Genetic and environmental influences on blood pressure variability

Xu, Xiaojing; Ding, Xiuhua; Zhang, Xinyan; Su, Shaoyong; Treiber, Frank A.; Vlietinck, Robert; Fagard, Robert; Derom, Catherine; Gielen, Marij; Loos, Ruth J. F.

Published in:
Journal of Hypertension

DOI:
10.1097/HJH.0b013e32835e2a4a

Publication date:
2013

Original Article

Genetic and environmental influences on blood pressure variability: a study in twins

Xiaojing Xu[a], Xiuhua Ding[a], Xinyan Zhang[b], Shaoyong Su[a], Frank A. Treiber[c], Robert Vlietinck[d], Robert Fagard[e], Catherine Derom[d], Marij Gielen[f,g], Ruth J.F. Loos[h,i,j], Harold Snieder[k], and Xiaoling Wang[a]

Objectives: Blood pressure variability (BPV) and its reduction in response to antihypertensive treatment are predictors of clinical outcomes; however, little is known about its heritability. In this study, we examined the relative influence of genetic and environmental sources of variance of BPV and the extent to which it may depend on race or sex in young twins.

Methods: Twins were enrolled from two studies. One study included 703 white twins (308 pairs and 87 singletons) aged 18–34 years, whereas another study included 242 white twins (108 pairs and 26 singletons) and 188 black twins (79 pairs and 30 singletons) aged 12–30 years. BPV was calculated from 24-h ambulatory blood pressure recording.

Results: Twin modeling showed similar results in the separate analysis in both twin studies and in the meta-analysis. Familial aggregation was identified for SBP variability (SBPV) and DBP variability (DBPV) with genetic factors and common environmental factors together accounting for 18–40% and 23–31% of the total variance of SBPV and DBPV, respectively. Unique environmental factors were the largest contributor explaining up to 82–77% of the total variance of SBPV and DBPV. No sex or race difference in BPV variance components was observed. The results remained the same after adjustment for 24-h blood pressure levels.

Conclusions: The variance in BPV is predominantly determined by unique environment in youth and young adults, although familial aggregation due to additive genetic and/or common environment influences was also identified explaining about 25% of the variance in BPV.

Keywords: blacks, blood pressure variability, heritability, meta-analysis, twin study

Abbreviations: ABP, ambulatory blood pressure; AIC, Akaike's information criterion; BP, blood pressure; BPV, blood pressure variability; CI, confidence intervals; DBPV, DBP variability; EFPTS, East Flanders Prospective Twin Survey; GEE, generalized estimating equations; MZm, onozygotic; SBPV, SBP variability

INTRODUCTION

Hypertension is the major risk factor for cardiovascular disease worldwide [1]. Traditionally, it was believed that blood pressure (BP) level on its own could account for all the hypertension-related cardiovascular risk, and for the reduction in risk due to antihypertensive drug treatment [2]. In recent years, researchers have paid more attention to BP variability (BPV), which is generally estimated by the SD of BP assessed by 24-h ambulatory BP (ABP) monitoring [3,4]. Increased 24-h BPV has been shown to be associated with a greater degree of target-organ damage [5]. Additionally, increased nighttime BPV was shown to be related with a higher rate of cardiovascular events [6,7], carotid atherosclerosis [8] and stroke [9]. Its prognostic value has been confirmed by randomized clinical trials for antihypertensive therapy that showed reductions in 24-h BPV in addition to reductions in mean BP in patients with normal BP levels [10,11].

It is well established that BP is a heritable trait with genetic factors contributing about 50% of its variance [12,13]. However, little is known about the heritability of BPV, despite its clinical importance. In the current study, we

Journal of Hypertension 2013, 31:690–697

[a]Department of Pediatrics, Georgia Prevention Institute, Georgia Health Sciences University, Augusta, [b]Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro, Georgia, [c]College of Nursing, Medical University of South Carolina, Charleston, South Carolina, [d]Department for Human Genetics, University Hospital Gasthuisberg, [e]Hypertension and Cardiovascular Rehabilitation Unit, Department of Cardiovascular Diseases, KU Leuven, Leuven, Belgium, [f]Research School for Nutrition, Toxicology and Metabolism (NUTRIM), [g]Cluster of Genetics and Cell Biology, Department of Complex Genetics, Maastricht University Medical Centre, Maastricht, The Netherlands, [h]Medical Research Council Epidemiology Unit, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK, [i]Faculty of Kinesiology and Rehabilitation Sciences, Department of Biomedical Kinesiology, University Hospital Gasthuisberg, KU Leuven, Leuven, Belgium, [j]Genetic of Obesity and Related Metabolic Traits Program, Institute for Personalized Medicine, Child Health and Development Institute, Department of Preventive Medicine, Mount Sinai School of Medicine, New York, New York, USA and [k]Department of Epidemiology, Unit of Genetic Epidemiology and Bioinformatics, University of Groningen, University Medical Center Groningen, The Netherlands

Correspondence to Dr Xiaoling Wang, MD, PhD, Department of Pediatrics, Georgia Prevention Institute, Georgia Health Sciences University, HS-1640, Augusta, GA 30912, USA. Tel: +1 706 721 6139; fax: +1 706 721 7150; e-mail: xwang@georgiahealth.edu

Received 7 September 2012 **Revised** 12 November 2012 **Accepted** 20 December 2012

J Hypertens 31:690–697

DOI:10.1097/HJH.0b013e32835e2a4a

analyzed ABP data from 1133 young individuals (495 twin pairs and 143 singletons) from two twin studies, including both white and black individuals, exploring for the first time the relative contribution of genetic and/or environmental sources of variance of BPV. We further examined whether these sources of variance of BPV are independent of mean BP. Finally, we investigated the extent to which these sources of variance depend on race or sex.

METHODS

Patients

The present study comprised twins from the Prenatal programming twin study, a nested study in East Flanders Prospective twin Survey (EFPTS), and the Georgia cardiovascular twin study.

The EFPTS study is a population-based survey, which is conducted in a homogenous white population. The EFPTS is still ongoing and contains data on all multiple births in the Belgian Province of East Flanders since 1964 [14]. Zygosity was determined at birth according to sequential analysis based on sex, fetal membranes, umbilical cord blood groups, placental alkaline phosphatase as well as DNA fingerprints [15]. The Prenatal programming twin study randomly contacted 803 pairs out of 2141 twin pairs registered between 1964 and 1982. Details of the selection process have been described previously [16]. Patients were excluded according to the following criteria: one or both twin pairs had died or suffered from major congenital malformation; one or both twin pairs had moved out of the area; participants were taking any kind of medication that could affect BP; female patients got pregnant before the start of the study, or twin pairs did not have accurate zygosity information. Eventually, 768 twins of 418 pairs (overall response, 52.1%) aged 18–34 years participated in the Prenatal programming twin study conducted from 1997 to 2000. The study was approved by the Local Medical Ethics Committee and all participants gave signed written informed consents. A total of 703 twins (308 pairs and 87 singletons, aged 18–34) with valid 24-h ambulatory BP (ABP) recordings were included in the current study.

The Georgia cardiovascular twin study was established in 1996, including roughly equal numbers of white and black youth (>500 twin pairs) with the purpose of exploring the change in relative influence of genetic and environmental factors on the development of cardiovascular risk factors [17,18]. All twin pairs were reared together and zygosity was determined using five standard microsatellite markers in DNA collected with buccal swabs. All the twins were recruited from the southeastern United States and were overtly healthy and free of any acute or chronic illness based on parental report. Study design, selection criteria and the criteria to classify twins as white or black for this study have been described previously [12,13]. During the second visit (from January 2001 to December 2003), ABP recording was offered to 678 twin patients between October 2001 to December 2003 with 493 patients taking this test. Compared with the patients who refused to take the ABP recording ($n = 185$), the patients who took this test were younger (17.3 vs. 18.2, $P < 0.01$) and more likely to be black (45 vs. 33%, $P < 0.01$). A total of 430 individuals including 187 pairs and 56 singletons aged 12–30 years of both races with valid 24-h ABP data were included in this study. The Institutional Review Board at the Medical College of Georgia had given approval for this study. Informed consent was provided by all patients and by parents if patients were less than 18 years.

Measurements

For the Prenatal programming twin study, the detailed measurement procedures have been reported for office BP, ABP recordings, as well as other characteristics [15]. Generally, all twins had a 2-h examination in the morning. Basic information was recorded, and clinical characteristics were measured according to established protocols. Office BP was measured on the right arm in triplicate, after 5 min rest in the supine position. The reported office BP was the average of these three recordings. The 24-h ABP monitoring device (SpaceLabs, Inc., Redmond, Washington, USA) was applied for 24-h BP and heart rate recordings. The cuff of the ABP monitor was applied to the nondominant arm by participants themselves after the investigator's introduction. This device was worn for one full 24-h period, starting in the morning (0600 to 0800 h) until they woke up the next day. The frequency of ABP monitoring was every 15 min from 0800 to 2200 h, and every 30 min between 2200 and 0800 h.

For the Georgia cardiovascular twin study, the recording procedures have also been described in detail [13,19]. Briefly, basic characteristics including height, weight and waist were measured and BMI was calculated. Office BP was measured at the 11th, 13th and 15th minute during a 15-min supine relaxation period. The average of the last two measures was reported as the office BP level. The cuff of the ABP monitoring device (Model 90207; SpaceLabs, Inc.) used in the Georgia cardiovascular twin study was also fitted to the nondominant arm to obtain ABP recordings for one full 24 h period. Between 0800 and 2200 h, measurements were taken every 20 min, and between 2200 and 0800 h, every 30 min.

For both of these studies, daytime was defined from 0800 to 2200 h, and night-time from 2400 to 0600 h. The transitional periods from 0600 to 0800 h and 2200 to 2400 h were not included in data analysis to diminish the interindividual variations in bed-rest time. The inclusion criteria of acceptable ABP recordings for both studies were based on guidelines from the European Society of Hypertension Working Group on BP Monitoring: SBP recording between 70 and 180 mmHg; DBP recording between 40 and 140 mmHg; pulse pressure between 20 and 140 mmHg; heart rate between 40 and 180 beats/min; at least 14 readings over the 14 h daytime period; at least six readings over the 6 h night period [20]. The 24-h weighted BP was defined as the mean of the daytime and night-time ambulatory BP weighted by the duration of daytime and night-time sub-periods. Likewise, the 24-h weighted BPV was defined as the mean of daytime and night-time ABP SDs weighted by the duration of daytime and night-time sub-periods.

Statistical analysis

The purposes of our analyses were to estimate the genetic and/or environmental sources of variance of BPV and the

extent to which they depend on sex, race and 24-h ABP level. We first conducted the analyses in each study separately, and then performed a meta-analysis of the two studies together. For the Georgia cardiovascular twin study, we conducted model-fitting analyses for black and white twins separately to estimate race-specific genetic and environmental variance components and investigate sex differences. Eventually, we combined both race groups into one model to test for potential differences in blacks and whites. For the Prenatal programming twins, sex differences were also tested.

Quantitative genetic model fitting

Structural equation modeling was used. Details of model fitting of twin data have been described elsewhere [21]. In short, the technique is based on the comparison of the variance-covariance matrices in monozygotic and dizygotic twin pairs and allows separation of the observed phenotypic variance into additive (A) or nonadditive (D) genetic components and shared (C) and unique (E) environmental components. The latter also comprises measurement error. Dividing each of these components by the total variance yields the different standardized components of variance, for example, the heritability (h^2), which can be defined as the ratio of additive genetic variance to total phenotypic variance.

Sex differences

Sex differences were examined by comparing a full model in which parameter estimates are allowed to differ in magnitude between men and women, with a reduced model in which parameter estimates are constrained to be equal across the sexes. In addition to those models, a scalar model was tested. In a scalar model, heritabilities are constrained to be equal across sexes, but total variances may be different. All (nonstandardized) variance components for women are constrained to be equal to a scalar multiple, k^2, of the male variance components, such that $h_f^2 = k^2 h_m^2$, $c_f^2 = k^2 c_m^2$, $e_f^2 = k^2 e_m^2$ and $d_f^2 = k^2 d_m^2$. As a result, the standardized variance components such as heritabilities are equal across sex, even though the unstandardized components differ.

Race differences

Race differences were, similar to sex differences, examined by comparing a full model in which parameter estimates are allowed to differ in magnitude between blacks and whites, with a reduced model in which parameter estimates are constrained to be equal across race. In addition to those models a scalar model was tested in a similar fashion as done for sex.

Meta-analysis of the two studies

This analysis was similar to the analysis testing sex or race differences. That is, we first examined differences between studies by comparing a full model in which parameter estimates are allowed to differ between the two studies, with a reduced model in which parameter estimates are constrained to be equal across studies. A scalar model was also tested in a similar fashion as done for race.

Effect of 24-h ambulatory blood pressure level

To explore whether the genetic and/or environmental sources of variance of BPV are dependent on BP level, we performed all model-fitting analyses before and after adjustment for 24-h ABP levels.

Model fitting procedure

Prior to analysis, effects of age were regressed out for all variables before using the residuals in model fitting. The significance of variance components A, C and E was assessed by testing the deterioration in model fit after each component was dropped from the full model. Standard hierarchic χ^2 tests were used to select the best fitting models in combination with Akaike's information criterion ($AIC = \chi^2 - 2df$). The model with the lowest AIC reflects the best balance of goodness of fit and parsimony.

Statistical software

Prior to analyses, all BPV parameters were log-transformed to obtain a better approximation of the normal distribution. Generalized estimating equations (GEEs) were used to analyze the sex and race difference in basic characteristics. Data management and the above statistics were performed by Stata SE, version 12 (StataCorp, College Station, Texas, USA). Genetic modeling was carried out with OpenMx Version 1.2 (http://openmx.psyc.virginia.edu/). OpenMx is a free and open source R-based software package, which is specifically designed for twin data analysis and allows estimation of a wide variety of advanced structural equation models [22].

RESULTS

The general characteristics of these two twin studies are presented in Table 1. In both twin studies, men had higher office BP, 24-h SBP and BPV than women. Men in the Georgia cardiovascular twin study also had higher 24-h DBP than women. In the Georgia cardiovascular twin study, blacks showed higher BMI, office BP and 24-h BP levels than whites. No significant differences were found for BPV between whites and blacks.

Table 2 presents intratwin pair correlation coefficients of BPV by race and zygosity. In both studies, twin correlations in monozygotic twin pairs were higher than those in dizygotic twin pairs, indicating there may be some genetic and/or common environment effect on BPV. We present the correlations collapsed over sex, because models that best explained the variance and covariance of BPV did not show any sex differences (see below).

The model fitting results were shown in Table 3. For both SBPV and DBPV, the model fitting suggested that there were no significant race or sex differences in variance component estimates (results not shown). In the Prenatal programming twin study, model fitting of SBPV showed ACE was the best-fitting model, which means the variance of SBPV depends on additive genetic factor (A), common environmental factor (C) as well as unique environmental factor (E). Although the model assuming the absence of the genetic component (CE vs. ACE model, $P = 0.39$) and the model assuming the absence of the common environmental factor fitted the data well (AE vs. ACE model, $P = 1.00$), the

TABLE 1. General characteristics of study subjects by sex and race for each of the two twin studies

Characteristics	Prenatal programming twin study ($n=703$)			Georgia cardiovascular twin study ($n=430$)				P	
	White male	White female	P Sex	White male	White female	Black male	Black female	Sex	Race
n	352	351		119	123	81	107		
Age (years)	25.6±4.7	25.4±4.6	0.89	17.0±3.6	17.0±3.0	16.8±3.0	17.6±3.8	0.80	0.69
BMI (kg/m^2)[a]	22.2±2.9	22.0±3.4	0.14	23.2±6.0	22.3±4.6	23.2±4.8	24.5±5.5	0.53	0.03
Office BP (mmHg)[a]									
SBP	129.8±11.1	120.0±11.1	<0.001	112.8±10.6	106.1±8.5	117.3±10.8	111.2±11.5	<0.001	<0.001
DBP	70.1±10.0	65.7±8.6	<0.001	56.6±6.5	58.2±5.8	60.2±7.1	62.6±8.2	0.001	<0.001
24-h weighted BP (mmHg)[a]									
SBP	119.3±7.6	114.3±7.8	<0.001	102.8±6.9	97.3±5.7	103.6±6.1	100.1±7.8	<0.001	0.01
DBP	68.2±6.0	68.7±6.2	0.30	81.7±6.1	79.7±5.2	82.9±5.3	82.0±7.4	0.01	0.01
SBPV	9.8±2.0	8.6±1.7	<0.001	9.6±2.0	8.5±1.7	9.5±1.7	8.9±1.8	<0.001	0.26
DBPV	8.7±1.7	8.2±1.6	<0.001	9.3±2.2	8.5±1.6	9.3±1.7	8.6±1.4	<0.001	0.50

BP, blood pressure; DBPV, diastolic blood pressure variability; SBPV, systolic blood pressure variability.
[a]Traits were adjusted for age prior to evaluation of sex and race differences.

model assuming the absence of both components (E vs. ACE model, $P<0.01$) was significantly worse. The ACE model was also the best model for DBPV in the Prenatal programming twin study. The Georgia cardiovascular twin study showed very similar results. Therefore, as expected, the meta-analysis for SBPV and DBPV of these two studies also showed similar results. That is, the model assuming either the absence of A component or the absence of C component fitted the data well (e.g, for SBPV, ACE vs. AE model, $P=0.26$, ACE vs. CE model, $P=0.63$), but the model assuming the absence of both components fitted the data significantly worse (e.g. for SBPV, ACE vs. E model, $P<0.01$). This indicates that BPV did show familial aggregation to some degree, either due to additive genetic and/or common environment influence and its variation in the population could not be explained by unique environment effects alone. The modeling fitting results remained the same after adjusting for 24-h BP levels (Table 3), indicating the familial aggregation identified in BPV is not caused by average BP levels. A scalar effect was identified for the meta-analysis of these two cohorts on 24-h SBPV with the Georgia twin cohort showing larger variability than the EFPTS cohort (Table 3).

As Table 3 demonstrates, the best fitting models in both the Prenatal programming twin and the Georgia cardiovascular twin study were ACE models for both BPV traits. Variance component parameters estimated from the best models before and after adjustment for 24-h ABP level are shown in Table 4 including 95% confidence intervals (95% CIs). The variances of BPV were predominantly due to unique environmental components (e.g. for SBPV, $e^2=0.82$ in the Prenatal programming twin study, $e^2=0.60$ in the Georgia cardiovascular twin study). The additive genetic component had a small contribution to BPV (e.g. for SBPV, $a^2=0.18$ in the Prenatal programming twin study, $a^2=0.17$ in the Georgia cardiovascular twin study), as did the shared environmental component (e.g., for SBPV, $c^2=0.00$ in the Prenatal programming twin study, $c^2=0.26$ in the Georgia cardiovascular twin study). However, as the 95% CI of unique environmental component does not include zero in both traits, the other part of the BPV variance must be genetic and/or common environmental components. This small influences of A and/or C combined did have a significant contribution to the total variance of BPV, accounting for 18–40% and 23–31% of the total variance of SBPV and DBPV, respectively. Meta-analysis of these two studies confirmed these results (for SBPV, $a^2=0.08$, $c^2=0.16$, $e^2=0.75$; for DBPV, $a^2=0.21$, $c^2=0.05$, $e^2=0.73$). The results remained unchanged after adjustment for BP levels. A figure (Supplementary Figure 1, http://links.lww.com/HJH/A230) was also provided displaying the source of variance in 24-h BPV before adjustment for 24-h BP level in each study as well as in the meta-analysis.

DISCUSSION

To our knowledge, this is the first study evaluating the relative impact of genetic and environmental influences on 24-h BPV. In this study, we used 24-h ABP data from two twin studies, the Prenatal programming twin and the Georgia cardiovascular twin study, to avoid regional

TABLE 2. Intra twin pair correlation coefficients of 24-h weighted ambulatory and blood pressure variability by race and zygosity

	Prenatal programming twin study		Georgia cardiovascular twin study			
	White MZ	White DZ	White MZ	White DZ	Black MZ	Black DZ
n (pairs)	194	114	52	56	34	45
24-h weighted BPV						
SBPV	0.27	0.22	0.43	0.29	0.51	0.38
DBPV	0.26	0.10	0.41	0.40	0.29	0.21

DZ, dizygotic; MZ, monozygotic.

TABLE 3. Model fitting results of univariate analysis of blood pressure variability before and after adjustment for 24-h ABP level

Models	Model fitting results					Models	Model fitting results				
	−2LL	AIC	$\Delta\chi^2$	Δdf	*P*		−2LL	AIC	$\Delta\chi^2$	Δdf	*P*
24-h weighted SBPV						24-h weighted SBPV after adjustment for 24-h SBP level					
Prenatal programming twin study						Prenatal programming twin study					
ACE	−283.92	−1679.92	–	–	–	ACE	−301.53	−1699.53	–	–	
AE	−283.92	−1681.92	<0.01	1	1.00	AE	−301.53	−1701.53	<0.01	1	0.95
CE	−283.20	−1681.20	0.73	1	0.39	CE	−301.13	−1701.53	0.41	1	0.52
E	−277.53	−1677.53	6.40	2	0.04	E	−295.60	−1697.60	5.93	2	0.05
Georgia cardiovascular twin study						Georgia cardiovascular twin study					
ACE	−248.80	−1094.80	–	–	–	ACE	−269.02	−1121.02	–	–	–
AE	−247.43	−1095.43	1.37	1	0.24	AE	−266.92	−1120.92	2.1	1	0.15
CE	−248.34	−1096.34	0.47	1	0.49	CE	−269.00	−1123.00	0.02	1	0.90
E	−225.32	−1075.32	23.48	2	<0.01	E	−250.99	−1106.99	18.03	2	<0.01
Meta-analysis						Meta-analysis					
SACE[a]	−525.16	−2779.16	–	–	–	SACE[a]	−566.83	−2820.83	–	–	–
SAE[a]	−523.91	−2779.91	1.25	1	0.26	SAE[a]	−564.79	−2820.79	2.04	1	0.15
SCE[a]	−524.93	−2780.93	0.23	1	0.63	SCE[a]	−566.83	−2822.83	<0.01	1	1.00
SE[a]	−501.44	−2759.44	23.72	2	<0.01	SE[a]	−546.59	−2804.59	20.24	2	<0.01
24-h weighted DBPV						24-h weighted DBPV after adjustment for 24-h DBP level					
Prenatal programming twin study						Prenatal programming twin study					
ACE	−330.47	−1726.47	–	–	–	ACE	−330.46	−1728.46	–	–	–
AE	−330.47	−1728.47	<0.01	1	1.00	AE	−330.46	−1730.46	<0.01	1	1.00
CE	−328.00	−1726.00	2.46	1	0.12	CE	−328.00	−1728.00	2.64	1	0.12
E	−318.47	−1718.47	12.00	2	<0.01	E	−318.44	−1720.44	12.01	2	<0.01
Georgia cardiovascular twin study						Georgia cardiovascular twin study					
ACE	−234.95	−1080.95	–	–	–	ACE	−243.95	−1095.95	–	–	
AE	−234.36	−1081.36	1.59	1	0.21	AE	−241.56	−1095.56	2.39	1	0.12
CE	−234.92	−1082.92	0.03	1	0.85	CE	−243.95	−1097.95	<0.01	1	1.00
E	−216.85	−1066.85	18.10	2	<0.01	E	−226.26	−1082.26	17.69	2	<0.01
Meta-analysis						Meta-analysis					
ACE	−561.27	−2817.27	–	–	–	ACE	−569.97	−2825.97	–	–	–
AE	−561.14	−2819.14	0.13	1	0.72	AE	−569.70	−2827.70	0.27	1	0.60
CE	−559.80	−2817.80	1.47	1	0.23	CE	−568.91	−2826.91	1.06	1	0.30
E	−534.50	−2794.50	26.77	2	<0.01	E	−543.99	−2803.99	25.98	2	<0.01

$\Delta\chi^2$, difference in chi-square; Δdf, difference in degrees of freedom; −2LL, minus twice the log likelihood; A, additive genetic; AIC, Akaike information criteria; C, common environment; E, unique environment.
[a]Meta-analysis for SBPV used scalar models (S).

TABLE 4. Parameters estimates of best fitting models of blood pressure variability before and after adjustment of 24-h ABP level

	Best model	Variance component estimates (95% confidence intervals)		
		a^2	c^2	e^2
24-h weighted BPV				
Prenatal programming twin study				
SBPV	ACE	0.18 (0.00–0.25)	0.00 (0.00–0.25)	0.82 (0.69–0.96)
DBPV	ACE	0.23 (0.00–0.35)	0.00 (0.00–0.25)	0.77 (0.65–0.90)
Georgia cardiovascular twin study				
SBPV	ACE	0.17 (0.00–0.55)	0.23 (0.00–0.46)	0.60 (0.44–0.78)
DBPV	ACE	0.05 (0.00–0.46)	0.26 (0.00–0.42)	0.69 (0.53–0.84)
Meta-analysis				
SBPV	ACE	0.08 (0.00–0.35)	0.16 (0.00–0.31)	0.75 (0.64–0.86)
DBPV	ACE	0.21 (0.00–0.36)	0.05 (0.00–0.30)	0.74 (0.64–0.84)
24-h weighted BPV after adjustment of BP				
Prenatal programming twin study				
SBPV	ACE	0.16 (0.00–0.30)	0.01 (0.00–0.25)	0.83 (0.70–0.97)
DBPV	ACE	0.23 (0.00–0.35)	0.00 (0.00–0.25)	0.77 (0.65–0.90)
Georgia cardiovascular twin study				
SBPV	ACE	0.03 (0.00–0.49)	0.29 (0.00–0.43)	0.68 (0.50–0.83)
DBPV	ACE	0.00 (0.00–0.43)	0.29 (0.00–0.42)	0.71 (0.55–0.84)
Meta-analysis				
SBPV	ACE	0.01 (0.00–0.32)	0.21 (0.00–0.30)	0.78 (0.67–0.88)
DBPV	ACE	0.18 (0.00–0.36)	0.08 (0.00–0.29)	0.74 (0.64–0.85)

A/a^2, additive genetic; C/c^2, common environment; E/e^2, unique environment; BPV, blood pressure variability.

influence. The Georgia cardiovascular twin study also included blacks and whites that enables us to compare racial differences. Despite the major contribution of unique environment factors to the variance of BPV, some familial aggregation (explaining about 25% of the variance) either due to additive genetic and/or common environment influences was identified for 24-h SBPV and DBPV. The Prenatal programming twin and the Georgia cardiovascular twin study showed similar results, which were confirmed by the meta-analysis of these two studies. The model fitting results remained virtually the same after adjusting for 24-h BP levels, which indicates that the familial aggregation identified in BPV is not caused by BP levels.

Twenty-four-hour BPV plays an important role in triggering vascular events [23]. Despite its great importance, this is the first study focusing on the genetic and/or environmental sources of variance of 24-h BPV. Previously we [24] reported a 15-year longitudinal study on BPV from childhood to early adulthood and observed that 24-h BPV showed low tracking stability with the tracking coefficient ranging from 0.08 to 0.28. This observation is consistent with our results, which found that unique environment plays the most important role in BPV variance. Although precise mechanisms responsible for BPV are not fully understood, it is proposed that behavioral, neural, reflex and humoral factors all participate in this phenomenon [25]. In this context, the unique environmental factors may include the frequent behavioral changes during the ABP recordings during which patients are free to go about their normal daily activities and the responsiveness of BP to external demands and internal homeostatic requirements unique to the patients [26]. Previous studies have identified several environmental factors related to 24-h BPV including alcohol intake [27], outdoor temperature, seasonal changes [28], and activity [29]. Nevertheless, BPV is still a trackable trait [24], which explains why we found a certain degree of familial aggregation of BPV.

BPV is a multifaceted trait influenced by BP, age, sex, and heart rate [30–32]. Among these, BP, a clearly heritable trait, is the major determinant of BPV with higher BP levels associated with higher BPV [33]. The heritability of 24-h BP is about 30–70% for SBP and 28–73% for DBP [34–37]. However, we adjusted for 24-h ABP levels in our model fitting process and the results remained virtually unchanged, which indicates that the familial aggregation identified for BPV is independent of BP level.

Traditionally, BPV is indexed by the SD of the ABP recordings over the entire 24 h [38]. However, this definition includes the circadian BP variation and will mainly reflect the day-night variation. As the magnitude of the nocturnal BP fall is positively related with 24-h BPV [31] and the clinical significance of these two parameters is opposite, with an increased BPV [39] and a reduced degree of nocturnal BP fall [40] both being associated with a greater degree of end-organ damage and cardiovascular events, we did not focus on the 24-h BPV in the present study. Instead, to account for the influence of the nocturnal BP fall on the 24-h BP SD and quantify 24-h BPV without including the circadian component, the weighted 24-h BP SD was used in this study, which is the mean of the daytime BPV and nighttime BPV weighted for the duration of daytime and nighttime sub-periods. Separate calculation of daytime BPV and night-time BPV were also suggested [41] and more recently, night-time BPV was considered as a more prominent risk factor for cardiovascular events compared with daytime BPV [6]. In consideration of the fact that nighttime BPV may be less influenced by physical activity and other external factors, we conducted the variance component analysis on daytime and nighttime BPV separately (Results shown in supplementary Table 1, http://links.lww.com/HJH/A230). However, we did not observe that genetic factors played a more important role in nighttime BPV. Results were similar to those for 24-h BPV with unique environment the primary determinant of both daytime BPV

and nighttime BPV. Recently, another BPV index, average real variability (ARV) of BP that calculates the average of the absolute differences between consecutive BP measurements over 24 h, was also observed to be a predictor of target organ damage and cardiovascular risk [42]. Therefore, we also conducted the variance component analysis on ARV of SBP and DBP. However, the results remained largely unchanged. That is, unique environment remained the primary determinant of ARV (Supplementary Table 1, http://links.lww.com/HJH/A230).

Consistent with our previous longitudinal study in youth [24], we observed that men had higher mean BPV values than women in both twin studies. The classic twin study is established as the ideal study design to estimate the relative importance of genetic and environmental factors to the variance of traits and diseases in human populations, but our study shows that the observed sex difference in mean values did not translate into differences in genetic and environmental variability in BPV between men and women. In our previous longitudinal study in youth, we also observed that blacks had higher BPV values than whites, but this difference disappeared after the adjustment for BP levels, which indicates that the higher BPV values observed are caused by the higher BP levels in blacks in comparisons with whites. In the current study, we did not observe that blacks had higher BPV values, which does not exclude the possibility that genetic or environmental factors contribute differently to the variance of BPV. However, we did not observe any race differences either.

Several limitations of the present study need to be recognized. First, although this study included data from two large twin studies with 24-h ABP recording, an even larger sample size is required to tease out the relative contribution of genetic or common environmental factors to the variance of BPV. Second, BPV in the present study represented 20-min or 15-min (daytime)/30-min (nighttime) intermittent BP variability, not beat-to-beat BP variability. Short-term BP variability, including sporadic and random variations as well as physiological variations, should be examined by beat-to-beat measurements of BP [31,43], although the BPV obtained by intermittent measurements was not significantly different from those from beat-to-beat measurements when the period between the intermittent measurements ranged from 5 to 20 min. [43]. Third, as both twin studies comprised youth and young adults, the generalizability of these results to adult populations remains to be determined.

In conclusion, 24-h BPV is predominantly determined by unique environmental factors in youth and young adults. In addition, BPV does show some familial aggregation that might be attributed to genetic and/or common environmental influence.

ACKNOWLEDGEMENTS

This study was supported by grants HL56622 from the National Heart Lung and Blood Institute. X.W. is funded by NHLBI (HL104125 & HL105689). S.S is funded by NHLBI (HLHL106333) and AHA (09SDG2140117). The Prenatal programming twin Study was supported by a grant (nr. 3.0269.97) from the National Fund for Scientific Research, Belgium.

Conflicts of interest

There are no conflicts of interests.

REFERENCES

1. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008; 371:1513–1518.
2. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, *et al*. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335:765–774.
3. Sega R, Corrao G, Bombelli M, Beltrame L, Facchetti R, Grassi G, *et al*. Blood pressure variability and organ damage in a general population: results from the PAMELA study (Pressioni Arteriose Monitorate E Loro Associazioni). *Hypertension* 2002; 39:710–714.
4. Mancia G, Bombelli M, Facchetti R, Madotto F, Corrao G, Trevano FQ, *et al*. Long-term prognostic value of blood pressure variability in the general population: results of the Pressioni Arteriose Monitorate e Loro Associazioni Study. *Hypertension* 2007; 49:1265–1270.
5. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-h blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens* 1987; 5:93–98.
6. Eguchi K, Ishikawa J, Hoshide S, Pickering TG, Schwartz JE, Shimada K, Kario K. Night time blood pressure variability is a strong predictor for cardiovascular events in patients with type 2 diabetes. *Am J Hypertens* 2009; 22:46–51.
7. Stolarz-Skrzypek K, Thijs L, Richart T, Li Y, Hansen TW, Boggia J, *et al*. Blood pressure variability in relation to outcome in the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome. *Hypertens Res* 2010; 33:757–766.
8. Kawai T, Ohishi M, Kamide K, Nakama C, Onishi M, Ito N, *et al*. Differences between daytime and nighttime blood pressure variability regarding systemic atherosclerotic change and renal function. *Hypertens Res* 2012. doi: 10.1038/hr.2012.162. [Epub ahead of print].
9. Rothwell PM. Does blood pressure variability modulate cardiovascular risk? *Curr Hypertens Rep* 2011; 13:177–186.
10. Zhang Y, Agnoletti D, Safar ME, Blacher J. Effect of antihypertensive agents on blood pressure variability: the Natrilix SR versus candesartan and amlodipine in the reduction of systolic blood pressure in hypertensive patients (X-CELLENT) study. *Hypertension* 2011; 58:155–160.
11. Safar ME. Blood pressure variability and arterial stiffness. *Artery Res* 2011; 5:119–121.
12. Wang X, Ding X, Su S, Harshfield G, Treiber F, Snieder H. Genetic influence on blood pressure measured in the office, under laboratory stress and during real life. *Hypertens Res* 2011; 34:239–244.
13. Wang X, Ding X, Su S, Yan W, Harshfield G, Treiber F, Snieder H. Genetic influences on daytime and night-time blood pressure: similarities and differences. *J Hypertens* 2009; 27:2358–2364.
14. Loos R, Derom C, Vlietinck R, Derom R. The East Flanders Prospective Twin Survey (Belgium): a population-based register. *Twin Res* 1998; 1:167–175.
15. Fagard RH, Loos RJ, Beunen G, Derom C, Vlietinck R. Influence of chorionicity on the heritability estimates of blood pressure: a study in twins. *J Hypertens* 2003; 21:1313–1318.
16. Loos RJ, Fagard R, Beunen G, Derom C, Vlietinck R. Birth weight and blood pressure in young adults: a prospective twin study. *Circulation* 2001; 104:1633–1638.
17. Snieder HTreiber FA. The Georgia Cardiovascular Twin Study. *Twin Res* 2002; 5:497–8.
18. Ge D, Dong Y, Wang X, Treiber FA, Snieder H. The Georgia Cardiovascular Twin Study: influence of genetic predisposition and chronic stress on risk for cardiovascular disease and type 2 diabetes. *Twin Res Hum Genet* 2006; 9:965–970.
19. Harshfield GA, Barbeau P, Richey PA, Alpert BS. Racial differences in the influence of body size on ambulatory blood pressure in youths. *Blood Press Monit* 2000; 5:59–63.
20. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, *et al*. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21:821–848.
21. McCaffery JM, Snieder H, Dong Y, de Geus E. Genetics in psychosomatic medicine: research designs and statistical approaches. *Psychosom Med* 2007; 69:206–216.

22. Boker SM, Neale MC, Maes HH, Wilde MJ, Spiegel M, Brick TR, *et al*. OpenMx: an open source extended structural equation modeling framework. *Psychometrika* 2011; 76:306–317.
23. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet* 2010; 375:938–948.
24. Li Z, Snieder H, Harshfield GA, Treiber FA, Wang X. A 15-year longitudinal study on ambulatory blood pressure tracking from childhood to early adulthood. *Hypertens Res* 2009; 32:404–410.
25. Mancia G, Grassi G. Mechanisms and clinical implications of blood pressure variability. *J Cardiovasc Pharmacol* 2000; 35: S15–S19.
26. Ward T, Johnston D. Temporal stability of ambulatory cardiovascular monitoring. *Ann Behav Med* 1994; 12:12–23.
27. Ohira T, Tanigawa T, Tabata M, Imano H, Kitamura A, Kiyama M, *et al*. Effects of habitual alcohol intake on ambulatory blood pressure, heart rate, and its variability among Japanese men. *Hypertension* 2009; 53:13–19.
28. Winnicki M, Canali C, Accurso V, Dorigatti F, Giovinazzo P, Palatini P. Relation of 24-h ambulatory blood pressure and short-term blood pressure variability to seasonal changes in environmental temperature in stage I hypertensive subjects. Results of the Harvest Trial. *Clin Exp Hypertens* 1996; 18:995–1012.
29. Crowther JH, Stephens MA, Koss PG, Bolen KG. Behavioral predictors of blood pressure variation in hypertensives and normotensives. *Health Psychol* 1987; 6:569–579.
30. Pringle E, Phillips C, Thijs L, Davidson C, Staessen JA, de Leeuw PW, *et al*. Systolic blood pressure variability as a risk factor for stroke and cardiovascular mortality in the elderly hypertensive population. *J Hypertens* 2003; 21:2251–2257.
31. Imai Y, Aihara A, Ohkubo T, Nagai K, Tsuji I, Minami N, *et al*. Factors that affect blood pressure variability. A community-based study in Ohasama, Japan. *Am J Hypertens* 1997; 10:1281–1289.
32. Li Z, Snieder H, Su S, Harshfield GA, Treiber FA, Wang X. A longitudinal study of blood pressure variability in African-American and European American youth. *J Hypertens* 2010; 28:715–722.
33. Rothwell PM, Howard SC, Dolan E, O'Brien E, Dobson JE, Dahlof B, *et al*. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. *Lancet Neurol* 2010; 9:469–480.
34. Fagard R, Brguljan J, Staessen J, Thijs L, Derom C, Thomis M, Vlietinck R. Heritability of conventional and ambulatory blood pressures. A study in twins. *Hypertension* 1995; 26:919–924.
35. Bochud M, Bovet P, Elston RC, Paccaud F, Falconnet C, Maillard M, *et al*. High heritability of ambulatory blood pressure in families of East African descent. *Hypertension* 2005; 45:445–450.
36. Fava C, Burri P, Almgren P, Groop L, Hulthen UL, Melander O. Heritability of ambulatory and office blood pressure phenotypes in Swedish families. *J Hypertens* 2004; 22:1717–1721.
37. Tomaszewski M, Debiec R, Braund PS, Nelson CP, Hardwick R, Christofidou P, *et al*. Genetic architecture of ambulatory blood pressure in the general population: insights from cardiovascular gene-centric array. *Hypertension* 2010; 56:1069–1076.
38. Ragot S, Herpin D, Siche JP, Poncelet P, Mallion JM. Relationship between short-term and long-term blood pressure variabilities in essential hypertensives. *J Hum Hypertens* 2001; 15:41–48.
39. Parati G, Mancia G. Blood pressure variability as a risk factor. *Blood Press Monit* 2001; 6:341–347.
40. Verdecchia P, Schillaci G, Guerrieri M, Gatteschi C, Benemio G, Boldrini F, Porcellati C. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. *Circulation* 1990; 81:528–536.
41. Parati G, Ochoa JE, Bilo G. Blood Pressure Variability, Cardiovascular Risk, and Risk for Renal Disease Progression. *Curr Hypertens Rep* 2012; 14:421–431.
42. Schillaci G, Bilo G, Pucci G, Laurent S, Macquin-Mavier I, Boutouyrie P, *et al*. Relationship between short-term blood pressure variability and large-artery stiffness in human hypertension: findings from 2 large databases. *Hypertension* 2012; 60:369–377.
43. di Rienzo M, Grassi G, Pedotti A, Mancia G. Continuous vs intermittent blood pressure measurements in estimating 24-h average blood pressure. *Hypertension* 1983; 5:264–269.

Reviewers' Summary Evaluations

Reviewer 1

The present classic twin study investigates the genetic and environmental determinants of short-term BP variability in two large cohorts of young twins (age 12 to 34 years) who underwent 24-h ABPM. The main finding is that, although unique environmental variables accounted for the majority of the variance of BPV, a sizeable (around 25%) contribution was attributable to genetic and/or common environmental (familial) factors. Strengths of the study include a large sample size, the use of two distinct populations, and a sound methodologic approach. The main limitation of studies like the present one is that the approach does not allow to define whether the familial aggregation of blood pressure variability is due to genetic factors or to common environmental variables.

Reviewer 2

Genetic influences on cardiovascular hemodynamics have always been a question remaining open for debate. In this study, the authors had the unique opportunity to study BP variability and the link to genetics in twins, followed over years in a superb protocol realized by the late Professor Robert Derom. Remarkably, results did only show a relatively minor influence of genetics on variability which showed to be much more influenced by all stimuli occurring in our daily life. We shall all have to realize that studying BP variability in 'controlled' conditions will be a very difficult task.