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Trajectories of systolic blood pressure in children: risk factors and cardiometabolic correlates

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Abstract

Objective—To identify systolic blood pressure (SBP) percentile trajectories in children and to describe the early-life risk factors and cardiometabolic correlates of those trajectories.

Study design—Using age-, sex-, and height-specific SBP percentiles based on the American Academy of Pediatrics reference, we examined SBP trajectories using latent class mixed models from ages 3 to 8y (n=844) from GUSTO-study, a Singaporean mother-offspring cohort study. We analyzed associations between SBP trajectories and early-life risk factors using multinomial logistic regression and differences across trajectories in cardiometabolic outcomes using multiple linear regressions.

Results—Children were classified into one of four SBP percentile trajectories: "low increasing" (15%), "high stable" (47%), "high decreasing" (20%), "low stable" (18%). Maternal hypertension during early pregnancy was a predictor of the "high stable" and "low increasing" SBP trajectories. Rapid child weight gain in the first 2y of life was only associated with the "high stable" trajectory. Compared with children in the "low stable" trajectory, children in the "high stable" SBP trajectory had higher BMI z-scores, sum of skinfold thicknesses, waist circumference from ages 3 to 8y and abdominal adipose tissue (mL) at 4.5y (adjusted mean difference [95%CI]: superficial and deep subcutaneous abdominal adipose tissue: 115.2[48.1,182.3] and 85.5[35.2,135.8]). Their fat mass (kg) (1.3[0.6,2.0]), triglycerides levels (mmol/L) (0.10[0.02,0.18]), HOMA1-IR (0.28[0.11,0.46]) at age 6y were also higher but not their arterial thickness and stiffness.

Conclusion—Reducing maternal BP during pregnancy and infant weight gain in the first 2y of life might help to prevent the development of high SBP.

Keywords

latent class mixed model; adiposity; maternal hypertension; rapid weight gain; GUSTO

Introduction

Hypertension is the leading risk factor for cardiovascular diseases (CVD) and accounted for 44% of all non-communicable disease-related deaths globally in 2016[1]. Evidence suggests that the association between hypertension and CVD is stronger in Asians than in Caucasians[6]. Asians represent about half of the world's population and thus comprise a major CVD global burden. Studies in mid-childhood suggest that high BP tracks into adulthood[7] and leads to adverse cardiometabolic outcomes[8–11]. BP trajectory, i.e. BP changes over time, was previously described in overall[12] or by sex and ethnicity[13, 14]. Different BP trajectories have been reported from mid-childhood to adulthood[8, 9, 15, 16] but early childhood contribution in is lacking. One challenge in studying BP in childhood is its

spontaneous increase with growth as children age. In most studies tracking childhood BP, growth was either not controlled or only poorly controlled for. The American Association of Pediatrics (AAP) has incorporated height as a marker of body size, in addition to age and sex, when estimating BP percentiles[20]. The resulting reference has been used globally for the diagnosis of elevated BP and hypertension (HTN) in children and adolescents.

Singapore is a multi-ethnic country comprising Chinese, Malay and Indian ethnic groups, who collectively represent 80% of the world's Asian population. Studying BP trajectories in this population could provide new insights into the development of hypertension in Asians. In the present study, we identify systolic BP (SBP) percentile trajectories in Singaporean children aged 3 to 8y. To further investigate the determinants and the health implications of the BP trajectories, we also examine the associations of pre-, peri- and postnatal risk factors with those trajectories and describe their correlations with several cardiometabolic outcomes.

Population and Methods

Study population

The Growing Up in Singapore Towards healthy Outcomes (GUSTO) is a multi-ethnic mother-offspring cohort study. A detailed study description has been published previously[21]. Briefly, pregnant women aged ≥18y who attended their first-trimester ultrasound scan at one of Singapore's two major public maternity units (National University Hospital (NUH) or KK Women's and Children's hospital (KKH)) between 2009 and 2010, were recruited. Institutional review board approval for the study was granted by both the National Healthcare Group Domain Specific Review Board (reference D/09/21) and SingHealth Centralized Institutional Review Board (reference 2009/280/D). Informed written consent was obtained from the women for themselves and their child.

A study flow chart is shown in Figure 1 **online**. Children with at least three encounters with successful BP measurements from age 3 to 8y were used in the main analysis (n=844).

Blood pressure measurement in children

From age 3 to 8y, BP was measured yearly by trained research staff using the DINAMAP CARESCAPE™ V100 (GE Healthcare, Milwaukee, WI), with an appropriate cuff size. The measurement was taken in a quiet environment from the right upper arm in a seated position, with legs uncrossed and the arm resting at heart level, after a five-minute rest. Two BP measurements were taken; if the second systolic or diastolic blood pressure differed from the first by >10 mmHg, a third measurement was taken. BP readings in moving or crying children were discarded. The two lowest BP readings were averaged and the highest BP was discarded to account for child anxiety.

Age-, sex-, and height-specific SBP percentiles were derived using the AAP BP reference[17]. DINAMAP devices have been reported to be inaccurate for measuring DBP in children[22, 23]. Given that DBP has a weaker tendency to track than SBP[7] and a lower predictive value for adult adverse health outcomes[24], we did not further analyse DBP measurements.

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Pre- and perinatal characteristics

At the recruitment visit, maternal educational attainment, ethnicity, pre-pregnancy weight and household income were collected through interviewer-administered questionnaires. At 24 or 36 months, paternal height was measured and diagnosis for hypertension was self-reported. Offspring sex, birth weight, and maternal BP before 20 weeks' gestation were extracted from the maternity hospital record. Gestational age (GA) was calculated based on first trimester ultrasound scans or hospital record. Sex- and GA-specific birth weight z-scores were derived[25]. Information on maternal pregnancy hypertensive disorders were collected from hospital records. From maternal BP before 20 weeks' gestation, mothers were classified as having normal BP (SBP<120 and DBP<80 mmHg), elevated BP (120≤SBP≤129 and DBP<80 mmHg), or HTN (130≤SBP or 80≤DBP mmHg). Maternal pre-pregnancy body mass index (BMI) was calculated based on self-reported pre-pregnancy weight and the height measured at 26-28 weeks' gestation. The WHO classification for Asian populations was applied (underweight: <18.5; normal weight 18.5-22.9; overweight 23-24.9; and obese ≥25.0 kg/m^2).

At 26-28 weeks' gestation, maternal active smoking was defined as a plasma cotinine level ≥3.0ng/mL[26] or self-reported active smoking in an interviewer-administered questionnaire. At the same clinic visit, a two-hour 75-g oral glucose tolerance test was performed in the mothers (further details in Appendix 1 **online**). Gestational diabetes mellitus (GDM) was defined using WHO 1999 definition.

Postnatal (before age 3y) child characteristics

Duration of any breastfeeding (exclusive or non-exclusive) was estimated through answers to interviewer-administered questionnaires at postnatal week three and at every three-month interval from months 3 to 12. At 18 months, mothers responded to a validated self-administered and semi-quantitative food frequency questionnaire[27] concerning their offspring's dietary intake during the past month. Subsequently, overall offspring dietary quality was assessed using the Diet Quality Index (DQI) (Appendix 1 online)[28]. Rapid weight gain in the first 2y of life was defined as a change of >+0.67SD (upward centile crossing through at least one of the growth charts centile bands) of age- and sex-specific weight z-scores at age 2y and birthweight z-scores.

Offspring cardiometabolic outcomes from ages 3 to 8y

From age 3 to 8y, anthropometric measurements were assessed yearly (detailed methods in Appendix 1 online). BMI age- and sex-specific z-scores were calculated based on the WHO standards and references[29, 30]. The sum of the subscapular and triceps skinfold thicknesses (SST) was calculated. Besides the routinely performed anthropometric assessment of all the participating children, consents were obtained at different time points from families who agreed to participate in more in-depth phenotyping evaluation (magnetic resonance imaging (MRI), quantitative magnetic resonance (QMR), blood sampling, vascular assessment).At age 4.5y, an abdominal MRI was performed on a subsample of GUSTO children (n≈300)[31]. Subcutaneous abdominal adipose tissue (SAT) and visceral adipose tissue (VAT) compartments were identified. SAT was further divided into deep subcutaneous adipose tissue (DSAT) and superficial subcutaneous adipose tissue (SSAT).

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In a subsample of GUSTO children aged 6y (n≈400), fat mass (kg) was estimated by QMR[32] (detailed methods in Appendix 1 online).

At age 6y, blood samples were collected after an overnight fast in a subsample of GUSTO children (n≈500). Venous plasma glucose, insulin, triglycerides, cholesterol, high-density lipoprotein, high-sensitivity C-reactive protein, creatinine were measured (detailed methods in Appendix 1 online). The homeostasis model assessment of insulin resistance (HOMA1-IR) was calculated as the ratio of fasting insulin to fasting glucose divided by 22.5.

At age 6y, about 500 children participated to a non-invasive vascular assessment. Carotid intima media thickness (cIMT) and carotid femoral pulse wave velocity (cfPWV) were assessed (detailed methods in Appendix 1 online).

Statistical analysis

T-tests and chi-square tests were used to compare baseline characteristics of included and non-included participants (**Table 1**). Similarly, as abdominal MRI, QMR, blood tests and vascular assessments were available only in sub-populations, we discussed differences between participants with and without these measurements.

SBP percentile trajectories from age 3 to 8y were identified using latent class mixed models (LCMM) for non-Gaussian outcomes[33]. Detailed method was described in Appendix 2 **online**.

Based on existing literature regarding potential determinants of childhood BP, we analysed associations of SBP trajectories with antenatal/perinatal maternal smoking status and environmental tobacco exposure during pregnancy, GDM, BMI before pregnancy, BP before 20 weeks' gestation, ethnicity, age at delivery, parity, educational attainment and household income at recruitment, study center, paternal self-reported hypertensive status and BMI at 24-36 months, child birthweight z-scores, child sex and postnatal factors (any breastfeeding duration, DQI at 18 months, rapid weight gain between birth and age 2y) using multinomial logistic regression.

Only 6% (n=46) of mothers in our study were diagnosed with pre-eclampsia, eclampsia or pregnancy induced hypertension. This low proportion was not adequate to study the association between child SBP trajectories with these hypertensive disorders. Instead, we performed a sensitivity analysis after removing mothers diagnosed for these hypertensive disorders. Apart from these hypertensive disorders, it has been suggested that elevated maternal BP overall during pregnancy, and especially in early pregnancy, might be a good predictor of offspring SBP[34, 35]. Hence, maternal BP before 20 weeks' gestation was included as for a risk predictor of child SBP trajectories.

In a sensitivity analysis, we assessed the influence of different periods of rapid child weight gain (0-6, 6-12, 12-24 and 24-36 months) on the SBP trajectories. Because rapid weight gain in children with lower birth size may lead to higher BP in mid-childhood[36, 37], we also tested interactions between birth weight and rapid weight gain on SBP trajectories.

To better understand the health implications of the SBP trajectories, we compared cardiometabolic outcomes measured repeatedly from 3 to 8y (BMI z-scores, SST, WC) or only at age 4.5 (DSAT, SSAT, VAT) or 6y (fat mass, blood lipids and glucose levels, HOMA1-IR, cIMT, cfPWV) across SBP trajectories identified from LCMM, using linear regression adjusted for a priori confounders based on prior knowledge (study center, child sex, household income, maternal characteristics (ethnicity, educational attainment, HTN, active smoking and tobacco exposure during pregnancy, GDM, BMI before pregnancy and parity) and paternal HTN and BMI at 24-36 months).

For logistic and linear regression models, missing values were assumed to be missing at random and handled using multiple imputations (n=20)[38](except for outcomes). Among the 844 children, missing values were present in following variables breastfeeding (n=36), maternal educational attainment (n=6), household income (n=51), pre-pregnancy BMI (n=51), GDM (n=40), maternal HTN (n=26), maternal active smoking (n=91), tobacco exposure during pregnancy (n=40), paternal HTN (n=171) and BMI (n=90). Twenty independent datasets were generated using the Markov Chain Monte Carlo method. LCMM was performed using the package “lcmm” in R software[39] (version 3.4.3; R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.). Analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R software.

Results

Baseline characteristics of the included and non-included participants are summarized in Table 1. The ethnicity distribution was 57% Chinese, 26% Malay and 17% Indian. Mothers with a secondary education or below were 30% of mothers. One-fourth of mothers were classified as obese and two-thirds were normotensive in early pregnancy. Only 10% of the fathers reported having been diagnosed with hypertension. Compared with non-included children, the 844 included children were more likely to be boys (52% vs 45%), their mean birth weight was higher (3.1±0.4kg vs 3.0±0.5kg) and they were breastfed for longer (42% vs 53% were breastfed for three months or less). Mothers in the subsamples of children with QMR data and vascular assessment, had lower rate of hypertension than their counterparts (data not shown). Children with blood tests and abdominal MRI were more likely to have siblings compared with children without blood tests (data not shown).

SBP trajectories

Based on the AAP reference, four SBP percentile trajectories were identified (Figure 2): “low increasing” (comprising 15% of the children), “high stable” (47%), “high decreasing” (20%) and “low stable” (18%).

Early-life predictors of SBP trajectories

Non-adjusted and adjusted associations of pre-, peri- and postnatal risk factors with SBP percentile trajectories from age 3 to 8y are shown in **Table 2 online & 3**, respectively. Compared with the unadjusted associations, those adjusted remained similar with reduced magnitude. We then described only the adjusted associations. Children of mothers classified

as hypertensive during their early pregnancy were more likely to be in the “low increasing” and “high stable” SBP percentile trajectory than in the “low stable” one. Children of smoking mothers during pregnancy were less likely to be in the “low increasing” SBP percentile trajectory. Children who underwent a rapid weight gain from birth to age 2y were more likely to be classified in the “high stable” SBP percentile trajectory. These associations remained for children in the “high stable” SBP percentile trajectory after removing mothers diagnosed with hypertensive disorders during pregnancy (**Table 4 online**). When considering narrower periods of rapid weight gain, only rapid weight gain in the first 6 months of life was associated with the “high stable” SBP percentile trajectory, although the magnitude of the association was higher between 12 to 24 months (OR[95% CI]: 1.66[1.07,2.58] from 0 to 6 months vs 1.08[0.50,2.35] from 6 to 12 months, 2.09[0.89,4.92] from 12 to 24 months and 1.47[0.63,3.43] from 24 to 36 months). No interactions were observed between birth weight and rapid weight gain during the studied age periods. No associations were observed between SBP trajectories and other pre-, peri- or postnatal factors.

Cardiometabolic outcomes across SBP trajectories between ages 3 to 8y

Comparisons of BMI z-scores, SST and WC across SBP trajectories from ages 3 to 8y are presented in Figure 3, 4 & 5 **online**. Children in the “high stable” SBP trajectory had higher BMI z-scores, SST and WC over time compared with children in the “low stable” one. Children in the “high decreasing” trajectory had also a higher BMI z-scores than children in the “low stable” trajectory. The magnitude of this difference remained stable over time and, lower than the one between children in the “high stable” and “low stable” trajectory. No differences in SST and little differences were observed in WC between children in the “high decreasing” trajectory and children in the “low stable” trajectory. Increasing differences in BMI z-scores, SST and WC were notable from 5y between children in the “low increasing” trajectory and children in the “low stable” one.

Comparisons of cardiometabolic outcomes across SBP trajectories at 4.5 and 6y are summarized in **Table 5**. Compared with children in the “low stable” SBP trajectory, children in the “high stable” SBP trajectory consistently had higher SSAT and DSAT at age 4.5y and fat mass at age 6y. Compared with children in the “low stable” SBP trajectory, children in the “high stable” SBP trajectory had higher fasting plasma glucose, insulin, HOMA1-IR and triglycerides at age 6y. Children in the “low increasing” trajectory had higher fasting plasma glucose and triglycerides at age 6y than children in the “low stable” trajectory. No differences in LDL cholesterol, total cholesterol, creatinine, hs-CRP, cIMT and cfPWV at age 6y were observed among the SBP trajectories.

Discussion

Nearly half of our GUSTO sample aged 3 to 8y was classified in a “high stable” SBP percentile trajectory. The two most prominent early-life predictors of being in the “high stable” SBP percentile trajectory were a mother with high BP during her early pregnancy and rapid postnatal weight gain from birth to age 2y, and particularly in the first 6 months of life. No associations with sociodemographic characteristics, breastfeeding and toddler’s

dietary quality index were found. Children in the “high stable” SBP percentile trajectory had a higher degree of adiposity from ages 3 to 8y, were more insulin resistant and had higher concentrations of triglycerides at age 6y compared with children in the “low stable” SBP trajectory.

Using the LCMM method, we identified four SBP percentile trajectories: low increasing” (15% of the children), “high stable” (47%), “high decreasing” (20%) and “low stable” (18%). Using a similar latent growth modelling approach, three previous studies have examined BP trajectories in children[8, 9, 15, 40]. Two to four SBP trajectories have been identified in these studies. Only one previous study has adjusted for the child’s height when analyzing latent BP trajectories[15] and only one study included three-year-old children[40].

High maternal BP in early pregnancy was associated with the “high stable” and “high decreasing” SBP trajectories. Previous evidence has consistently shown that maternal BP during pregnancy, and particularly in the first trimester, is associated with higher offspring BP[34, 35]. It has been suggested that higher maternal BP in early pregnancy could be a marker of maternal and placental maladaptation[41], leading to fetal growth restriction and abnormal fetal vascular development that may subsequently affect childhood BP[42].

Consistent with previous studies, we found that rapid postnatal weight gain, particularly in the first 6 months of life, was associated with higher BP in childhood [36, 37, 43]. By contributing to greater adiposity at later ages, early rapid weight gain may lead to elevated BP[44].

Children in the “high stable” SBP trajectory had higher BMI z-scores, SST and WC from ages 3 to 8y but also more abdominal subcutaneous adipose tissue at age 4.5y, higher fat mass, insulin resistance and triglycerides levels at age 6y compared with children in the “low stable” trajectory. These results are consistent with the robust association between elevated BP and overweight and obesity in children[45, 46]. Compared with children in the “low stable” trajectory, children in the “high decreasing” trajectory had little to no differences in adiposity markers except for BMI z-scores. Children in the “high decreasing” trajectory had a slightly higher BMI z-scores than children in the “low stable” trajectory and the difference in their BMI z-scores remained stable over time. This could be protective of an increase in their blood pressure. Conversely, children in the “low increasing” SBP trajectory had a noteworthy increase in their BMI z-scores, SST and WC from 5y. It is plausible that these children encountered an early adiposity rebound contributing to an increasing blood pressure. Our cardiometabolic outcomes were measured concomitantly with BP. Hence, we cannot draw any firm conclusions on the temporal relationships and directionality of the observed associations. However, these findings provide some evidence that cardiometabolic outcomes and SBP are correlated over the same range of ages. Besides, from our post hoc analysis, other reported chronic health conditions (such as asthma or atopic symptoms) and their medications were not affecting our findings.

Our study has several other limitations. Globally, the AAP BP reference is often recommended for the interpretation of BP in children[17, 19]. The AAP reference is based on BP values obtained by the auscultatory method, while BP was measured using an

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oscillometric device in our study. Compared with auscultatory BP values, SBP values from our study are underestimated[23]. However, as any underestimation is systematic, the broad phenotypic associations with SBP trajectories should still be valid.

Current BP references are descriptive, rather than prescriptive. That is, they describe the general population and use arbitrary cut off values to define hypertension, rather than being based on the risks of adverse health outcomes in childhood or adulthood. It is unclear, therefore, whether the distribution of BP should be similar in different populations. Finally, GUSTO children not included in our analysis were more often girls, were lighter at birth, breastfed for a shorter duration and had younger mothers. As these factors were not associated with SBP trajectories, selection bias is unlikely to have affected our findings. We cannot exclude selection bias of subjects in our analyses of abdominal MRI, QMR, blood tests and vascular assessment. Some of these sub-populations differed by either lower maternal hypertension rate during pregnancy or higher rate of primiparity which are associated with BP trajectories in our study. These differences might have reduced the magnitude of the observed associations in these sub-populations.

Our study is the first to explore latent BP trajectories from age 3y with a relatively large sample size. Unlike conventional models, latent growth modelling assumes that population is heterogeneous, and that multiple trajectories, rather than a single one, may better fit the entire population. Compared with studies using BP at a single time point to assess children's BP, we used longitudinal modelling. Owing to the inherent variability in BP, identifying a hypertensive child using BP measurement at a single time point is far from ideal. Our study is the first to use age-, height- and sex-specific SBP percentiles to monitor child BP, which better accounts for child growth. Finally, our findings are strengthened by the prospective design of our study and the comprehensive information collected on the participants' early-life predictors and later cardiometabolic status at multiples ages.

Conclusion

Our study adds to existing evidence that maternal blood pressure during pregnancy, child adiposity, and early childhood weight gain are all important contributors to children's blood pressure. Monitoring BP during pregnancy and infant weight gain might help prevent the development of later high BP. Because group-based approaches assign children to a latent group based on their highest estimated group-membership probability for each latent group, these latent classes should be considered as approximations of complex developmental patterns[47]. Further studies on BP trajectories are needed for an in-depth understanding of BP developmental patterns, using multiple approaches and particularly in Asians. As the GUSTO study is ongoing, cardiometabolic outcomes measured at later ages should help disentangle the implications of these SBP trajectories for later cardiometabolic health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAP	American Academy of Pediatrics
BP	blood pressure
SBP	systolic blood pressure
DBP	diastolic blood pressure
GUSTO	Growing Up in Singapore Towards healthy Outcomes
NUH	National University Hospital
KKH	KK Women's and Children's hospital
BIC	Bayesian information criterion
EBP	elevated blood pressure
HTN	hypertension
BMI	body mass index
FPG	fasting plasma glucose
2-h PPPG	2-h postprandial plasma glucose
MRI	magnetic resonance imaging
SAT	abdominal subcutaneous adipose tissue
SSAT	superficial abdominal subcutaneous adipose tissue
DSAT	deep abdominal subcutaneous adipose tissue
VAT	visceral adipose tissue
QMR	quantitative magnetic resonance
HOMA	homeostasis model assessment of insulin resistance
cIMT	carotid intima media thickness
cfPWV	carotid femoral pulse wave velocity
LCMM	Latent Class Mixed Models

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Figure 1. Study flow chart

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Figure 2.

Sex-, age- and height-specific SBP percentile trajectories from age 3 to 8 years, results from LCMM. 95% confidence intervals are represented with shades. “High stable” SBP trajectory is represented by a dashed line, the “high decreasing” trajectory by a dotted line, the “low increasing” trajectory by a solid line and the “low stable” trajectory by a dotted-dashed line.

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Figure 3.

Comparisons of age- and sex-specific BMI z-score (SD) across SBP percentile trajectories from age 3 to 8 years (adjusted means difference [95%CI]).

Models were adjusted for study center, child sex, household income, maternal characteristics (ethnicity, educational attainment, HTN, active smoking and tobacco exposure during pregnancy, GDM, BMI before pregnancy and parity) and paternal HTN and BMI at 24-36 months. Abbreviations: LOW: low stable, HIGH: high stable, INC: low increasing, DEC: high decreasing.

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Figure 4.

Comparisons of sum of skinfold thicknesses (mm) across SBP percentile trajectories from age 3 to 8 years (adjusted means difference [95%CI]).

Models were adjusted for study center, child sex, household income, maternal characteristics (ethnicity, educational attainment, HTN, active smoking and tobacco exposure during pregnancy, GDM, BMI before pregnancy and parity) and paternal HTN and BMI at 24-36 months. Abbreviations: LOW: low stable, HIGH: high stable, INC: low increasing, DEC: high decreasing.

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Figure 5.

Comparisons of waist circumference (cm) across SBP percentile trajectories from age 3 to 8 years (adjusted means difference [95%CI]).

Models were adjusted for study center, child sex, household income, maternal characteristics (ethnicity, educational attainment, HTN, active smoking and tobacco exposure during pregnancy, GDM, BMI before pregnancy and parity) and paternal HTN and BMI at 24-36 months. Abbreviations: LOW: low stable, HIGH: high stable, INC: low increasing, DEC: high decreasing.

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