Hypertension Research (2011) 34, 173–179

www.nature.com/hr

ORIGINAL ARTICLE

Genetic and environmental influences on blood pressure and body mass index in Han Chinese: a twin study

Ting Wu[1,2], Harold Snieder[2,3], Liming Li[1], Weihua Cao[1], Siyan Zhan[1], Jun Lv[1], Wenjing Gao[1], Xiaoling Wang[3], Xiuhua Ding[3] and Yonghua Hu[1]

The familial aggregation of blood pressure (BP) may be partly due to the familial aggregation of obesity, caused by genetic and/or environmental factors that influence both. Gene–obesity interactions are expected to result in different heritability estimates for BP at different obesity levels. However, the latter hypothesis has never been tested. The present study included 1243 monozygotic and 833 dizygotic Han Chinese twins (mean ± s.d. age: 37.81 ± 9.82; range: 19.1–81.4) from the Chinese National Twin Registry. Body mass index (BMI) was used as the index of general obesity. The outcome measures were systolic BP (SBP) and diastolic BP (DBP). Quantitative genetic modeling was performed using Mx software. The SBP and DBP heritabilities were 46 and 30%, respectively. The positive correlations of BMI with SBP (r=0.26) and with DBP (r=0.27) were largely due to genetic factors (approximately 85%). Genetic factors, which also influence BMI, account for 6 and 7% of the total variance for SBP and DBP, respectively. The gene–obesity interaction analysis showed that both common and unique environmental influences on SBP increased with increasing levels of BMI, resulting in a lower heritability at higher BMI levels, whereas for DBP the heritability remained unchanged at higher BMI levels. Our results suggest that higher BMIs may reduce SBP heritability through a larger impact of environmental effects. These conclusions may be valuable for gene-finding studies.
Hypertension Research (2011) **34,** 173–179; doi:10.1038/hr.2010.194; published online 4 November 2010

Keywords: blood pressure; heritability; interaction; obesity; twin

INTRODUCTION

Hypertension affects a large proportion of the adult population,[1] and is caused by complex interactions of environmental and genetic factors that vary across populations. Obesity is a well-established risk factor for hypertension.[2–4]

Twin studies have shown that underlying continuous traits for both hypertension and obesity are significantly heritable. Heritability estimates for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) are between 40 and 60%,[5] and the heritability for body mass index (BMI) is also substantial.[6–8] These estimates raise the possibility that common genetic susceptibility may account for the association. Several previous twin and family studies have shown that the association between blood pressure (BP) and BMI is partly attributed to a common set of genetic factors,[5,9–11] although another study investigating the differences in monozygotic (MZ) twins showed that even in the absence of genetic influences, obesity may still be significantly associated with BP.[12] Moreover, most of these studies were performed in Caucasians and with relatively small sample sizes; studies conducted with Asian twins are rare.[13] Another possibility of interest is that obesity modifies the genetic susceptibility to hypertension. However, no study has hitherto quantified, such an effect of BMI, on the relative contribution of genetic and environmental factors on BP.

Twin studies provide a unique opportunity to provide evidence regarding genetic and environmental influences not only on the variation of individual traits but also on cross-trait correlations. Furthermore, study designs involving twins can examine evidence for gene–environment interactions.[14] Such information will help direct molecular, clinical and epidemiological studies on specific underlying causes of the disease. The present twin study is among the very few studies that investigate the shared genetic and environmental influences on BP and obesity, as well as the effect of gene–obesity interactions on these influences. Moreover, our study is the first to report such analyses in the Han Chinese population and uses a

[1]Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing, China; [2]Department of Epidemiology, Unit of Genetic Epidemiology and Bioinformatics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands and [3]Department of Pediatrics, Georgia Prevention Institute, Medical College of Georgia, Augusta, GA, USA
Correspondence: Dr H Snieder, Department of Epidemiology, Unit of Genetic Epidemiology & Bioinformatics, University Medical Center Groningen, University of Groningen, Hanzeplein 1 (9713 GZ), PO Box 30.001, Groningen 9700 RB, The Netherlands
E-mail: h.snieder@epi.umcg.nl or
Dr Y Hu, Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, Beijing 100083, China.
E-mail: yhhu@bjmu.edu.cn
Received 22 March 2010; revised 29 June 2010; accepted 28 July 2010; published online 4 November 2010

comparatively large sample size. The aims of this study were to (1) examine the relative influence of genetic and environmental factors on SBP, DBP and BMI; (2) investigate the extent to which the phenotypic correlations between BP and BMI may be explained by genetic or environmental factors using bivariate variance component models; and (3) investigate the extent to which BMI may modify the genetic influence on SBP and DBP in a large sample of adult twins from the Chinese National Twin Registry.

METHODS

Subjects

The present study comprised subjects from the Chinese National Twin Registry, which was established in 2001.[15,16] In total, 2111 subjects were recruited from Qingdao and Lishui, two cities located in the north and south of China, respectively. In this study, we excluded three triplets (nine individuals), 20 individuals who had type 2 diabetes, two pairs of twins who did not have sex information and one pair of twins who did not have BP measures. After the exclusions, 1243 MZ (620 pairs and three singletons) and 833 dizygotic (DZ) (414 pairs and five singletons) twins, including pairs of the same and the opposite sex (age, mean ± s.d.: 37.81 ± 9.82; range: 19.1–81.4), were included. Gender and ABO blood type were used for an initial screen of zygosity, and those twin pairs showing differences were categorized as DZ. Then ⩾4 Short Tandem Repeat markers were used to determine zygosity in the remaining twins.[16,17] Written informed consent was obtained from all participants before they entered the study, which was approved by the Ethics Committee for Human Subject Studies of the Peking University Health Science Center.

Measurements

BP was measured in seated subjects with a mercury-gravity sphygmomanometer according to standard protocols.[18] Each individual of a pair of twins was measured on the same day in the morning and was seated quietly for at least 5 min before measurement. Three measurements were taken for each subject with an interval of at least 30 s between measurements, and the mean value of the three measurements was used in the analysis. Subjects were asked to refrain from alcohol, coffee and vigorous exercise during the 24 h before the measurements, and they were also asked to fast for 12 h before the measurements. Height was measured to the nearest cm using a wall-mounted stadiometer. Weight (light clothing only) was measured to the nearest 0.1 kg using digital scales. BMI was calculated as weight divided by the square of the height ($kg\,m^{-2}$).

Statistical analysis

Structural equation modeling was the primary method of analysis. Structural equation modeling is based on the comparison of the variance–covariance matrices in MZ and DZ twin pairs and allows the separation of the observed phenotypic variance into its genetic and environmental components: additive (A) or dominant (D) genetic components and common (C) or unique (E) environmental components. Dividing each of these components by the total variance yields the different standardized components of the variance. For example, the heritability (h^2) can be defined as the proportion of the total variance attributable to additive genetic variation.[19] We focused on the additive genetic effects and common and unique environmental effects because there was little evidence that correlations among MZ twins substantially exceeded twice those among DZ twins, which would indicate dominance variance.[19]

Sex differences were examined by comparing a full model, in which parameter estimates were allowed to differ in magnitude between men and women, with a reduced model, in which parameter estimates were constrained to be equal across the sexes. In addition to those models, a scalar model was tested. In the scalar model, the heritabilities were constrained to be equal across sexes, but total variances could be different.[20]

For the second purpose of the study, a bivariate path model, which is shown in Figure 1, was used. With this model, which made use of the 'Cholesky decomposition,' we can not only estimate the heritability of BMI ($(a_{11}^2/(a_{11}^2+c_{11}{}^2+e_{11}^2)$) and BP ($(a_{21}^2+a_{22}^2)/(a_{21}^2+a_{22}^2+c_{21}^2+c_{22}^2+e_{21}^2+e_{22}^2)$) but also test whether the magnitude of the genetic influence differs for BMI and BP. We can further test whether the genes influencing BP are the same (that is, a_{22}=0?), partly the same (that is, $a_{21}\neq 0$ and $a_{22}\neq 0$?) or entirely different (that is, a_{21}=0?) from those for BMI. If they are partly the same, this bivariate model allows further determination of the amount of overlap between the genes that influence BP and BMI by calculating the genetic correlation between the two traits (r_g=COV_A (trait 1, trait 2)/$\sqrt{}$($V_A$trait1*$V_A$trait2)). The shared and unique environmental correlations can be calculated in a similar manner.[19,21]

We then fit the gene–environment interaction models as described by Purcell[14] using BMI as a continuous moderator and incorporating all available twin pairs (Figure 2). In this gene–environment interaction model, the phenotypic variance of the outcome variables (SBP and DBP) was portioned into A, C and E components, with the path coefficients associated with each variable expressed as linear functions of the moderator (for example, A+T×M1, C+U×M1 and E+V×M1), in which M1 represents the value of the moderator

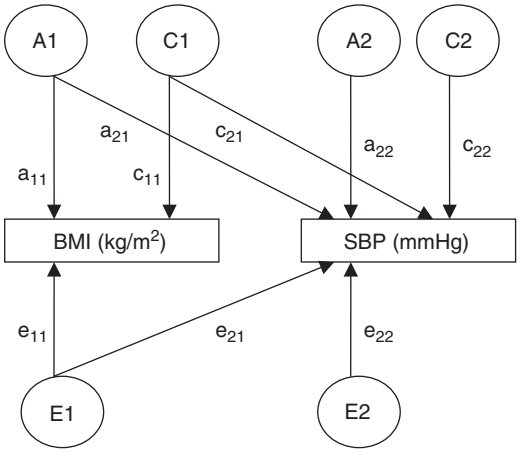

Figure 1 Path diagram for a bivariate model. For clarity only one twin is depicted. A1, A2=genetic variance components; C1, C2=common environmental variance components; E1, E2=unique environmental variance components; a_{11} through a_{22}=genetic path coefficients (or factor loadings) of which a_{22} represents specific genetic influences on SBP; c_{11} through c_{22}=common environmental path coefficients (or factor loadings) of which c_{22} represents specific common environmental influences on SBP; e_{11} through e_{22}=unique environmental path coefficients (or factor loadings), of which e_{22} represents specific unique environmental influences on SBP. Formulas for the different heritability estimates are as follows:

h^2 total (BMI) = $a_{11}^2/(a_{11}^2+c_{11}^2+e_{11}^2)$

h^2 total (SBP) = $(a_{21}^2+a_{22}^2)/(a_{21}^2+a_{22}^2+c_{21}^2+c_{22}^2+e_{21}^2+e_{22}^2)$

h^2 shared (SBP explained by BMI) = $a_{21}^2/(a_{21}^2+a_{22}^2+c_{21}^2+c_{22}^2+e_{21}^2+e_{22}^2)$

h^2 specific (SBP) = $a_{22}^2/(a_{21}^2+a_{22}^2+c_{21}^2+c_{22}^2+e_{21}^2+e_{22}^2)$

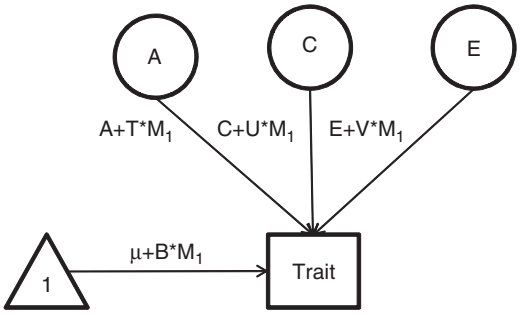

Figure 2 Partial path diagram for the basic gene–environment interaction model. A=additive genetic effects; C=common environmental effects; E=unique environmental effects; M=moderator (BMI in the present study); T=moderated component of A; U=moderated component of C; V=moderated component of E; B=linear effects of moderator on mean (forced entry).

and B represents the linear effects on the outcome. Because we were primarily interested in the effects of BMI on the variance components, we forced B into the model to guard against model misspecification. That is, by forcing the effect of BMI into the model, we guarded against detecting the GxE that is actually due to gene–environment correlation (r_{GE}). A significant compromise of model fit when parameters T, U and V were fixed to zero reflected evidence of significant moderation of additive genetic, common environmental and unique environmental variance by BMI, respectively. For example, a significant moderation of additive genetic variance alone would suggest that the magnitude of the heritability of SBP changes as the moderator increases or decreases. Variance components were only tested for significance if the respective interaction terms had been dropped from the model; for example, A was not tested unless T was not significant, to avoid modeling interactions in the absence of the main effects. In the final model, each parameter contributed significantly to the model fit ($P<0.05$). BMI may be correlated with the genetic effects on BP (r_{GE}) rather than modifying the genetic effects on BP (G×E). However, entering BMI in the means model to allow for a main effect would effectively remove from the covariance model any genetic effects that may be shared between BP and BMI (a_{21} in Figure 1). Thus, any interactions detected will not be due to gene–environment correlation (r_{GE}), but will instead be interactions between BMI and the variance components specific to BP. We further performed stratified analyses in twin pairs concordant for normal weight or overweight to confirm the results from the above analysis. Overweight in our population of Han Chinese was defined as BMI $\geqslant 24\,kg\,m^{-2}$.[22,23]

Before the analysis, 15 and 10 mm Hg were added to SBP and DBP, respectively, for individuals using antihypertensive medication because this addition was shown to reduce bias and improve statistical power.[24,25] However, performing all analyses after the exclusion of 39 subjects who were currently taking antihypertensive medication yielded virtually identical results. SBP, DBP and BMI were log-transformed to obtain a better approximation of the normal distribution. The effects of age, gender and study site were regressed for the log-transformed SBP and DBP before using the residuals in model fitting. To obtain the heritabilities for SBP and DBP independent of obesity, we adjusted for BMI in the univariate analysis. For the gene–BMI interaction analysis, only SBP and DBP were log-transformed. The significance of moderator effects T, U and V and variance components A and C were assessed by testing the deterioration in model fit after each term 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 (χ^2-2d.f.). The model with the lowest Akaike's Information Criterion reflects the best balance of goodness of fit and parsimony.[19] Preliminary analyses were done using STATA 10.0 (Stata Corp., College Station, TX, USA). Genetic modeling was conducted with Mx, a computer program specifically designed for the analysis of twin and family data.[26]

RESULTS

Sample and demographics

The general characteristics of the male and female twins are presented in Table 1. Men had higher SBPs and DBPs than women. More women lived in the city of Qingdao compared with men. Subjects who lived in Qingdao had higher SBPs and DBPs ($Ps<0.001$) than those living in the city of Lishui. None of the traits showed significant differences between MZ and DZ twins.

Table 2 presents the twin correlations for all traits of each sex-by-zygosity group. For SBP and DBP, the results are shown before and after adjustment for BMI. The MZ correlations were consistently higher than the DZ correlations, indicating an important contribution of genetic factors. The DZ correlations for all traits were more than half of the corresponding MZ correlations, suggesting an absence of dominance (D) effects. There was no substantial change in the correlations after adjustment for BMI.

Univariate model

Parameter estimates of the best-fitting models for SBP, DBP and BMI are shown in Table 3. All three traits were significantly heritable, with heritabilities of 46% for SBP, 30% for DBP and 74% for BMI. For SBP and DBP, the model, including additive genetic, common and unique environmental (ACE) effects without sex differences, provided the best fit. Heritability of SBP and DBP decreased after adjustment for BMI, indicating that BP shared some genetic factors with BMI to some extent. For BMI, we also tested for the presence of a common environmental effect, but dropping this effect had virtually no effect on the model fit. A scalar sex effect was observed for BMI, with women showing larger total variability than men, but there was equal heritability across the sexes.

Table 1 General characteristics and blood-pressure related variables of study subjects by gender

	Male	*Female*	*Sex difference,* P
Subjects, *n* [a]	1092	984	
Age, years	38.73 ± 10.6	36.79 ± 8.71	NS
Study site (Qingdao %)	47.5%	58.5%	<0.001
Zygosity (MZ %)	61.1%	58.7%	NS
BMI, $kg\,m^{-2}$	22.9 ± 3.02	23.0 ± 3.39	NS
SBP, mm Hg	123.0 ± 16.9	114.8 ± 15.7	<0.001
DBP, mm Hg	82.6 ± 11.1	77.3 ± 10.4	<0.001
Antihypertensive medication use[b]	22 (1.99%)	17 (1.71%)	NS

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DZ, dizygotic; MZ, monozygotic; SBP, systolic blood pressure.
Data are mean ± s.d. unless stated otherwise.
[a]Eight singletons; 620 MZ and 414 DZ pairs; two missing values for BMI in male and one in female; one missing value (outlier) for SBP in male.
[b]Antihypertensive medication use in the most recent 2 weeks.

Table 2 Twin correlations of each sex-by-zygosity group for SBP, DBP and BMI

Measure	*MZM*	*DZM*	*MZF*	*DZF*	*DOS*
N, pairs	332	111	288	103	200
SBP, mm Hg[a]	0.70/0.70	0.46/0.43	0.65/0.63	0.47/0.49	0.42/0.43
DBP, mm Hg[a]	0.66/0.64	0.50/0.46	0.60/0.58	0.42/0.43	0.40/0.39
BMI, $kg\,m^{-2}$	0.73	0.50	0.76	0.42	0.29

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DOS, dizygotic opposite sex; DZM, dizygotic male; DZF, dizygotic female; MZF, monozygotic female; MZM, monozygotic male; SBP, systolic blood pressure.
[a]Twin correlations for SBP and DBP are shown before and after adjustment for BMI. All measures were log-transformed and adjusted for age, sex and study site.

Bivariate model

We performed a bivariate model fitting to estimate to what extent the phenotypic correlations can be explained by genetic or environmental factors that influence both BP and obesity (Figure 1). BMI was significantly correlated with both SBP (0.26) and DBP (0.27), reflecting higher levels of BP at higher levels of BMI. Genetic correlations for BP and BMI were substantial (0.38 and 0.48 for SBP and DBP, respectively), whereas unique environmental correlations were somewhat weaker, but still highly significant (0.17 and 0.12 for SBP and DBP, respectively) (Table 4). The decomposition of the phenotypic correlations into their genetic and environmental parts showed that they were largely (82% for SBP and BMI, 86% for DBP and BMI) due to genetic factors.

Figure 3 presents sources of variance of BP based on the best-fitting bivariate models. Around 38% percent of the total variance for SBP and 24% for DBP could be attributed to specific genetic factors that

Table 3 Parameter estimates and 95% CIs of best-fitting models for SBP, DBP and BMI

Measures		*h^2 (95%CI)*	*c^2 (95%CI)*	*e^2 (95%CI)*	*Sex effects*
SBP, mm Hg	Model 1	0.46 (0.30–0.62)	0.22 (0.06–0.36)	0.32 (0.29–0.37)	
	Model 2	0.41 (0.26–0.58)	0.25 (0.09–0.39)	0.34 (0.30–0.38)	
DBP, mm Hg	Model 1	0.30 (0.14–0.48)	0.31 (0.15–0.46)	0.38 (0.34–0.43)	
	Model 2	0.27 (0.10–0.45)	0.32 (0.16–0.47)	0.41 (0.37–0.46)	
BMI, kg m^{-2}		0.74 (0.71–0.77)		0.26 (0.23–0.29)	k^2=0.81

Abbreviations: BMI, body mass index; c^2, common environmental effects; CI, confidence interval; DBP, diastolic blood pressure; e^2, unique environmental effects; h^2, heritability; k^2, scalar sex effect; SBP, systolic blood pressure.
All (non-standardized) variance components for males are constrained to be equal to a scalar multiple, k^2, of the female variance components, such that $h_m^2=k^2h_f^2$, $c_m^2=k^2c_f^2$ and $e_m^2=k^2e_f^2$. As a result, the standardized variance components, such as heritabilities, are equal across sexes.
BMI was log-transformed and adjusted for age, sex and study site.
Model 1: SBP and DBP were log-transformed and adjusted for age, sex and study site.
Model 2: Model 1+ adjustment for BMI.

Table 4 Phenotypic (r_P), genetic (r_A) and unique environmental (r_E) correlations from 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*
SBP and BMI	0.26	0.22–0.31	0.38	0.28–0.49	0.17	0.10–0.24	0.82/0.18
DBP and BMI	0.27	0.22–0.31	0.48	0.35–0.68	0.12	0.05–0.19	0.86/0.14

Abbreviations: A, additive genetic factor; CI, confidence interval; E, unique environmental factor; h^2, heritability.
All phenotypes were log-transformed and adjusted for age, sex and study site.

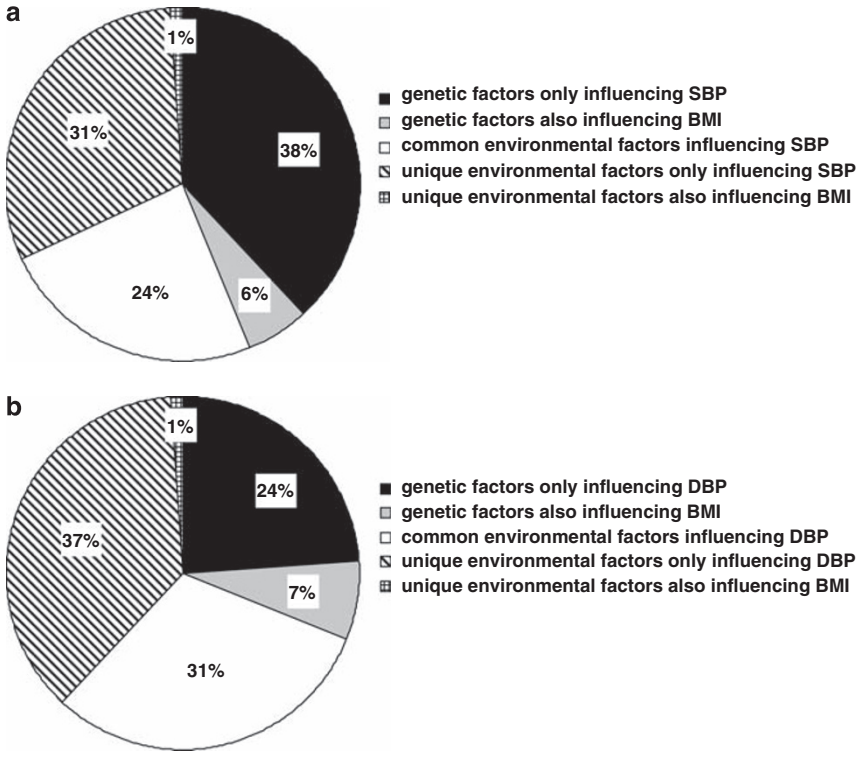

Figure 3 A decomposition of the variance of BP in its genetic and environmental components (that is, genetic and environmental sources of individual differences in BP) is shown for SBP (**a**) and DBP (**b**). We could further discriminate between genetic and environmental factors that also influenced BMI or were specific to BP.

only influenced BP. Genetic factors that also influenced BMI contributed 6% to the total variance for SBP and 7% for DBP. Comparatively, environmental factors that also influenced BMI contributed very little to the total variance for SBP and DBP (1%).

Gene–environmental interaction model

Comparative model fittings that tested the extent to which BMI served as a moderator of SBP and DBP are presented in Table 5. Gene–BMI analyses were collapsed across genders because heritability estimates of

Table 5 Comparative model fitting for BMI as a continuous moderator of SBP and DBP

	Model fitting			*Comparative model fitting*			
	Model	*−2LL*	*d.f.*	*Δ-2LL*	*Δd.f.*	P-*value*	*AIC*
SBP							
1.Full	ACETUVB	6067.531	2054				
2.T=U=V=0	ACEB	6092.519	2057	24.988	3	<0.001	18.988
3.V=0	ACETUB	6074.529	2055	6.999	1	0.008	4.999
4.U=0	ACETVB	6068.573	2055	1.042	1	0.307	−0.958
5.T=0	**ACEUVB**	**6067.540**	**2055**	**0.010**	**1**	**0.922**	**−1.990**
6.U=V=0	ACETB	6074.561	2056	7.031	2	0.030	3.031
7.T=V=0	ACEUB	6077.025	2056	9.494	2	0.009	5.494
8.T=U=0	ACEVB	6074.966	2056	7.436	2	0.024	3.436
DBP							
1.Full	ACETUVB	6355.688	2054				
2.T=U=V=0	**ACEB**	**6363.211**	**2057**	**7.524**	**3**	**0.057**	**1.524**

Abbreviations: −2LL, −2-log likelihood; A, additive genetic variance; AIC, Akaike's Information Criterion; B, linear effects of BMI on means of the outcome variables; BMI, body mass index; C, common environmental variance; DBP, diastolic blood pressure; d.f., degrees of freedom; E, unique environmental variance; SBP, systolic blood pressure; T, moderation of additive genetic variance by BMI; U, moderation of common environmental variance by BMI; V, moderation of unique environmental variance by BMI.
All models were compared with the full model (model 1).
SBP and DBP were log-transformed and adjusted for age, sex and study site.
Best fitting models are in bold.

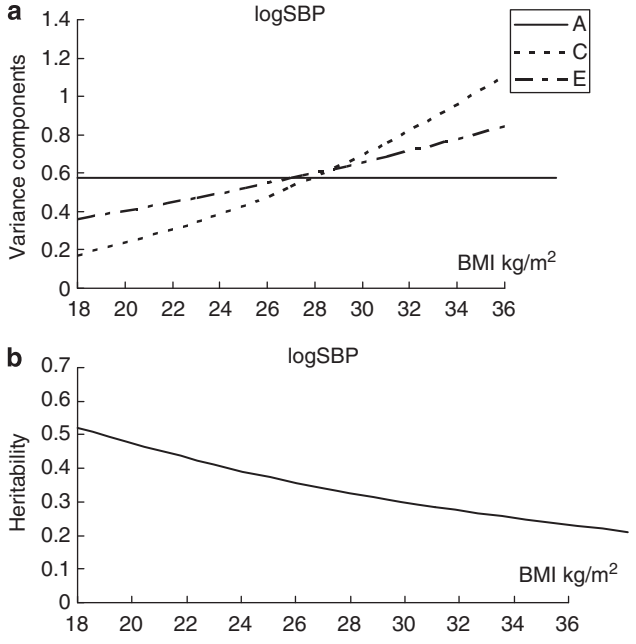

Figure 4 (**a**) Change of additive genetic, common environmental and unique environmental variances of SBP with increasing level of BMI. (**b**) Change of heritability of SBP with increasing level of BMI.

SBP and DBP were not significantly different between men and women (Table 3). The best-fitting model for SBP was the ACEUVB model in which the moderators of the common (U) and unique environment (V) components contributed significantly. As shown in Figure 4a, both the common and the unique environmental influences on SBP increased with BMI, which resulted in a lower heritability estimate for SBP at higher BMI levels; for example, the heritability for SBP is 0.47 at BMI=20 kg m^{-2} and 0.32 at BMI=30 kg m^{-2} (Figure 4b). For DBP, the best-fitting model was the ACEB model in which none of the moderators contributed significantly.

Table 6 Twin pair correlations and univariate twin structural equation model parameter estimates (unstandardized) for BP, normal weight and overweight subjects

	N *(pairs)*	*Correlations*					
Variables	*MZ/DZ*	r_{MZ}	r_{DZ}	a^2	c^2	e^2	*Total* variance
SBP							
Normal weight	357/195	0.68	0.43	0.53	0.27	0.40	1.20
Overweight	140/76	0.65	0.52	0.53	0.60	0.58	1.71
P-value[a]				0.989	0.293	0.006	
DBP							
Normal weight	357/195	0.59	0.42	0.41	0.46	0.63	1.50
Overweight	140/76	0.63	0.50	0.33	0.62	0.59	1.54
P-value[a]				0.796	0.588	0.526	

Abbreviations: a^2, additive genetic effects; BP, blood pressure; c^2, common environmental effects; DBP, diastolic blood pressure; DZ, dizygotic; e^2, unique environmental effects; MZ, monozygotic.
[a]*P*-value: *P*-value is shown for the χ^2 difference (1 d.f.) between the full ACE model with BMI differences and the ACE sub–model, in which normal weight and overweight parameter estimates are set equal, that is, a^2 (normal weight)=a^2 (overweight), then c^2 (normal weight)=c^2 (overweight) and then e^2 (normal weight)=e^2 (overweight), respectively.
Normal weight: BMI <24 kg m^{-2}; overweight: BMI $\geqslant 24$ kg m^{-2}.
SBP and DBP were log-transformed and adjusted for age, sex and study site.

The change in variance components of SBP with different BMI levels was confirmed by stratified analysis in twin pairs concordant for normal weight and for overweight, as shown in Table 6. As a result, the heritability was 14 percentage points lower for SBP among twins concordant for overweight (h^2=0.31) relative to twins concordant for normal weight (h^2=0.45). Moreover, the unchanged heritability of DBP in the interaction model was confirmed by stratified analysis, which showed the same heritability (h^2=0.26) in subjects with normal weight and overweight.

DISCUSSION

The aims of this study included estimating the relative influence of genetic and environmental factors on BP and BMI. Furthermore, we investigated the genetic and environmental overlap between BP and BMI and the extent to which BMI may modify the effect of genetic factors on SBP and DBP in a large sample of adult twins from the Han Chinese population. The current study suggests that genetic and environmental influences on SBP may vary as a function of BMI.

The present study, for the first time, reported the heritability of BP in a large sample of adult Han Chinese twins and further investigated sex effects. The major difference between this study and former twin studies is that we found a significant contribution of the common environment to BP. The environmental factors common to twins for SBP and DBP explained 22 and 31%, respectively, of the total variance. Because familial resemblance could be explained by sharing the environment in addition to sharing genes, the heritability estimates for BP in the present study were somewhat lower than those reported in the previous twin studies.[5,27] Part of the explanation might be the diversity of genetic backgrounds and/or differences in the environmental effects between populations. The present study was performed in Han Chinese, whereas previous studies were mostly performed in white twins.[5] In addition, the common environmental influences detected in this study may be attributable to different sample sizes. Hopper[28] convincingly argued that most twin studies simply lacked the power to detect moderate-size influences of the common environment. A few studies that either had large sample sizes or used a

more powerful multivariate approach did find a small contribution by the common environment of approximately 10–20%.[5] For example, a large family study, including two-generation families, reported that common environmental effects accounted for 31 and 23% of the variance in SBP and DBP, respectively.[11] The present study is one of the largest twin studies to date that investigates the relative contribution of genes and environment on BP. Thus, our results confirm that large sample sizes are needed to detect moderate influences of the common environment in twin studies. However, we did not observe any sex differences for BP. Our results were in line with most previous twin studies in which heritability estimates for men and women are remarkably similar.[5] We also detected a substantial heritability of 0.74 for BMI, which is consistent with previous findings.[6,29,30] The heritability estimates of BP decreased after adjustment for BMI, suggesting that the heritability of BP is partly dependent on BMI.

We further confirmed the above conclusion by performing bivariate variance components analyses. Our results showed that genetic factors accounted for a large portion of the correlations between BP and BMI (approximately 85%), indicating that these phenotypes, as expected, had a set of genes in common.[31] The percentage of total BP variance caused by genetic effects common to BP and BMI was 6 and 7% for SBP and DBP, respectively. Schieken *et al*.[32] addressed the same issue in a pediatric population of 11-year-old twins. They observed a significant correlation between SBP and BMI (0.29) that could largely be explained by common genes rather than common environmental effects influencing both traits. The percentage of total SBP variance caused by genetic effects common to SBP and BMI was 8%, which is consistent with our results. McCaffery *et al*.[9] also reported that genetic and, to a lesser extent, non-shared environmental factors contribute to the covariation of SBP and BMI in young adult twins. Another study performed in African-American twins found sex differences, showing that 3.1% of the total variance in SBP was in common with BMI in males and 6% in females, while for DBP, 6.1% was in common with BMI in males and 3.7% in females.[10] The consistent results of these studies across different ethnicities and age groups confirm that part of the genetic variation in BP can be explained by genes for obesity.

A novel finding of this study is that the genetic and environmental influences on SBP vary as a function of general obesity. The influence of common and unique environmental factors increases with increasing levels of BMI, resulting in a decreased level of heritability. This result seems to suggest that higher BMI levels may reduce the penetrance of genetic vulnerability to SBP through a larger impact of environmental effects. Using models similar to the present study, McCaffery *et al*.[33] reported a higher heritability of hypertension with more years of education. Typically, socioeconomic status, as indexed by education attainment, occupation and income, is inversely associated with BMI levels, even in developing countries.[34,35] In other words, our results are consistent with those from McCaffery's study, showing reduced heritability in the high-risk environment; that is, heritability was reduced with higher BMIs in our study and lower education levels in McCaffery's. Although the specific mechanism by which BMI affects the heritability of BP cannot be determined from this study, it is well known that several environmental and behavioral factors that predict BP levels, such as unhealthy diets and lack of physical activity, are more prevalent among groups with higher BMIs. Within the twin design, this type of effect may manifest itself as an enhancement of the environmental effect relative to the genetic effect, resulting in reduced heritability.

Our results have some implications for further efforts to find genes underlying BP levels. Although BP shows a substantial heritability of approximately 40–60%,[5] the findings for candidate genes have been difficult to consistently replicate. Two recent large-scale genome-wide association studies[36,37] identified common variants in 13 loci associated with BP that each explained only 0.05–0.10% of the variance,[36] and only about 1% was associated with BP when aggregated over all the loci.[37] Thus, the vast majority of the genetic contributions to variation in BP remain unexplained. One explanation for the difficulty in finding genes for BP is that the expression of genes may vary as a function of environmental exposures. This would mean that their effects could only be found in the presence of certain environments. Our results provided some evidence for this because genetic variation of SBP was higher in subjects with normal BMI. This suggests that in the Han Chinese, the selection of subjects with normal BMIs would increase the power required to find genes for SBP. Future genome-wide association studies may want to rigorously measure environmental exposures and perform gene–environment interaction analyses to enhance the chances of finding genes.[38]

There are many strengths of this paper. First, our study was based on a large sample of adult male and female twins of Han Chinese ethnicity and is one of the largest twin studies for BP.[5,27] Second, BMI was measured in an objective way rather than self-reported. In our study, BP was measured three times according to standard procedures, and we used the mean values in the analyses to decrease measurement error. There are also some potential limitations. First, the Chinese Twin National Registry is predominantly of Han ethnicity. Thus, the generalizability of these results to other ethnicities remains to be determined. Second, although we treated BMI as an environmental moderator in the statistical models, BMI is not a purely environmental factor. We have shown in our study that BMI is both substantially heritable and shows genetic and environmental overlap with BP. At the same time, however, the interaction model suggests that BMI influenced SBP heritability through a larger impact of environmental effects. By entering BMI into the means model to allow for a main effects model, we effectively removed from the covariance model any genetic effects that are shared between SBP and BMI (a_{21} in Figure 1). Any interactions detected were not due to gene–obesity correlation, which is essential when interpreting and generalizing our results. Third, the model used to test for interactions, including a continuously measured environmental variable, is relatively new. However, splitting the sample into a normal and an overweight group confirmed our findings. Fourth, we did not include other risk factors for hypertension (for example, smoking, alcohol consumption and salt intake), which may have some influence on the modifying effects of BMI on BP.

In conclusion, our findings show that genes for obesity explain part of the genetic variation in BP. These results will provide important information for strategies for the discovery of specific genes or environmental factors that impact BP, BMI or both, especially in Asian populations. Our results further suggest that BMI levels are associated with the heritability of SBP. In this regard, we expect that performing gene–obesity interaction analyses in future genome-wide association studies will enhance the efficiency of detecting BP susceptibility genes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This work was partly supported by the China Medical Board of New York (01-746) and the National Natural Science Foundation of China (30070672).

1 Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, Kjeldsen S, Luscher T, Mallion JM, Mancia G, Poulter N, Rahn KH, Rodicio JL, Ruilope LM, van Zwieten P, Waeber B, Williams B, Zanchetti A. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. *J Hyperten* 2003; **21**: 1779–1786.
2 Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. *Circulation* 2000; **101**: 329–335.
3 Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 1978; **240**: 1607–1610.
4 Harsha DW, Bray GA. Weight loss and blood pressure control (Pro). *Hypertension* 2008; **51**: 1420–1425.
5 Wang X, Snieder H. Familial aggregation of blood pressure. In: Flynn JT, Ingelfinger JR, Portman RJ (eds). *Clinical Hypertension and Vascular Diseases: Pediatric Hypertension*, 2nd edn. Humana Press Inc.: Totowa, NJ, 2010 (in press).
6 Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet* 1997; **27**: 325–351.
7 Nelson TL, Brandon DT, Wiggins SA, Whitfield KE. Genetic and environmental influences on body-fat measures among African-American twins. *Obes Res* 2002; **10**: 733–739.
8 Schousboe K, Visscher PM, Erbas B, Kyvik KO, Hopper JL, Henriksen JE, Heitmann BL, Sorensen TI. Twin study of genetic and environmental influences on adult body size, shape, and composition. *Int J Obes Relat Metab Disord* 2004; **28**: 39–48.
9 McCaffery JM, Pogue-Geile MF, Debski TT, Manuck SB. Genetic and environmental causes of covariation among blood pressure, body mass and serum lipids during young adulthood: a twin study. *J Hyperten* 1999; **17**: 1677–1685.
10 Nelson TL, Brandon DT, Wiggins SA, Whitfield KE. Genetic and environmental influences on body fat and blood pressure in African-American adult twins. *Int J Obes (Lond)* 2006; **30**: 243–250.
11 Cui J, Hopper JL, Harrap SB. Genes and family environment explain correlations between blood pressure and body mass index. *Hypertension* 2002; **40**: 7–12.
12 Newman B, Selby JV, Quesenberry Jr CP, King MC, Friedman GD, Fabsitz RR. Nongenetic influences of obesity on other cardiovascular disease risk factors: an analysis of identical twins. *Am J Public Health* 1990; **80**: 675–678.
13 Sung J, Lee K, Song YM. Heritabilities of the metabolic syndrome phenotypes and related factors in Korean twins. *J Clin Endocrinol Metab* 2009; **94**: 4946–4952.
14 Purcell S. Variance components models for gene-environment interaction in twin analysis. *Twin Res* 2002; **5**: 554–571.
15 Yang H, Li X, Cao W, Lu J, Wang T, Zhan S, Hu Y, Li L. Chinese National Twin Registry as a resource for genetic epidemiologic studies of common and complex diseases in China. *Twin Res* 2002; **5**: 347–351.
16 Li L, Gao W, Lv J, Cao W, Zhan S, Yang H, Hu Y. Current status of the Chinese National Twin Registry. *Twin Res Hum Genet* 2006; **9**: 747–752.
17 Huang AQ, Hu YH, Zhan SY, Xu B, Pang ZC, Cao WH, Lu J, Qin Y, Lee LM. Lipoprotein lipase gene S447X polymorphism modulates the relation between central obesity and serum lipids, a twin study. *Int J Obes (Lond)* 2006; **30**: 1693–1701.
18 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hyperten* 1999; **17**: 151–183.
19 Neale MC, Cardon LR. *Methodologies for Genetic Studies of Twins and Families*. Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992.
20 Reynolds CA, Hewitt JK. Issues in the behavior genetic investigation of gender differences. In: Turner JR, Cardon LR, Hewitt JK (eds). *Behavior Genetics Approaches in Behavioral Medicine*. Plenum Press: New York, 1995, pp 189–199.
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 Cheng TO. Chinese body mass index is much lower as a risk factor for coronary artery disease. *Circulation* 2004; **109**: e184.
23 Bei-Fan Z. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Asia Pac J Clin Nutr* 2002; **11**: S685–S693.
24 Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. *Stat Med* 2005; **24**: 2911–2935.
25 De Geus EJ, Kupper N, Boomsma DI, Snieder H. Bivariate genetic modeling of cardiovascular stress reactivity: does stress uncover genetic variance? *Psychosom Med* 2007; **69**: 356–364.
26 Neale MC, Boker SM, Xie G, Maes HH. *Mx: Statistical Modeling*. Department of Psychiatry, Virginia Commonwealth University: Richmond, VA, 1999.
27 Evans A, Van Baal GC, McCarron P, DeLange M, Soerensen TI, De Geus EJ, Kyvik K, Pedersen NL, Spector TD, Andrew T, Patterson C, Whitfield JB, Zhu G, Martin NG, Kaprio J, Boomsma DI. The genetics of coronary heart disease: the contribution of twin studies. *Twin Res* 2003; **6**: 432–441.
28 Hopper JL. Why 'common' environmental effects' are so uncommon in the literature. In: Spector TD, Snieder H, MacGregor AJ (eds). *Advances in Twin and Sib-Pair Analysis*. Greenwich Medical Media: London, 2000, pp 151–165.
29 Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr* 2008; **87**: 398–404.
30 Mustelin L, Silventoinen K, Pietilainen K, Rissanen A, Kaprio J. Physical activity reduces the influence of genetic effects on BMI and waist circumference: a study in young adult twins. *Int J Obes (Lond)* 2009; **33**: 29–36.
31 Hong Y, Pedersen NL, Brismar K, de Faire U. Genetic and environmental architecture of the features of the insulin-resistance syndrome. *Am J Hum Genet* 1997; **60**: 143–152.
32 Schieken RM, Mosteller M, Goble MM, Moskowitz WB, Hewitt JK, Eaves LJ, Nance WE. Multivariate genetic analysis of blood pressure and body size. The Medical College of Virginia Twin Study. *Circulation* 1992; **86**: 1780–1788.
33 McCaffery JM, Papandonatos GD, Lyons MJ, Niaura R. Educational attainment and the heritability of self-reported hypertension among male Vietnam-era twins. *Psychosom Med* 2008; **70**: 781–786.
34 Yu Z, Nissinen A, Vartiainen E, Song G, Guo Z, Zheng G, Tuomilehto J, Tian H. Associations between socioeconomic status and cardiovascular risk factors in an urban population in China. *Bull World Health Organ* 2000; **78**: 1296–1305.
35 Monteiro CA, Moura EC, Conde WL, Popkin BM. Socioeconomic status and obesity in adult populations of developing countries: a review. *Bull World Health Organ* 2004; **82**: 940–946.
36 Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, Najjar SS, Zhao JH, Heath SC, Eyheramendy S, Papadakis K, Voight BF, Scott LJ, Zhang F, Farrall M, Tanaka T, Wallace C, Chambers JC, Khaw KT, Nilsson P, van der Harst P, Polidoro S, Grobbee DE, Onland-Moret NC, Bots ML, Wain LV, Elliott KS, Teumer A, Luan J, Lucas G, Kuusisto J, Burton PR, Hadley D, McArdle WL, Brown M, Dominiczak A, Newhouse SJ, Samani NJ, Webster J, Zeggini E, Beckmann JS, Bergmann S, Lim N, Song K, Vollenweider P, Waeber G, Waterworth DM, Yuan X, Groop L, Orho-Melander M, Allione A, Di Gregorio A, Guarrera S, Panico S, Ricceri F, Romanazzi V, Sacerdote C, Vineis P, Barroso I, Sandhu MS, Luben RN, Crawford GJ, Jousilahti P, Perola M, Boehnke M, Bonnycastle LL, Collins FS, Jackson AU, Mohlke KL, Stringham HM, Valle TT, Willer CJ, Bergman RN, Morken MA, Doring A, Gieger C, Illig T, Meitinger T, Org E, Pfeufer A, Wichmann HE, Kathiresan S, Marrugat J, O'Donnell CJ, Schwartz SM, Siscovick DS, Subirana I, Freimer NB, Hartikainen AL, McCarthy MI, O'Reilly PF, Peltonen L, Pouta A, de Jong PE, Snieder H, van Gilst WH, Clarke R, Goel A, Hamsten A, Peden JF, Seedorf U, Syvanen AC, Tognoni G, Lakatta EG, Sanna S, Scheet P, Schlessinger D, Scuteri A, Dorr M, Ernst F, Felix SB, Homuth G, Lorbeer R, Reffelmann T, Rettig R, Volker U, Galan P, Gut IG, Hercberg S, Lathrop GM, Zelenika D, Deloukas P, Soranzo N, Williams FM, Zhai G, Salomaa V, Laakso M, Elosua R, Forouhi NG, Volzke H, Uiterwaal CS, van der Schouw YT, Numans ME, Matullo G, Navis G, Berglund G, Bingham SA, Kooner JS, Connell JM, Bandinelli S, Ferrucci L, Watkins H, Spector TD, Tuomilehto J, Altshuler D, Strachan DP, Laan M, Meneton P, Wareham NJ, Uda M, Jarvelin MR, Mooser V, Melander O, Loos RJ, Elliott P, Abecasis GR, Caulfield M, Munroe PB. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet* 2009; **41**: 666–676.
37 Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Kottgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FU, Smith AV, Taylor K, Scharpf RB, Hwang SJ, Sijbrands EJ, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JC, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009; **41**: 677–687.
38 Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, Kong A, Kruglyak L, Mardis E, Rotimi CN, Slatkin M, Valle D, Whittemore AS, Boehnke M, Clark AG, Eichler EE, Gibson G, Haines JL, Mackay TF, McCarroll SA, Visscher PM. Finding the missing heritability of complex diseases. *Nature* 2009; **461**: 747–753.