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Genetic influence on blood pressure and underlying hemodynamics measured at rest and during stress

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Abstract

Objective—This study examined genetic and environmental contributions to the individual differences in blood pressure (BP) levels and underlying hemodynamic characteristics at rest and during mental challenge tasks in a large twin cohort of youth. Including both European American (EA) and African American (AA) twins further allowed examination of potential ethnic differences.

Methods—We studied CVR to two stressors (car driving simulation and a social stressor interview) in 308 EA and 223 AA twin pairs including monozygotic twin pairs and same-sex as well as opposite-sex dizygotic twin pairs (mean [SD] age: 14.7 [3.1]). Variables included systolic and diastolic BP, heart rate (HR), stroke volume, cardiac output and total peripheral resistance.

Results—Heritability indices for levels at rest and during stress were high (31% – 73%) and comparable between ethnic groups. A common genetic factor accounted for both resting and stress levels explaining 23% to 58% of the total variance. The increases in heritability indices for BP and HR from rest to stress are mostly explained by newly emerging genetic influences on the added stress component. Indices for hemodynamic variables remained stable from rest to stress owing to a simultaneous decrease in genetic and environmental variances.

Conclusions—Cardiovascular measures obtained during rest and stress show substantial heritability that is comparable between individuals of African and European descent. Most of the variance in both resting and stress levels is explained by common genetic factors, although other genetic factors that only contribute to cardiovascular levels during stress are also important.

Keywords

blood pressure; hemodynamics; reactivity; heritability; ethnicity; twin

INTRODUCTION

Cardiovascular reactivity (CVR), defined as the magnitude or pattern of an individual's hemodynamic responses to behavioral stressors, has been identified as potentially playing a role in the development of coronary artery disease (CAD) and hypertension (1). Large

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stress-induced blood pressure (BP) or heart rate (HR) elevations are hypothesized to lead, over time, to elevation of the tonic BP level and the development of CAD (2).

BP measured under certain standardized environmental challenges such as mental or physical stress may be more heritable than its unchallenged counterpart, potentially offering important advantages for gene-finding studies (3). However, a downside of expressing CVR as a change score is that its heritability reflects an inseparable mixture of genetic and environmental influences already present at rest with those newly emerging during stress. These influences can only be separated if both resting and challenged *levels* (as opposed to a change score) are analyzed in a bivariate model, i.e., a model including two dependent variables. De Geus et al. (4) recently used such an approach to investigate BP during a stress challenge and test for the existence of gene-by-stress interaction within the context of a classic twin study. Genetic factors significantly contributed to individual differences in resting SBP and DBP in the adolescent and middle aged twin cohorts of Northern European ancestry included in this study. The effect of these genetic factors was amplified by stress for both SBP and DBP in the adolescent cohort and for SBP in the middle-aged cohort. In addition, stress-specific genetic variation emerged for SBP in the adolescent cohort. It was concluded that exposure to stress may uncover new genetic variance and amplify the effect of genes that already influence the resting level.

The aim of the current study was to replicate the work by De Geus et al. (4) in adolescents and extend it in two important ways. First, we extended it to another ethnic group by including not only European American (EA) but also a group of African American (AA) twins. Second, we extended it to include cardiac output (CO) and total peripheral resistance (TPR) of the systemic vasculature as hemodynamic determinants of BP, because a given increase in BP can be the result of an increase in CO, an increase in TPR, or a combination of alterations in both parameters (5).

The goal of this study, therefore, was to estimate the contribution of genes and environment to the individual differences in levels of BP and underlying hemodynamic characteristics at rest and during stress using a bivariate approach in a large twin cohort of youth. Unlike previous studies, inclusion of both EA and AA twins further allowed examination of potential ethnic differences.

METHODS

Subjects

The present study comprised participants from the Georgia Cardiovascular Twin Study, which was established in 1996 (6, 7). Participants were 308 EA and 226 AA twin pairs from the southeastern United States, including pairs of the same and the opposite sex (mean $\pm$ SD age, 14.7 ± 3.1 years; range, 10.0–25.9 years). See Table 2 for the number of pairs for each sex by zygosity group in EAs and AAs. Zygosity was determined using five standard microsatellite markers in DNA collected with buccal swabs (8). Recruitment of twin pairs into the Georgia Cardiovascular Twin Study has been described previously (7) as have been the criteria to classify participants as AA or EA (9). The study was approved by the institutional review board, and all participants (or parents if participants were <18 years) provided written informed consent.

All twin pairs were reared together and were apparently healthy based on (parental) report of the child's medical history. Three twin pairs were excluded because 1 twin of each pair had an SBP > 160 mmHg or a DBP > 90 mmHg (10). None of the participants used any antihypertensive medication.

Measurements

All participants were asked to refrain from tobacco use and drinking alcohol for 11 hours prior to the visit. After arrival in the laboratory, anthropometric data were collected using established protocols (11). As a measure of general obesity, body mass index (BMI) was computed as weight/height². Participants were instrumented for the recording of SBP, DBP and mean arterial pressure (MAP) by using a Dinamap 1864 SX (Criticon Incorporated, Tampa, FL) and HR by electrocardiograph (EKG). In addition, SV was measured by bioimpedance cardiography (NCCOM, BoMed Medical Manufacturing Ltd., Irvine, CA). The NCCOM yields reliable and valid measures of cardiac output when compared with simultaneous thermodilution and Fick-derived measures of cardiac output obtained from supine individuals (12, 13). CO (SV*HR) was indexed by body surface area (i.e., cardiac index). Total peripheral resistance (TPR) index was calculated as MAP/cardiac index. Bioimpedance measures were not available for 8 participants because of equipment failure.

Baseline hemodynamics were calculated based on the average of minutes 11, 13 and 15 while participants lay (supine) on a hospital bed. After the resting evaluation period, the participants engaged in the virtual reality car driving simulation test (5 min) and the social stressor interview (10 min) using a standardized protocol during which hemodynamics were recorded and BP measured every 2 minutes. The two stressors have been successfully used in our laboratory studies for over 10 years (14–16).

The virtual reality car driving stressor—Briefly, the participant wore a Kaiser-Optic Visual Immersion Monitor (VIM 500) fitted on his/her head. The VIM 500 was interfaced with a Panasonic Real 3DO Interactive Multiplayer System. The participant played “Need for Speed” under the condition of challenge (i.e., money incentive) without harassment for 5 minutes.

The social competence interview was administered using an established protocol (17). Briefly, participants discussed a recent interpersonal interaction, which resulted in significant anger and/or frustration. A 10 minute structured interview was used to guide the participant in describing the event, including his/her affective and behavioral responses and summarization of outcome of the event.

Analytical Approach

Previous studies have shown increased reliability of interindividual differences in the response to stress when multiple stressors are aggregated to a single stress level (18). In the present study, we summed the levels of BP and hemodynamics across all observations for each stressor and then averaged the values for both of the stressors. This result yielded a single score for the mean stress level for each parameter. CV reactivity (change score) was calculated as average stress level minus resting level.

Genetic modeling of Twin Data—Univariate analysis for each dependent variable separately was firstly used to estimate the relative influence of genetic and environmental factors on individual differences of BP and underlying hemodynamic characteristics at rest and during stress. Sex differences in (co)variance were examined by comparing the full model, in which parameter estimates are allowed to differ in magnitude between males and females, 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 (19).

Subsequently, we used a bivariate analysis of rest and stress levels corresponding to the path diagram shown in Figure 1. This path diagram depicts the typical structural equation modeling approach to twin resemblances, which has been described previously (20, 21). In this approach, the variance in the observed traits (e.g., SBP at rest and SBP during stress) is decomposed into latent additive genetic, shared environmental and unique environmental components. The effect of A represents the relative contribution of genetic variance to the total variance (heritability) in SBP at rest calculated as $a_{11}^2/(a_{11}^2 + c_{11}^2 + e_{11}^2)$. The heritability of SBP during stress is the summed effect of A and As and is calculated as $(a_{21}^2 + a_{22}^2)/(a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2)$. We can further test whether the genes influencing SBP at rest are the same (i.e. $a_{22}=0$?), partly the same (i.e. $a_{21} \neq 0$ and $a_{22} \neq 0$?) or entirely different (i.e. $a_{21}=0$?) from SBP during stress. If they are partly the same, this bivariate model allows further determination of the amount of overlap between genes influencing SBP at rest and during stress by calculating the genetic correlation between the two traits [$r_g = \text{COV}_A(\text{trait 1, trait 2}) / \sqrt{(V_A \text{ trait 1} * V_A \text{ trait 2})}$]. Shared and unique environmental correlations can be calculated in a similar fashion (19, 22).

When going from rest to stress, the effects of the genetic differences between subjects may be amplified ($a_{21} > a_{11}$) or dampened ($a_{21} < a_{11}$) by the stressors. In addition, entirely new genetic variation between subjects may emerge only during stress, depicted by factor As. In this case, the path-coefficient a_{22} will differ significantly from zero ($a_{22} > 0$). This part of the total heritability of the stress level represents the influence of novel genetic effects only expressed during stress and is equal to $a_{22}^2/(a_{21}^2 + a_{22}^2 + c_{21}^2 + c_{22}^2 + e_{21}^2 + e_{22}^2)$. Both amplification/dampening and emergence effectively constitute forms of gene-by-stress interaction (23). For comparison with previous studies, we also computed heritability of reactivity as a change score as described previously (4).

Model Fitting Procedure—All quantitative genetic modeling was carried out separately for EAs and AAs. Before genetic analysis, SBP, DBP and TPR index were log-transformed to obtain better approximations of normal distributions. Effects of age, sex, ethnicity and body mass index (BMI) were regressed out for all variables and the residuals were used in model fitting and the calculation of twin correlations. Models were fitted to the raw data using normal theory maximum likelihood allowing inclusion of incomplete data. For genetic modeling, a series of submodels nested within the full parameter ACE triangular (Cholesky) model were fitted to the multivariate variance-covariance matrices (an ADE model was not considered based on inspection of the twin correlations). 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. Emergence of new genetic factors was tested by a submodel that constrains the a_{22} parameter to zero. Amplification (or dampening) of genetic factors was tested by a submodel that constrains a_{21} and a_{11} to be equal.

Standard hierarchic chi-squared 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—Ethnic and sex effects on mean values were tested by generalized estimating equations (GEE) in regression models that included age as a covariate in addition to ethnicity, sex and their interaction. GEE takes the nonindependence between twins into account and yields unbiased standard errors and p-values (24). Data handling, preliminary analyses, and GEEs were performed with STATA software (StataCorp., College Station, TX). Quantitative genetic modeling was performed with Mx software, a computer program specifically designed for the analysis of twin and family data (25).

RESULTS

Table 1 shows mean values of general characteristics and CV reactivity measures for EA and AA males and females in the twin sample. The mean age of the sample was 14.7 years (range, 10.0 to 25.9 years). As shown in Table 1, age, height, weight and BMI were very similar for AAs and EAs. Males were taller and heavier than females. At rest, AAs showed significantly higher SBP, DBP and TPR index levels but lower cardiac index than EAs. Females had higher DBP, HR and cardiac index but lower SBP and TPR index levels than males. During stress, EAs showed significantly higher cardiac index and HR but lower DBP and TPR index levels than AAs. Males had higher SBP and TPR index but lower DBP, HR, SV and cardiac index than females. EAs showed significantly higher SBP, DBP, HR and SV reactivity to stress compared with AAs. Males showed higher SBP, cardiac index and TPR index reactivity to stress than females. There was no significant interaction between ethnicity and sex on any of the measures.

Table 2 shows the twin correlations for each sex-by zygosity group in EAs and AAs. For rest and stress levels in both EAs and AAs, MZ correlations showed consistently higher values than did DZ correlations, and mostly the MZ correlations exceeded DZ correlations by almost half, suggesting genetic factors as the main source of familial resemblance in these traits. Correlational patterns for hemodynamics change scores were less clear-cut compared with those for levels, which highlights the advantage of modeling all information available in the resting and stress levels using a bivariate approach rather than modeling the change scores.

We first used univariate models to estimate heritabilities and to test potential sex effects (data not shown). The best fitting models included additive genetic and unique environmental components (AE models) for all measures, except for cardiac and TPR index at rest in EAs and SV and TPR index change score in AAs, in which models including common and unique environmental components (CE models) were shown to have the best fit. In EAs, scalar sex effects were found in cardiac index change score with females showing larger total variability than males and in all TPR index variables with males showing larger total variability than females but equal heritability across sexes. In AAs, scalar effects were detected in both resting and stress levels of SV, all cardiac index variables and resting levels for TPR index with females showing larger total variability than males, while for TPR index change score, males showed larger total variability than females. Thus, a number of variables showed differences in total variances between males and females, but no significant sex differences in genetic or environmental parameter estimates were observed. On the basis of these results, we equalized total variances of SV, cardiac index and TPR index in males and females prior to bivariate modelling and estimated all parameters by combining data from males and females in these models.

Results from bivariate testing, using the model depicted in Figure 1, are shown in Table 3, Table 4, Figures 2 and Figure 3. Models including only an additive genetic and unique environmental component (AE models) gave the best overall fit to the data for all six traits in both EAs and AAs. That is, significant heritabilities were found for resting and stress levels for all variables in both ethnic groups. The heritability estimates were highly comparable across EA and AA subjects. As can be judged from the overlap of 95% confidence intervals, neither for resting nor for stress levels were any ethnic effects on heritability observed.

A common genetic factor was found to influence both resting and stress levels for all variables. This factor represents genes that act on both resting and stress levels and corresponds to factor A in Figure 1. As shown in Figure 2, 39%–52% of the total variance of

stress BP could be attributed to genes that also influenced resting BP. A somewhat larger common genetic factor was found for HR (58%) in both EAs and AAs. For SV and cardiac index in EAs, the heritability of stress levels could entirely be explained by genetic factors that also influenced resting level (53% and 51%). Forty eight percent and 28% of the total variance in EAs and AAs, respectively, were attributed to genes that also influenced resting TPR index (Figure 3).

The effect of this common genetic factor was dampened for SV in both EAs and AAs, and for cardiac and TPR index in AAs only. Furthermore, new genetic factors corresponding to factor As in Figure 1 emerged for SBP, DBP, HR and TPR index in EAs and all variables in AAs (Table 3). These factors accounted for 6% to 28% of the total variance of these variables during stress. Comparing this to the total heritability of the stress levels, which varied from 31% to 73%, shows that this emergent genetic factor accounts for a smaller part of the total variance during stress than the effect of the common genetic factor also acting on the resting level. Regarding the reactivity, the heritability of change scores varied from 21% to 50%, except for SV and cardiac index in EAs, which showed no significant heritability for the change scores (Table 3).

When estimating to what extent phenotypic correlations between rest and stress levels can be explained by genetic or environmental factors that influence variables both at rest and during stress, genetic correlations were substantial, while unique environmental correlations were somewhat weaker but still highly significant (Table 4).

Compared to the rest condition, the total variance during stress increased for SBP, DBP and HR in both EAs and AAs but, with the single exception of TPR index in EAs, decreased for all others. The increase in total variance for SBP, DBP and HR in both ethnic groups was mostly due to an increase in the genetic variance whereas environmental variance decreased or stayed about the same (Supplementary Digital Content 1, Supplementary Table 1). Together with the results from Table 3 this confirms that increases in heritabilities of BP and HR from rest to stress in both EAs and AAs are mostly due to newly emerging genetic influences during stress. For the hemodynamic parameters heritabilities stayed fairly stable from rest to stress mostly caused by simultaneous decreases in genetic and environmental variances (Supplementary Table 1).

DISCUSSION

The intent of this study was to estimate the contribution of genes and environment to the individual differences in levels of BP and underlying hemodynamics at rest and during stress and examine ethnic differences in a large sample of young twins. The results were in line with previous univariate analyses for resting levels of cardiovascular variables (10). The current bivariate analysis shows that results are comparable across ethnicity groups not only for rest as shown before, but also for stress. Most genetic variance was explained by a common genetic factor influencing both resting and stress levels. Increases in heritabilities of BP and HR from rest to stress in both EAs and AAs were mostly due to newly emerging genetic influences, while the heritabilities of hemodynamics stayed fairly stable from rest to stress due to simultaneous decreases in genetic and environmental variances. CVR heritability varied from 21% to 50%, except for SV and cardiac index in EAs, which showed no significant heritability.

Previous studies of BP and HR reactivity simply used univariate models to estimate heritabilities of change scores (i.e., stress minus rest levels) as an inherent test of gene-stress interaction. We recently used meta-analysis to summarize results of all available twin studies that measured such BP and HR reactivity to mental stress in white participants (26).

The pooled heritability estimate for change in HR was 43% with no effects of gender, very similar to our estimate of 42% in the current study. However, the present study showed higher heritabilities for SBP (0.48) and DBP reactivity (0.38) than Wu et al.'s meta-analysis (26), which estimated SBP reactivity at 0.26 and 0.38 for males and females, respectively, and at 0.29 for DBP reactivity. A major difference between the current and previous studies is that estimates for CVR heritabilities were derived from the best fitting bivariate model of rest and stress levels. This has the important advantage that all available information in the bivariate variance/covariance matrices is used, providing more power to select the best fitting model (27). Interestingly, our study is the first to present heritability estimates of BP and HR reactivity in AAs, which were found to be comparable to those in EAs.

The limitation of the studies using univariate analysis of change scores is that heritability estimates will reflect an inseparable mix of newly emerging genetic or environmental influences during stress and an amplification or dampening of genetic or environmental influences already present at rest (4). To explicitly test for emergence and amplification/dampening, we used bivariate analysis of resting and aggregated stress levels. We found that a single genetic factor (or set of genes) influenced both resting and stress levels for all variables. However, we also observed emergence of new genes under stress conditions for BP, HR, all hemodynamic variables in AAs, and TPR index in EAs. In line with these findings, using the same Georgia Cardiovascular Twin cohort measured 4 years later, Wang et al. (28) found that substantial overlap exists between genes that influence BP measured in the office, under laboratory stress and during real life, but that significant genetic components specific to each BP measurement also exist. These findings confirm that partly different genes or sets of genes contribute to BP regulation under different conditions. The study by de Geus et al (4) in a Dutch adolescent and middle-aged twin cohort is the only other study that used bivariate analyses of rest and stress levels of BP and HR. Apart from being on average 2 years older, their young cohort is highly comparable to our EA twins. Heritabilities of rest and stress levels of SBP, DBP and HR were very similar between these two young cohorts as were the newly emerging genetic factors and CVR heritability estimates for SBP and HR. In contrast to de Geus et al. (4) we observed newly emerging genetic effects for DBP during stress, whereas we were unable to confirm a significant amplification during stress of the genes that also acted on the resting levels for BP and HR. Taken together, our findings indicate that there will be some genes that show an effect on BP and underlying hemodynamics at rest as well as during stress, whereas others are expressed only when these traits are measured in stressful conditions.

Variation in genes within a number of pathways may moderate CV reactions to mental stressors, with genes encoding components of the parasympathetic and sympathetic nervous system, the renin-angiotensin-aldosterone system and endothelial function as likely candidates (9, 29, 30). For example, Wang et al. (31) showed that a variant in the endothelin receptor Type A gene led to higher SBP levels at rest and during acute mental stress. This gene, therefore, would be part of factor A in Figure 1. On the other hand, two variants in the endothelin-1 gene did not influence resting SBP but led to greater SBP increases to stress. This variation in the gene seems to be expressed only during stress and would be part of factor As in Figure 1. Other studies that reported associations with stress-elicited BP levels focused on candidate genes from the sympathetic nervous system (32) and the renin-angiotensin-aldosterone system (33), whereas association studies with CVR were reviewed in Wu et al. (26).

Our Georgia Cardiovascular Twin study is one of the very few studies that investigated the genetic and environmental contribution to underlying hemodynamic regulators of BP (SV, CO and TPR) for which we previously reported resting heritabilities (10) and emergence of novel genetic influences during adolescence (34). Heritabilities of these hemodynamic

parameters were substantial for both rest and stress (between 31% and 58%), remained stable between conditions and were comparable between ethnic groups. Stress-specific genetic effects were either small or absent in both EAs and AAs, whereas the effect of the common genetic factor influencing both resting and stress levels dampened for all hemodynamic variables and reached significance for SV in both EAs and AAs and cardiac and TPR index in AAs only. CVR heritability varied from 21% to 35%, except for SV and cardiac index in EAs, which showed no significant heritability.

Taken together, the present study has many strengths. First, we performed the analyses in both EAs and AAs to explore potential ethnic differences, which was seldom investigated by previous studies. Second, cardiovascular responses that were aggregated across the two mental stress tasks were used instead of the responses to each of the stressors separately. The former is more reliable as it reduces the relative influence of unique situational variance (18, 35). Finally, the genetic and environmental influences of SV, CO and TPR under stress were explored, providing more insight into the underlying hemodynamic regulators of BP.

Some limitations of the present study also need to be mentioned. First, as the Georgia Cardiovascular Twin Study is comprised of youth and young adults, the generalizability of these results to other adult populations remains to be determined. Second, our overall sample size was substantial for BP and underlying hemodynamics heritability estimates, but might not have had enough power to detect small ethnic or sex differences in heritabilities of the studied traits. Further twin studies with large sample sizes involving multiethnic groups would be needed to detect those.

In conclusion, we have shown that levels of BP and underlying hemodynamic variables at rest and during stress show substantial heritabilities comparable between ethnic groups. Our findings are in line with those from De Geus et al. (4) in suggesting that there will be some genes that show an effect on BP, HR and underlying hemodynamic regulators at rest as well as during stress, whereas others are expressed only when these traits are measured in stressful conditions, suggesting that exposure to stress uncovers new genetic variance. In this regard, we expect that performing gene-by-stress interaction analyses in future gene finding studies will be a promising way forward for detecting genes underlying BP regulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Glossary

AA	African American
A or a^2	Additive Genetic Effects
BP	Blood Pressure
C or c^2	Shared Environmental Effects
CAD	Coronary Artery Disease
CO	Cardiac Output

CV	Cardiovascular
CVD	Cardiovascular Disease
CVR	Cardiovascular Reactivity
DBP	diastolic blood pressure
DZ	Dizygotic
E or e²	Non-shared Environmental Effects
EA	European American
GEE	Generalized Estimating Equation
h²	Heritability
HR	Heart Rate
MAP	Mean Arterial Pressure
MZ	Monozygotic
SBP	Systolic Blood Pressure
SV	Stroke Volume
TPR	Total Peripheral Resistance

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Figure 1.

Bivariate twin model for genetic and environmental influences on systolic blood pressure (SBP). Biometrical genetic theory specifies that the additive genetic factors (denoted by A and As) of (monozygotic) MZ twins are perfectly correlated (1.0), whereas those of dizygotic (DZ) twins are correlated 0.5. Common environmental factors shared by twins from the same family (denoted by C and Cs) are correlated unity for both types of twins, whereas the unique environmental influences (E and Es) are always uncorrelated. Path coefficient a_{11} quantifies the effect of genetic influence A on SBP at rest, a_{21} quantifies the effect of A on SBP during stress, and a_{22} quantifies the effect of emergent genes in As on SBP during stress. In a similar way, path coefficients e_{11} , c_{11} , e_{21} , and c_{21} quantify the effects of common and unique environmental influences E and C on SBP at rest and during stress. e_{22} and c_{22} quantify the effect of emergent environmental influences in Es and Cs on SBP during stress.

European Americans **African Americans** **Figure 2.**

Sources of variance in stress SBP, DBP and HR in comparison with resting SBP, DBP and HR in EAs and AAs

Figure 3.
Sources of variance in stress SV, cardiac index and TPR index in comparison with resting SV, cardiac index and TPR index in EAs and AAs

General characteristics and hemodynamic measures at rest and during stress of European- and African-American males and females

Table 1

Characteristic	European Americans		African Americans		Ethnicity and Sex effects ^a	
	Males	Females	Males	Females	Ethnicity, <i>P</i>	Sex, <i>P</i>
Participants, n	294	322	202	244		
Age, y	14.8±2.9	14.9±3.1	14.2±2.7	14.9±3.5	NS	NS
Height, m	1.64±0.14	1.58±0.07	1.63±0.13	1.59±0.77	NS	<0.001
Weight, kg	59.1±19.5	54.5±15.9	60.3±22.0	58.1±16.7	NS	<0.05
BMI, kg/m ²	21.5±4.8	21.5±5.0	22.2±5.8	22.9±5.6	NS	NS
Cardiovascular measures						
SBP at rest, mmHg	110.1±9.3	105.7±8.2	112.9±10.8	110.2±10.2	<0.001	<0.001
SBP during stress [*] , mmHg	124.1±12.8	117.1±10.8	124.1±13.0	118.6±11.5	NS	<0.001
SBP change score [†] , mmHg	14.0±8.32	11.3±7.37	11.2±8.36	8.33±8.06	<0.001	<0.001
DBP at rest, mmHg	56.2±5.8	57.6±5.4	59.5±5.9	61.0±7.0	<0.001	<0.01
DBP during stress, mmHg	68.4±7.01	69.8±6.25	70.4±7.44	70.7±7.41	<0.01	<0.05
DBP change score, mmHg	12.1±5.54	12.3±5.20	10.9±5.44	9.69±5.23	<0.05	NS
HR at rest, beats/min	67.2±11.7	71.9±11.7	65.8±10.9	70.7±10.9	NS	<0.001
HR during stress, beats/min	77.0±12.5	82.7±12.0	73.1±11.1	79.6±11.6	<0.01	<0.001
HR change score, beats/min	9.25±6.13	9.95±6.38	6.86±5.48	7.71±6.38	<0.001	NS
SV at rest, mL/beat	87.1±20.1	88.9±19.3	83.3±20.1	85.2±18.4	NS	NS
SV during stress, mL/beat	76.2±18.3	79.1±17.3	75.5±18.3	77.5±16.6	NS	<0.05
SV change score, mL/beat	-11.0±8.88	-9.82±8.62	-8.22±8.43	-7.66±8.89	<0.01	NS
Cardiac index at rest, L/min/m ²	3.62±0.78	4.17±0.78	3.39±0.69	3.87±0.83	<0.01	<0.001
Cardiac index during stress, L/min/m ²	3.59±0.77	4.21±0.75	3.35±0.62	3.87±0.79	<0.001	<0.001
Cardiac index change score, L/min/m ²	-0.05±0.38	0.03±0.48	-0.05±0.35	0.01±0.44	NS	<0.05
TPR index at rest, mmHg/L/min/m ²	21.5±5.20	18.3±3.95	23.9±5.47	21.1±5.60	<0.001	<0.001
TPR index during stress, mmHg/L/min/m ²	25.6±6.11	21.1±4.10	27.3±5.56	23.6±5.49	<0.001	<0.001
TPR index change score, mmHg/L/min/m ²	4.08±3.23	2.81±2.73	3.55±3.50	2.33±3.19	NS	<0.001

Note: Data are mean±SD unless stated otherwise; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; TPR = total peripheral resistance.

^a Ethnic and sex effects on mean values were tested by generalized estimating equations (GEE) in regression models that included age as a covariate in addition to ethnicity, sex and their interaction; Ethnic and sex interactions on mean values were not significant.

Cardiac index= cardiac output/body surface area; TPR index=mean arterial pressure/cardiac index

* Stress levels were aggregated values of two stress tasks.

[†] change score= aggregated stress level – level at rest

Table 2

Twin Correlations for Each Sex by Zygosity group in European and African Americans

Measure	European Americans						African Americans					
	MZM	DZM	MZF	DZF	DOS	MZM	DZM	MZF	DZF	DOS	MZM	DZM
Pairs, n	73	35	89	33	78	50	26	58	39	50		
SBP												
Rest	0.59	0.48	0.58	0.36	0.10	0.69	0.30	0.50	0.35	0.14		
Stress	0.78	0.38	0.71	0.45	0.05	0.86	0.31	0.67	0.38	0.05		
Reactivity	0.60	0.35	0.41	0.39	0.13	0.59	0.18	0.52	0.38	0.08		
DBP												
Rest	0.47	-0.07	0.49	0.27	0.25	0.64	0.36	0.54	0.17	0.30		
Stress	0.70	0.31	0.64	0.39	0.18	0.75	0.30	0.74	0.47	0.25		
Reactivity	0.54	0.29	0.47	0.22	0.05	0.49	0.27	0.57	0.36	-0.16		
HR												
Rest	0.67	0.38	0.70	0.42	0.34	0.70	-0.02	0.66	0.35	0.39		
Stress	0.81	0.40	0.67	0.38	0.36	0.71	0.22	0.70	0.24	0.48		
Reactivity	0.42	0.23	0.39	0.22	0.15	0.35	0.33	0.38	0.05	-0.08		
SV												
Rest	0.50	0.41	0.56	0.24	0.29	0.62	0.34	0.54	0.57	0.02		
Stress	0.51	0.31	0.63	0.06	0.29	0.59	0.44	0.52	0.62	0.06		
Reactivity	0.18	0.12	0.19	0.14	0.03	0.21	0.03	0.14	0.60	0.24		
Cardiac index												
Rest	0.60	0.45	0.45	0.55	0.27	0.48	0.05	0.31	0.26	0.03		
Stress	0.55	0.47	0.43	0.28	0.16	0.31	0.16	0.29	0.24	0.07		
Reactivity	0.06	0.23	0.21	0.03	0.01	0.45	0.20	0.22	0.29	0.18		
TPR index												
Rest	0.49	0.43	0.46	0.58	0.29	0.55	0.02	0.40	0.29	0.09		
Stress	0.57	0.55	0.51	0.20	0.17	0.43	0.15	0.31	0.35	0.12		
Reactivity	0.25	0.50	0.21	-0.14	0.04	0.21	0.12	0.15	0.39	0.23		

SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; SV=stroke volume and TPR=total peripheral resistance; MZM=monozygotic males; DZM=dizygotic males; MZF=monozygotic females; DZF=dizygotic females; DOS=dizygotic opposite sex.

Residuals were used after effects of age, sex, ethnicity and BMI were regressed out for all measures.

Table 3

Bivariate Heritability Estimates in European- and African-Americans

	Rest Level h^2 (95% CI)	Stress Level h^2 (95% CI)	Amplification or dampening of genes acting on resting level	Specific h^2 due to genes emerging during stress (95% CI)	Reactivity * h^2 (95% CI)
European Americans					
SBP	0.61 (0.52–0.68)	0.68 (0.60–0.75)	No, $a_2/a_1=1.19$	0.25 (0.19–0.31)	0.48 (0.37–0.57)
DBP	0.40 (0.30–0.49)	0.67 (0.58–0.73)	No, $a_2/a_1=0.85$	0.28 (0.20–0.35)	0.38 (0.27–0.47)
HR	0.66 (0.58–0.72)	0.70 (0.64–0.76)	No, $a_2/a_1=1.01$	0.12 (0.08–0.16)	0.42 (0.29–0.53)
SV	0.51 (0.40–0.60)	0.53 (0.42–0.62)	Yes, $a_2/a_1=0.86$	NS	NS
Cardiac index	0.49 (0.39–0.58)	0.51 (0.41–0.59)	No, $a_2/a_1=0.89$	NS	NS
TPR index	0.49 (0.40–0.58)	0.55 (0.46–0.64)	No, $a_2/a_1=0.96$	0.08 (0.04–0.13)	0.21 (0.09–0.33)
African Americans					
SBP	0.60 (0.49–0.68)	0.72 (0.63–0.79)	No, $a_2/a_1=1.07$	0.24 (0.17–0.31)	0.50 (0.37–0.60)
DBP	0.53 (0.42–0.62)	0.73 (0.65–0.80)	No, $a_2/a_1=0.91$	0.22 (0.14–0.29)	0.37 (0.24–0.50)
HR	0.66 (0.56–0.74)	0.68 (0.58–0.75)	No, $a_2/a_1=1.04$	0.10 (0.05–0.15)	0.34 (0.18–0.48)
SV	0.58 (0.46–0.68)	0.58 (0.45–0.67)	Yes, $a_2/a_1=0.84$	0.06 (0.02–0.10)	0.28 (0.11–0.42)
Cardiac index	0.38 (0.22–0.51)	0.31 (0.14–0.45)	Yes, $a_2/a_1=0.70$	0.08 (0.03–0.12)	0.35 (0.20–0.49)
TPR index	0.44 (0.29–0.57)	0.39 (0.23–0.52)	Yes, $a_2/a_1=0.77$	0.10 (0.05–0.16)	0.34 (0.18–0.48)

h^2 , heritability; CI, confidence interval;

SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; SV=stroke volume and TPR=total peripheral resistance.

Residuals were used after effects of age, sex, ethnicity and BMI were regressed out for all measures

* Reactivity was defined as change score calculated as average stress level minus resting level. Based on parameter estimates of the best fitting bivariate models the heritability of reactivity can be derived as $((a_2 - a_1)^2 + a_2^2) / ((a_2 - a_1)^2 + a_2^2 + (c_2 - c_1)^2 + c_2^2 + (e_2 - e_1)^2 + e_2^2)$

Table 4

Phenotypic (r_P), genetic (r_A), and environmental (r_E) correlations between rest and stress levels as well as the proportion of r_P explained by genetic (A) or environmental (E) factors based on the best fitting bivariate models

	Phenotypic correlation			Additive genetic correlation			Unique environmental correlation			Proportions of r_P	
	r_P	95% CI		r_A	95% CI		r_E	95% CI		A/E*	
European Americans											
SBP	0.73	0.69–0.77		0.86	0.79–0.91		0.52	0.41–0.62		0.75/0.25	
DBP	0.62	0.57–0.67		0.71	0.60–0.81		0.54	0.43–0.63		0.60/0.40	
HR	0.85	0.83–0.87		0.91	0.88–0.95		0.72	0.65–0.78		0.73/0.27	
SV	0.86	0.84–0.88		0.96	0.92–1.00		0.75	0.68–0.80		0.58/0.42	
Cardiac index	0.83	0.81–0.86		0.95	0.91–1.00		0.71	0.64–0.77		0.57/0.43	
TPR index	0.80	0.77–0.83		0.92	0.86–0.96		0.68	0.60–0.75		0.59/0.41	
African Americans											
SBP	0.74	0.69–0.79		0.84	0.76–0.90		0.59	0.47–0.69		0.74/0.26	
DBP	0.70	0.65–0.75		0.81	0.72–0.89		0.53	0.39–0.65		0.73/0.27	
HR	0.85	0.82–0.88		0.93	0.89–0.97		0.69	0.59–0.77		0.73/0.27	
SV	0.88	0.85–0.90		0.95	0.90–0.98		0.78	0.71–0.84		0.63/0.37	
Cardiac index	0.85	0.83–0.88		0.86	0.73–0.94		0.85	0.80–0.89		0.35/0.65	
TPR index	0.82	0.78–0.85		0.85	0.74–0.93		0.79	0.72–0.85		0.43/0.57	

h^2 = heritability; A = additive genetic factor; E = unique environmental factor; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; SV=stroke volume and TPR=total peripheral resistance.

Residuals were used after effects of age, sex, ethnicity and BMI were regressed out for all measures.

* A/E: the percentage of the phenotypic correlation that is due to genes (A) or to environment (E), calculated from: $r_P = (\sqrt{h^2} * r_A * \sqrt{h^2}) + (\sqrt{e^2} * r_E * \sqrt{e^2})$.