

Research Article

The Relationship between Birthweight and Longitudinal Changes of Blood Pressure Is Modulated by Beta-Adrenergic Receptor Genes: The Bogalusa Heart Study

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This study examines the genetic influence of β -adrenergic receptor gene polymorphisms (β_2 -AR Arg16Gly and β_3 -AR Trp64Arg) on the relationship of birthweight to longitudinal changes of blood pressure (BP) from childhood to adulthood in 224 black and 515 white adults, aged 21–47 years, enrolled in the Bogalusa Heart Study. Blacks showed significantly lower birthweight and frequencies of β_2 -AR Gly16 and β_3 -AR Trp64 alleles and higher BP levels and age-related trends than whites. In multivariable regression analyses using race-adjusted BP and birthweight, low birthweight was associated with greater increase in age-related trend of systolic BP (standardized regression coefficient $\beta = -0.09$, $P = .002$) and diastolic BP ($\beta = -0.07$, $P = .037$) in the combined sample of blacks and whites, adjusting for the first BP measurement in childhood, sex, age, and gestational age. Adjustment for the current body mass index strengthened the birthweight-BP association. Importantly, the strength of the association, measured as regression coefficients, was modulated by the combination of β_2 -AR and β_3 -AR genotypes for systolic ($P = .042$ for interaction) and diastolic BP age-related trend ($P = .039$ for interaction), with blacks and whites showing a similar trend in the interaction. These findings indicate that the intrauterine programming of BP regulation later in life depends on β -AR genotypes.

1. Introduction

Low birthweight is an indicator of intrauterine growth retardation. The relationship between low birthweight and elevated blood pressure (BP) levels later in life and the mechanisms of fetal programming have been extensively studied since the fetal origins hypothesis was proposed [1–4]. However, evidence for the developmental programming of adult hypertension thus far is still inconsistent, particularly in pediatric populations [5–7]. Recently, researchers have outlined substantive challenges to the birthweight-BP association. One of the criticisms is the inappropriate use of statistical methodology and improper interpretation of epidemiologic analyses in support of the fetal origins hypothesis [3, 8–12].

β -adrenergic receptors (β -ARs) play a pivotal role in regulation of cardiac, pulmonary, vascular, endocrine, and

sympathetic nervous systems [13, 14]. Three β -AR subtypes (β_1 -AR, β_2 -AR, and β_3 -AR) are pharmaceutically characterized [14, 15]. Polymorphisms of the β -AR genes have been found to be associated with multiple cardiovascular risk variables, including hemodynamic factors such as heart rate, vasodilation, and BP [16]. Further, the β -AR genes are associated with preterm birth and modulate the relationship between birthweight and insulin resistance in later life [17–20]. However, whether genetic variations in the β -AR genes modulate the influence of birthweight on BP is not known, especially for BP longitudinal changes.

As part of the Bogalusa Heart Study, a long-term biracial (black-white) community-based epidemiologic study of the early natural history of cardiovascular disease beginning in childhood since 1973 [21], the present study examines the modulating effect of β_2 -AR Arg16Gly and β_3 -AR Trp64Arg polymorphisms on the association between birthweight and

longitudinal changes of BP from childhood to adulthood in black and white asymptomatic younger adults enrolled in the Bogalusa Heart Study.

2. Methods

2.1. Study Cohort. In the community of Bogalusa, LA, 9 cross-sectional surveys of children aged 4–17 years between 1973 and 1994 and 10 cross-sectional surveys of young adults aged 18–48 years between 1987 and 2009, who had been previously examined as children, were conducted for cardiovascular risk factors. This panel design of repeated cross-sectional examinations conducted approximately every 3 years has resulted in serial observations from childhood to adulthood. A total of 739 adult subjects (515 whites and 224 blacks; 42.2% males; age range = 21–47 years; mean age = 36.7 years) who had β -AR gene polymorphism genotype data formed the study cohort for this report. The study subjects have been serially examined 4–14 times (at least 2 times each in childhood and adulthood) for BP over an average of 26.7 years, with 5793 observations. Birthweight records of the participants were obtained from the Office of Health Statistics in New Orleans, Louisiana. All subjects in this study gave informed consent at each examination, and for those under 18 years of age, consent of a parent/guardian was obtained. Study protocols were approved by the Institutional Review Board of the Tulane University Health Sciences Center.

2.2. General Examinations. All surveys since 1973 followed the same protocols, and procedures for the general examinations were described elsewhere [22]. Height and weight were measured twice to ± 0.1 cm and to ± 0.1 kg, respectively. Body mass index (BMI, weight in kilograms divided by the square of the height in meters) was used as a measure of overall adiposity. BP levels were measured on the right arm of subjects in a relaxed, sitting position by 2 nurses (3 replicates each). The first and fourth Korotkoff phases were used to determine systolic (SBP) and diastolic (DBP) blood pressures, respectively. Means of replicate readings were used for analyses. For subjects ($n = 57$) who were on medications for hypertension at the time of examination, we adjusted the recorded BP levels by adding 10 mm Hg to SBP and 5 mm Hg to DBP, based on average treatment effects [23, 24].

2.3. Genotyping. Genotyping of β_2 -AR Arg16Gly and β_3 -AR Trp64Arg polymorphisms was performed using the TaqMan assay (Applied Biosystems, Inc., Foster, CA) in the laboratory of the Human Genetics Center, University of Texas School of Public Health, 1200 Hermann Pressler, E447, Houston. Amplification conditions and information on primer and probe sequences have been previously described [25, 26]. The reproducibility of genotyping of the three polymorphisms was 100% assessed by 64 blind duplicates.

2.4. Statistical Methods. Cubic growth curves of BP measured repeatedly at multiple time points from childhood to adulthood were established by race and sex groups using a

random effects model by SAS Proc MIXED. As shown in Figure 1 using SBP of two white males as an example, the area under the curve (AUC) was calculated as the integral of the growth curve parameters during the follow-up period for each individual [27, 28]. Total AUC (baseline AUC + incremental AUC) is considered a measure of long-term levels. Incremental AUC determined by within-individual variability represents a combination of linear and nonlinear longitudinal trends and was used as the measure of age-related trend. Since individuals had different follow-up periods, the AUC values were divided by the number of follow-up years for further analyses. The AUC measures have advantages over other longitudinal analysis models in that they measure both the long-term levels and trends.

Race differences in distributions of genotypes and allele frequencies were tested using a contingency chi-square test. Differences in mean values of continuous study variables between race-sex groups were tested by analysis of covariance models. The rate of fetal growth was calculated as birthweight in kilograms/gestational age in weeks for each individual, and then multiplied by the mean gestational age of the sample to make the scale close to the original values. The gestational age-adjusted birthweight was used in all subsequent analyses. The impact of genotype and birthweight on BP was examined by multiple regression models by race and in the total sample, adjusting for sex, current age, and race (for the total sample). In order to examine the impact of BMI adjustment on the relation between birthweight and BP, two types of regression analyses were performed, with and without adjustment for current BMI. In addition to the above covariates, the baseline BP (the first measurement in childhood) was also included in the regression models for the age-related trend analyses to control for the regression-to-the-mean bias because the baseline values were closely associated with the age-related trend measured by incremental AUC. The differences in slopes (birthweight-genotype interaction on BP) were tested using a homogeneity-of-slopes model, a regression interaction model, among genotype groups. Due to significant differences in BP levels, birthweight and gene allele frequencies between blacks and whites, BP measures (childhood, adulthood, AUC, and age-related trend), and birthweight were standardized into Z-scores (mean = 0 and SD = 1) by race groups prior to regression analyses to remove the influence of population stratification.

3. Results

Table 1 shows the mean levels of study variables in childhood, adulthood, and at birth, and AUC values by race and sex. The first measurement of childhood SBP and DBP did not significantly differ between races or sexes. The last measurement of adulthood SBP and DBP differed significantly by race (blacks > whites) and by sex (males > females) except for sex difference in blacks. Total AUC and age-related trend of SBP showed significant race (blacks > whites) and sex (males > females) differences; significant sex differences (males > females) were noted for total DBP AUC in both races and a significant race difference (blacks > whites) in females only. The age-related trend of DBP showed

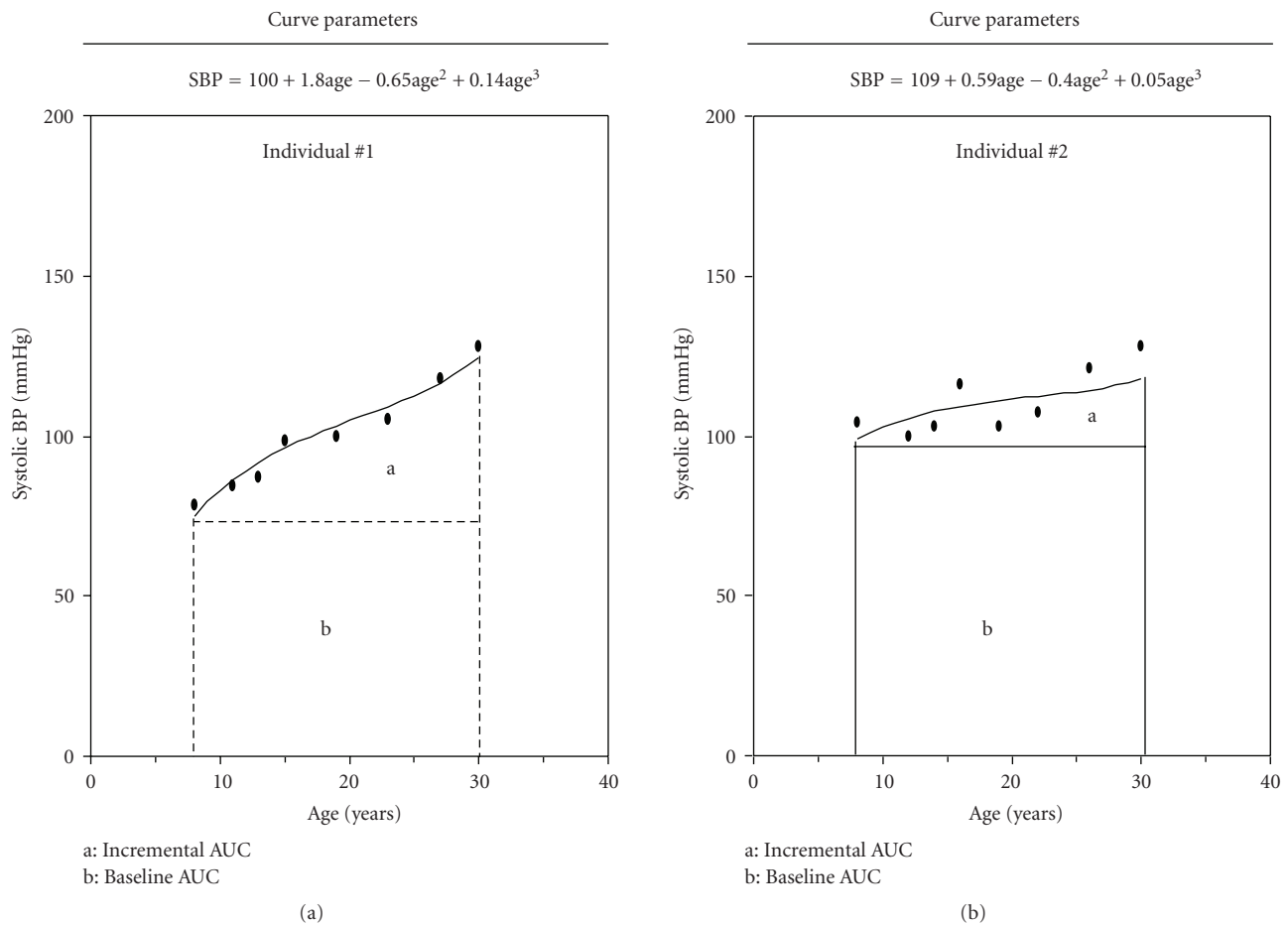


FIGURE 1: Illustration for Calculation of Area under the Curve of Systolic Blood Pressure: The Bogalusa Heart Study.

a significant race difference (blacks > whites) among females only and a sex difference (males > females) among whites only. Blacks had significantly lower birthweight than whites, but males had significantly higher birth weight than females only among whites.

Blacks displayed a lower alleles frequencies of β_2 -AR Gly16 (0.507 versus 0.630, $P < .001$) and β_3 -AR Trp64 (0.895 versus 0.925, $P = .008$) than whites. The genotype distributions were in accordance with Hardy-Weinberg equilibrium expectations in blacks and whites (data not shown).

Standardized regression coefficients for β -AR genotypes, race-adjusted birthweight, and covariates for race-adjusted BP are presented in two models in Table 2. Since race-birthweight and race-gene interactions on BP were not significant, the results of the total sample with blacks and whites combined are displayed. Race was not included in the models because birthweight and BP were adjusted for race by standardization prior to the regression analyses. The associations between race and Z-scores of BP measures (childhood, adulthood, AUC and age-related trend) were no longer significant ($P = .725-.896$). In model I with current BMI included, childhood age and current BMI, but not birthweight, were associated with the first SBP measurement in childhood. Female sex, older age, higher adulthood BMI,

and lower birthweight were significantly associated with higher values of the last SBP measurement in adulthood, total SBP AUC, and SBP age-related trend. Birthweight was significantly associated with adulthood DBP levels and age-related trend; however, the association was weaker than for SBP. In addition, the first BP measurement in childhood (the baseline value) was also a significant predictor of the age-related trend of both SBP and DBP. In model II without current BMI included, the effect of birthweight on SBP was attenuated to some extent for adulthood SBP, SBP AUC, and the age-related trend, but they were still significant; the regression coefficients for other covariates did not considerably changed compared with those in model I. Birthweight was associated with the age-related trend only for DBP in model II. The main effect of individual β_2 -AR and β_3 -AR polymorphism genotype on SBP and DBP was not significant in both model I and model II without any interaction terms included.

Figure 2 illustrates the magnitude of the association of birthweight with SBP age-related trend, measured as standardized regression coefficients, by the combination of β_2 -AR and β_3 -AR genotypes. The regression coefficients of SBP age-related trend on birthweight were derived from multiple regression models using race-adjusted birthweight and BP

TABLE 1: Mean Levels and SD of Study Variables by Race and Sex.

	Whites				Blacks				<i>P</i> -value for difference	
	Males (<i>n</i> = 226)		Females (<i>n</i> = 289)		Males (<i>n</i> = 86)		Females (<i>n</i> = 138)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Race	Sex
Childhood										
Age (year)	10.3	2.9	9.7	3.0	10.0	2.9	9.6	2.7	NS	<.05 w
Systolic BP (mm Hg)	100.8	9.4	99.4	9.1	99.8	11.8	99.0	9.6	NS	NS
Diastolic BP (mm Hg)	61.7	8.2	62.2	8.8	62.4	8.0	61.0	8.6	NS	NS
Adulthood										
Age (year)	37.6	5.1	36.7	5.5	35.0	5.9	35.9	5.7	<.01 m	NS
Systolic BP (mm Hg)	117.1	10.7	109.5	10.8	122.8	15.2	119.3	17.3	<.01	<.05 w
Diastolic BP (mm Hg)	78.9	8.0	73.8	7.9	81.2	11.8	78.7	11.5	<.05	<.05
AUC Values (mm Hg)										
Systolic BP total	113.1	7.2	106.9	5.5	115.0	7.6	110.7	6.8	<.05	<.01
Systolic BP trend	11.8	5.1	7.5	5.3	15.6	6.6	11.8	6.2	<.01	<.01
Diastolic BP total	72.3	5.8	69.7	4.5	72.3	6.2	70.8	5.0	<.01 f	<.05
Diastolic BP trend	10.8	3.3	8.1	4.0	10.8	3.8	9.7	4.2	<.01 f	<.01 w
At Birth										
Gestational age (week)	39.8	1.6	39.6	2.0	39.2	2.3	39.5	1.8	<.05 m	NS
Birth weight (kg)	3.46	0.5	3.34	0.6	3.09	0.6	3.00	0.6	<.01	<.05 w
Birth weight (kg) [†]	3.44	0.5	3.33	0.5	3.10	0.5	3.00	0.5	<.01	<.05 w

BP: blood pressure; AUC: area under the curve.

NS : *P* > .05; f : females only; m: males only; w : whites only.

[†] adjusted for gestational age.

TABLE 2: Standardized regression coefficients of race-adjusted blood pressure on birth weight, β -adrenergic receptor genotypes, and covariates.

	Systolic BP				Diastolic BP			
	First	Last	AUC	Trend	First	Last	AUC	Trend
Model I								
Childhood BP	—	—	—	-0.43**	—	—	—	-0.44**
Female sex	-0.05	-0.24**	-0.37**	-0.38**	0.02	-0.22**	-0.19**	-0.28**
Age	0.22**	0.19**	0.17**	-0.20**	0.28**	0.25**	0.34**	-0.02
BMI	0.16**	0.36**	0.26**	0.23**	0.06	0.34**	0.21**	0.26**
Birth weight [†]	-0.004	-0.11**	-0.11**	-0.10**	0.04	-0.07*	-0.07*	-0.08*
β_2 -AR genotype	-0.04	-0.03	-0.04	0.01	-0.05	-0.02	-0.03	-0.01
β_3 -AR genotype	-0.04	-0.01	-0.02	0.02	-0.05	-0.01	-0.05	-0.01
Model II								
Childhood BP	—	—	—	-0.40**	—	—	—	-0.42**
Female sex	-0.05	-0.25**	-0.38**	-0.39**	0.01	-0.24**	-0.20**	-0.29**
Age	0.23**	0.22**	0.19**	-0.19**	0.28**	0.28**	0.36**	-0.01
Birth weight [†]	-0.004	-0.09**	-0.10**	-0.09**	0.04	-0.05	-0.06	-0.07*
β_2 -AR genotype	-0.05	-0.05	-0.05	-0.02	-0.05	-0.04	-0.04	-0.02
β_3 -AR genotype	-0.04	-0.01	-0.02	0.02	-0.05	-0.01	-0.05	-0.01

First: the first measurement in childhood; last: the last measurement in adulthood; BP: blood pressure;

AUC: area under the curve; BMI: body mass index.

β_2 -AR genotype = β_2 -adrenergic receptor Arg16Gly (coding: 0, 1, and 2 of Arg alleles).

β_3 -AR genotype = β_3 -adrenergic receptor Trp64Arg (coding: 0 = Arg/Arg and Trp/Arg, 1 = Trp/Trp).

[†] adjusted for gestational age.

* *P* < .05; ** *P* < .01.

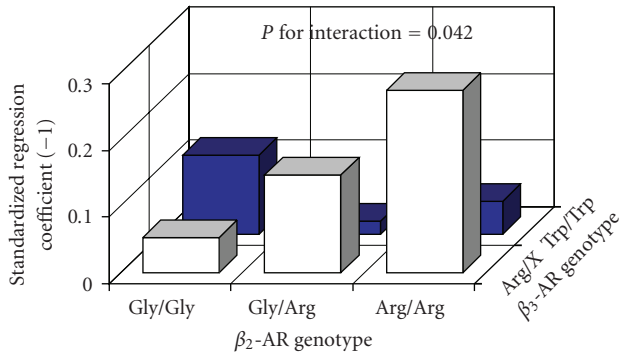


FIGURE 2: Relationship between Age-related Trend of Systolic Blood Pressure and Birth Weight by β_2 -AR Arg16Gly and β_3 -AR Trp64Arg Genotypes: The Bogalusa Heart Study Arg/x stands for Arg/Trp and Arg/Arg genotypes combined.

in terms of race-specific Z-scores, adjusting for the first SBP measurement in childhood, adulthood age, and sex, without any interaction terms. Because the regression coefficients were all negative, standardized regression coefficients $\times (-1)$ were presented in Figure 2 for convenience. The regression coefficients showed opposite trends with increasing number of the β_2 -AR Arg16 alleles in the two β_3 -AR genotype groups. The birthweight effect on SBP trend ($\beta = -0.12$, $P = .014$, $n = 224$) was the greatest among individuals who had β_3 -AR Trp/Trp and β_2 -AR Gly/Gly genotypes; having β_3 -AR Arg/x and β_2 -AR Arg/Arg genotypes was associated with the highest effect of $\beta = -0.28$ ($P = .257$, $n = 21$). The overall 3-way interaction (birthweight- β_2 -AR- β_3 -AR) was significant ($P = .042$), suggesting that the relationship between SBP age-related trend and birthweight depends on the combination of β_2 -AR and β_3 -AR genotypes. Further, the interaction of individual polymorphisms with birthweight on SBP trend was not significant in the 2-way interaction models without a 3-way interaction term included (data not shown).

Figure 3 presents the strength of the association of birthweight with SBP age-related trend by the combination of β_2 -AR and β_3 -AR genotypes in blacks and whites using the race-specific Z-scores of birthweight and SBP age-related trend. The pattern of the standardized regression coefficients of SBP age-related trend on birthweight by β_2 -AR and β_3 -AR genotypes was similar in the two race groups; the four-way interaction (race-birthweight- β_2 -AR- β_3 -AR) was not significant ($P = .523$).

For DBP age-related trend, a similar pattern of regression coefficients to SBP was observed with respect to β_2 -AR and β_3 -AR genotypes; the birthweight- β_2 -AR- β_3 -AR interaction on DBP age-related trend was significant ($P = .039$) in the total sample. Blacks and whites did not show any difference in the birthweight-genotype interaction on DBP age-related trend ($P = .682$).

4. Discussion

Many studies have shown that low birthweight is inversely associated with high BP and hypertension in later life [1–4]

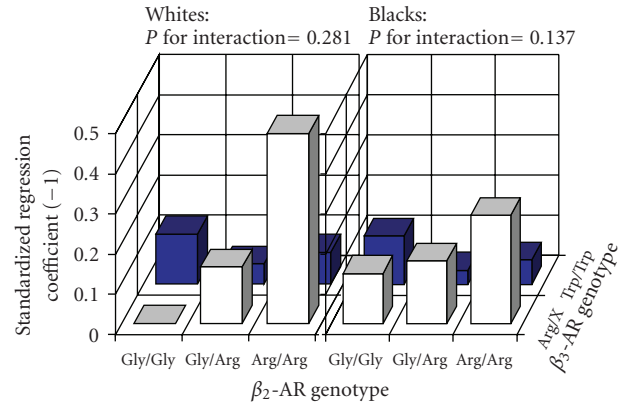


FIGURE 3: Relationship between Age-related Trend of Systolic Blood Pressure and Birth Weight by β_2 -AR Arg16Gly and β_3 -AR Trp64Arg Genotypes in Blacks and Whites: The Bogalusa Heart Study Arg/x stands for Arg/Trp and Arg/Arg genotypes combined.

although there exist criticisms and concerns [3, 8–12]. Systematic reviews of the literature suggest an inverse linear relationship between SBP and birthweight of ~ 1 – 2 mm Hg/kg [29]. However, most previous studies in this regard focused on BP levels; limited information is available on the influence of birthweight on longitudinal changes of BP. The present community-based study demonstrates an adverse effect of low birthweight on BP in terms of adulthood BP, the long-term levels, and increasing trend from childhood to young adulthood, especially for SBP. However, the birthweight-BP association was not noted in childhood in the study cohort.

The hypothesis of the fetal origins of hypertension proposed several possible mechanisms linking reduced fetal growth and elevated BP in later life, such as persisting changes in vascular structure, including loss of elasticity in vessel walls, effects of glucocorticoid hormones, and abnormalities of nephrogenesis [1, 2]. Furthermore, low birthweight may be associated with elevated sympathetic nervous system activity in adulthood, as measured by heart rate, pre-ejection period, and respiratory sinus arrhythmia [30, 31]. These findings suggest that increased sympathetic nervous system activity established in utero may be one of the mechanisms linking low birthweight with high BP in adults. Although genetic factors have been found to play a role in the birthweight-BP relationship in family and twin studies [31–33], limited information on specific genes has become available. We noted in the current study that the association between birthweight and age-related trend of BP was dependent on the combination of β_2 -AR and β_3 -AR genotypes, suggesting that β -AR gene variants play a role, in an interactive manner, in BP regulation of adults who have a low birthweight, an indicator of fetal growth restriction.

It is well established that both BP regulation and birthweight are genetically determined [34, 35]. Candidate genes and chromosomal regions have been identified for birthweight [36, 37]. β -ARs are an important component of the sympathetic nervous system [13, 14]. Polymorphisms of the β -AR genes have been found to be associated with

multiple cardiovascular risk factors, including hemodynamic status and obesity measures. Previous studies have shown that β_2 -AR Gly16 and β_3 -AR Arg64 alleles were associated with BP elevation or hypertension, although the findings on β_2 -AR Gly16 allele have been questioned [16, 38]. In the present study, we did not find a significant association of β_2 -AR Arg16Gly and β_3 -AR Trp64Arg polymorphisms, individually, with BP in terms of childhood, adulthood, and long-term BP levels, and the age-related trend. However, the two genes were found to interactively influence the relationship of birthweight to longitudinal changes of BP. Individuals who were born a lower weight and have β_2 -AR Arg/Arg and β_3 -AR Arg allele or β_2 -AR Gly/Gly and β_3 -AR Trp/Trp genotypes are prone to have a faster increase in BP after birth compared with those having a normal birthweight and other β_2 -AR and β_3 -AR genotypes. Data on 3-way interaction (birthweight- β_2 -AR- β_3 -AR) on BP, which is a complex interplay, have not been previously reported. Further studies with multiple polymorphisms of the two genes are needed to confirm the findings in this study with respect to the possible important loci which are in linkage disequilibrium with β_2 -AR Arg16Gly and β_3 -AR Trp64Arg polymorphisms.

In the United States, blacks have a greater prevalence of both low birthweight and hypertension than whites; however, it is not yet established that excess risk of hypertension in blacks is programmed in utero [39]. In some studies black children showed a weaker birthweight-BP association than white children, or none at all [40–43]. A weaker birthweight-BP association in blacks was also observed in our previous study in a separate cohort [44]. However, the modulating effect of β_2 -AR and β_3 -AR genes, individually or in combination, on the association between birthweight and longitudinal changes of BP did not differ between blacks and whites in the present study. In addition to race differences in birthweight and BP, β_2 -AR and β_3 -AR gene allele frequencies also differed significantly between blacks and whites in this study cohort. Strong correlations among these study variables would lead to a serious bias resulted from population stratification when blacks and whites were combined for analysis. For this reason, BP and birthweight were standardized by race groups, and then race-specific Z-scores were used in association and interaction analyses in the present study.

It is well known that size at birth is strongly related to fetal genotype, uterine environment, and a number of maternal factors including parity, length of gestation, mother's adult size, mother's own birthweight, as well as mother's genotype [34, 45]. Because of the correlation of maternal and fetal genotypes of multiple relevant genes, maternal genotypes are expected to have a confounding effect on the birthweight-BP relationship as well as its genetic modulation by β_2 -AR and β_3 -AR gene polymorphisms noted in this study. However, mother's genotype data are not available in our cohort. Another limitation of this community-based study is that only one single polymorphism was typed in each of the two genes under study.

In summary, we found in the current study that low birth weight was associated with a greater increase in BP levels

from childhood to adulthood. This relationship was modulated by the combination of β_2 -AR and β_3 -AR genotypes. These findings support the emerging concept of intrauterine programming and its pathophysiologic consequences after birth and underscore the role of genetic factors in the fetal origins of hypertension later in life. Since no data in this regard are available for comparison, our findings need to be replicated in other populations.

Acknowledgments

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