] A recently published study examined global trends in childhood obesity using data from school-age populations in 25 countries and pre-school populations in 42 countries.[67] The study included three countries from Asia (Thailand, Japan and Taiwan). Using these data, the authors estimated the global prevalence of overweight and obesity among school-age children for 2006 and likely prevalence levels for 2010. The authors concluded that prevalence of childhood overweight has increased in almost all countries (except school age populations in Russia and Poland) for which data were available.[67]

Given the association of adiposity to high BP, it is natural to expect a similar (increasing) secular trend for high BP among children based on these observations. Logically, an increasing trend in adiposity can also influence the pattern of BP distribution among children due to association of adiposity and blood pressure in children. The Bogalusa heart study looked at the two trends in the same population across time to see if the secular trend of adiposity and blood pressure in children were linked to each other.[68]

The Bogalusa heart study included 7 cross-sectional studies of school children (1973–1994). Data from 11 478 children (24092 examinations) were used for analysis. The table below presents the changes in mean values of body mass index and BP along with the changes in prevalence of high BP (BP more than 90th percentile of reference).[68]

Table.17 .Trends in the distribution of adiposity and blood pressure during childhood[68]

	Boys					Girls				
	Age	**BMI**	**SBP**	**DBP**	**HBP%**	**Age**	**BMI**	**SBP**	**DBP**	**HBP%**
1974	10.3	17.5	100	62	5.8	10.3	17.8	100	63	8.1
1977	11.6	18.7	102	62	4.7	11.5	18.7	101	62	7.3
1979	11.3	18.6	104	63	7.2	11.1	18.5	103	64	10.0
1982	11.2	18.7	104	63	5.4	11.1	18.8	103	64	10.8
1985	11.3	19.0	104	60	5.0	11.5	19.5	103	63	8.7
1988	11.0	19.1	101	59	3.5	11.0	19.6	100	60	5.0
1993	11.4	20.0	103	62	4.1	11.4	20.2	102	62	5.8

All values presented are mean except for HBP. Age in years, BMI in Kg/m^2, SBP and DBP in mm Hg and HBP in prevalence percentage. BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, HBP high blood pressure (BP more than 90th p of Fourth task force recommendations for pediatric blood pressure).

While the mean body mass index levels showed a steady increase in successive surveys, no such increase was seen in either mean BP levels or prevalence of high BP. On the contrary, there was a steady decrease in the prevalence of high BP across various levels of adiposity.

Section Summary - Secular trends in adiposity and its association with BP trends

Available data indicates that the long term time trends in body mass index and those in BP (both during childhood and adolescence) are discordant. The currently prevailing increasing trends in childhood and adolescent obesity are not associated with a similar increasing trend for mean BP as well as high BP prevalence.

4.H. *High blood pressure in South Asian children*

Several researchers have examined the role of ethnicity in the distribution of BP among children, adolescents and young adults.[21, 69, 70] South Asian ethnicity was associated with higher BP in children as reported by Jafar et al.[21] This study from Pakistan reported higher body mass-adjusted BP levels for South Asian children than white (Caucasian) children in the United States.

The study collected data from 5641 South Asian children 5 to 14 years old included in the nationally representative National Health Survey of Pakistan (NHSP) (1990 –1994) and on 4756 Caucasian children 5 to 14 years old included in Third National Health and Nutrition Examination Survey (NHANES III) (1988 –1994). Blood pressure was measured twice in the seated position with a mercury sphygmomanometer. The study reported that Caucasian children had lower mean systolic and diastolic BP compared to south Asian children in spite of the fact that the former were taller and heavier than the latter.[21]

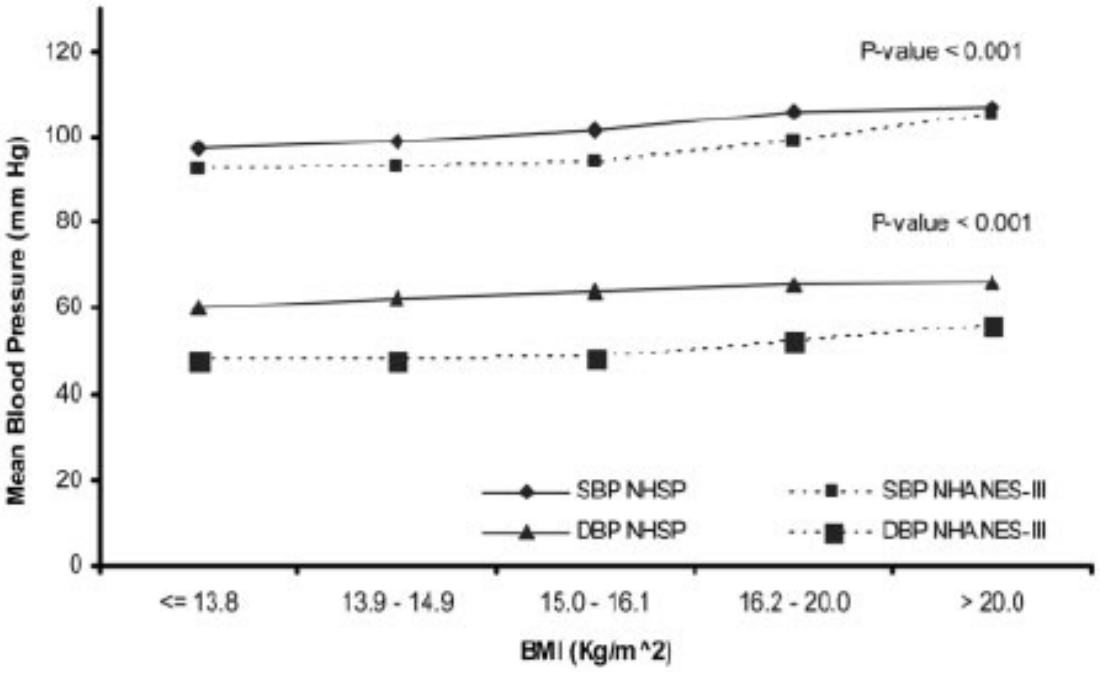
The details of the comparison done in the study are presented as **Table 18** below.

TABLE.18. Comparison of children in South Asia and children in the United States.[21]

	Boys			Girls		
Characteristics						
	NHSP	**NHANES**		**NHSP**	**NHANES**	
	(n= 2974)	**(n=2343)**		**(n=2667)**	**(n=2413)**	
			P Value			**P Value**
Age	**9.0 (2.8)**	**8.6 (2.7)**	**< 0.001**	**9.0 (2.8)**	**8.7 (2.8)**	**< 0.001**
Height, cm	**127.7 (17.9)**	**135.1 (18.4)**	**< 0.001**	**126.7 (17.4)**	**134.6 (18.3)**	**< 0.001**
Weight, kg	**24.9 (9.1)**	**28.5 (17.4)**	**< 0.001**	**25.2 (9.7)**	**28.9 (17.8)**	**< 0.001**
BMI, kg/m2	**15.2 (4.3)**	**18.3 (3.9)**	**< 0.001**	**15.3 (4.3)**	**18.5 (4.1)**	**< 0.001**
SBP, mm Hg	**101 (10)**	**99 (11)**	**< 0.001**	**99 (12)**	**97 (10)**	**< 0.001**
DBP, mm Hg	**65 (9)**	**52 (13)**	**< 0.001**	**60 (10)**	**52 (12)**	**< 0.001**

NHSP - National Health Survey of Pakistan, 1990–1994; NHANES III, - Third National Health and Nutrition Examination Survey, 1988–1994. BMI body mass index, SBP systolic blood pressure, DBP –diastolic blood pressure.

As per the study, the mean body mass index-adjusted systolic BP levels (SD) were 100 (11) versus 99 (11) mm Hg (*P*< 0.001), and diastolic BP levels (SD) were 63 (10) versus 52 (12) mm Hg (*P*<0.001) in NHSP versus NHANES III, respectively. The differences in systolic BP (100 mm Hg vs 99 mm Hg) between the comparison groups appear minimal even though the differences in mean levels were statistically significant. The differences in diastolic BP (63 mm Hg vs 52 mm Hg) appear to be much higher in magnitude.[21] The body mass index specific mean blood pressure levels across selected body mass index cutoffs are presented as **Figure 6** below.



BMI cutoffs are based on 25th, 50th, 75th, and 95th percentiles of values in NHSP data. P values are based on ANOVA among children in NHSP vs NHANES III surveys. BMI body mass index

Figure.6. Body mass index-specific systolic and diastolic blood pressure levels in children in South Asia (Pakistan) vs children in the United States.[21]

Even though the study by Jafar et al reported higher body mass index adjusted systolic and diastolic BP levels for children from Pakistan compared to those from US, we cannot confirm this conclusion. The comparability of the two datasets (NHSP and NHANES III) is unknown with available evidence from the published paper.[21] Studies that identified higher BP levels for Indian children compared to children from other ethnic groups were reported by researchers from India as well.[71, 72] These comparisons too have methodological issues.

Section summary – High blood pressure in South Asian children
Current evidence suggesting higher BP levels for South Asian children compared to other ethnic groups has methodological issues. The existence of a real difference in age, gender and height adjusted BP levels for children and adolescents from South Asia compared to others can only be confirmed by a direct comparison study that used the same methodology in various ethnically different study populations including South Asian children. Such studies are currently not available.

Summary of review of literature

Theme	Summary
Age related changes in BP from childhood to adolescence	Pooled data analysis of 79 studies shows similarity in summary values for BP across age groups. The overall trend of age related progression of BP appears similar across studies.
Childhood growth trajectories and BP status in later life	Childhood growth factors and their trajectories can influence BP in later life. The most dominant factor appears to be recent weight gain.
Tracking of BP in children and adolescents.	BP exhibits tracking from childhood and adolescence to adulthood. Repeated measures, short periods of follow up and higher age at baseline increases tracking correlations. Systolic BP tracks better than diastolic BP.
Measurement protocols and variations in BP measurement	Measurement protocols can influence conclusions of longitudinal follow up studies in childhood BP. There needs to be consensus on the ideal approach to BP measurement in children.
Predicting future BP levels from childhood measurements.	Future BP levels can be predicted from BP and anthropometric measures recorded during childhood. Baseline BP appears to predict follow up BP better, followed by change in BMI.
Childhood BP and its relation to future cardiovascular risk	Childhood BP correlates with future cardiovascular risk profile in adulthood.
Secular trends in childhood adiposity and childhood BP	The relationship between secular trends in adiposity and those in BP during childhood and adolescence is discordant.
High blood pressure in South Asian children	Evidence is currently lacking to support the conclusion that South Asian children have higher BP compared to children from other ethnically different regions.

5. Rationale for the study

Most previous work in this area has spanned several decades during which both measurement of blood pressure in children and its categorization have undergone important changes. It is unknown whether the current more rigorous approaches to measuring BP in children would impact the observed association shown in previous studies.

Most studies that reported the relationship of childhood growth trajectories to child, adolescent or adult BP have done so based on infancy or early childhood growth trajectories. There appears to be a shortage of studies linking late childhood growth and adolescent growth trajectories to future BP levels. None of the studies had paired BP values which would have provided more information. Prediction models described by Cook et al (1997) and Bao et al (1995) clearly show that baseline BP predicts most of the variations in future blood pressure.[60, 61] Examining the impact of growth patterns on blood pressure needs paired BP values for better understanding of the complex interaction of growth and blood pressure evolution.

The three pooled analysis described in the review of literature are predominantly represented by studies from Americas and Europe.[6, 19, 58] The pooled analysis of Brotons et al has very few studies from South Asia.[19] In addition, none of the longitudinal studies reported in the two meta-analyses by Chen et al were from South Asian children.[6, 58] These observations suggest that there is a paucity of information from longitudinal studies of pediatric BP in South Asian countries.

A study that provides data on age related changes in BP and growth from childhood to adolescence can contribute to bridging some of the gaps identified in the review of literature. Such data will add to the current information of child to adult longitudinal studies and provide better understanding of the dynamic process of BP evolution with age.

The area of age related progression of BP needs to have studies that are methodologically sound and relevant to current clinical and public health approaches. Paired values of BP and anthropometric variables collected using currently recommended, standardized measurement instruments can add to quality of data and minimize measurement related errors.

This study is from South Asia where there is the need for data describing most of the themes discussed in the review.

6. Study hypothesis and objectives

6.A Study hypothesis:

Systolic and diastolic blood pressure exhibits age related changes from childhood to adolescence.

6.B Study objectives

Primary objective: *To investigate the changes in systolic and diastolic blood pressure among South Asian children aged 6 to 11 years who were followed for a period of six years.*

Secondary objectives:

(a) To examine the influence of changes in body mass index on age related changes in systolic and diastolic blood pressure from childhood to adolescence.

(b) To examine the influence of gender on age related changes in systolic and diastolic blood pressure from childhood to adolescence.

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METHODS

1. Study Methods

1.A Study design

The current study is a prospective cohort study with a follow up period of 6 years (2005-2011).

1.B Study population.

One urban school from the district of Ernakulam, province of Kerala, India was selected for this study. The school was selected as there was an ongoing annual school health program. Two school health screenings were conducted as part of the study. The first screening was done in 2005 and covered 1560 children (age group 6-16 years). The second screening was done in 2011 and covered 1654 children (age group 6-17 years). Combined, the two screenings provided a cohort of 703 children who were 5 to 11 years of age in 2005 and followed up for a period of six years (age range of 11 to 17 years in 2011).

1.C Study measurements

Blood pressure and anthropometric data (weight and height) were collected from study participants during the two screening years for the study (1560 children in 2005 and 1654 children in 2011). Consent was obtained from parents for younger children (below 12 years) and from parents and children for older children (above 12 years) to enroll them to the study. Verbal assent was obtained from all children prior to study measurements.

All measurements included in the study were conducted in the school campus during school hours. The research team made visits to the selected school on school days. Children were invited to come to the medical examination room in batches based on grade divisions. All children were requested to rest for ten minutes in the examination room. During this time, one team member explained the process of all measurements and clarified the students' queries. Children who reported having medical problems (fever, infections, or short term medications) on

the day of screening were asked to report for another examination at a subsequent time once the medical problem was over.

All three measurements (height, weight and blood pressure) were measured during single visits for both survey periods. Height and weight was measured only once per visit. Height was measured by a wall mounted stadiometer (Seca) to the nearest centimeter. Standing weight was measured by an electronic weighing balance (Seca) to nearest 0.5 kilogram.

The mid-arm circumference (MAC) was determined by having the subject stand erect with feet together and the right arm flexed 90^0 at the elbow with the palm facing up. A non-stretchable measuring tape was used to measure MAC. On the right scapula, the observer located the upper most edge of the posterior border of the acromion process where the zero end of the measuring tape was fixed. From this landmark, the tape was extended down to the posterior surface of the arm to the tip of the olecranon process. The observer made a horizontal mark with a cosmetic pencil at the midpoint at the posterior aspect of the arm and measured the arm circumference at this point.

During both surveys, blood pressure was measured using a mercury sphygmomanometer as per methodology recommended by The Fourth Report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents.[1]Blood Pressure was measured in sitting position with the subject's right hand resting on the examining table. Chairs of adequate height were made available to adjust seating as per the child's height. The arm and back were supported, and the children were requested to keep their legs uncrossed with both feet flat on the floor. The subject's arms were bared and unrestricted by clothing. The palm of the hand was turned up and kept relaxed on the examining table. The cubital fossa of the right hand was positioned and supported at heart level. The bell of the stethoscope was

placed over the brachial artery pulse, proximal and medial to the cubital fossa and below the bottom edge of the cuff (that is about 2 cm above the cubital fossa). Cuffs having a bladder width that is approximately 40% of the arm circumference midway between the olecranon and the acromion were used. Tables for cuff selection and various sizes of cuffs were available with all observers. The appropriate cuffs were selected using the table provided by the fourth task force report. The criteria for cuff selection based on mid arm circumference (MAC) is presented below as **Table 1**.

Table.1 Recommended dimensions for blood pressure cuff bladders[1]

Age Range	Width (cm)	Length (cm)	MAC (cm)
Newborn	**4**	**8**	**10**
Infant	**6**	**12**	**15**
Child	**9**	**18**	**22**
Small Adult	**10**	**24**	**26**
Adult	**13**	**30**	**34**
Large Adult	**16**	**38**	**44**
Thigh	**20**	**42**	**52**

MAC – mid arm circumference, cm centimeters

The blood pressure measurements were taken at the right arm for consistency. The appropriate blood pressure cuff was applied using predetermined arm circumference ranges as per the table presented above. The radial pulse was palpated and the cuff inflated (while noting the pressure column) till the radial pulse disappeared. The cuff was inflated to 30 mm Hg above the disappearance of the radial pulse (peak inflation level). The cuff was then slowly deflated at the rate of 2 mm Hg per second. The pressure readings on the mercury sphygmomanometer that matched the appearance and disappearance of the Korotkoff sounds were identified and recorded.

Two readings of blood pressures of each child were taken at an interval of 2 minutes by one single observer using the same instrument. At the end of the first measurement, the cuff was deflated and removed from the child's arm. The cuff was reapplied two minutes later after ensuring that the mercury column in the sphygmomanometer steadied at zero level. A second reading was taken as per the same methodology. If the observer was unable to get the readings, the child was asked to rest for another ten minutes and examined by another observer who repeated the same methodology explained earlier. Average of two readings of the blood pressure of each child was taken for analysis. All measurements were made by study personnel (three nurses & two physician assistants) who were trained as per standard training modules available for blood pressure and anthropometric measurements in children. All measurements were made under the supervision of a pediatrician who ensured adherence of the observers to the procedure protocols.

2. Statistical analysis plan

2.A Primary analysis

Children for this study will be divided into 7 age categories; 5, 6, 7, 8, 9, 10 &11 years. Assessment for heterogeneity of mean subject specific blood pressure changes across age group (mentioned above) will be done using the Analysis of Variance (ANOVA). If heterogeneity is detected, then in each age group, the mean subject specific blood pressure changes will be evaluated using the paired t-test at 0.05 alpha level (adjusting for multiple comparisons). If not, to increase the study power, all age categories will be combined together and a single paired t-test will be performed.

Rationale of the Paired t-test

The paired t-test is used when there are two repeated measurements coming from a normally distributed continuous outcome. So it fits well with the design of this study. In addition to this, there are additional advantages. By using the paired t-test each person is used as his/her own control thereby controlling for both known and unknown underlying individual differences. Compared with the independent t-test, the paired t-test will tend to have a smaller random error (in most situations the correlation will tend to be positive) and hence more power to detect the change and less number needed to achieve the same power. Further, the number needed for the paired t-test will always be smaller. This has economic implications in studies like school health screenings which are usually conducted in the community setting (limited time and minimum resources). Such a method will reduce the required number of subjects for an accurate measurement of the difference if any of the study variable/s for any given study and will substantially reduce the cost and time required to collect data in the field. Graphs from previously published study of blood pressure from the same population showed that the

distribution of blood pressure among children was normal, thereby validating the normality assumption needed for the test.

Prediction models for blood pressure in the proposed study

If blood pressure changes are statistically significant, a general linear regression model with subject specific blood pressure change as a dependent variable and sex, weight, height and body mass index as independent variables will be fitted to assess the association of these factors with an outcome. Scatter plots of blood pressure change versus each of the factors will be drawn to determine an appropriate functional form of the regression model. The non-parametric curves will be fitted to aid with the determination of this functional form.

The outcome variables (dependent variables) planned for the modeling will be final blood pressure and change in blood pressure (δ BP). If our non parametric curves are consistent with the linear model as suggested in literature, **s**eparate linear regression models will be used for both outcomes.[2,3] The predictor variables will be baseline values (blood pressure, weight, height, body mass index) as well as change in variables from baseline to follow up (weight, height and body mass index).

2.B Secondary analysis

The role of change in body mass index on age related progression of blood pressure will be analyzed by looking at mean blood pressure change (δ BP) across categories of body mass index change (δ BMI). The relationship of δ BP with δ BMI will be examined by non parametric curve fitting using LOWESS (Locally weighted scatter plot smoothening) method. The sample will then be divided into categories based on δ BMI as per the results of LOWESS curve fitting. The mean δ BP across various categories of δ BMI will be compared by ANCOVA (Analysis of Covariance). ANCOVA evaluates whether population means of a dependent variable (δ SBP and δ DBP in this case) are equal across levels of a categorical independent variable (δ BMI in

this case), while controlling for extraneous factors that are not of primary interest (age, baseline BMI & gender in this case).

The role of gender in age related progression of blood pressure and their interaction will also be assessed by ANCOVA. The means of δ SBP and δ DBP across each age group will be compared using ANCOVA (adjusting for δ BMI and baseline BP) and a p for interaction will be reported.

2.C Power of the study

The total number of subjects available for the study was 703. The standard deviation (SD) for systolic and diastolic blood pressure reported for the same population was in the range of 8-11 mm Hg.[3] The correlations (mean) reported by Chen et al in a recent meta-analysis were 0.38 for systolic and 0.28 for diastolic blood pressure.[4] With these inputs and 5% type I error, this study will have 80% or 90% power to detect the following change in systolic and diastolic blood pressure values for a number of scenarios shown in **Table 2** below.

Table. 2 Effect sizes for blood pressure that can be detected for possible combination of parameters (n= 703)

SD of BP measures *	Correlation coefficient between BP measures	Min. detectable BP difference (mm Hg)	
		80% power	90% power
11	0.5	1.2	1.3
11	0.4	1.3	1.5
11	0.3	1.4	1.6
10	0.5	1.1	1.2
10	0.4	1.2	1.3
10	0.3	1.3	1.5
9	0.5	0.95	1.1
9	0.4	1.0	1.2
9	0.3	1.2	1.3
8	0.5	0.85	0.98
8	0.4	0.93	1.1
8	0.3	1.0	1.2

** assuming first and second BP measures have the same SD. SD- standard deviation, calculated at 80% power. BP–blood pressure.*

The calculated effect size is in the range of 0.85 to 1.6 mm Hg. With a conservative trend estimate of 1 mm Hg per year for systolic and 0.5 mm Hg per year for diastolic blood pressure, we expect a minimum of 6 mm Hg increase for mean systolic blood pressure and 3 mm Hg increase for mean diastolic blood pressure at the end of the study period (6 years). The sample size of 703 appears to be sufficient in this scenario.

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RESULTS

1. Participant characteristics

A total of 703 children (359 boys, 344 girls) were included in the study. The age range was 5 to 11 years at baseline. At the time of follow up, the ages ranged from 11 to 17 years. The mean follow up period was 6.01 years. The descriptive data from the initial baseline survey and the final follow up survey are presented below as **Tables 1A & I B.**

Table 1.A. Participant characteristics at baseline by age group

Age	n	Boys (%)	Weight* (Kg)	Height* (cms)	BMI* (Kg/m^2)	SBP* (mm Hg)	DBP* (mm Hg)
5	28	14 (50)	20.2(3.2)	114.7 (5.2)	15.3 (2.1)	93.9 (8.9)	59.5 (9.0)
6	135	77 (57)	21.2(3.6)	118.7 (5.5)	15.0 (1.7)	95.3 (8.0)	60.5 (7.2)
7	123	66 (53.7)	24.7(5.3)	124.3 (5.6)	15.9 (2.6)	96.4 (7.5)	62.6 (8.8)
8	132	63 (47.7)	26.7(6.1)	129.2 (6.7)	15.9 (2.7)	94.3 (11.3)	60.4 (8.9)
9	107	57 (53.3)	30.9(6.4)	135.7 (5.6)	16.7 (2.7)	100.6 (8.1)	63.4 (7.7)
10	102	47 (46.1)	33.9(7.5)	140.9 (6.3)	17.0 (2.9)	103.4 (8.5)	66.7 (7.4)
11	75	35 (46.7)	38.2(9.5)	146.2 (7.1)	17.7 (3.3)	103.4 (8.3)	68.8 (7.0)

*BMI body mass index (Kg/m^2), SBP systolic blood pressure (mm Hg), DBP diastolic blood pressure (mm Hg). Age in completed years at baseline, weight in kilograms, height in centimeters. One child was not included in the tabulated data as she was 12 years of age at baseline. * values are mean (SD) except when indicated.*

Table 1.B. Participant characteristics at follow up by age group

Age	n	Boys (%)	Weight* (Kg)	Height* (cms)	BMI* (Kg/m^2)	SBP* (mm Hg)	DBP* (mm Hg)
11	**23**	**11(47.8)**	**42.7(9.7)**	**149.2(9.4)**	**19.1 (3.3)**	**106.2 (9.2)**	**69.4 (8.7)**
12	**139**	**81(58.3)**	**42.9(9.9)**	**152.5(8.1)**	**18.3 (3.4)**	**107.7 (9.2)**	**70.5 (8.9)**
13	**127**	**65(51.2)**	**47.0(10.4)**	**156.2(7.7)**	**19.2 (3.7)**	**110.0 (8.7)**	**72.2 (8.1)**
14	**127**	**62(48.8)**	**50.5(12.0)**	**160.3(8.6)**	**19.6 (4.0)**	**109.8 (8.7)**	**72.2 (7.9)**
15	**108**	**58(53.7)**	**53.8(10.5)**	**165.0(8.2)**	**19.7 (3.2)**	**113.0 (8.7)**	**73.5 (8.4)**
16	**99**	**45(45.5)**	**56.8(12.3)**	**166.1(9.6)**	**20.6 (3.8)**	**116.8 (10.7)**	**78.0 (7.8)**
17	**80**	**37(46.3)**	**56.6(11.9)**	**164.4(10.0)**	**20.9 (4.2)**	**116.7 (9.7)**	**77.6 (8.4)**

*BMI body mass index (Kg/m^2), SBP systolic blood pressure (mm Hg), DBP diastolic blood pressure (mm Hg). Age in completed years at follow up, weight in kilograms, height in centimeters. * values are mean (SD) except when indicated.*

Overall, the mean increments in weight (Kg), height (cm) and body mass index (Kg/m^2) were 22.2 Kg (SD 7.5), 29.4 cm (SD 8.1) and 3.4 Kg/m^2 (SD 2.3) during the follow up period. Mean systolic BP increased from 98.1 mm Hg to 111.6 mm Hg (difference 13.4, $p < 0.001$) and mean diastolic BP from 63.1 mm Hg to 73.4 mm Hg (difference 10.3 mm Hg, $p < 0.001$) during the same period. Boys showed higher increments compared to girls for weight (23.6 vs 20.8 Kg, $p < 0.001$), height (32.2 vs 26.4 cm, $p<0.001$), systolic BP (15.0 vs 11.8 mm Hg, $p < 0.001$) and diastolic BP (10.5 vs 10.1 mm Hg, p 0.525) while girls showed more increment for body mass index (3.6 vs 3.2 Kg/m^2, p 0.005).

There were no major differences in baseline parameters between children who were absent for the follow up survey vs those who were present for the follow up survey. The details are presented as **Table 2** below.

Table 2. Comparison of baseline characteristics among children without follow up and children with completed follow up

Variable	No follow up	Completed follow up
n	47 (6.3%)	703 (93.7%)
Boys	20 (42.6%)	359 (51.1%)
Age*, years	9.0 (1.9)	8.6 (1.7)
Weight*, Kg	28.5 (8.1)	28.0 (8.3)
Height*, cms	132.1 (10.1)	130.3 (11.3)
BMI*, Kg/m^2	16.1 (2.9)	16.2 (2.7)
SBP*, mm Hg	100.4 (14.4)	98.1 (9.5)
DBP*, mm Hg	64.8 (11.1)	63.0 (8.5)

*BMI body mass index (Kg/m^2), SBP systolic blood pressure (mm Hg), DBP diastolic blood pressure (mm Hg). Age in completed years at baseline, weight in kilograms, height in centimeters. * values are mean (SD) except when indicated.*

The mean change in the variables (from baseline to follow up) across various age groups is presented as **Table 3** below.

Table 3. Change in Participant characteristics from baseline to follow up by age group

Age group	n	Weight* (Kg)	Height* (cms)	BMI* (Kg/m^2)	SBP* (mm Hg)	DBP* (mm Hg)
5-11	28	21.7 (7.8)	33.9 (5.2)	3.5 (2.7)	11.7 (7.7)	9.4 (7.6)
6-12	135	21.6 (7.1)	34.1 (4.9)	3.2 (2.2)	12.7 (8.2)	10.3 (8.4)
7-13	123	22.8 (7.1)	32.1 (4.5)	3.5 (2.4)	13.6 (7.6)	9.7 (7.9)
8-14	132	23.5 (7.6)	30.9 (5.9)	3.6 (2.3)	15.5 (10.3)	11.6 (9.6)
9-15	107	22.9 (6.4)	29.2 (6.4)	3.0 (1.8)	12.2 (7.6)	10.1 (7.5)
10-16	102	23.0 (8.0)	25.0 (8.4)	3.7 (2.4)	13.6 (8.5)	11.2 (7.8)
11-17	75	18.8 (8.5)	18.5 (9.8)	3.3 (2.6)	13.1 (9.4)	8.7 (7.3)

*BMI body mass index (Kg/m2), SBP systolic blood pressure (mm Hg), DBP diastolic blood pressure (mm Hg). Age group from baseline to follow up in completed years, weight in kilograms, and height in centimeters. * values are mean (SD).*

2. Change in blood pressure from baseline to follow up

The changes in systolic and diastolic BP from baseline to follow up were examined at the level of individual age groups. All age groups demonstrated significant increases in mean values for both systolic and diastolic BP from baseline to follow up ($p < 0.0001$ for all age groups). The change in BP during the follow up period ranged from 11.7 mm Hg to 15.6 mm Hg for systolic and 8.6 mm Hg to 11.6 mm Hg for diastolic blood pressure across age groups. Children who were 8 years at baseline (14 years at follow up) showed the maximum increase in both systolic and diastolic BP at follow up (15.5 mm Hg and 11.6 mm Hg respectively).

The details are presented in **Tables 4 & 5** below.

Table.4. Change in systolic blood pressure from baseline to follow up by age group

Age	n	Mean SBP at baseline(mm Hg)	Mean SBP at Follow up (mm Hg)	Mean difference (99% CI)	P value*
5	**28**	**93.9**	**105.6**	**11.7 (7.6, 15.7)**	**< 0.0001**
6	**135**	**95.3**	**108.0**	**12.7 (10.8, 14.5)**	**< 0.0001**
7	**123**	**96.4**	**110.0**	**13.6 (11.8, 15.4)**	**< 0.0001**
8	**132**	**94.3**	**109.8**	**15.5 (13.2, 17.9)**	**< 0.0001**
9	**107**	**100.6**	**112.8**	**12.2 (10.3, 14.2)**	**< 0.0001**
10	**102**	**103.4**	**117.0**	**13.6 (11.4, 15.8)**	**< 0.0001**
11	**75**	**103.4**	**116.5**	**13.1 (10.3, 16.0)**	**< 0.0001**

SBP systolic blood pressure (mm Hg). P value from Paired t test at α 0.01. Age in completed years at baseline. CI – confidence interval

Table.5. Change in diastolic blood pressure from baseline to follow up by age group

Age	n	Mean DBP at baseline (mm Hg)	Mean DBP at Follow up (mm Hg)	Mean difference (99% CI)	P value *
5	**28**	**59.5**	**68.9**	**9.4 (5.4,13.4)**	**< 0.0001**
6	**135**	**60.5**	**70.8**	**10.3 (8.4, 12.2)**	**< 0.0001**
7	**123**	**62.6**	**72.3**	**9.7 (7.8, 11.5)**	**< 0.0001**
8	**132**	**60.4**	**71.9**	**11.6 (9.4, 13.8)**	**< 0.0001**
9	**107**	**63.4**	**73.5**	**10.1 (8.2, 12.0)**	**< 0.0001**
10	**102**	**66.7**	**77.9**	**11.2 (9.2, 13.3)**	**< 0.0001**
11	**75**	**68.8**	**77.5**	**8.6 (6.4, 10.9)**	**< 0.0001**

DBP diastolic blood pressure (mm Hg) Age in completed years at baseline. P value from Paired t test at α 0.01. CI confidence interval

Overall, there was good correlation between baseline vs follow up values of weight (0.79), height (0.72) and body mass index (0.80). The correlation coefficients (Pearson's correlation coefficients) for BP was lower than those for weight, height and body mass index. Overall, systolic BP (0.60) had better correlation than diastolic BP (0.55).

The correlations for systolic and diastolic BP according to age group at baseline are presented as **Table 6** below.

Table 6. Correlations* of baseline vs follow up blood pressure by age group

Age at baseline	n	Systolic BP		Diastolic BP	
		R*	P value	*R**	P value
5	28	0.61	0.001	0.61	0.001
6	135	0.56	< 0.0001	0.47	< 0.0001
7	123	0.58	< 0.0001	0.58	< 0.0001
8	132	0.50	< 0.0001	0.36	< 0.0001
9	107	0.60	< 0.0001	0.58	< 0.0001
10	102	0.61	< 0.0001	0.46	< 0.0001
11	75	0.47	< 0.0001	0.55	< 0.0001

** Pearson's correlation. Mean follow up period is 6.01 years. Age at baseline in completed years.*

The change in BP with age was assessed by examining two outcomes i.e., follow up BP and change in BP separately for systolic and diastolic BP. The relationship between the two outcomes and the other variables (weight, height, body mass index, age, gender, change in weight, change in height and change in body mass index) were examined by correlation matrix. The correlations are presented graphically in **Appendix as Figures 1-4.**

3. Prediction models for blood pressure from baseline variables

The relationship between the dependent variables (follow up BP & change in BP) and the independent (predictor) variables was examined separately using linear regression models based on the input from the correlation matrix presented above as well as from previously published studies. Weight and height were not used in the regression models to avoid colinearity with body mass index.

3. A Models for *follow up* systolic blood pressure

The details of the univariable and multivariable regression models for follow up systolic BP are presented in **Table 7 A** and **Table 7 B** below.

Table 7. A Linear regression modeling of independent predictors of *follow up* systolic blood pressure

Variable	Univariable		Multivariable	
	Beta coefficient	95%CI	Beta coefficient	95%CI
Baseline SBP	0.621	0.560, 0.682	0.543	0.478, 0.608
Change in BMI	0.641	0.327, 0.955	0.592	0.349, 0.835
Baseline BMI	1.137	0.884, 1.390	0.273	0.052, 0.494
Age	1.951	1.549, 2.353	0.825	0.472, 1.178
Gender	-2.633	- 4.078, -1.188	-3.379	-4.49, -2.268

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values. CI confidence interval

Table 7. B Linear regression modeling of independent predictors of *follow up* systolic blood pressure

Variable	Multivariable	
	Standardised Beta coefficient	*P* value
Baseline SBP	0.526	< 0.001
Change in BMI	0.138	< 0.001
Baseline BMI	0.076	0.016
Age	0.143	< 0.001
Gender	-0.172	< 0.001

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the univariate model for predicting follow up systolic BP, baseline systolic BP, baseline body mass index, change in body mass index, age at baseline and gender were independently associated with follow up BP. In the multivariate model each mm Hg difference in systolic BP at baseline predicted a change of 0.5 mm Hg of follow up systolic BP when adjusted for other variables in the model. A change in body mass index (from baseline to follow up) appeared to predict more change (0.6 mm Hg per unit change of delta BMI) in follow up systolic BP compared to baseline body mass index (0.3 mm Hg per unit change of baseline BMI). When adjusted for other variables, each one year difference in age at baseline predicted a change of 0.8 mm Hg of systolic BP at follow up. Boys showed higher follow up systolic BP (3.4 mm Hg) compared to girls when adjusted for other variables in the multivariate model.

3. B Models for *follow up* diastolic blood pressure

The details of the univariable and multivariable regression models for follow up diastolic BP are presented in **Table 8 A and Table 8 B** below.

Table 8.A Linear regression modeling of independent predictors of *follow up* diastolic blood pressure

Variable	Univariable		Multivariable	
	beta	95%CI	beta	95%CI
Baseline DBP	0.562	0.499, 0.625	0.520	0.453, 0.587
Change in BMI	0.303	0.023, 0.583	0.236	-0.001, 0.473
Baseline BMI	0.563	0.330, 0.796	-0.010	-0.222, 0.202
Age	1.456	1.093, 1.819	0.658	0.317, 0.999
Gender	0.042	-1.25, 1.334	-0.436	-1.514, 0.642

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.CI confidence intervals

Table 8. B Linear regression modeling of independent predictors of *follow up* diastolic blood pressure

Variable	Multivariable	
	Standardised Beta coefficient	***P* value**
Baseline DBP	**0.507**	**< 0.001**
Change in BMI	**0.062**	**0.051**
Baseline BMI	**-0.003**	**0.924**
Age	**0.129**	**< 0.001**
Gender	**-0.025**	**0.428**

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the univariable model for predicting follow up diastolic BP, baseline diastolic BP, baseline body mass index, change in body mass index and age at baseline were independently associated with follow up BP. Gender showed no statistically significant association with follow up diastolic BP in both univariate and multivariate models.

In the multivariable model each mm Hg difference in diastolic BP at baseline predicted a change of 0.5 mm Hg of follow up diastolic BP when adjusted for other variables in the model. When adjusted for other variables, each one year difference in age at baseline predicted a change of 0.7 mm Hg of diastolic BP at follow up. Change in body mass index (delta BMI) and baseline body mass index failed to predict any statistically significant change in follow up diastolic BP in the multivariable model.

3. C Models for *change* in systolic blood pressure

The details of the univariable and multivariable regression models for change in systolic BP (baseline to follow up) are presented in **Table 9 A and Table 9 B** below.

Table 9. A Linear regression modeling of independent predictors of *change* in systolic blood pressure

Variable	Univariable		Multivariable	
	beta	95%CI	beta	95%CI
Baseline SBP	-0.379	-0.44, -0.318	-0.457	-0.522, -0.392
Change in BMI	0.489	0.213, 0.765	0.592	0.349, 0.835
Baseline BMI	-0.048	-0.283, 0.187	0.273	0.052, 0.494
Age	0.028	-0.348, 0.404	0.825	0.472, 1.178
Gender	-3.180	-4.440, -1.920	-3.379	-4.49, -2.268

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m2) Age in years. Change in body mass index is the difference between baseline and follow up values.

Table 9. B Linear regression modeling of independent predictors of *change* in systolic blood pressure

Variable	Multivariable	
	Standardised Beta coefficient	*P* value
Baseline SBP	-0.503	< 0.001
Change in BMI	0.157	< 0.001
Baseline BMI	0.086	0.016
Age	0.163	< 0.001
Gender	-0.195	< 0.001

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the univariable model for predicting δ SBP, baseline systolic BP, δ BMI and gender were associated with follow up BP. In the multivariable model each mm Hg increase in systolic BP at baseline predicted a decrease of 0.5 mm Hg in δ SBP and vice versa when adjusted for other variables in the model. The beta coefficients of other variables in the multivariable model (baseline BMI, δ BMI, age and gender) were same as that of multivariable model for follow up systolic BP.

3.D. Models for *change* in diastolic blood pressure

The details of the univariable and multivariable regression models for change in diastolic BP (baseline to follow up) are presented in **Table 10 A and Table 10 B** below.

Table 10. A Linear regression modeling of independent predictors of *change* in diastolic blood pressure

Variable	Univariable		Multivariable	
	beta	95%CI	beta	95%CI
Baseline DBP	-0.438	-0.501, -0.375	-0.480	-0.547, -0.413
Change in BMI	0.163	-0.102, 0.428	0.236	-0.001, 0.473
Baseline BMI	-0.253	-0.474, -0.031	-0.010	-0.222, 0.202
Age	-0.098	-0.453, 0.257	0.658	0.317, 0.999
Gender	-0.393	-1.606, 0.820	-0.436	-1.514, 0.642

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m2) Age in years. Change in body mass index is the difference between baseline and follow up values.

Table 10. B Linear regression modeling of independent predictors of *change* in diastolic blood pressure

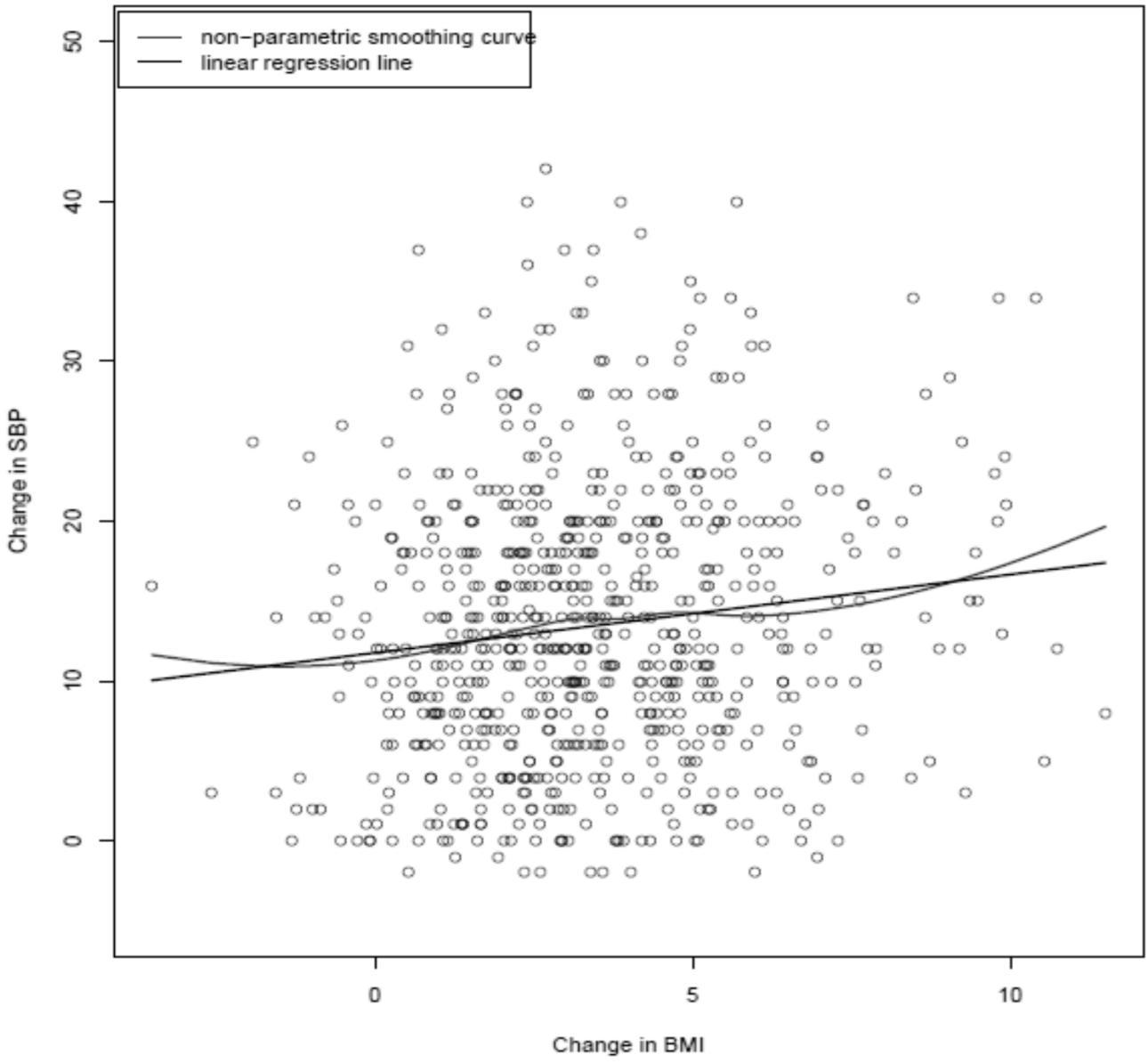
Variable	Multivariable	
	Standardised Beta coefficient	***P* value**
Baseline DBP	**-0.499**	**< 0.001**
Change in BMI	**0.066**	**0.051**
Baseline BMI	**-0.003**	**0.924**
Age	**0.137**	**< 0.001**
Gender	**-0.027**	**0.428**

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the univariable model for predicting δ DBP, both baseline diastolic BP and baseline body mass index showed a statistically significant association with δ DBP. δ BMI as well as gender showed no statistically significant association with δ DBP in both univariable and multivariable models. In the multivariable model, each mm Hg increase in diastolic BP at baseline predicted a decrease of 0.5 mm Hg of δ DBP and vice versa when adjusted for other variables in the model. The beta coefficients of other variables in the multivariable model were same as that of multivariable model for follow up diastolic BP.

4. Change in blood pressure vs change in body mass index

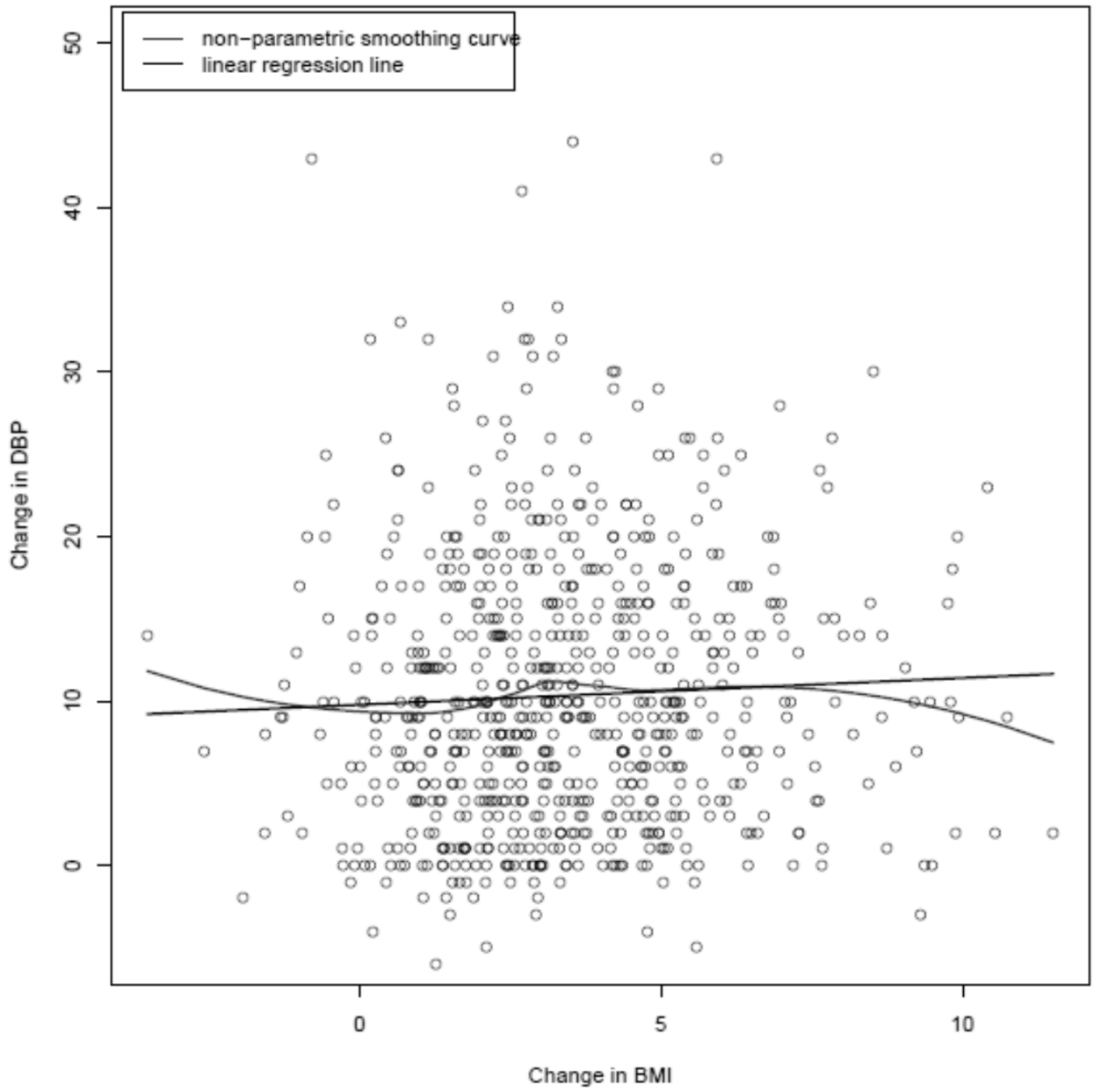
The association of change in body mass index (δ BMI) and age related change of BP (δ SBP and δ DBP) was studied in detail by using a non parametric curve fitting method (LOWESS). The details of this analysis are presented as **Figure 1**and **Figure 2** below.



SBP Systolic blood pressure (mm Hg), BMI body mass index (Kg/m^2).

R^2=0.17, P = 0.001

Figure. 1. Change in systolic blood pressure from baseline to follow up as a function of change in body mass index



DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m^2).

R^2 = 0.002, P = 0.228

Figure. 2. Change in diastolic blood pressure from baseline to follow up as a function of change in body mass index

The analysis suggested that the relationship between δ BMI and δ BP (both systolic and diastolic) were linear. The data was then divided into seven categories based on δ BMI.

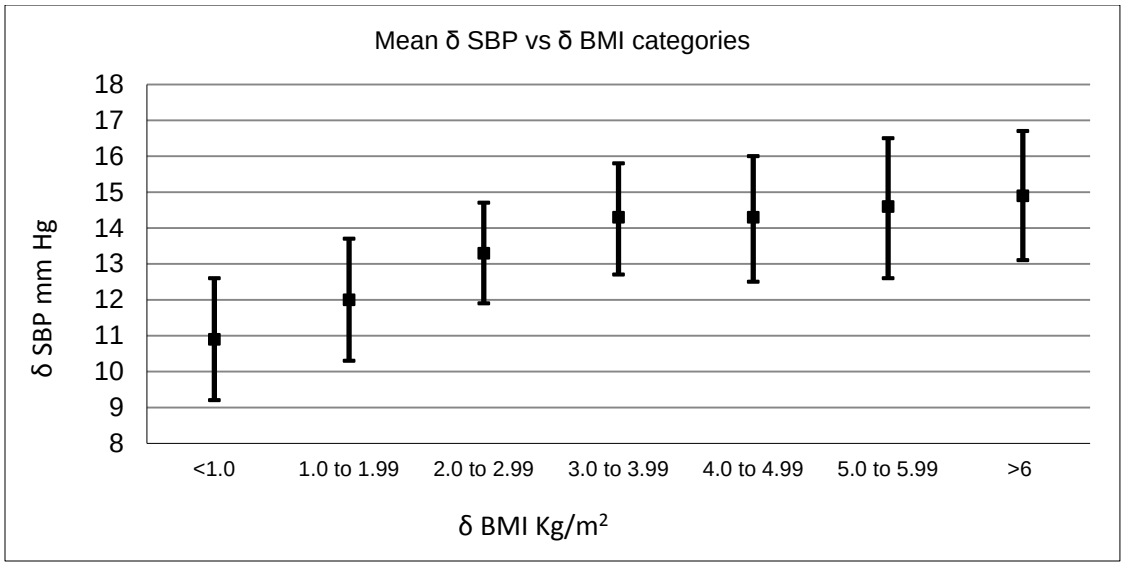
The mean systolic and diastolic BP (adjusted for baseline age, body mass index at baseline and gender) for each δ BMI category is presented in **Table 11** below.

Table. 11 Change in systolic and diastolic blood pressure from baseline to follow up by change in body mass index

BMI change Kg/m^2	Change in systolic BP, mm Hg		Change in diastolic BP, mm Hg	
	Mean	95% CI	Mean	95% CI
<1.0	10.9	9.2, 12.6	9.9	8.2, 11.6
1.0 to 1.99	12.0	10.3, 13.7	8.5	6.9, 10.1
2.0 to 2.99	13.3	11.9, 14.7	10.3	8.9, 11.6
3.0 to 3.99	14.3	12.7, 15.8	11.3	9.8, 12.8
4.0 to 4.99	14.3	12.5, 16.0	10.4	8.7, 12.0
5.0 to 5.99	14.6	12.6, 16.5	11.2	9.3, 13.1
≥ 6	14.9	13.1, 16.7	10.9	9.1, 12.6

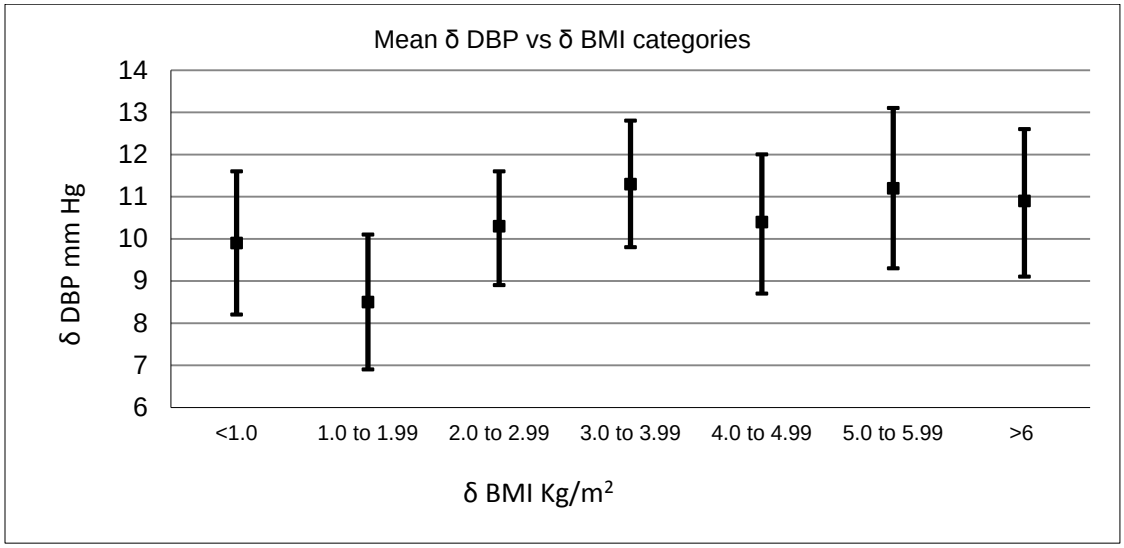
Adjusted for age at baseline, BMI at baseline and sex. Values for BMI change are units of BMI change from baseline to follow up. BMI body mass index(Kgm^2). CI confidence interval.

The change in δ BP across categories of δ BMI showed a linear trend for systolic BP (p for liner trend <0.0001) which was absent for diastolic BP (p for linear trend 0.71). The details are presented as **Figure 3** and **Figure 4** below.



δ SBP – change in systolic blood pressure (mm Hg) , δ BMI change in body mass index (Kg/m2) Error bars are predicted means of delta SBP with 95% confidence intervals (Adjusted for age at baseline, BMI at baseline and sex). P for linear trend <0.0001.

Figure. 3. Change in systolic blood pressure from baseline to follow up by change in body mass index

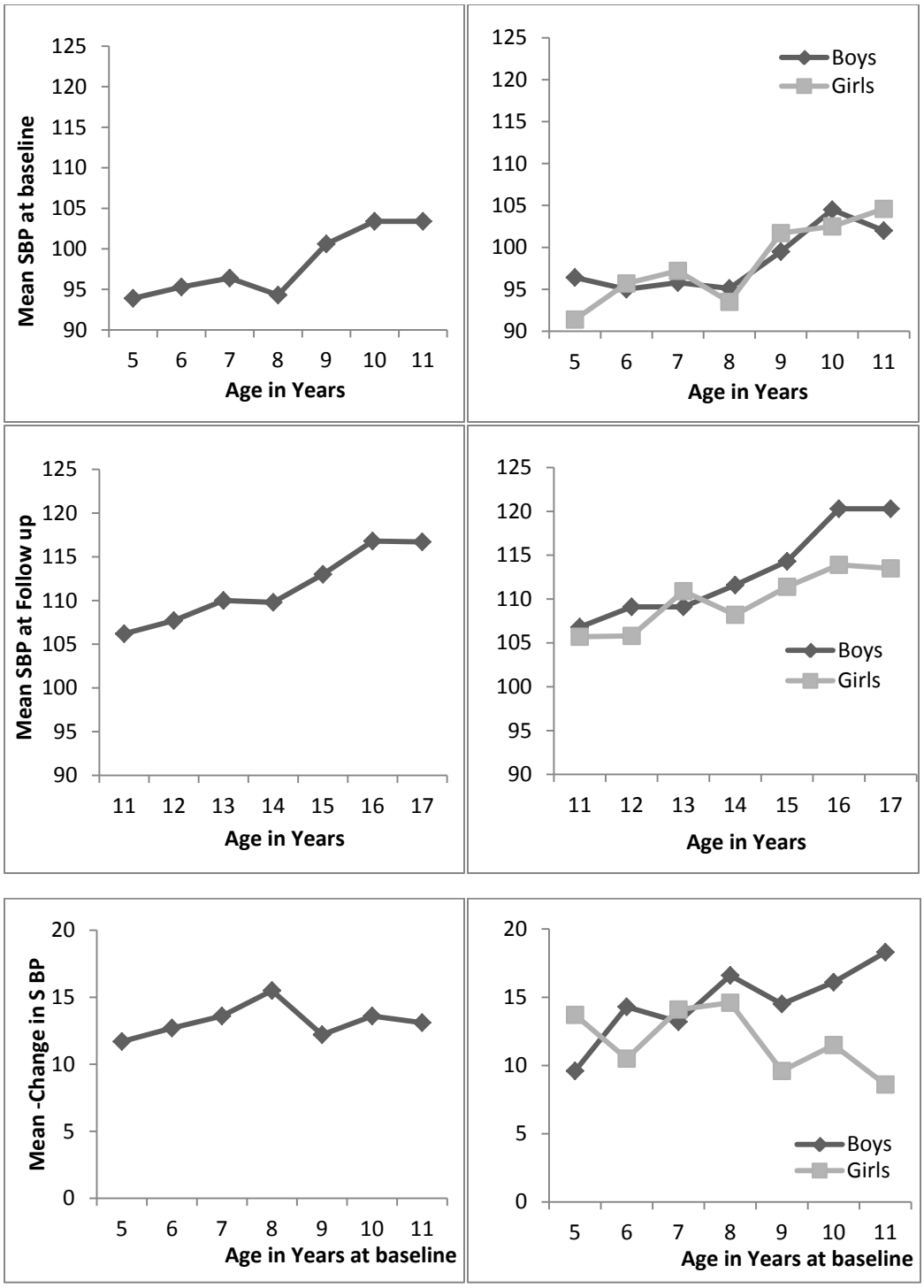


δ DBP – change in diastolic blood pressure (mm Hg) , δ BMI change in body mass index (Kg/m2). Error bars are predicted means of delta DBP with 95% confidence intervals (Adjusted for age at baseline, BMI at baseline and sex). P for linear trend 0.071.

Figure. 4. Change in diastolic blood pressure from baseline to follow up by change in body mass index

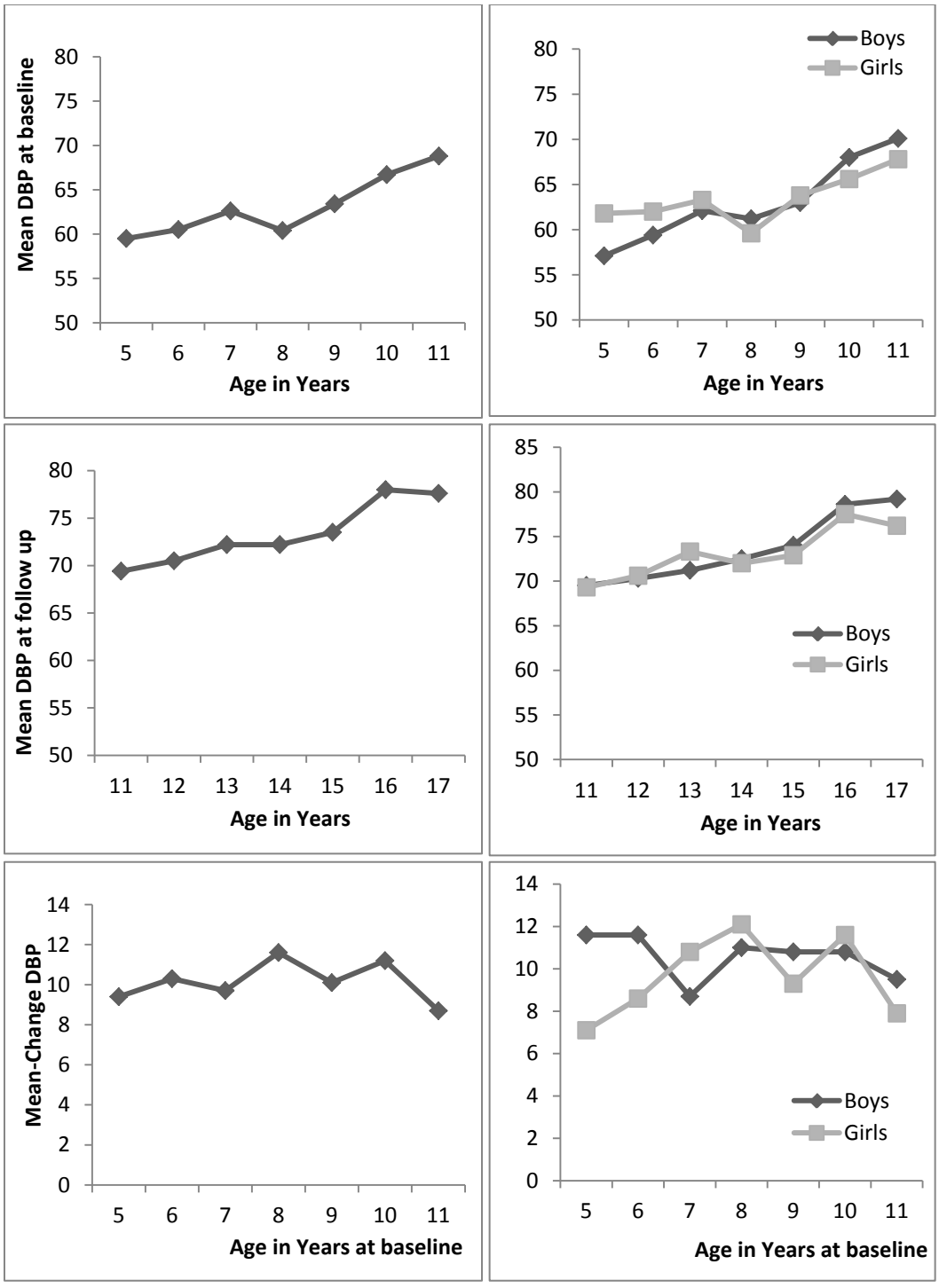
5. Role of sex in age related change in blood pressure

The role of sex in age related change of BP was examined by plotting the progression of BP separately for boys and girls. At baseline survey boys and girls appeared to have similar levels for systolic and diastolic BP. At follow up, there appeared to be a different pattern of systolic BP distribution for girls compared to boys. The change in BP also showed a different pattern in girls compared to boys in the case of systolic BP. The difference in systolic BP levels between boys and girls appeared by the age of 13 years. The details are presented as **Figures 5** and **6**.



SBP, Systolic blood pressure (mm Hg)

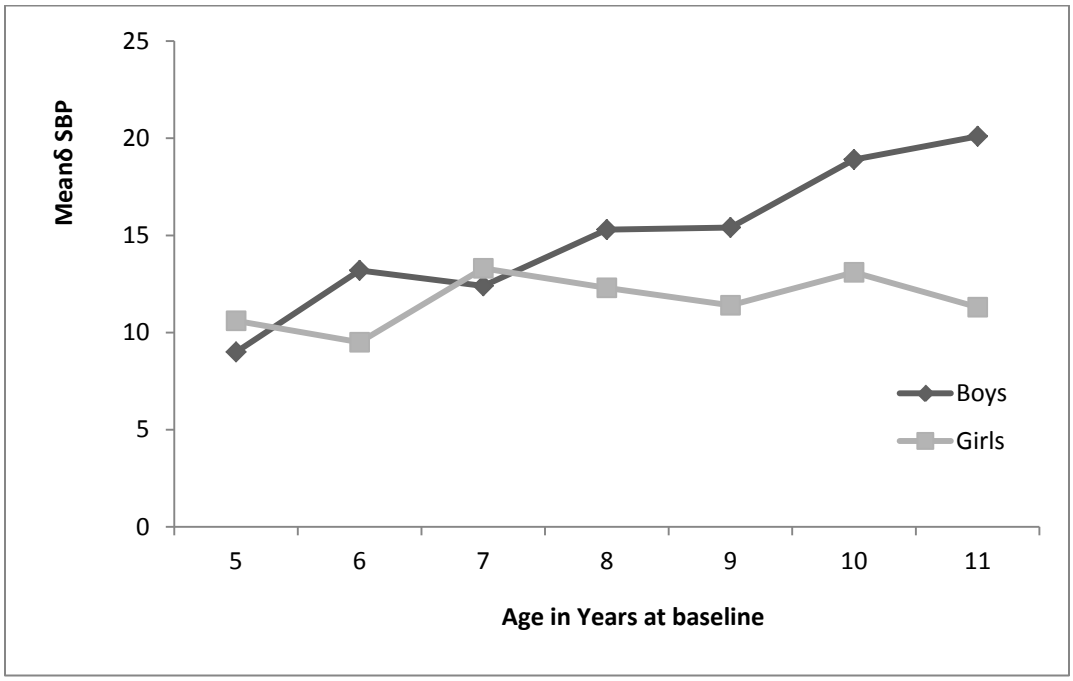
Figure.5 Age related level and change in systolic blood pressure by age and sex



DBP diastolic blood pressure (mm Hg).

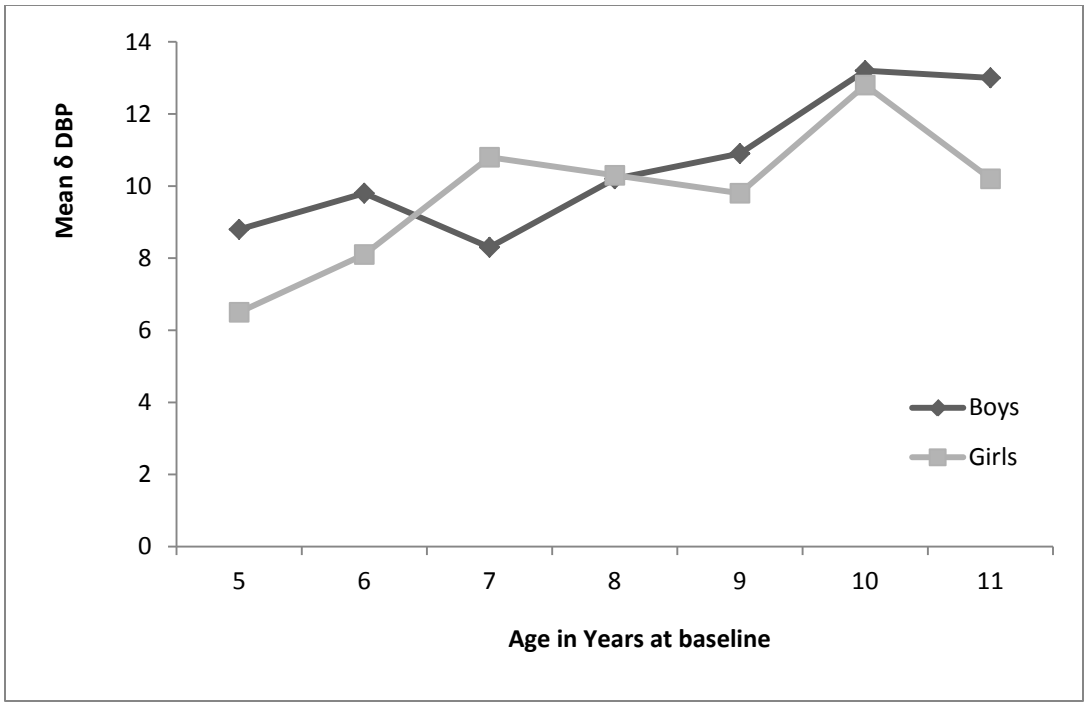
Figure.6 Age related level and change in diastolic blood pressure by age and sex

The difference in δ SBP between boys and girls was examined in detail by repeating the comparison for δ SBP after adjusting for other variables (δ BMI and baseline BP). The adjusted comparisons are presented as **Figure 7** and **Figure 8**.



**Marginal means of δ SBP are derived from ANCOVA (Adjusted for change in body mass index & baseline systolic blood pressure.) δ SBP - change in systolic blood pressure from baseline to follow up (mm Hg).*

Figure 7. Change in systolic blood pressure from baseline to follow up by age and sex*



**Marginal means of δ DBP are derived from ANCOVA (Adjusted for change in body mass index & baseline diastolic blood pressure.) δ DBP - change in diastolic blood pressure from baseline to follow up (mm Hg).*

Figure 8. Change in diastolic blood pressure from baseline to follow up by age and sex*

There was an interaction between sex and age for δ SBP (p for interaction < 0.0001) which was absent for δ DBP (p for interaction = 0.163). In view of the interaction of sex with age in the case of δ SBP even after controlling for baseline systolic BP and δ BMI, additional analysis was done to examine whether change in height (δ height) during adolescence influenced the sex based difference in δ SBP.

The comparison of the two models with and without additional adjustment for δ height is presented as **Figure 9** below.

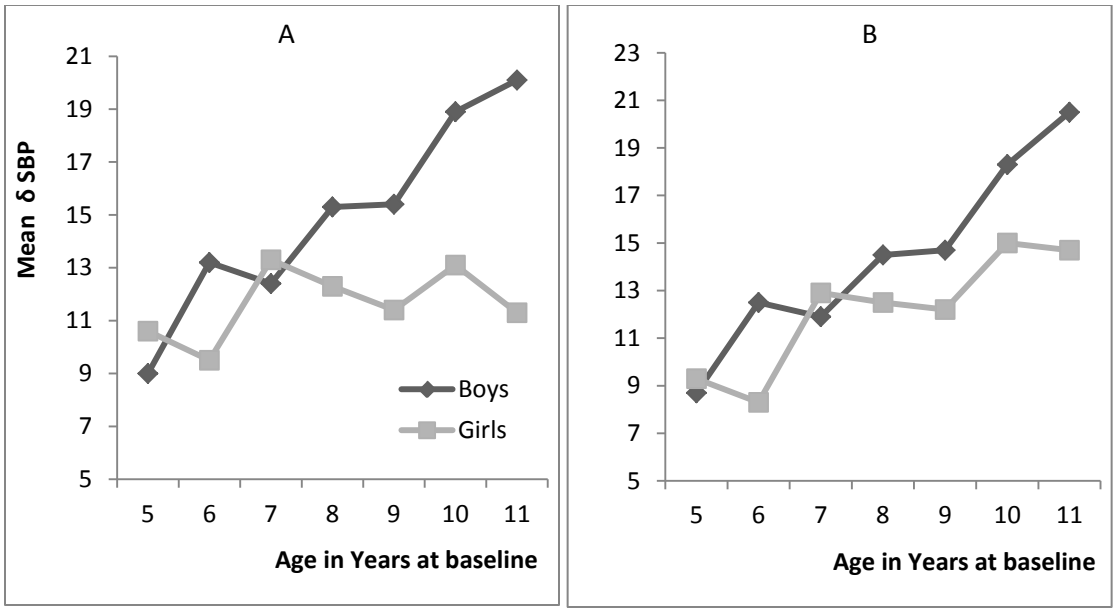


Figure 9 A is sex specific difference in δ systolic blood pressure across age groups adjusted for baseline systolic blood pressure & change in body mass index. Figure 9 B is sex specific difference in δ systolic blood pressure with additional adjustment for change in height. δSBP – change in systolic blood pressure (mm Hg) from baseline to follow up.

Figure 9. Change in systolic blood pressure by age and sex - adjusting for usual covariates plus change in height.

6. Sex specific regression models for change in blood pressure

Separate regression models were plotted for boys and girls to examine whether the magnitude of association of the predictor variables (baseline BMI, change in BMI and age) differed by sex. This approach was taken due to the presence of interaction between age and sex for change in blood pressure. The details of the sex specific regression models for change in systolic BP are presented as **Table 12 A** & **Table 12 B** below.

Table 12. A Linear regression modeling of independent predictors of *change* in systolic blood pressure – stratified by sex

Model	Boys		Girls	
	beta coefficient	95%CI	beta coefficient	95%CI
Intercept	42.261		46.222	
Baseline SBP	-0.477	-0.565, -0.388	-0.431	-0.521, -0.341
Change in BMI	0.665	0.330, 1.000	0.467	0.120, 0.814
Baseline BMI	0.220	-0.072, 0.512	0.418	0.087, 0.749
Age	1.621	1.135, 2.107	-0.049	-0.551, 0.453

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m2) Age in years. Change in body mass index is the difference between baseline and follow up values.CI confidence interval

Table 12. B Linear regression modeling of independent predictors of *change* in Systolic blood pressure – stratified by sex

Variable	Multivariable			
	Boys		Girls	
	Standardised Beta coefficient	*P* value	*Standardised Beta coefficient*	*P value*
Baseline SBP	**-0.519**	**< 0.001**	**-0.498**	**< 0.001**
Change in BMI	**0.176**	**< 0.001**	**0.127**	**0.009**
Baseline BMI	**0.071**	**0.142**	**0.132**	**0.014**
Age	**0.313**	**< 0.001**	**-0.010**	**0.850**

SBP systolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the sex specific multivariable models for change in systolic BP, each mm Hg change in baseline systolic BP predicted similar change among boys and girls for δ SBP (decrease of 0.5 mm Hg in boys vs 0.4 mm Hg in girls per mm Hg increase of baseline SBP). Change in body mass index at baseline predicted greater change in δ SBP for boys compared to girls. (0.7 mm Hg for boys vs 0.5 mm Hg for girls per unit change in δ BMI). Body mass index at baseline showed a statistically significant association with δ SBP only for girls (0.4 mm Hg per unit change in BMI at baseline) in the multivariable model. Age at baseline showed a statistically significant association with δ SBP only for boys in the multivariable model. An increase of one year for baseline age among boys predicted an increase of 1.6 mm Hg for δ SBP.

The details of the sex specific regression models for change in diastolic BP are presented as **Table 13 A** & **Table 13 B** below.

Table 13. A Linear regression modeling of independent predictors of *change* in diastolic blood pressure – stratified by sex

Model	**Boys**		**Girls**	
	beta	**95%CI**	**beta**	**95%CI**
Intercept	32.431		36.743	
Baseline DBP	-0.452	-0.548, -0.356	-0.515	-0.609, -0.421
Change in BMI	0.380	0.037, 0.723	0.080	-0.243, 0.403
Baseline BMI	-0.028	-0.32, 0.264	0.031	-0.277, 0.339
Age	0.678	0.164, 1.192	0.595	0.138, 1.052

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m2) Age in years. Change in body mass index is the difference between baseline and follow up values.CI confidence interval

Table 13. B Linear regression modeling of independent predictors of *change* in diastolic blood pressure – stratified by sex

Variable	Multivariable			
	Boys		Girls	
	Standardised Beta coefficient	*P* value	*Standardised Beta coefficient*	*P value*
Baseline DBP	-0.476	< 0.001	-0.526	< 0.001
Change in BMI	0.103	0.031	0.023	0.627
Baseline BMI	-0.009	0.853	0.010	0.842
Age	0.134	0.010	0.131	0.011

DBP diastolic blood pressure (mm Hg), BMI body mass index (Kg/m^2) Age in years. Change in body mass index is the difference between baseline and follow up values.

In the sex specific multivariable models for change in diastolic BP, each mm Hg change in baseline diastolic BP predicted similar change among boys and girls for δ DBP (decrease of 0.5 mm Hg in boys and girls per mm Hg increase of baseline DBP and vice versa). A difference in δ BMI predicted change in δ DBP only for boys in the multivariable model. (0.4 mm Hg increase per unit increase in δ BMI and vice versa). Body mass index at baseline showed no statistically significant association with δ DBP for both boys and girls in the multivariable model. Age at baseline showed a statistically significant association with δ DBP for both boys and girls in the multivariable model. An increase of one year for baseline age predicted an increase of 0.7 mm Hg for δ DBP in boys. The corresponding figure for girls was 0.6 mm Hg in the multivariable model.

DISCUSSION

1. Overview of main findings

1.A Age related changes in blood pressure during longitudinal follow up

The longitudinal anthropometric and blood pressure data from children enrolled in the study sheds light into the intricate association of BP with growth during childhood and adolescence. During the study period, systolic BP increased by 13.4 mm Hg and diastolic BP by 10.3 mm Hg. The study results correspond to an average annual increase of 2.2 mm Hg for systolic BP (boys 2.5 mm Hg, girls 2.0 mm Hg) and 1.7 mm Hg for diastolic BP (boys 1.8 mm Hg, girls 1.7 mm Hg).

In a previously published study on Asian children (556 children, mean age at baseline 8.35, 4 year follow up), Tan et al reported average annual increases of 2.6 mm Hg for systolic BP (boys 3 mm Hg, girls 2.2 mm Hg) and 1.4 mm Hg for diastolic BP (boys 1.3 mm Hg, girls 1.6 mm Hg).[1] Overall, the results of the two studies appear to be comparable. In general, systolic BP appears to increase more with age compared to diastolic BP both in boys and girls during adolescence.

The study results confirm the observation that there is a strong correlation between BP levels from childhood to adolescence. The baseline to follow up BP correlations of the current study (follow up period of 6 years) are better than the predicted five year correlations of systolic and diastolic BP (correlation coefficients of 0.42 and 0.32 respectively for SBP & DBP) reported by a recent meta-analysis by Chen et al.[2] Better correlations for systolic BP when compared to diastolic BP could be due to true biological difference, higher chance of measurement error for diastolic BP or a combination of both.[3]

Follow up BP as well as change in BP appears to be influenced by baseline BP, change in BMI, baseline BMI, age and sex. Of these factors, baseline BP appears to exert maximum influence on follow up BP as well as change in BP. While follow up BP was higher for children with higher baseline BP, change in BP was lower for children with higher BP at baseline. Boys had higher follow up BP compared to girls.

1.B Change in body mass index and its influence on blood pressure

The study results suggest that change in BP during childhood to adolescence is influenced by change in body mass index during the same time. The change in systolic BP was more among children in higher categories of BMI change from baseline to follow up. This finding suggests that there is a dose response effect of change in BMI on change in systolic BP during childhood and adolescence. Such a dose response effect was not seen for diastolic BP across categories of BMI change.

Change in BMI appears to have more influence on systolic BP than diastolic BP. While each unit of BMI change predicted a change of 0.6 mm Hg of systolic BP at follow up, the same predicted only 0.2 mm Hg change for diastolic BP. Similar results were published earlier. In a recent study, Mirzaei et al compared the change of systolic and diastolic BP across categories of change in BMI in a longitudinal cohort of children (mean age at baseline 12 years, follow up period 3 years).[4] The authors reported that the change in Systolic BP was higher than the change in diastolic BP across various categories of children based on change in BMI.

1.C Sex specific differences in blood pressure change during adolescence

The results suggest a sex specific difference for change in systolic BP during adolescence. Overall, the mean systolic BP of boys increased more than that seen for girls

during the study period. The change in diastolic BP was similar for boys and girls. There was a statistically significant interaction between age and sex for systolic BP in the current study. A similar interaction was reported by Dasgupta et al.[5]

The sex specific differences of systolic BP during adolescence were reported earlier by other researchers.[5-9] The findings from the current study appear to be consistent with these published studies. A recently published study by Shankar et al reported that during pubertal growth period, systolic BP increased significantly in both males and females and the increase was more among males.[7] In another study by Tu et al, the change in systolic BP was more among boys than girls.[8] The authors reported that the rates of systolic BP change were accompanied by more pronounced peaks in boys compared to girls. They also reported that the peak of systolic BP increase in girls appeared earlier than in boys, even though boys were able to reach a much higher rate at a later age during adolescence. The studies by Dasgupta et al & Maximova et al both reported that systolic BP changed more during adolescence compared to diastolic BP and that changes in systolic BP were more in boys than girls during this period.[5, 6]

Overall, all studies (including the current study) mentioned above suggest that there is a sex based difference for systolic BP change during adolescence with boys exhibiting more change than girls. The mechanisms of this sex based difference of systolic BP are not well established, though most research studies implicate sex hormones.[10] During puberty, males increase production of testosterone and females increase generation of estradiol. Long term exposure to testosterone is thought to result in higher BP. The suggested mechanisms include altered renal function, impaired vascular reactivity, enhanced vasoconstriction and activation of the sympathetic nervous system as a result of higher testosterone levels in boys during pubertal period.[10-13]

In summary,

- ***Systolic and diastolic blood pressure increases from childhood to adolescence.***
- ***Systolic blood pressure appears to increase more with age compared to diastolic blood pressure during adolescence.***
- ***Baseline blood pressure appears to be the strongest predictor of follow up blood pressure among the variables studied.***
- ***Change in body mass index influences blood pressure more than baseline body mass index and the influence is more for systolic blood pressure than diastolic blood pressure.***
- ***Boys showed higher levels of change in systolic blood pressure when compared to girls confirming a sex specific difference for change in systolic blood pressure during adolescence.***
- ***Age showed an interaction with sex for change in systolic blood pressure. The sex specific difference in systolic blood pressure change was higher with increasing age. Boys exhibited higher change in systolic blood pressure than girls in older age groups compared to younger age groups.***

2. Methodological issues

2.A Selection bias

The study intended to create an all-inclusive cohort of children who were students of the selected school during both the surveys (baseline and follow up). Of the 750 children who were students in the school during the time of both the baseline and follow up surveys as per the school roster, 47 children (27 girls, 20 boys) missed the measurements in the follow up survey as they were absent on the follow up survey dates. This gives a follow up rate of 93.7%. There were no major differences between children who were present for the follow up survey vs those who were absent as per **Table 2** in the Results section. The all-inclusive nature of the cohort, low level of lost to follow up and comparability of baseline variables between those present and those who were absent for the follow up survey suggests that there is minimal selection bias in the study.

2.B Measurement error

Systematic errors in blood pressure measurement

Systematic error in measurement occurs when the measurement error, after multiple measurements, does not average out to zero. For example, this would occur if the measurements are consistently wrong in a particular direction i.e., they tend to be consistently higher or consistently lower than the true values in any given scenario. In the case of BP measurement, systematic error may be due to improper calibration of the measuring instrument, improper arm cuff size, deviations from standard measurement protocols or measuring children in unsuitable environments.

In a recent study, researchers compared the accuracy of aneroid and mercury sphygmomanometers to a recently calibrated and standardized mercury sphygmomanometer. Significantly more aneroid devices had systematic errors of > 5mmHg (19 versus 3%, P< 0.05).[14] All sphygmomanometers in the current study were standardized by specially trained service personnel every two weeks during the current study. Defective instruments were replaced with new instruments from the same manufacturer.

A recent study compared indirect measurement (by three separate cuff selection criteria) to direct measurement of BP in subjects aged 5 days to 22 years. Strict adherence to the 40% arm circumference criteria showed the least systematic error for systolic BP measurement as per the study.[15] All measurements in the current study were done using cuffs that approximated the 40% mid arm circumference criteria.[16] In addition, other reasons can also induce systematic errors in BP measurement. Using muffling of Korotkoff sounds (K4) instead of disappearance of Korotkoff sounds (K5), rapid deflation of inflated bladder (rate faster than 2 mm Hg per second) and measuring BP in children immediately following physical exertion can all result in systematically elevated BP readings. Strict adherence to the Fourth task force report protocol was enforced to avoid errors in these categories in the current study.[16]

Even in the presence of a systematic error for BP measurement, this error would have been consistent throughout in all participants for both surveys. Such an error is unlikely to affect associations between the dependent variables (follow up BP & change in BP) and their predictors in the current study.

Random errors in blood pressure measurement

Random error occurs when measurements fluctuate unpredictably around their true values and is caused by imprecise measurement tools or true biological variability, or both.[17] When BP is

measured using a sphygmomanometer, random error may arise from imprecise measurement due to rounding error (approximating the last digit of the reading to zero) or from true diurnal or day to day variation in BP.[18, 19] Due to this phenomenon, a BP reading obtained at a single occasion may differ by an unpredictable (random) amount from an individual's usual BP.[19] This random error in BP measurement can result in serious statistical issues in longitudinal studies for BP. Two such issues are regression dilution and low precision of estimates from regression models.

Regression dilution

Blood pressure studies in children have a high probability of random error. If regression models are used to interpret data with high random error, this can bias the results and conclusions of the study. The bias introduced by random measurement error will be different depending on whether the error is in a predictor variable or outcome variable.[17] Random measurement error in a predictor variable will bias the estimates of regression slope coefficients towards the null. This phenomenon where the observed regression slope (beta coefficient of the regression model) is shifted closer to horizontal (X axis) is termed regression dilution.[17] In the current study, the predictor variable that is prone for maximum random error is baseline BP. The steps taken to reduce random error of this predictor variable in the current study include use of regularly standardized mercury sphygmomanometers, paired BP measurements at each visit and strict adherence to standard methodology.[16]

Low precision of regression model estimates due to random error

Random measurement error in an outcome variable will increase the standard error of the estimates from regression models and widen the corresponding confidence intervals, making results less likely to be statistically significant.[17] The outcome variable in the current study is follow-up BP. If this variable is measured with high random error, we may end up with a

confidence interval wider enough to conclude that the association between baseline BP and follow up BP is non-significant while in reality there may be a true association.

If the outcome variable is prone to random measurement error, the solution is to increase either the sample size or the number of measurements taken per subject to account for the increased standard error of the coefficient estimate. This increase will compensate for the precision lost as a result of random error.[17] It is expected that the large sample size of the current study as well as paired measurements of the outcome variable (follow up BP) might have minimized the effect of random error in outcome variable measurement.

2.C Confounding

Confounding occurs when a factor or combination of factors other than the study factor is responsible for at least part of the association we observe for the association between the study factor and the outcome.[20] In the event of confounding, the crude data give us an inappropriate profile of the relationship between the exposure and outcome. Other factors may be exaggerating or obscuring the magnitude of the relationship studied.[20] If confounding is present, desirable options at the analysis stage are either to present data using appropriate methods (stratified analysis, average estimates or standardized measures of frequency) or compute an adjusted measure of association that controls for the effects for the confounding variables using multiple regression models.[20]

In the present study while examining for changes in systolic BP and diastolic BP across categories of δ BMI, potential confounders were identified (baseline BMI, age and gender) and appropriate adjustments made during the comparison. Similarly appropriate adjustments to tackle confounding were done for other comparisons listed in the results section. It is accepted that residual confounding is still possible in the results presented due to the confounding by

covariates not measured by the current study (e.g., waist circumference) which are known to influence BP levels as well as unknown confounders of blood pressure.

2.D Effect modification

Effect measure modification is a situation where the measure of effect for an exposure on the outcome varies across levels of another factor. Effect modification means that there are important differences between groups in the relationship between the exposure and the outcome on the current scale of measurement.[20]

In the current study, there was a statistically significant interaction (effect modification) between age and sex for change in systolic blood pressure (δ SBP) with age. If we interpret the summary measure for δ SBP from the regression model (**Tables 9A & 9B** of Results section), we assume that if adjusted for baseline BP and δ BMI, boys and girls should have an increase of 0.8 mm Hg per year of increase in baseline age and the difference in SBP at any age is 3.4 mm Hg between the genders (higher SBP in boys). Separate summary measures were presented for boys and girls for δ SBP due to the presence of a significant interaction between age and sex (**Tables 12A & 12B** of Results section). These separate summaries show that while each year increase in baseline age increases δ SBP by 1.6 mm Hg in boys, there is no significant change in δ SBP (-0.05 mm Hg per year) with baseline age for girls (when adjusted for other variables in the model). The summary value of 0.8 mm Hg per year is different from the true sex stratified values (1.6 mm Hg in boys, -0.05 mm Hg in girls) due to interaction of age and gender for δ SBP

2.E Analysis methods

The ***paired t test*** and ***independent t test*** were used for unadjusted analysis. The ***linear regression models*** were used for both adjusted and unadjusted analysis. Compared to the independent t test, the paired t test is better suited for the primary analysis of this study due to the study design (repeated measures design). The preference for paired t test in this study is due to its inherent property of *reduction in variance* (as repeated measures in blood pressure tend to be positively correlated), *better power* and *automatic control of between individual differences*.

Other methods used in the secondary analysis were LOWESS curve fitting, ANCOVA, tests for linear trend and tests for interaction. The LOWESS curve fitting was done for δ SBP vs δ BMI and δ DBP vs δ BMI comparisons to explore the functional relationship between each pair of the variables. As to our knowledge, no function has been suggested in previous studies. The LOWESS curve fitting suggested a linear relationship between the variables (**Figures 1**& **2** of the Results section). The subsequent analysis assumed a linear relationship. The ANCOVA approach was used to compare means of δ BP across categories of δ BMI as this approach permits adjustment for covariates to reduce the effect of confounding due to measured variables.

The regression model for linear trend was used to identify the presence of a dose response effect between δ SBP and δ BMI by using the ordinal categories of δ BMI as a predictor variable for δ SBP. The statistical test for interaction was done to identify the presence (or absence) of an effect modification by age on gender for δ SBP which was indicated as per the results from the ANCOVA approach for comparison of δ SBP across age groups plotted separately for boys and girls.

2.F Study Power

As per the calculations for study power described in the methods section earlier, the study had sufficient power (more than 90%) to detect the differences (any difference more than 1.6 mm Hg) in both systolic and diastolic BP between the two surveys for the follow up period of 6 years. The observed differences of 13.4 mm Hg for systolic BP and 10.3 mm Hg for diastolic BP between the two surveys are much higher than the required minimum difference of 1.6 mm Hg for 90% power described in the effect size calculation table (**Table 2** of the Methods section) described earlier.

2.G Generalizability

The study findings may not be generalizable to all children in India considering that the children in the study were predominantly from middle socioeconomic status and only from urban areas. For instance, it is possible that children from other regions of India with lower socio economic status may have varying environmental exposures during childhood (i.e., nutritional deficiency) and the findings may differ. However the study findings are consistent with previous studies from other parts of the world.[4-8] It is likely that the study findings can be applicable to children from other regions.

3. Summary of Strengths and Limitations of the study

3.A Strengths of the study

The major strengths of this study include a large sample size, low attrition rate and adherence to standard blood pressure measurement methodology recommended by the Fourth task force report.[16] A repeated measures design is the best approach to study age related changes in BP during adolescence. In this design, BP levels in adolescents are compared to their own BP values measured earlier during childhood which makes results of these comparisons more accurate. The large sample size and its accompanying power clearly increased the reliability of these results. The low attrition rate makes results more internally valid. Strict adherence to standard BP measurement methodology recommended by the fourth task force probably have played a major role in reducing measurement errors and thereby reducing the effect of regression dilution and improving precision of prediction estimates.

3.B Study limitations

Blood pressure measurements were recorded in school premises under conditions which may have resulted in minor deviations from actual blood pressure readings. Measurements of variables like waist circumference, dietary patterns and physical activity levels would have added more depth to the information collected by the present study. These variables are known to influence blood pressure levels in children and it is likely that they may also influence age related changes in blood pressure. Measuring these variables would have permitted us to study their independent role in the age related changes of blood pressure. These measurements were not done due to limitations in resources.

Follow up measurements at more than one time point during the follow up period would have added more depth to the information and might have identified any non-linear nature of the relationships studied. The study findings may not be applicable to the rural pediatric population

who may have a different age related trend pattern for blood pressure due to variations in growth and nutritional levels compared to urban children.

4. Implications of the study results

Currently there is debate on the reliability of BP values during childhood to predict BP levels during follow up visits. Many researchers have suggested that the predictive value of childhood BP levels were poor and questioned the relevance of school based BP screenings. These researchers probably based their conclusions on studies that reported low tracking of BP in longitudinal studies done during childhood. The findings of this study suggest that there is good tracking of both systolic and diastolic BP from childhood to adolescence and there is relevance for childhood BP screening programs. Children with high risk for high blood pressure during adolescence can be identified with reasonable accuracy by means of these childhood BP screenings if appropriate methodology is adopted and practiced during these studies.

The study also suggests that a change in BMI is more influential in modifying BP compared to baseline BMI. This finding identifies an opportunity for school health programs that attempt to improve cardiovascular health by means of modifying gains in weight and BMI. The study also suggests that we should be conservative in our expectations for reductions in diastolic BP by means of modifying BMI trends during adolescence.

5. Recommendations for future research

Future studies on age related changes in BP from childhood to adolescence should adhere to standard methodology to minimize issues related to high measurement error. Multiple longitudinal follow up screens are recommended as there is a probability of differential progression of BP during a long period of follow up. Measurement of additional variables like waist circumference, physical activity levels, dietary patterns and sexual maturity status may permit us to reduce confounding by these variables and provide us with results that are more likely to represent the actual role played by age and all the measured variables in the progression of BP from childhood to adolescence.

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APPENDIX

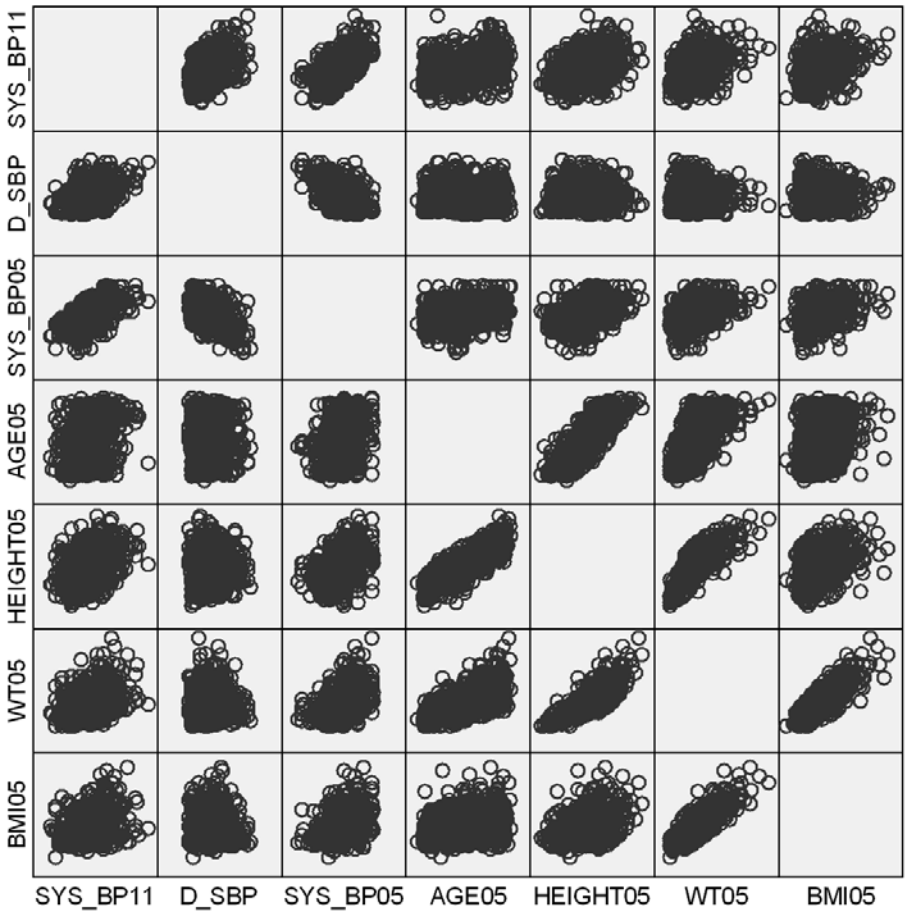

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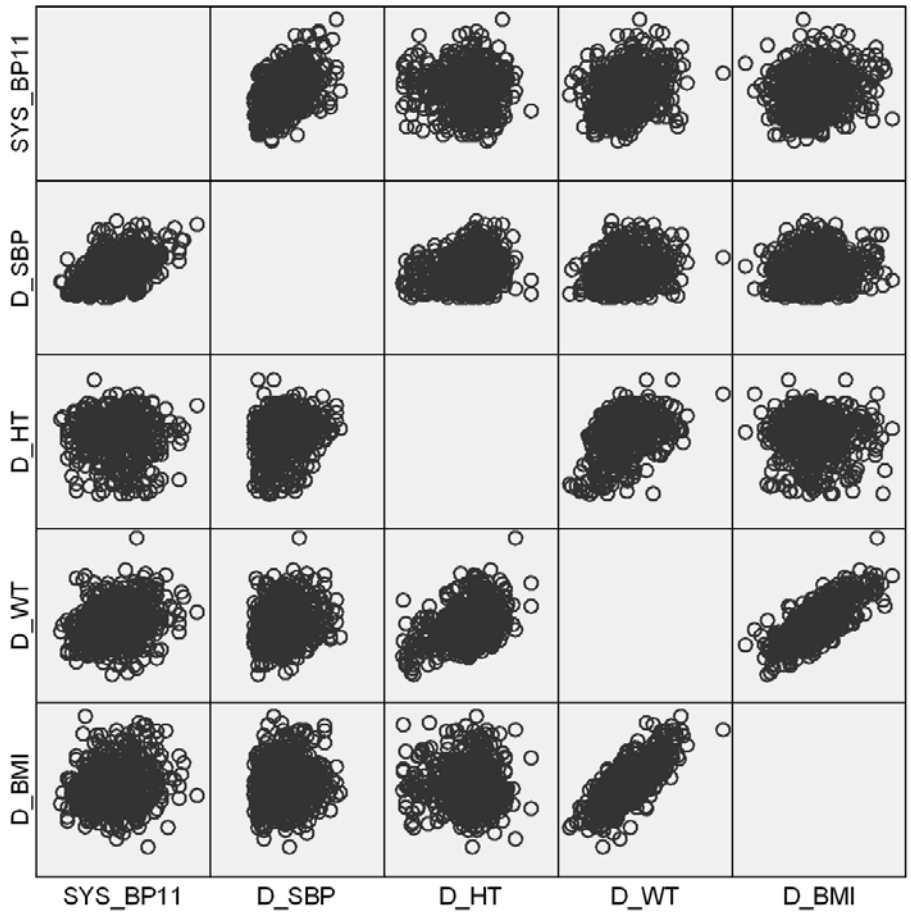
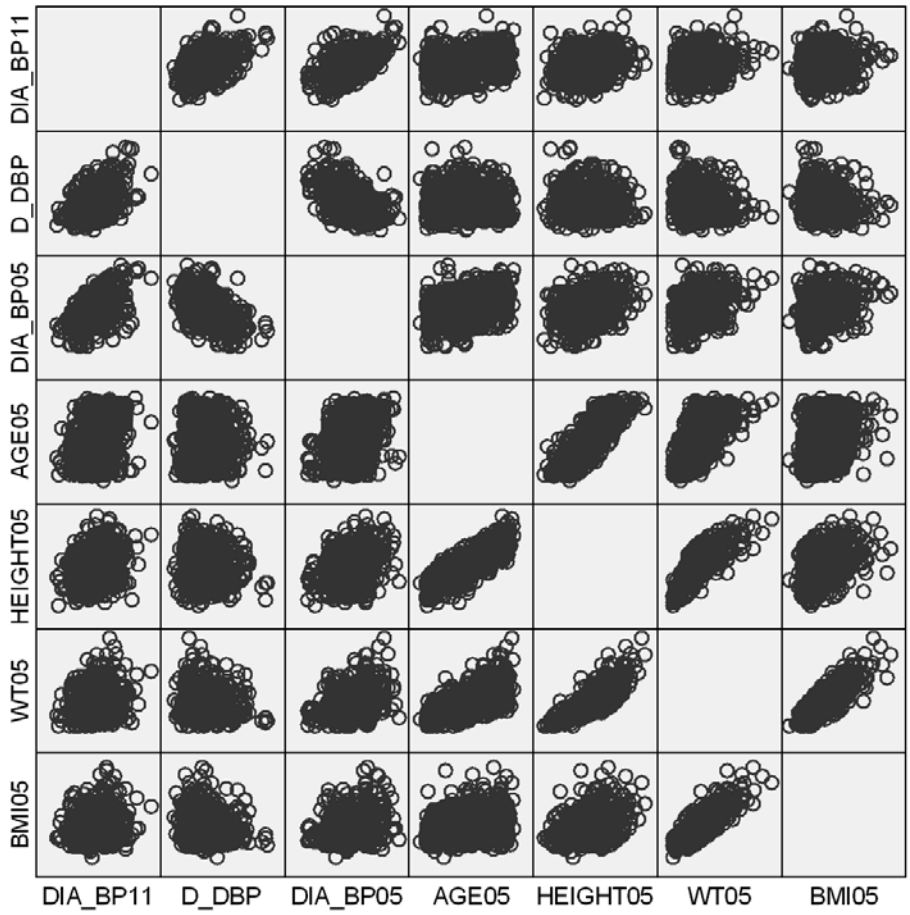
Figure 1. Correlations of follow up systolic blood pressure and change in systolic blood pressure to baseline systolic blood pressure and baseline anthropometric variables



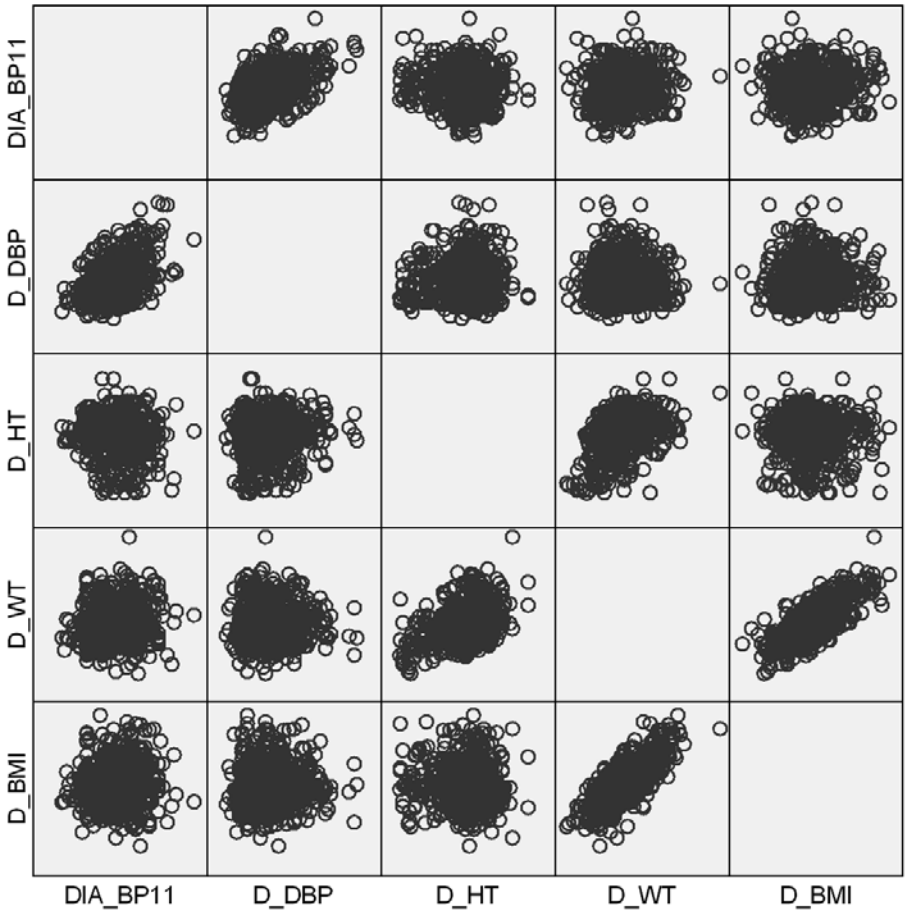
SYS_BP 11 – follow up Systolic BP, D_SBP – change in Systolic BP from baseline to follow up, D_HT – change in height from baseline to follow up, D_WT – change in weight from baseline to follow up, D_BMI – change in body mass index from baseline to follow up.

Figure 2. Correlations of follow up systolic blood pressure and change in systolic blood pressure to change in anthropometric variables



DIA_BP 11 – follow up Diastolic BP, D_DBP – change in Diastolic BP from baseline to follow up, DIA_BP 05 – baseline diastolic BP, AGE 05 – baseline age, HEIGHT05 – Height at baseline, WT05 – weight at baseline, BMI 05 – body mass index at baseline.

Figure 3. Correlations of follow up diastolic blood pressure and change in diastolic blood pressure to baseline diastolic blood pressure and baseline anthropometric variables



DIA_BP 11 – follow up Diastolic BP, D_DBP – change in Diastolic BP from baseline to follow up, D_HT – change in height from baseline to follow up, D_WT – change in weight from baseline to follow up, D_BMI – change in body mass index from baseline to follow up.

Figure 4. Correlations of follow up diastolic blood pressure and change in diastolic blood pressure to change in anthropometric variables