Genes and Family Environment Explain Correlations Between Blood Pressure and Body Mass Index

Jisheng Cui, John L. Hopper, Stephen B. Harrap

Abstract—The correlations between systolic blood pressure (SBP) and diastolic blood pressure (DBP), and between SBP and body mass index (BMI), might result from genetic or environmental factors that determine variation in 2 or more phenotypes and are shared by family members. In 767 adult nuclear families (n=2912 individuals, including 66 pairs of monozygotic twins and 84 pairs of dizygotic twins), we used a multivariate normal model and the software FISHER to estimate genetic and environmental components of variation and covariation. Mean phenotypes were adjusted for age, gender, and generation, and for antihypertensive treatment. Genetic and shared family environmental factors accounted for 46% and 31% of total variance in SBP, respectively. Adjustment of SBP for DBP reduced considerably both the additive genetic (86.7 to 21.0) and shared environmental (59.7 to 21.0) components of variance. Smaller reductions in genetic (86.7 to 84.9) and shared environmental (59.7 to 51.1) components were observed after adjustment of SBP for BMI. For SBP and DBP, the correlation between the effects of genes was 1.00 and between shared environmental effects was 0.52. For SBP and BMI the correlations were 0.30 for genetic and 0.22 for shared environmental effects. Our findings suggest that the same gene and many of the same family environmental factors determine variation in both SBP and DBP. In contrast, SBP and BMI share genetic and family environmental determinants to a lesser degree. These observations are relevant to multifactorial cardiovascular risk reduction based on genetic and family environmental approaches. (Hypertension. 2002;40:7-12.)

Key Words: systole □ diastole □ body mass index □ genetics □ risk factors □ twins

High blood pressure and body mass index (BMI) predispose independently to death from coronary artery disease and stroke.¹² However, hypertension and obesity also often coincide, and cardiovascular risk is augmented under these circumstances. The coincidence of these clinical conditions reflects the underlying correlation between blood pressure and body weight that has been observed at different ages and in a variety of populations.³–⁶ Why there is an association between blood pressure and weight is unclear, although a number of specific physiological hypotheses have been advanced,⁷ including the concept of insulin resistance and the metabolic syndrome.⁸⁹ If common causes of hypertension and obesity can be identified, they offer potentially important targets for more efficient and effective strategies for reduction in cardiovascular risk.

Family and twin studies can provide evidence regarding genetic and environmental influences, not only on variation of individual traits, but also on covariation between traits. Such information will help direct molecular, clinical, and epidemiological searches for specific underlying causes. For example, evidence of genetic factors that determine both blood pressure and BMI might lead to more efficient and targeted molecular searches for the specific genes that might determine variation in both traits.

For many years it has been known that the blood pressures, both systolic (SBP) and diastolic (DBP), and BMI are correlated between and within parents and offspring to varying extents.¹⁰ The relative contributions of genes and environment to describing this familial aggregation of blood pressure and BMI separately have been estimated by biometric pedigree analyses.¹¹–¹³ For example, in the Victorian Family Heart Study (VFHS), a study of healthy adult families enriched with monozygotic and dizygotic twins, we estimated that genetic factors accounted for 41%, 46%, and 42% of the variation in SBP, DBP, and BMI, respectively.¹³ Family environmental factors shared during cohabitation accounted for 13%, 19%, and 35% of adult variance in the same phenotypes.¹²

Parents with high blood pressure often have high BMI, and in general their offspring tend to share these characteristics.¹³ However, there are examples of dissociation of blood pressure and BMI within families. For example, there are offspring and parents of large weight but without high blood pressure, who presumably share genetic and environmental factors specific to weight alone.¹⁴ In contrast, there are young adult offspring with high blood pressure and high BMI whose parents who have low blood pressure and BMI.¹⁵ In such cases, individual-specific environmental factors rather than...
familial influences are likely to explain the similarity of the traits within individuals but not between relatives. The question is what are the relative contributions of the genetic and environmental factors that account for the observed intertrait correlations across the population. To answer this, studies of relatives are essential.

In an early analysis of Framingham data, it was observed that the modest correlation in blood pressure between spouses was reduced when blood pressure was adjusted for weight.\(^{16}\) Notwithstanding the genetic similarity between spouses that might arise as a result of assortative mating, this finding suggested that environmental factors shared by spouses might influence both blood pressure and body weight. Unfortunately, the authors did not report similar analyses of other relative pairs that might have addressed the effects of shared genetic factors. However, in a longitudinal multivariate analysis of 998 children (full siblings and first cousins) from 261 families in the Muscatine Study, Hanis and colleagues\(^{17}\) reported that, within the limits of available power, the association between SBP and weight could not be attributed to genes that directly affect both traits. Genes that affected weight directly and SBP secondarily were thought to explain a small proportion of the covariance between these 2 traits. To date, no studies have reported bivariate analyses of familial associations between blood pressure and weight in adults.

Of potential interest also are the genetic and environmental factors that might determine both SBP and DBP. Although the correlation between SBP and DBP within individuals is high, differences exist in relation to the molecular, physiological, and epidemiological associations of these 2 traits.

In this study we have used data from the VFHS to address the familial correlations between SBP, DBP, and BMI. As a study of adult parents and offspring, the VFHS avoids the confounding effects of adolescent growth. VFHS families are enriched with those containing twins, thereby increasing the informativeness of biometric analyses. We conducted 2 analyses. In one, we performed biometric analyses of SBP before and after adjustment of mean for DBP and/or BMI. A fall in the genetic/environmental components of variance after such adjustments implies that SBP shares genetic/environmental determinants with the other trait(s). In the second, we used a bivariate method, in which we determined the correlation between genetic or environmental determinants of pairs of traits. This approach provides two independent perspectives for explaining the correlations between blood pressure and BMI.

### Methods

#### Subject Recruitment and Phenotype Measurement

The details of the recruitment of subjects for the VFHS have been published previously.\(^{13}\) In brief, a volunteer sample of families exhibiting a broad range of cardiovascular risk factor levels was recruited from a variety of community-based sources, including the Australian Twin Registry. As a result the VFHS is enriched with families containing twins in both the parental and offspring generations. A family history of heart disease was not a prerequisite for recruitment. Families comprised both parents aged between 40 and 70 years and at least one natural offspring aged between 18 and 30 years. Recruitment was limited to white families to reduce the possible confounding effect of racially determined genetic differences in pedigree, DNA, and genomic analyses.\(^{18,19}\)

The study was approved by the Ethics Review Committee of the Alfred Hospital, Melbourne, and informed consent was obtained from all participants. Detailed descriptions of research clinic procedures and standardized measures of blood pressure, weight, and height have been published previously.\(^{13}\)

The total of 767 nuclear families included in this analysis comprised 2912 individuals, of whom 1431 were male and 1481 female. The mean age was 55.2 years (SD 6.4) for fathers, 52.5 years (SD 5.8) for mothers, and 24.0 (SD 3.7) years for offspring. One hundred and fifty offspring twin pairs were included, of which 66 were monozygotic (MZ) and 84 dizygotic (DZ).

A total of 250 subjects (132 males and 118 females) was receiving treatment with an antihypertensive medication at the time of phenotype measurement. The recorded pressures in these individuals were, therefore, likely to be lower than their inherent untreated levels. Based on known average treatment effects,\(^{20}\) for the purpose of these analyses, we empirically adjusted the recorded pressures in treated individuals by adding 10 mm Hg to SBP and 5 mm Hg to DBP. Compared with approaches in which no or different (5/2 mm Hg, 20/10 mm Hg) adjustments were made, there were only slight differences in the heritability estimates of individual phenotypes (J. Cui, J.L. Hopper, S.B. Harrip, unpublished observations, 2002), but no material difference in the estimates of variance component analyses of phenotype correlations.

#### Statistical Methods

Statistical analyses were carried out under a multivariate normal model for pedigree analysis using the software FISHER.\(^{21,22}\) The means of all phenotypes were adjusted for age by gender within each generation, and the variances and correlations between relatives, or variance components, were estimated under maximum likelihood theory. Standard errors and 95% confidence intervals were calculated using large sample normal approximations.\(^{23}\) Correlations in adjusted trait values between relatives were estimated separately for MZ twin, DZ twin, nontwin sibling, parent-offspring, and spouse pairs. Variance components were defined previously.\(^{13}\) The variance of each phenotype \(Y\) was given by \(\sigma^2_Y = \sigma^2_g + \sigma^2_e + \sigma^2_s\), where \(\sigma^2_g\), \(\sigma^2_e\), and \(\sigma^2_s\) are the genetic, shared environmental, and individual-specific variances, respectively. The covariance between traits was decomposed by allowing the variance components for the individual traits to be correlated.

#### Univariate Analysis

All correlation coefficients for different pairs were estimated simultaneously from the data by modeling the respective covariances using FISHER.\(^{22}\) Univariate variance component analyses were conducted for each phenotype separately. All phenotypes were first adjusted for age by gender within each generation through linear regression about their respective means. Specifically, the variance components of SBP were further analyzed by adjusting the mean for DBP or BMI separately, and then for both DBP and BMI. The covariance between a pair of individuals depended on the type of relationship. For nonsib pairs, the covariance was given by \(2\phi e^{-\gamma}\), where \(\phi\) is the kinship coefficient between the 2 individuals and \(\gamma\) (0≤\(\gamma\)≤1) was the coefficient for shared environmental effect. For both MZ and DZ twin pairs, we let \(\gamma_{MD} = 1\), following the critical assumption of the classic twin model that the effects of shared environment are independent of zygosity. The coefficients for nontwin sibling pairs, \(\gamma_{NS}\), and parent-offspring pairs, \(\gamma_{PO}\), were estimated under the realistic constraint that the effect of shared environment in these pairs was no greater than in twin pairs. The covariance between spouses was modeled separately by \(\rho_{PS}(\sigma^2_g + \sigma^2_e + \sigma^2_s)\), where \(\rho_{PS}\) is the correlation coefficient between spouses for that trait. Because it is unlikely that the effect of shared environmental factors would be in the opposite directions between parents and offspring or between siblings, we set a lower bound of zero for parameter estimates.
TABLE 1. Descriptive Statistics of Measured Phenotypes in the Victorian Family Heart Study According to Generation and Gender

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parents</th>
<th>Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>n (individuals)</td>
<td>767</td>
<td>767</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132 (16.4)</td>
<td>126 (16.1)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>83.1 (9.3)</td>
<td>78.9 (9.2)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.0 (3.4)</td>
<td>26.1 (4.5)</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SD). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index.

Bivariate Analysis

Bivariate correlation coefficient for different pairings of family members was defined as ρ = cov(Y_iZ_j)/[SD(Y_i)SD(Z_j)], where Y_i is phenotype 1 of one individual and Z_j is phenotype 2 of the other individual. As for the univariate analyses, both Y_i and Z_j were adjusted for age by gender within each generation using linear regression. Similarly, correlation coefficients of different pairs were estimated simultaneously from the data by modeling the respective cross-trait covariances using FISHER.22

As an extension to the univariate analysis, bivariate component analysis considers the covariation of 2 phenotypes simultaneously. Here, the covariance of 2 phenotypes for an individual (in contrast to 1 phenotype in 2 individuals in the univariate analysis), is given by

\[ \text{cov}(Y_1, Y_2) = \sigma_{a12} + \sigma_{e12} \]

where \( \sigma_{a1} \) and \( \sigma_{a2} \) are the parameters for the additive genetic component, \( \sigma_{e1} \) and \( \sigma_{e2} \) are the parameters for the individual-specific factors. In terms of the shared environmental component, the covariance for 2 phenotypes is given by \( \gamma_{se} \).

Results

Descriptive Statistics

Table 1 shows the gender- by generation-specific means and standard deviations of SBP, DBP, and BMI in fathers, mothers, male offspring, and female offspring. SBP, DBP, and BMI were greater in the parental than in the offspring generations \((P<0.001)\), and within generations these phenotypes were greater in males than in females \((P<0.001)\).

Univariate Analyses

The univariate correlation coefficients for SBP, DBP, and BMI in different relative pairs are shown in Table 2. For SBP, DBP, and BMI, the magnitude of the correlations was greatest for MZ twin pairs and least for spouse pairs. The contrasting correlations between different relative pairs are indicative of genetic and environmental effects. Under the assumptions of the classical twin model, the higher correlations in MZ than in DZ twins for SBP (by 0.28), DBP (by 0.15), and BMI (by 0.19) (Table 2) would reflect the greater genetic similarity between MZ (100%) than between DZ twins (average 50%). For relative pairs of comparable genetic similarity, differences in correlations reflect the influence of shared family environments. Such influences were observed for SBP, DBP, and BMI where there were both greater correlations between DZ twins than between nontwin sibling pairs and greater correlations between nontwin siblings than between parent-offspring pairs (Table 2).

Table 3 shows the estimates from the univariate variance component analysis for SBP, DBP, and BMI. For SBP, the genetic and shared environmental components of variance accounted for 46% and 31% of the total variance, respectively. The remaining 23% was accounted for by individual-specific factors. For DBP a greater proportion of variance (46%) resulted from individual-specific factors, whereas genetic and shared environmental factors accounted for 31% and 23% of the total variance. For BMI, the greatest proportion of variance (46%) was attributed to shared environmental factors, compared with 37% for genetic and 17% for individual-specific factors. In terms of the shared environmental factors, the coefficients were greater within the generations \((\gamma_{se})\) than between the generations \((\gamma_{se})\) for SBP, DBP, and BMI (Table 3). The analyses suggested that the environment shared by parents and offspring in the family

TABLE 2. Univariate Correlation Coefficients for SBP, DBP, and BMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spouse-Spouse</th>
<th>Parent-Offspring</th>
<th>Nontwin Siblings</th>
<th>DZ Twins</th>
<th>MZ Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (pairs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.12 (0.06, 0.17)</td>
<td>0.22 (0.18, 0.27)</td>
<td>0.44 (0.35, 0.54)</td>
<td>0.50 (0.30, 0.69)</td>
<td>0.78 (0.70, 0.86)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.15 (0.08, 0.21)</td>
<td>0.23 (0.19, 0.27)</td>
<td>0.27 (0.19, 0.34)</td>
<td>0.39 (0.23, 0.54)</td>
<td>0.54 (0.39, 0.70)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.26 (0.20, 0.32)</td>
<td>0.29 (0.25, 0.34)</td>
<td>0.37 (0.29, 0.45)</td>
<td>0.64 (0.52, 0.76)</td>
<td>0.83 (0.76, 0.89)</td>
</tr>
</tbody>
</table>

Means were adjusted for age by gender, within generation; 95% confidence intervals are given in parentheses.

TABLE 3. Univariate Genetic and Environmental Components of Variance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SBP</th>
<th>DBP</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_a^2 )</td>
<td>86.7 (10.1)</td>
<td>25.3 (17.7)</td>
<td>5.3 (2.0)</td>
</tr>
<tr>
<td>( \sigma_e^2 )</td>
<td>59.7 (10.6)</td>
<td>18.8 (14.2)</td>
<td>6.7 (1.9)</td>
</tr>
<tr>
<td>( \sigma_{se}^2 )</td>
<td>44.0 (7.7)</td>
<td>36.9 (6.2)</td>
<td>2.5 (0.5)</td>
</tr>
<tr>
<td>( \gamma_{se} )</td>
<td>190.4</td>
<td>81.0</td>
<td>14.5</td>
</tr>
<tr>
<td>( \gamma_{po} )</td>
<td>0.70 (0.17)</td>
<td>0.47 (0.24)</td>
<td>0.41 (0.10)</td>
</tr>
<tr>
<td>( \rho_{po} )</td>
<td>0.00 (bound)</td>
<td>0.31 (0.28)</td>
<td>0.24 (0.10)</td>
</tr>
</tbody>
</table>

Means were adjusted for age by gender, within generation. The model estimates the following components of the total phenotype variance \((\sigma^2)\): additive genetic \((\sigma_a^2)\), shared environment \((\sigma_{se}^2)\), and individual-specific \((\sigma_{ei}^2)\) effects; shared environment coefficients for nontwin sibling pairs \((\gamma_{se})\) and parent-offspring pairs \((\gamma_{po})\) and the correlation coefficient between spouse pairs \((\rho_{po})\). For \( \gamma_{po} \), the value zero represents the lower bound set for the estimate (see Methods). Standard errors of estimates are given in parentheses.
The within-individual correlation between SBP and DBP was 0.68 (Table 5). The cross-trait correlations between SBP and DBP in relative pairs show evidence suggestive of genetic home does not produce variation in SBP ($\gamma_{po}=0$) after offspring have moved away (Table 3).

Table 4 shows the estimates from variance component analyses for SBP (adjusted for age, gender, age-gender interaction, and generation) after adjustment for DBP and/or BMI. After adjustment for DBP only, the total variance of SBP was reduced by just over half (190.4 to 93.9), reflecting the strong cross-sectional correlation between these 2 blood pressure traits. Of the variance components, the genetic component showed the greatest reduction after adjustment for DBP (86.7 to 21.0). There was also substantial reduction in the shared environment component of variance (59.7 to 21.0). The individual-specific component remained virtually unchanged (Table 4).

In contrast, when SBP was adjusted for BMI, there was only a relatively small fall in the total variance (190.4 to 177.9), with reductions of 2% (86.7 to 84.9) and 14% (59.7 to 51.1) for the genetic and shared environmental factors, respectively (Table 4). There was only a small effect of adjustment for BMI (44.0 to 41.9) on the individual-specific factors that determine variation in SBP. When adjusted for both DBP and BMI, the variance components were similar to those seen after adjustment for DBP alone.

**Bivariate Analyses**

The within-individual correlation between SBP and DBP was 0.68 (Table 5). The cross-trait correlations between SBP and DBP in relative pairs show evidence suggestive of genetic influences (higher correlations between MZ than between DZ twins) and shared environmental (greater correlations between DZ twins than between nontwin siblings and greater correlations between nontwin siblings than between parent-offspring pairs) influences (Table 5). Within individuals the correlation coefficient between SBP and BMI was 0.36, and the cross-trait correlations between relative pairs also suggested genetic and shared environmental influences (Table 5). For DBP and BMI, the within-individual correlation coefficient was 0.41. In contrast to the familial patterns of the other cross-trait correlations, there was little evidence of genetic influences (MZ cross-trait correlations were no greater than in DZ twins) but a suggestion of shared environmental influences.

The Figure illustrates the magnitude of the correlations between age by gender within generation-adjusted SBP and DBP, SBP and BMI, and DBP and BMI with respect to genetic, shared environmental, and individual-specific components of variance. The diameter of each circle for a phenotype is proportional to its univariate variance component, and the overlap represents the correlation between the variance components for the phenotype pair. Bivariate analyses found that there was estimated to be a perfect correlation ($R=1.0$) between the genetic factors for SBP and DBP. There was also a substantial correlation between the shared environmental factors for the 2 blood pressures ($R=0.52$, 95% CI: 0.32 to 0.72). The correlation between the individual-specific factors for SBP and DBP was 0.27 (95% CI: 0.11 to 0.43).

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### TABLE 4. Univariate Variance Components of SBP, Adjusted for DBP and BMI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DBP</th>
<th>BMI</th>
<th>DBP and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma^2$</td>
<td>21.0 (4.3)</td>
<td>84.9 (9.4)</td>
<td>22.6 (4.3)</td>
</tr>
<tr>
<td>$\sigma_{se}^2$</td>
<td>21.0 (7.6)</td>
<td>51.1 (10.0)</td>
<td>19.8 (7.5)</td>
</tr>
<tr>
<td>$\sigma_i^2$</td>
<td>51.9 (7.4)</td>
<td>41.9 (7.4)</td>
<td>50.2 (7.3)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>93.9</td>
<td>177.9</td>
<td>92.6</td>
</tr>
<tr>
<td>$\gamma_{sb}$</td>
<td>0.33 (0.22)</td>
<td>0.71 (0.20)</td>
<td>0.35 (0.24)</td>
</tr>
<tr>
<td>$\gamma_{po}$</td>
<td>0.0 (bound)</td>
<td>0.0 (bound)</td>
<td>0.0 (bound)</td>
</tr>
<tr>
<td>$\rho_{ip}$</td>
<td>0.05 (0.03)</td>
<td>0.11 (0.03)</td>
<td>0.05 (0.03)</td>
</tr>
</tbody>
</table>

Means were adjusted for age by gender within generation. The model estimates the following components of the total phenotype variance ($\sigma^2$): additive genetic ($\sigma^2_g$), shared environment ($\sigma_{se}^2$), and individual-specific ($\sigma_i^2$) effects; shared environment coefficients for nontwin sibling pairs ($\gamma_{sb}$) and parent-offspring pairs ($\gamma_{po}$) and the correlation coefficient between spouse pairs ($\rho_{ip}$). For $\gamma_{po}$, the value zero represents the lower bound set for the estimate (see Methods). Standard errors of estimates are given in parentheses.

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### TABLE 5. Cross-Trait Correlation Coefficients for SBP and DBP, SBP and BMI, and DBP and BMI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Spouse-Spouse</th>
<th>Parent-Offspring</th>
<th>Nontwin Siblings</th>
<th>DZ Twins</th>
<th>MZ Twins</th>
<th>Within Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (pairs)</td>
<td>2767</td>
<td>473</td>
<td>84</td>
<td>66</td>
<td>2912</td>
<td></td>
</tr>
<tr>
<td>SBP and DBP</td>
<td>0.11 (0.06, 0.16)</td>
<td>0.21 (0.17, 0.25)</td>
<td>0.35 (0.28, 0.42)</td>
<td>0.42 (0.28, 0.55)</td>
<td>0.53 (0.45, 0.61)</td>
<td>0.68</td>
</tr>
<tr>
<td>SBP and BMI</td>
<td>0.06 (0.02, 0.11)</td>
<td>0.05 (0.01, 0.09)</td>
<td>0.11 (0.04, 0.18)</td>
<td>0.14 (0.04, 0.24)</td>
<td>0.21 (0.15, 0.28)</td>
<td>0.36</td>
</tr>
<tr>
<td>DBP and BMI</td>
<td>0.06 (0.01, 0.11)</td>
<td>0.07 (0.03, 0.11)</td>
<td>0.12 (0.06, 0.18)</td>
<td>0.18 (0.08, 0.28)</td>
<td>0.14 (0.06, 0.22)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Means were adjusted for age by gender within generation; 95% confidence intervals are given in parentheses.
The correlations were less for SBP and BMI, estimated to be 0.30 (95% CI: 0.10 to 0.50) for the genetic correlation and 0.22 (95% CI: 0.04 to 0.40) for the shared environmental correlation. The individual-specific correlation was 0.18 (95% CI: −0.06 to 0.42).

Discussion

Our observations confirm the influence of genes and shared environment in the separate determination of variation in the individual traits SBP, DBP, and BMI, and extend the biometric analyses to show that the correlations between 3 related major cardiovascular risk factors depend on familial factors. The influence of familial factors varies between the particular pairs of risk factors and is most obvious between SBP and DBP and less apparent between SBP and BMI. The magnitude of the effects also seems to vary depending on whether genetic or shared environmental components are considered.

For the 2 blood pressures, our findings suggest that there are genes that determine variation in both SBP and DBP, and that the other genes that determine SBP or DBP separately explain less variance of the respective trait. In contrast, for SBP and BMI we found evidence for genes that determine some of the variation in both phenotypes, but the genes that influence SBP or BMI separately explain a greater variance of the respective trait. For the effects of shared environmental factors, those that influence both SBP and DBP explained as much variance of the respective traits as did those that influenced either SBP or DBP separately.

The finding of close genetic correlation for SBP and DBP raises a number of interesting issues. From the physiological perspective, SBP and DBP result from the combined effects of variation in the underlying phenotypes of mean arterial pressure and pulse pressure. Changes in mean arterial pressure will see parallel changes in SBP and DBP, whereas changes in pulse pressure will result in opposite changes in SBP and DBP. Therefore, genetic correlation between SBP and DBP would be expected if genetic factors influenced mean arterial pressure through, for example, cardiac output or total peripheral resistance.

Interestingly, the results of our biometric analyses might appear to contradict the findings of genome scans, including our own. Quantitative trait loci (QTLs) for blood pressure have been suggested from genomic mapping, but most studies have detected QTLs for SBP yet failed to identify QTLs for DBP. For example, in the Victorian Family Heart Study, we found 4 QTLs for SBP but none for DBP. One explanation that might reconcile the high genetic correlation between SBP and DBP from our present analysis with the evidence of QTLs for SBP, but not for DBP, is that it may be more difficult to detect QTLs for DBP. Our present analyses revealed that the individual-specific variation for DBP, which includes measurement error, is a proportionally greater component of DBP variance (36.9/81.0 = 46%) than SBP variance (44.0/190.4 = 23.1%) (Table 3). Furthermore, and maybe even in part as a consequence, the heritability (defined as the proportion of variance attributed to genetic factors) was also greater for SBP than for DBP (Table 3). The latter characteristic will in theory reduce the power of QTL analyses for DBP compared with those for SBP. Based on the results of the present study, more specific investigation is warranted of the association or linkage of SBP genetic candidates with DBP.

In terms of etiological shared family environmental factors, the overlap between SBP and DBP and between SBP and BMI is more evident within the offspring generation between nontwin siblings than it is across generations between parents and offspring. This observation emphasizes the importance of shared generational factors. It is important to recognize that the effects of shared environment between nontwin siblings reflect the period during which they lived together. At the time of this study, offspring (aged 18 to 30 years) mostly lived away from the family home and away from their siblings. Therefore, for offspring, the effects of shared environment represent the persistent influence of the time when offspring lived as infants and children in the family home. Such a persistent effect does not appear to exist for SBP as a result of the environment shared by parents and offspring.

The links between blood pressure and BMI have been topical in relation to the metabolic syndrome. Indeed, it has been suggested that genes, such as the insulin receptor substrate-1, could simultaneously influence related phenotypes such as BMI, cholesterol, insulin resistance, and blood pressure. However, a recent review concluded that the relationship between blood pressure and the metabolic syndrome was not as strong as the links between the other phenotypes, including BMI, lipids, and insulin resistance. Nevertheless, the concept that some, but not all, genes that determine BMI might also determine SBP is supported by both the biometric analyses in this study and the genomic studies in the VFSH. Of the four QTLs for SBP suggested on chromosomes 1, 4, 18, and X, evidence of linkage was reduced substantially (a reduction in the Z score from 3.2 to 1.4) for the QTL on chromosome 16 when SBP was adjusted for BMI. This suggests that the chromosome 16 QTL might determine both SBP and BMI, whereas the loci on chromosomes 1, 4, and X determined SBP, but not BMI. This partial overlap of genetic influences in molecular analyses is consistent with the findings of biometric analyses in the present study.

In this study we attempted to adjust for the expected average effects of antihypertensive treatment by adding 10 mm Hg and 5 mm Hg to the treated SBP and DBP levels. This adjustment was applied to 250 individuals (8.6%) and obviously increased the total variances for SBP and DBP. Interestingly, however, this increase was accounted for almost entirely by an augmentation of the genetic component of variance with no appreciable change in either the shared environmental or individual-specific components of variance (data not shown). This shows that the adjustment of pressure for antihypertensive treatment was correlated in families and that correlation was likely to be due to genetic factors. Consequently, it suggests that the lowering of blood pressure by treatment blunts the proportional contribution of genetic factors to blood pressure. In other words, antihypertensive treatment might preferentially affect genetically determined components of blood pressure. Nevertheless, the presence or absence of this adjustment made no material difference to the
conclusions regarding the genetic and shared environmental variance components of the correlations between phenotypes.

The design of the VFHS as a general population sample of families enriched with twins, whose range of cardiovascular risk factors is representative of the general community, is unusual, if not unique. It not only provides a substrate for both informative biometric analyses, such as those presented here, but also permits specific testing of genetic hypotheses and identification of candidate genes and DNA variants. From these analyses we might predict that gene variants associated with SBP will also be associated with DBP and that those associated with SBP will, in part, be associated with BMI also.

Perspectives

These analyses provide some insight into the etiological similarity between related cardiovascular risk factors. They provide an indication of the magnitude of the similarity and also its quality, in terms of shared genes and shared environment. This information will influence strategies for the discovery of specific genes or environmental factors impacting on blood pressure and BMI and prompt more formal testing of precise relationships, including those related to the metabolic syndrome.6 Gene discovery using linkage analyses might be better directed at combinations of these risk factors, rather than on single, easily measured entities. In the future, etiological factors may be defined as unique or combinations of cardiovascular risk determinants. This research design of the VFHS also allows for the incorporation of specific genetic variants or environmental factors into comprehensive variance components analyses and subsequent linkage analyses. Such analyses are especially rigorous, because they assess the impact of individual factors in the ultimate forum of the general community. Although many factors deemed “significant” by case-control comparisons will fail this test,25 those robust enough to survive will achieve public health significance. The hope is for new, more efficient and effective means of prevention and treatment of cardiovascular disease based on underlying multifactorial targets.

Acknowledgments

This study was supported by the Victoria Health Promotion Foundation and the National Health and Medical Research Council. The hope is for new, more efficient and effective means of prevention and treatment of cardiovascular disease based on underlying multifactorial targets.

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