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Published in:
Twin Research and Human Genetics

DOI:
10.1017/thg.2014.83

Publication date:
2015

Document version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Multivariate Modeling of Body Mass Index, Pulse Pressure, Systolic and Diastolic Blood Pressure in Chinese Twins

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Systolic and diastolic blood pressure, pulse pressure (PP), and body mass index (BMI) are heritable traits in human metabolic health but their common genetic and environmental backgrounds are not well investigated. The aim of this article was to explore the phenotypic and genetic associations among PP, systolic blood pressure (SBP), diastolic blood pressure (DBP), and BMI. The studied sample contained 615 twin pairs (17–84 years) collected in the Qingdao municipality. Univariate and multivariate structural equation models were fitted for assessing the genetic and environmental contributions. The AE model combining additive genetic (A) and unique environmental (E) factors produced the best fit for each four phenotypes. Heritability estimated in univariate analysis ranged from 0.42 to 0.74 with the highest for BMI (95% CI 0.70–0.78), and the lowest for PP (95% CI 0.34–0.49). The multivariate model estimated (1) high genetic correlations for DBP with SBP (0.87), PP with SBP (0.75); (2) low–moderate genetic correlations between PP and DBP (0.32), each BP component and BMI (0.24–0.37); (3) moderate unique environmental correlation for PP with SBP (0.68) and SBP with DBP (0.63); (4) there was no significant unique environmental correlation between PP and BMI. Overall, our multivariate analyses revealed common genetic and environmental backgrounds for PP, BP, and BMI in Chinese twins.

Keywords: blood pressure, pulse pressure, body mass index, twin study, multivariate model

Hypertension, obesity, and elevated PP are important components of risk to metabolic and cardiovascular diseases and to mortality (Benetos et al., 1997; Berrington de Gonzalez et al., 2010). Both clinical and epidemiological studies have shown that these disorders are also interconnected (De Pergola et al., 2012; Wu et al., 2011). The exploration of the genetic and environmental relationships underlying these conditions is one approach to resolving the biological basis for the association. Several twin studies have shown that the associations between blood pressure (BP) components and BMI are partly attributed to a common set of genetic factors (Tarnoki et al., 2013; Wu et al., 2011). However, most of these studies were performed by using a bivariate model. Meanwhile, multivariate genetic models have been applied in twin studies of complex human traits, including, for example, metabolic syndrome (Zhang et al., 2009), cardiovascular disorders (Williams et al., 2004), and cognitive aging (Tucker-Drob et al., 2013), and have revealed common genetic and environmental factors underlying the subphenotypes associated with these composite phenotypes. Multivariate genetic analysis can be employed to provide a complete and objective description of the underlying genetic and environmental architecture of the relationship between traits. In addition to partitioning, the phenotypic variance into genetic and environmental components, phenotypic covariance between the traits can be partitioned in a similar fashion. In this study, data from 615 twin pairs aged from 17 to 84 years were collected from the Qingdao twin...
registry (QTR), which was established by Qingdao center for disease control and prevention, China. Univariate and multivariate structural equation models were fitted to explore the genetic associations between PP, SBP, DBP, and BMI.

Materials and Methods

Study Population
The study participants were recruited from the QTR, a population-based registry established in Qingdao, China (Duan et al., 2013; Pang et al., 2006). Briefly, all twins were taken from the most recent wave of a twin sample for a heritability study on multiple phenotypes associated with the metabolic syndrome, conducted by the Qingdao center for disease control and prevention in 2008. All the participants were invited to a clinical investigation. Those who were pregnant, breastfeeding, had known diabetes and/or cardiovascular disease, or were taking antihypertensive medication or weight-reducing medication within 1 month, were excluded from participation; and incomplete twin pairs with one twin missing were excluded from sampling.

Zygosity of like-sex twin pairs was determined by DNA testing using 16 short tandem repeat DNA markers. A total of 401 pairs of monozygotic (MZ) and 214 pairs of dizygotic (DZ) twins who were aged from 17 to 84 years were sampled. The age and gender distribution of the sample is shown in Table 1.

Phenotypes
Brachial BP was taken in a sitting position by using a mercurial table stand model sphygmomanometer. SBP and DBP were determined by the first and fifth Korotkoff sounds, respectively. Measurements were taken twice for each subject, with at least 5 min between each measurement, and the average of the two measurements was recorded. PP was calculated as the difference between systolic and DBP. Weight and height were measured with the subject in lightweight clothes and their shoes removed. BMI was calculated as weight (kg) divided by square of height (m). All the anthropometrics, including height, weight, and brachial BP, were carried out by well-trained clinicians in a face-to-face manner at the Qingdao center for disease control and prevention. Participants were examined at 8:00–10:00 am after an overnight fast of at least 10 hours. All phenotype values were log-transformed (natural log) to avoid skewed distributions. There were two samples missing BMI and one sample missing sex. Phenotype values more than three standard deviations below or above phenotype means were set to missing.

Data Analysis

Basic analyses. We described PP, SBP, DBP, and BMI in raw data by sex and zygosity using means and standard deviations.

Univariate genetic analyses. After adjusting for age and sex, intra-class correlation coefficients (ICC) were calculated to show twin correlations on each of the four phenotypes. Since our DZ correlation is more than one half the MZ correlations for all phenotypes, an ACE model was preferred, with A representing the additive genetic effects, C the shared, and E the non-shared environmental effects. Comparisons on performances between the full ACE model and its nested models (AE, CE, E) were done using the likelihood ratio test. The likelihood ratio test calculates twice the difference in the log likelihoods for the full and the nested models, and can be approximated by a chi-squared distribution with degree of freedom equaling the difference in the number of parameters in the two models. When no statistical significance is observed between two models, the parsimonious one is preferred. The model with the lowest akaike information criteria (AIC) reflects the best balance between goodness of fit and parsimony.

Multivariate genetic analyses. Cross-trait, cross-twin correlations for each of the four phenotypes were estimated separately in MZ and DZ twins. We then performed a multivariate genetic model fitting by constructing a Cholesky decomposition model (Figure 1) with age and sex correction. The first set of factor loadings (i.e., A1, C1, and E1) had an impact on all the four phenotypes. The second set of factor loadings (i.e., A2, C2, and E2) had an impact on the second, third, and fourth phenotype, with the third set (i.e., A3, C3, and E3) on the third and fourth phenotype, and the final set (i.e., A4, C4, and E4) on the fourth phenotype only. We performed genetic modeling analysis by removing parts of factors loading from the full Cholesky model, leading to a submodel with fewer parameters. The best fitting and most parsimonious model was also selected based on the likelihood ratio test and AIC.

All of the phenotypic analysis, including descriptive statistics and correlation calculation, were performed by using the free R software (http://www.r-project.org/). All twin models were fitted by including age and sex as covariates for adjustment using the Mx package.

Ethics Statement
Written informed consent was obtained from the adult twins and from parents or legal guardians of twins aged under 18 years. Ethical approval was obtained from the ethics committee of the Qingdao center for disease control and prevention.

Results

Basic Analyses
A total of 615 pairs of twin (401 MZ, 214 DZ pairs) were sampled. The basic statistics for all subjects are shown in Table 1 for male and female, MZ and DZ twins separately. For all the phenotypes, no significant difference ($p > 0.05$).
TABLE 1
Descriptive Statistics by Sex and Zygosity

<table>
<thead>
<tr>
<th>Groups</th>
<th>Male</th>
<th>Female</th>
<th>MZ</th>
<th>DZ</th>
<th>All</th>
<th>Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>470</td>
<td>760</td>
<td>802</td>
<td>428</td>
<td>1230</td>
<td></td>
</tr>
<tr>
<td>Age(years)</td>
<td>39.87 (10.55)</td>
<td>40.60 (8.99)</td>
<td>40.30 (9.55)</td>
<td>40.36 (9.76)</td>
<td>40.32 (9.62)</td>
<td>17–84</td>
</tr>
<tr>
<td>PP(mmHg)</td>
<td>41.73 (9.52)</td>
<td>39.54 (9.70)</td>
<td>39.60 (9.22)</td>
<td>41.82 (10.36)</td>
<td>40.37 (9.68)</td>
<td>20–85</td>
</tr>
<tr>
<td>SBP(mmHg)</td>
<td>123.84 (10.69)</td>
<td>116.49 (15.36)</td>
<td>117.68 (15.13)</td>
<td>122.33 (16.29)</td>
<td>119.3 (15.69)</td>
<td>75–195</td>
</tr>
<tr>
<td>DBP(mmHg)</td>
<td>82.11 (10.69)</td>
<td>76.95 (10.30)</td>
<td>78.07 (10.52)</td>
<td>80.51 (10.99)</td>
<td>78.92 (10.75)</td>
<td>50–120</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>24.05 (3.37)</td>
<td>23.38 (3.37)</td>
<td>23.49 (3.34)</td>
<td>23.91 (3.45)</td>
<td>23.64 (3.39)</td>
<td>15.63–37.76</td>
</tr>
</tbody>
</table>

Note: Values are mean (SD) and range as indicated.

Figure 1
Multivariate Cholesky ACE model with specified parameters.

in mean or SD was found between the two zygosity groups, fulfilling the basic assumptions for classic twin analyses. No significant differences (p > 0.05) in mean or SD were found between the first-born and second-born twins, suggesting no birth order effect on these measures. After removing the samples with missing value and measurements above or below 3 SDs of the mean, 607 pairs of twin were available for the genetic model fitting.

Univariate Genetic Analyses
ICCs for MZ and DZ pairs are summarized in Table 2. For all phenotypes, MZ correlations were consistently larger than those in DZ twins, suggesting genetic contributions. We started our twin modeling with testing sex difference in phenotype variance by fitting the scalar sex-limitation model, a model that allows for sex differences in phenotype variances by assuming that the additive genetic, shared, and unique environmental components are proportionally equal in males and females with a scalar factor. Performance of the sex-limitation model was compared with the sex-invariant model (scalar factor set to 1) using the likelihood ratio (chi-squared) test. Our results showed no significant sex difference in the variance of each phenotype with p values 0.79, 0.14, 0.95, and 0.11 for PP, SBP, DBP, and BMI, respectively. The subsequent twin models were then fitted assuming no sex difference in phenotype variances and simply including sex as a covariate. The full univariate ACE model was first fitted, and then the reduced model was constructed by removing a specific parameter and comparing the result with the full ACE model. For each phenotype, the AE model with the lowest AIC did not result in a significant deterioration of the model fit except that the SBP AE sub-model is very close to misfit (p = .053). Table 2 also shows the AE models for all phenotypes. Heritability ranged from 0.42 to 0.74 with the highest for BMI (95% CI 0.70–0.78), and the lowest for PP (95% CI 0.34–0.49).

Multivariate Genetic Analyse
Considering that multivariate modeling of gender differences with opposite-sex DZ twins is problematic (Neale et al., 2006), a sex-specific multivariate ACE model using MZ and like-sex DZ twins (opposite-sex DZ twins dropped) was fitted. Comparing this model with the multivariate ACE model ignoring sex difference (also with opposite-sex DZ
Table 2
Twin Intra-Class Correlations (95% CI) and the Proportion of Phenotypic Variance (95% CI) of Traits

<table>
<thead>
<tr>
<th>Traits</th>
<th>MZ</th>
<th>DZ</th>
<th>( a^2 )</th>
<th>( e^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP (mmHg)</td>
<td>0.41 (0.31–0.49)</td>
<td>0.22 (0.09–0.34)</td>
<td>0.42 (0.34–0.49)</td>
<td>0.58 (0.50–0.66)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.60 (0.54–0.66)</td>
<td>0.35 (0.23–0.45)</td>
<td>0.61 (0.55–0.67)</td>
<td>0.39 (0.33–0.45)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.57 (0.51–0.63)</td>
<td>0.31 (0.19–0.42)</td>
<td>0.58 (0.52–0.64)</td>
<td>0.42 (0.36–0.48)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.73 (0.69–0.77)</td>
<td>0.42 (0.30–0.51)</td>
<td>0.74 (0.70–0.78)</td>
<td>0.26 (0.22–0.30)</td>
</tr>
</tbody>
</table>

Table 3
Cross-Trait Cross-Twin Correlations (95% CI) in MZ and DZ Twins

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Traits</th>
<th>PP1</th>
<th>SBP1</th>
<th>DBP1</th>
<th>BMI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZ PP2</td>
<td>0.43 (0.35, 0.51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ SBP2</td>
<td>0.40 (0.29, 0.50)</td>
<td>0.23 (0.15, 0.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ DBP2</td>
<td>0.24 (0.19, 0.30)</td>
<td>0.37 (0.28, 0.45)</td>
<td>0.36 (0.27, 0.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MZ BMI2</td>
<td>0.32 (0.27, 0.41)</td>
<td>0.35 (0.24, 0.47)</td>
<td>0.20 (0.08, 0.32)</td>
<td>0.19 (0.03, 0.35)</td>
<td></td>
</tr>
<tr>
<td>DZ PP2</td>
<td>0.27 (0.11, 0.41)</td>
<td>0.31 (0.19, 0.44)</td>
<td>0.20 (0.08, 0.32)</td>
<td>0.19 (0.03, 0.35)</td>
<td></td>
</tr>
<tr>
<td>DZ SBP2</td>
<td>0.14 (-0.02, 0.28)</td>
<td>0.25 (0.12, 0.37)</td>
<td>0.14 (0.01, 0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ DBP2</td>
<td>0.19 (0.07, 0.38)</td>
<td>0.25 (0.12, 0.37)</td>
<td>0.14 (0.01, 0.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ BMI2</td>
<td>0.24 (0.19, 0.39)</td>
<td>0.35 (0.24, 0.47)</td>
<td>0.20 (0.08, 0.32)</td>
<td>0.19 (0.03, 0.35)</td>
<td></td>
</tr>
</tbody>
</table>

Note: ‘1’ and ‘2’ refer to measures made on first and second twin, respectively.

Table 4
Goodness of Fit Statistics from Multivariate Analyses of Studied Traits

<table>
<thead>
<tr>
<th>Number</th>
<th>Model Tested against</th>
<th>-2LL</th>
<th>df</th>
<th>AIC</th>
<th>△ -2LL</th>
<th>△ df</th>
<th>Prob.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full model (ACE)</td>
<td>6892.0</td>
<td>4878</td>
<td>-2863.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Drop C (off-diagonal)</td>
<td>6898.2</td>
<td>4884</td>
<td>-2869.84</td>
<td>6.15</td>
<td>6</td>
<td>0.406</td>
</tr>
<tr>
<td>3*</td>
<td>Drop all C (AE)</td>
<td>6899.7</td>
<td>4888</td>
<td>-2876.34</td>
<td>1.50</td>
<td>4</td>
<td>0.827</td>
</tr>
<tr>
<td>4</td>
<td>Drop A (off-diagonal)</td>
<td>6929.8</td>
<td>4884</td>
<td>-2838.16</td>
<td>37.84</td>
<td>6</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note: -2LL – 2 times log-likelihood of data, △ difference.
*The best fitting model.

In the best fitting multivariate model, correlations shown in Table 5 were as follows: (1) high genetic correlations for DBP with SBP (0.87), PP with SBP (0.75); (2) low–moderate genetic correlations between PP and DBP (0.32), each BP component and BMI (0.24–0.37); (3) moderate unique environmental correlation for PP with SBP (0.68) and SBP with DBP (0.63); (4) there was no significant unique environmental correlation between PP and BMI. The standardized path coefficients are presented in Figure 2.

Discussion
This twin study documented three major findings. First, the heritability estimates for BMI, SBP, DBP, and PP suggested an important genetic component in the development of obesity and hypertension. A recent systematic review reported that BMI heritability is sensitive to age, time period of observation, average BMI, GDP, and rapid economic growth. (Min et al., 2013). However, our high heritability of BMI was consistent with previous studies in Chinese and European as well as American populations (Tarnoki et al., 2013; Wu et al., 2011). MZ twin discordance for BMI suggests epigenetic modification induced by accumulated stimulation caused by internal and external factors, including environmental exposure (Zhang et al., 2012). An inter-
TABLE 5
Genetic and Unique Environmental Correlations from a Multivariate (AE, the Best Fitted) Model with Sex and Age Justified Between Studied Traits

<table>
<thead>
<tr>
<th>Traits</th>
<th>(r_A)</th>
<th>(r_E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP &amp; SBP</td>
<td>0.75 (0.68–0.80)</td>
<td>0.68 (0.62–0.73)</td>
</tr>
<tr>
<td>PP &amp; DBP</td>
<td>0.32 (0.19–0.45)</td>
<td>-0.13 (-0.22–0.04)</td>
</tr>
<tr>
<td>PP &amp; BMI</td>
<td>0.24 (0.12–0.35)</td>
<td>0.06 (-0.04–0.15)</td>
</tr>
<tr>
<td>SBP &amp; DBP</td>
<td>0.87 (0.83–0.91)</td>
<td>0.63 (0.57–0.68)</td>
</tr>
<tr>
<td>SBP &amp; BMI</td>
<td>0.37 (0.28–0.46)</td>
<td>0.15 (0.06–0.25)</td>
</tr>
<tr>
<td>DBP &amp; BMI</td>
<td>0.37 (0.28–0.45)</td>
<td>0.15 (0.06–0.24)</td>
</tr>
</tbody>
</table>

Figure 2
(Colour online) Best multivariate model for four phenotypes (standardized path coefficients with 95% CI).

Interesting study found that the heritability of BP measured in the office, under laboratory stress and during real life is different (Wang et al., 2011). In this study, all the participants were examined at 8:00–10:00 am after an overnight fast of at least 10 hours. Variations in SBP and DBP were primarily explained by additive genetic factors, accounting for 61% and 58% of their total variances, with residual variances explained by unique environmental factors, which was consistent with previous studies (Jermendy et al., 2011; Wu et al., 2011). Although low–modest heritability has been estimated in many different ethnic populations (Bochud et al., 2005; DeStefano et al., 2004; Tarnoki et al., 2012), our heritability estimate of PP (0.42) is close to a recent study reported by Tarnoki et al. (2013) in Italian, Hungarian, and American twins, reflecting that maybe the heritability of PP does not vary considerably by race.

Second, there were significant pair-wise phenotypic correlations among PP, SBP, DBP, and BMI. We identified that PP was highly correlated with SBP and weakly correlated with DBP. Based on Framingham-data, DBP first increases with age and then levels off or decreases after the age of 50 years, whereas SBP increases throughout life. (De Pergola et al., 2011, Franklin et al., 1997). PP therefore increases with age and is correlated with SBP. The significant phenotypic association between PP and BMI is consistent with those from an early study. A study performed in a cohort of overweight and obese patients, never treated by antihypertensive treatment, showed that obesity is associated with the tendency to higher SBP and lower DBP, at least before the hypertension becomes stable, corresponding to profound alterations in artery structural and functional characteristics. (De Pergola et al., 2011). Our study proved once again that BMI correlates with BP, supporting the concept that obesity poses a major risk for hypertension.

Third, by decomposing phenotypic correlation into additive genetic and unique environmental correlations, the variable estimates by Cholesky decomposition further revealed that the phenotype correlation among BP components (PP, SBP, and DBP) and BMI had genetic backgrounds. The genetic correlation indicates the extent to which genetic effects on one trait correlate with genetic effects on another trait, independently of the heritability of the two traits. A genetic correlation of 1.0 would indicate that genetic influences on the two traits completely overlap, whereas a genetic correlation of zero would indicate that entirely different genes influence the two traits. High genetic correlations are estimated to explain the phenotypic correlations of SBP with PP and DBP, suggesting that genes identified as affecting SBP may overlap with those associated with PP and DBP. And this opinion was supported by a recent BP genome-wide association study (Ehret et al., 2011). Our results could indicate that cross-phenotype correlations between BMI and each BP measure may lack a strong genetic background. The estimate of genetic correlation between SBP and BMI (0.37) was much closer to the results of another Chinese twin study (0.38; Wu et al., 2011). The genetic correlations between BMI with DBP (0.37, 95% CI: 0.28–0.46) were higher than those reported by an early bivariate analysis in Western twins (0.15, 95% CI: 0.03–0.28; Tarnoki et al., 2013). Whether the difference reflects an ethnic disparity or is only due to the differences in methodology of BP and BMI measurements requires further replication studies.

To our knowledge, this is the first multiple genetic analysis of the correlations between PP, BP, and BMI. Although several previous studies have analyzed the genetic associations of BP components with BMI in different ethnic populations, this is the first time that a multivariate model for related phenotypes has been used. Moreover, we are the first to report the genetic association of PP with BP and BMI in a Chinese population. In our study, BP was measured twice according to standard procedures, and we used the mean values in the analyses to reduce measurement error. BMI was measured in an objective way rather than self-reported. Despite the multiple strengths, there are also some potential limitations. First, body composition evaluation was limited to BMI. Second, we did not examine in detail dietary habits, physical activity or other lifestyle factors that may also

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influence BP and BMI. Third, our samples in this study were collected in north China, where the composition of food and geographical environment are different from those in the southern part of the country. Given the importance of the environmental effect on BP and BMI, similar twin-based studies conducted in south China should help to reveal the interplay between genetics and environment as a result of environmental adaptation for the same ethnic population. Fourth, there is no known causal order among PP, SBP, DBP, and BMI, so we are unable to discriminate the causative orders in our Cholesky decomposition model.

In conclusion, our multivariate analyses revealed common genetic and environmental backgrounds for PP, SBP, and BMI in Chinese twins. Our results could provide useful information for the discovery of specific genes or environmental factors that impact PP, BP, and BMI, especially in northern Han Chinese.

Acknowledgments
The authors are grateful to Dr Gu Zhu at the Genetic Epidemiology Unit, QIMR Berghofer Institute of Medical Research, Australia, for excellent technical help.

References


