ORIGINAL ARTICLE

Birth weight, puberty, and systolic blood pressure in children and adolescents: a longitudinal analysis

C Li[1,5], TT-K Huang[2], ML Cruz[3] and MI Goran[4]

[1]*Department of Preventive Medicine and Public Health, University of Kansas Medical Center, Kansas City, KS, USA;* [2]*Endocrinology, Nutrition, and Growth Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA;* [3]*College of Health Sciences, University of Texas at El Paso, El Paso, TX, USA and* [4]*Institute for Health Promotion and Disease Prevention Research, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*

We examined the association between birth weight and systolic blood pressure (SBP) from pre-puberty to late puberty in a cohort of American children. Ninety-eight children aged 4–12 years at baseline were followed annually for 2–6 years with at least two Tanner stages. Annual measures included SBP, age, gender, race, birth weight, Tanner stage, and body composition using dual-energy X-ray absorptiometry and computed tomography. Birth weight was inversely correlated with SBP in pre-pubertal children ($r = -0.23$, $P < 0.05$), especially in white children. SBP persisted at a higher level from pre-puberty through late puberty among children with low birth weight (< 2500 g). However, SBP significantly increased from pre-puberty to early or late puberty among children with high birth weight ($\geqslant 4000$ g). After adjusting for visceral fat, one unit change of birth weight category was associated with a 2.6 mm Hg reduction in SBP ($P < 0.05$), but this association was attenuated as puberty progressed. The changes in SBP across puberty followed different trajectories in children with low vs high birth weight. Attenuation in the association between birth weight and SBP from pre-puberty to late puberty may be influenced by sexual maturation.
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Introduction

The fetal origins hypothesis proposes that growth retardation *in utero* and during infancy may lead to persisting changes in blood pressure in adult life.[1] The relationship between birth weight and systolic blood pressure (SBP) may amplify from childhood to adulthood.[2] A large number of studies have shown that birth weight, a proxy indicator of total fetal growth *in utero*, is inversely associated with SBP in young children and adults.[3] However, findings of the association between birth weight and SBP during adolescence have been inconsistent.[3] Previous studies have reported inverse,[3–5] nonsignificant,[3,6,7] or positive[3,8] associations between birth weight and SBP in early and late adolescence.

Adolescents may experience complex physiological, body composition and hormonal changes during puberty, which may confound or mask the relationship between birth weight and SBP.[9] Previous studies have shown that body size[10] and sexual maturation[11] during adolescence may be positively associated with SBP. Thus far, no study has examined the role of pubertal status as a potential effect modifier in the relationship between birth weight and SBP longitudinally. Therefore, the aim of this study was to use longitudinal data to examine changes in SBP across different pubertal stages as a function of birth weight in white and black children. We hypothesized that the relations between birth weight and SBP would be influenced by puberty such that birth weight would be inversely associated with SBP in pre-pubertal children, but this association would be attenuated during puberty.

Correspondence: Dr MI Goran, Institute for Prevention Research, Department of Preventive Medicine, University of Southern California Keck School of Medicine, 1540 Alcazar Street, Room 208-D, Los Angeles, CA 90033, USA.
E-mail: goran@hsc.usc.edu
[5]Current address: Centers for Disease Control and Prevention, 4770 Buford Highway, NE, Mail Stop K-66, Atlanta, GA 30341.
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Materials and methods

Study design and subjects
Study subjects were part of an ongoing longitudinal study on intra-abdominal fat and disease risk in children in Birmingham, Alabama, USA.[12] Children who experienced at least two pubertal stages in the entire follow-ups were analysed ($n = 98$; mean age, 8.5 years at baseline). The children included in this study had 2–6 annual visits with available data (one with two visits, 24 with three visits, 24 with four visits, 33 with five visits, and 16 with six visits; mean, 4.4 visits), which resulted in a total of 431 observations. The majority of children excluded from analyses were pre-pubertal (96.6%) at baseline. The final analytic sample had higher proportion of older children and boys, but had similar percentage of white children and mean values of birth weights, SBP, and body composition compared to those excluded. The children were free of any major illnesses since birth. Ethnicity was determined by self-report based on both parents and both sets of grand parents reporting to be of the same ethnicity. The nature, purpose, and possible risks of the study were carefully explained to the parents before consent was obtained. This study was approved by the Institutional Review Board at the University of Alabama at Birmingham (UAB). All measurements were performed at the General Clinical Research Center (GCRC) and the Department of Nutritional Sciences at UAB during the school year (fall and spring) between 1994 and 2000.

Protocol
The detailed protocol has been reported previously.[13] In brief, three readings of blood pressure were taken from the right arm, at 1-min intervals, after a 5-min rest in the supine position with an automated device (Dynamap 8100 T; Critikon, Tampa, FL, USA). The blood measures were obtained in a quiet area and standard guidelines were used in selection of cuff size and inflation range. The average of the second and third measures was used in the present study. The original data on birth weight were obtained by parental recall. It was re-categorized into three groups: low birth weight = 1 (< 2500 g), normal birth weight = 2 (2500 g $\sim$ 3999 g), and high birth weight = 3 ($\geqslant 4000$ g). Tanner stage was determined by the three paediatricians who were trained with the identical guideline and was based on breast stage and pubic hair development in girls[14] and genitalia development in boys.[15] Pubertal stage on the scale of 1–5 was estimated using the Tanner criteria, with stage 1 being pre-puberty and 5 being adult. In the present study, pubertal status was defined as 1 = pre-puberty (Tanner stage I), 2 = early puberty (Tanner stage II), and 3 = late puberty (Tanner stage III–V).

Each subject wore a hospital gown without shoes at the time of testing. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using an electronic scale (Toledo Scale, Worthington, OH, USA). Body mass index (BMI) was calculated based on measured weight (kg) and height (m). BMI percentile and z-score were generated by using the Centers for Disease Control and Prevention growth charts.[16] Body composition (fat and lean mass) was assessed at the Energy Metabolism Laboratory in the Department of Nutrition Sciences at UAB by dual-energy X-ray absorptiometry (DXA; Lunar DPX-L densitometer; LUNAR Radiation, Madison, WI, USA; Pediatric software, v. 1.5).[17] Subjects were scanned in light clothing while lying flat on their backs with arms at their sides. Percent fat mass was calculated as the percentage of total fat mass (kg) over the body weight (kg). Visceral fat (intra-abdominal adipose tissue, IAAT) and subcutaneous abdominal adipose tissue (SAAT) were measured by computed tomography (CT) scanning with a HiLigh/Advantage Scanner (General Electric, Milwaukee, WI, USA) as previously described.[13]

Statistical analysis
T-test and χ^2-test were used for descriptive analyses. Pearson and Spearman correlation coefficients were provided for continuous and categorical variables, respectively. Mixed-effects analyses for repeated measures were performed using the PROC MIXED procedure in SAS[18,19] to take into account the correlations between repeated measures within the same individual over time and allow time-varying covariates and incomplete outcome data with an assumption of missing at random.[19]

In multivariable mixed-effects models, the intercept and time-varying variables were modeled as random effects, which allowed the effects of these variables to vary randomly across individuals in the population. Specifically, the slope of SBP with pubertal status (or the linear change in SBP with a unit change in pubertal status) was allowed to vary by birth weight (by adding an interaction term between birth weight and pubertal status) to test whether the rate of changes in SBP with pubertal status varied according to birth weight categories. Age and other time-varying covariates such as total fat mass, % fat mass, visceral fat, SAAT, and BMI z-score were also allowed to vary randomly in the model to adjust for their potential concurrent confounding effects on the association between birth weight, pubertal status, and SBP. The Bayesian Information Criterion (BIC) was used as a goodness-of-fit statistic for comparing models with varying covariates.[19]

Results

At baseline, among black children, there were fewer female participants and higher BMI percentiles than

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among whites (Table 1). About 90% of children were at their pre-puberty at baseline. In the total sample, birth weight category was inversely correlated with SBP (Spearman correlation coefficient $r_s = -0.23$, $P < 0.05$) at baseline survey.

Mean systolic blood pressure by pubertal status and birth weight

Average SBP across the entire range of birth weight at baseline was 108.6 mm Hg with a 95% confidence interval (CI) of 106.0–111.2 mm Hg for white children and 109.5 mm Hg with a 95% CI of 105.7–113.2 for black children. Among white children (Figure 1, upper panel), the mean SBP was significantly higher among pre-pubertal children with low birth weight (mean, 110.0 mm Hg) compared to those with high birth weight (mean, 102.8 mm Hg; $P < 0.05$). Among black children (Figure 1, lower panel), no significant association between birth weight and SBP was found among pre-pubertal or early and late pubertal children. Interestingly, in contrast with white children, the association between birth weight and SBP appeared to show a positive trend among late pubertal black children. The association between birth weight and SBP appeared to be attenuated most in early puberty (Tanner stage II) in both white and black children.

Unadjusted changes of mean systolic blood pressure across pubertal stages by birth weight categories

Overall, the unadjusted mean SBP was higher among black children than white children (111.9 vs 109.3 mm Hg). The mean ages of white children at pre-puberty (mean, 8.1 years; range, 4.8–12.1 years),

Table 1 Demographic and anthropometrical characteristics in white and black children at Baseline ($n = 98$)

Characteristic	White (n = 57)	Black (n = 41)	P-value[a]
Gender (girls/boys)	44/13	20/21	<0.01
Tanner stage (n (%))			NS
Stage I	53 (93.0)	36 (87.8)	
Stage II	4 (7.0)	3 (7.3)	
Stage III–V	0 (0.0)	2 (4.9)	
Age (years)	8.8 ± 1.3[b]	8.2 ± 1.6	NS
SBP (mm Hg)	108.6 ± 9.8	109.5 ± 11.2	NS
Birth weight (kg)	3.3 ± 0.8	3.2 ± 0.7	NS
Weight (kg)	33.0 ± 9.7	37.0 ± 13.0	NS
Height (cm)	133.5 ± 9.7	133.6 ± 11.6	NS
BMI percentile (%)	66.6 ± 25.1	79.2 ± 24.0	<0.05
Total fat mass (kg)	9.9 ± 5.0	12.0 ± 8.1	NS
SAAT (cm²)	99.3 ± 73.8	113.5 ± 109.9	NS
IAAT (cm²)	31.8 ± 17.0	31.2 ± 23.8	NS

Abbreviations: BMI, body mass index; IAAT, intra-abdominal adipose tissue or visceral fat; NS, not significant; SAAT, subcutaneous abdominal adipose tissue; SBP, systolic blood pressure.
[a]Tests or χ^2-tests between white and black children.
[b]Mean ± s.d.

early puberty (mean, 10.1 years; range, 8.5–13.4 years), and late puberty (mean, 11.6 years; range, 10.0–14.5 years) were similar to those of black children (mean ages, 8.8 years, 10.9 years, and 12.4 years; ranges, 4.2–11.0 years, 7.5–13.3 years, and 10.2–14.1 years, respectively).

Among white children, a noticeably elevated mean SBP was observed for those with low birth weight at pre-puberty (mean, 110.0 mm Hg) and persisted through early and late puberty. The significant change of mean SBP occurred from pre-puberty (PP) to early puberty (EP) (PP→EP; $\Delta_{SBP} = 8.1$ mm Hg; $P < 0.01$) in white children with high birth weight, whereas significant changes of mean SBP did not occur until early and late puberty for those with normal birth weight (EP→LP; $\Delta_{SBP} = 4.5$ mm Hg; $P < 0.05$) (Table 2).

In black children, mean SBP remained fairly high and stable across pubertal status in those with low birth weight. On the other hand, among those with high birth weight, a significant increase in SBP was observed from early to late puberty (EP→LP; $\Delta_{SBP} = 7.5$, $P < 0.05$) rather than from pre-puberty to early puberty (as in white children). In black children with normal birth weight, a significant change of SBP was only detectable from pre-puberty to late puberty (PP→LP; $\Delta_{SBP} = 4.7$, $P < 0.05$).

Multivariable longitudinal linear mixed-effects analysis

After initial adjustment for gender, ethnicity, age, and pubertal status, birth weight was marginally inversely associated with SBP at pre-puberty (Model 1, $\beta = -1.9$, $P < 0.10$), but the interaction term between birth weight and pubertal status was not statistically significant (Table 3; Model 1, $\beta = 0.8$, $P > 0.10$). However, the inverse relation between birth weight and SBP at pre-puberty became stronger after additional adjustment for body composition measures such as total fat mass ($\beta = -2.4$, $P < 0.05$), percent fat ($\beta = -2.3$, $P < 0.05$), visceral fat ($\beta = -2.6$, $P < 0.05$), subcutaneous fat ($\beta = -2.9$, $P < 0.05$), or BMI z-score ($\beta = -2.3$, $P < 0.05$). In addition, the effect of the interaction term between birth weight and pubertal status became larger and marginally significant after adjusting for total fat mass ($\beta = 1.6$, $P < 0.10$), visceral fat ($\beta = 2.0$, $P < 0.10$), subcutaneous fat ($\beta = 2.0$, $P < 0.10$), or BMI z-score ($\beta = 1.6$, $P < 0.10$), suggesting that the association between birth weight and SBP varied by pubertal stages.

Discussion

The present study used longitudinal data to examine the association between birth weight, puberty, and the changes of SBP in a cohort of white and black children. The results demonstrated that birth weight was inversely associated with SBP in children during pre-pubertal stage, but this association was
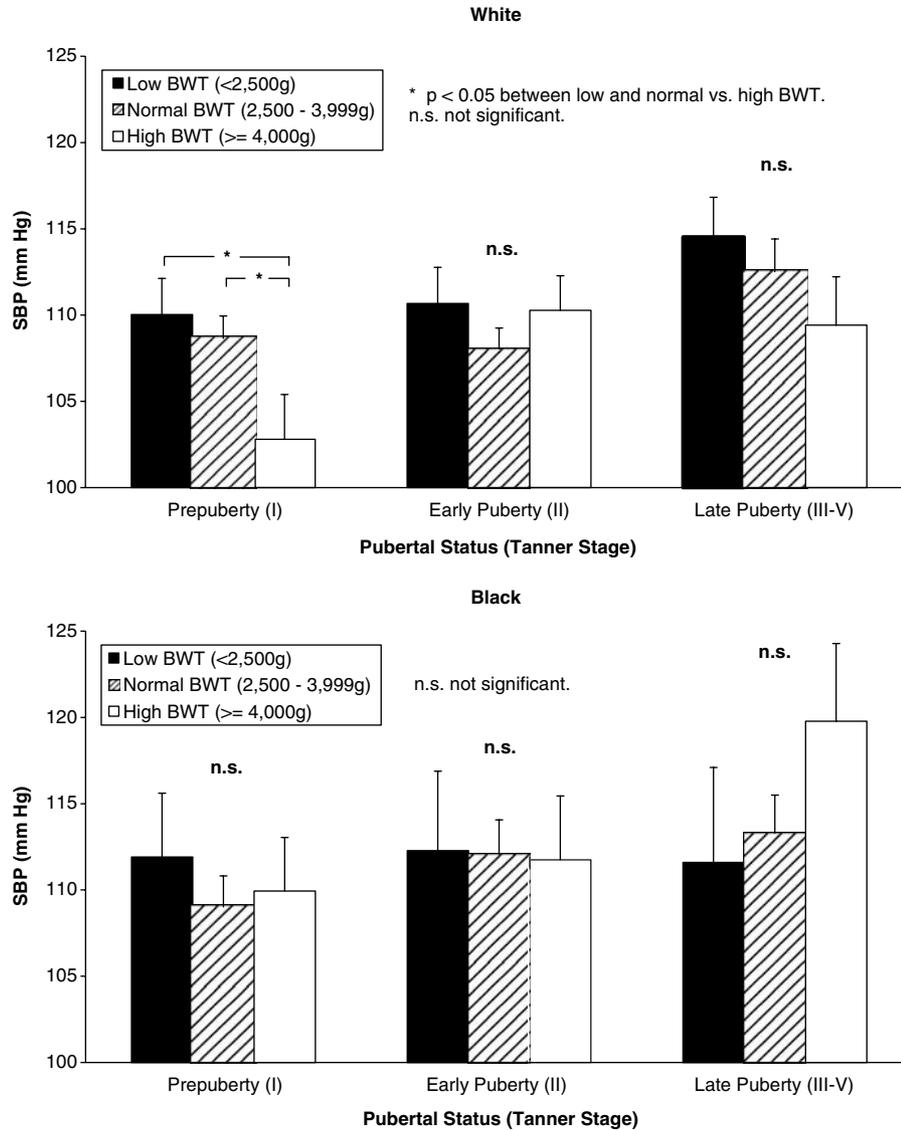
Figure 1 Unadjusted means of SBP by pubertal status and birth weight categories for white and black children. *T*-tests were performed to compare the differences of SBP between birth weight categories at each pubertal stage using PROC MIXED procedure in SAS. Pubertal status was defined as pre-puberty (Tanner stage I), early puberty (Tanner stage II), and late puberty (Tanner stages III–V). Abbreviations: BWT, birth weight; NS, not significant; SBP, systolic blood pressure. $P<0.05$ between low and normal vs high BWT.

Table 2 Unadjusted mean changes of SBP (mm Hg) from pre-puberty to early and late puberty by birth weight categories in white and black children and adolescents

| Birth weight | n | White (n = 57) | | | | Black (n = 41) | | | |
| | | | Δ_{SBP} | | | | Δ_{SBP} | | |
		Mean at PP	PP→EP	PP→LP	EP→LP	Mean at PP	PP→EP	PP→LP	EP→LP
Low (<2500 g)	19	110.0	0.8	3.4	2.6	111.9	0.2	0.2	0.0
Normal (2500–3999 g)	61	108.6	-0.5	4.0+	4.5*	109.0	3.1	4.7*	1.6
High (⩾4000 g)	18	102.8	8.1**	6.5*	−1.6	109.9	2.0	9.5*	7.5*

Abbreviations: EP, early puberty; LP, late puberty; PP, pre-puberty; SBP, systolic blood pressure.
+$P<0.1$, *$P<0.05$, **$P<0.01$ for testing null hypothesis that the change score of SBP is zero.

Table 3 Fixed effects of birth weight and pubertal status on SBP (mm Hg) adjusting for demographic and body composition measures

Predictor	Basic model[a]	Adjusted for total fat mass	Adjusted for % fat	Adjusted for IAAT	Adjusted for SAAT	Adjusted for BMI z-score
Time-invariant variable						
Gender, 1 = male 0 = female	−1.1 (1.1)	−0.6 (1.1)	−0.5 (1.1)	−2.1 (1.2)+	−1.0 (1.2)	−2.5 (1.0)*
Race, 1 = white 0 = black	−3.3 (1.1)**	−2.7 (1.0)**	−3.2 (1.0)**	−3.8 (1.2)**	−3.1 (1.2)*	−1.7 (1.0)+
Birth weight, -1 = LBW 0 = NBW 1 = HBW[b]	−1.9 (1.1)+	−2.4 (1.0)*	−2.3 (1.1)*	−2.6 (1.2)*	−2.9 (1.2)*	−2.3 (1.1)*
Time-variant variable						
Age (years)	0.5 (0.4)	0.3 (0.3)	0.7 (0.4)+	0.5 (0.4)	0.4 (0.4)	1.3 (0.4)**
Pubertal status, 0 = PP 1 = EP 2 = LP[c]	1.4 (0.9)	0.2 (0.9)	0.9 (0.9)	0.5 (1.1)	−0.1 (1.1)	−0.6 (0.8)
Total fat mass (log, kg)	—	4.99 (0.71)**	—	—	—	—
% Fat	—	—	0.03 (0.01)**	—	—	—
IAAT (log, cm²)	—	—	—	4.26 (1.03)**	—	—
SAAT (log, cm²)	—	—	—	—	3.29 (0.69)**	—
BMI percentile (%)	—	—	—	—	—	3.40 (0.47)**
Interaction term						
BWT × Tanner	0.8 (1.0)	1.6 (0.9)+	1.2 (1.0)	2.0 (1.1)+	2.0 (1.2)+	1.6 (1.0)+
Model fit statistic (BIC)[d]	3107	3058	3070	2344	2346	2893

Abbreviations: BMI, body mass index; IAAT, intra-abdominal adipose tissue; SAAT, subcutaneous abdominal adipose tissue; SBP, systolic blood pressure.
[a]Parameter estimates in the basic model were obtained using a mixed-effects procedure in SAS. Dependent variable = SBP; time-invariant variables included gender, race, and birth weight; time-variant variable included age, pubertal status; interaction term was the product of birth weight and pubertal status. The values in the table represent regression coefficients (standard errors).
[b]LBW = low birth weight (<2500 g), NBW = normal birth weight (2500–3999 g), HBW = high birth weight (⩾4000 g).
[c]Pubertal status was defined as PP = pre-puberty (Tanner stage I), EP = early puberty (Tanner stage II), and LP = late puberty (Tanner stage III through V).
[d]BIC = Bayesian Information Criterion; a smaller BIC represents a better model fit.
+$P<0.1$; *$P<0.05$; **$P<0.01$.

not statistically significant as they progressed to early or late puberty. SBP appeared to be at a persistently higher level from pre-puberty through puberty among children with low birth weight. However, SBP increased steadily from pre-puberty to early and late puberty in children with high birth weight, indicating a 'catch-up' increase along with sexual maturation in this group. Overall, the association between birth weight and SBP appeared to be attenuated from pre-puberty to early or late puberty.

Previous studies have shown that birth weight was inversely related to SBP in diverse populations.[3] The results in our study that low birth weight was associated with higher SBP, especially in white pre-pubertal children, add support for the fetal origins hypothesis which proposes that undernutrition *in utero* and during infancy could permanently programme risk for developing cardiovascular diseases and the insulin resistance syndrome, including raised blood pressure.[20] One mechanism may be that children with lower birth weight have a reduced renal mass owing to poor maternal nutrition *in utero*, which predisposes them to the greater risk of raised blood pressure and hence essential hypertension in adulthood.[21]

There is little evidence thus far to support this hypothesis in black children. The insignificant correlation between birth weight and SBP in black children in the present study is similar to previous studies in black children,[22] adolescents,[6,7] and

adults.[23] Furthermore, high rather than low birth weight may be related to a higher blood pressure in late pubertal black children as shown in the current study and one previous study.[8] Previous studies have shown that high birth weight may be associated with increased risk of diabetes.[24] and obesity[25,26] The mechanism for this inconsistency in the black population is unknown. The disparity in the association between birth weight and SBP in white and black children may suggest a role of complex genetic predispositions or environmental influences,[27] or an interaction between these two factors. A recent study on the relationship between growth *in utero* and blood pressure in the next generation by Barker *et al.*[28] suggests possible contributions of both environmental and genetic factors to raised SBP.

Previous observations suggested that the lack of or weaker association between birth weight and blood pressure in adolescents may be owing to confounding effects of sexual maturation or growth.[29,30] Results of the present study showing that the association between birth weight and SBP was strong in pre-puberty but became attenuated in early and late puberty provided some evidence in support of this suggestion. Many factors such as pubertal changes in physiological, hormonal, or body composition variables may have contributed to this attenuation.[9,31] A previous longitudinal analysis from our group showed that the pubertal transition from Tanner stage I to Tanner stage III was associated with a 30% reduction in insulin sensitivity.[32] We

previously reported that birth weight was inversely associated with insulin resistance,[33] which may be, in turn, related to raised SBP.[34]

The association between birth weight and SBP appeared to be partially confounded by body composition. When one of the body composition measures (total fat mass, % fat mass, visceral fat, SAAT or BMI z-score) was adjusted in the multivariable mixed-effects models in addition to demographic variables, the association between birth weight and SBP became stronger, particularly for the model adjusting for visceral fat. This notion was supported by previous studies showing that visceral fat was strongly related to both birth weight[33] and SBP.[35] This finding suggests that when examining the association between birth weight and SBP, adjustment for body composition, particularly visceral adiposity, is essential.

There were several strengths in our study. First, our study used longitudinal data of a cohort of white and black children and adolescents aged 4–12 years at baseline to examine the relation between birth weight, puberty, and SBP prospectively for an average of 4.4 years. Second, sexual maturation of adolescents was assessed directly by a paediatrician. Third, we assessed the body composition using DXA and CT scanning and examined the possible confounding effects of these body composition measures in the association between birth weight and SBP. Finally, we used a mixed-effects modelling approach to analyse our longitudinal data, which appropriately accounted for the correlations among repeated measures within each subject and for randomly missing values of SBP.

One weakness of this study was that we were unable to distinguish children with normal gestation time from those with premature delivery. However, the interpretation of our findings might not be affected by this limitation because previous studies showed that the effect of birth weight on SBP was independent of duration of gestation.[36] Another limitation of this study was based on the use of parental recall of birth weight. However, several previous studies have suggested that recalled birth weights are sufficiently accurate for use in children up to 16 years of age regardless of socioeconomic status and maternal education.[37,38] Thus, parent-reported birth weights were used in numerous previous studies.[23,30,33,36] In addition, the sample size at our baseline survey was relatively small, particularly for black children; therefore, cautions may be needed for interpreting the nonsignificant association between birth weight and SBP among black children. However, our results were in agreement with that of previous studies, which reported nonsignificant relations of birth weight to SBP among black children and adolescents.[3,6,7] Furthermore, the longitudinal design of our study with upto six repeated measures for SBP could improve power for detecting the differences in SBP among birth weight categories or pubertal stages.[39]

Despite these limitations, the present study for the first time examined the role of puberty as a potential effect modifier in the association between birth weight and SBP in children. SBP changes across pubertal stages with different patterns between those with low vs high birth weight. In addition, puberty may modify the association between birth weight and SBP such that birth weight was significantly associated with SBP in pre-pubertal children, but this association was attenuated in early or late pubertal children. The inconsistent findings on the association between birth weight and SBP during adolescence may be partially attributed by sexual maturation.

What is known about the topic

- The fetal origins hypothesis proposes that growth retardation *in utero* and during infancy may lead to persisting changes in blood pressure in adult life.[1]
- A large number of studies have shown that birth weight, a proxy indicator of total fetal growth *in utero* is inversely associated with SBP in young children and adults.[3]
- This association is inconsistent during adolescence.[3]

What this study adds

- Using longitudinal data, we demonstrated that birth weight was inversely associated with SBP in children during pre-pubertal stage, but this association was not statistically significant as children progressed to early or late puberty.
- SBP appeared to be at a persistently higher level from pre-puberty to late puberty among children with low birth weight.
- Puberty may serve as an effect modifier for the association between birth weight and SBP during adolescence.

Acknowledgements

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