Biological and Cultural Determinants of Blood Pressure

ULF DE FAIRE, M.D., LENNART ISELIUS, M.D., AND TORBJÖRN LUNDMAN, M.D.

SUMMARY A path analytic study of blood pressure in Swedish families gave evidence for genetic heritability (0.18 for systolic, 0.13 for diastolic) and for cultural heritability, with evidence for an intergenerational difference giving higher estimates of cultural heritability in adults (0.19 for systolic, 0.08 for diastolic). A maternal effect for cultural inheritance was evident for systolic blood pressure but not for diastolic pressure. (Hypertension 4: 725-728, 1982)

KEY WORDS • blood pressure • path analysis • heritability

HYPERTENSION is one of the major risk factors for coronary heart disease, and the familial aggregation of elevated blood pressure has stimulated several workers to look for a genetic contribution to arterial pressure. Environmental factors, such as obesity, smoking, and alcohol consumption, are also known to affect blood pressure. Few attempts, however, have been made to discriminate between biological and cultural inheritance. NonCaucasian population studies have been carried out on families of Japanese-American, Brazilian nordestino, and Tokelau ancestry. Estimates of genetic heritability have been similar, but studies have differed with respect to cultural heritability, intergenerational differences, and maternal effects. To help resolve these questions of genetic and cultural heritability, we applied path analysis to the study of systolic and diastolic blood pressures in a population of Swedish families.

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Methods

Population

Subjects included in the study were ascertained through the Swedish Twin Registry. The sampling procedure has been described elsewhere. The target population consisted of married twins with at least one adult child (> 20 years). A total sample of 909 subjects was selected, 548 from the twin generation (twins and their spouses) and 361 from the progeny generation (adult children of twins). Blood pressure was measured in 905 family members.

Procedure

The subjects were investigated either in Stockholm or Gothenburg. A standard questionnaire was filled out by each subject, which included questions on earlier diseases, hospital treatment, medication, smoking habits, and use of alcoholic beverages. Blood pressures were measured in the right arm with the subject in the seated position after 5 minutes' rest, using a mercury sphygmomanometer with a cuff size of 12 × 23 cm. The same observer performed all measurements. The pressure was read to the nearest 5 mm Hg.

Path Analysis

The object of path analysis was to study the relative contributions of genes and environment to family resemblance, including maternal effects, assortative mating, and cultural inheritance. We used a modification of the path analytic model of Rao et al. It was assumed that the environment acts additively with genotype, without interactions, to produce the blood pressure phenotype. Since family environment is not observable, an estimate of the environment was cre-
ated for the two blood pressure variables (systolic and diastolic blood pressure) by stepwise multiple regression. The part of the environment so estimated was called the "indexed environment" and the remainder the "residual environment." Nuclear families yield 16 correlations when an environmental index is created for father, mother, and child. There are 15 correlations between pairs of the following six variables: phenotype of father (P_F); environmental index of father (I_F); phenotype of mother (P_M); environmental index of mother (I_M); phenotype of child (P_c); environmental index of child (I_c) (average of index values for a sibling); and the sibling phenotypes generate an additional correlation. We assumed no dominance deviation, no direct effect of parental phenotype on child’s phenotype, and no genetic correlation between mates. The parameters estimated were:

- c  effect of child’s indexed environment on child’s phenotype
- cy effect of adult’s indexed environment on adult’s phenotype
- h  effect of genotype on child’s phenotype
- hz  effect of genotype of adult’s phenotype
- u  correlation between indexed environments of spouses
- f_F effect of father’s indexed environment or child’s indexed environment
- f_M effect of mother’s indexed environment or child’s indexed environment
- i  effect of child’s indexed environment on the index
- i_F effect of father’s indexed environment on his index
- i_M effect of mother’s indexed environment on her index

The parameters are diagrammed in figure 1, and the expected correlations are given in table 1. The genetic and cultural heritabilities in children are \( h^2 \) and \( c^2 \) respectively; they become \( (hz)^2 \) and \( (cy)^2 \) in adults. Special cases of interest include:

- \( f_F = f_M = f \) (no maternal effect)
- \( y = z = 1 \) (no intergenerational differences)
- \( u = 0 \) (no marital correlation)
- \( h = z = 0 \) (no genetic heritability)
- \( c = y = 0 \) (no cultural heritability).

The 16 correlations \( r_{ij} \) in nuclear families and the appropriate sample sizes \( N_i \) in terms of independent pairs were estimated by maximum likelihood. The correlations are treated as independent, giving the equation:

\[
\chi^2 = \sum_{i=1}^{16} N_i (z_i - \bar{z})^2
\]

where \( \bar{z} \) is the z transform of the expected correlation \( \rho_{ij} \) and \( N_i \) is the sample size. Ignoring correlations of correlations has not led to unreliable results. Estimation of parameters and tests of hypotheses were carried out in terms of the log-likelihood \( (\ell n L) \) function:

\[
\ell n L = -\chi^2/2 + \text{constant}
\]

The residual \( \chi^2 \) after estimating \( k \) parameters followed a chi-square distribution with \( 16-k \) df. By specifying \( \rho_{ij} \) as functions of parameters (table 2), we made \( \chi^2 \) a function of the parameters. Therefore, by minimizing \( \chi^2 \), we could estimate all or some parameters and use the residual \( \chi^2 \) for tests of hypotheses. The general model involving 10 parameters was tested by the residual \( \chi^2 \) with \( 16-10 = 6 \) df. If \( \chi^2_{10} \) is the value of \( \chi^2 \) after estimating all the 10 parameters, and \( \chi^2_{10-\omega} \) is another value after estimating only \( 10-\omega \) of

<table>
<thead>
<tr>
<th>Relation</th>
<th>Variables</th>
<th>Correlation</th>
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</thead>
<tbody>
<tr>
<td>Marital</td>
<td>P_F, P_M, c</td>
<td>(cy)^2 u</td>
</tr>
<tr>
<td></td>
<td>P_F, I_M, u</td>
<td>i_F, I_M, u</td>
</tr>
<tr>
<td></td>
<td>P_F, I_F, cy</td>
<td>u cy</td>
</tr>
<tr>
<td></td>
<td>P_M, I_F, u</td>
<td>i_F, I_M, u</td>
</tr>
<tr>
<td></td>
<td>I_F, I_M, I_F</td>
<td>i_F, I_M, I_F</td>
</tr>
<tr>
<td></td>
<td>P_F, I_C, I_C</td>
<td>ic</td>
</tr>
<tr>
<td></td>
<td>P_F, C, C_{C2}</td>
<td>h^2/2 + c^2</td>
</tr>
<tr>
<td></td>
<td>P_F, P_C, I_C</td>
<td>h^2/2 + c^2 u + uf_M</td>
</tr>
<tr>
<td></td>
<td>P_M, P_C, I_C</td>
<td>h^2/2 + c^2 u + uf_F</td>
</tr>
<tr>
<td></td>
<td>P_F, I_C, u</td>
<td>i_F, I_C, u</td>
</tr>
<tr>
<td></td>
<td>P_M, I_C, u</td>
<td>i_M, I_C, u</td>
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<td></td>
<td>I_F, I_C, u</td>
<td>i_F, I_C, u</td>
</tr>
<tr>
<td></td>
<td>I_M, I_C, u</td>
<td>i_M, I_C, u</td>
</tr>
</tbody>
</table>

\( P = \) phenotype; \( I = \) index; subscripts \( F, M, C \) refer to father, mother, child respectively; subscripts \( C_1, C_2 \) denote siblings.
the 10 parameters, the other \( \omega \) parameters being fixed under a null hypothesis, \( \chi^2 = \chi^2_{\omega+1} - \chi^2_{\omega} \), provide the likelihood-ratio test for the null hypothesis on the other parameters.

Each phenotype \( y \) (systolic and diastolic pressure) was approximately normalized by the power transformation

\[
x = \frac{6}{\sigma} \left( \frac{x - \mu}{\sigma} + 1 \right)^p - 1
\]

where \( \mu \) and \( \sigma \) are the means and variances within each of three classes: fathers, mothers, and children (table 2). For each standardized and normalized \( x \), an environmental index \( f(z) \) was created by incremental stepwise multiple regression on Quetelet’s index (weight/height\(^2\)), smoking (number of cigarettes per day), and alcohol [grams of absolute alcohol (beer, wine, liquor) per month per kilogram body weight]. Simultaneously, an age-sex adjustment \( f(a,s) \) was created stepwise using a cubic polynomial in age and sex. Only significant terms were retained in the regression equation, giving

\[
x = f(z) + f(a,s) + \varepsilon,
\]

where \( \varepsilon \) is random error. The phenotype used for the path analysis was defined as \( P = x - f(a,s) \), with \( f(z) \) as Index I.

**Results**

Descriptive statistics for systolic and diastolic blood pressure are given in table 2. Both systolic and diastolic blood pressure increases significantly with obesity, as defined by Quetelet’s index. Together with age and sex effects, obesity gave a multiple correlation coefficient of 0.322 for systolic pressure and 0.224 for diastolic pressure. Obesity alone accounted for 3.8% of the variation in systolic pressure in our population. The corresponding figure for diastolic pressure was 2.3%. Smoking and alcohol did not produce any significant effects.

The observed correlations are given in table 3. Goodness-of-fit \( \chi^2 \) values are presented in table 4 under various subhypotheses. Estimates of some parameters are given in table 5 under the most parsimonious

<table>
<thead>
<tr>
<th>Variable</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_F, f_F )</td>
<td>0.206</td>
<td>0.169</td>
</tr>
<tr>
<td>( P_F, P_M )</td>
<td>0.142</td>
<td>0.117</td>
</tr>
<tr>
<td>( P_F, f_M )</td>
<td>0.046</td>
<td>0.012</td>
</tr>
<tr>
<td>( f_F, P_M )</td>
<td>0.118</td>
<td>0.078</td>
</tr>
<tr>
<td>( f_F, f_M )</td>
<td>0.018</td>
<td>0.038</td>
</tr>
<tr>
<td>( f_F, P_C )</td>
<td>0.087</td>
<td>0.020</td>
</tr>
<tr>
<td>( f_F, f_C )</td>
<td>0.213</td>
<td>0.213</td>
</tr>
<tr>
<td>( f_F, f_C )</td>
<td>-0.049</td>
<td>-0.016</td>
</tr>
<tr>
<td>( f_F, f_C )</td>
<td>0.082</td>
<td>0.082</td>
</tr>
<tr>
<td>( P_M, f_M )</td>
<td>0.325</td>
<td>0.261</td>
</tr>
<tr>
<td>( P_M, P_C )</td>
<td>0.081</td>
<td>0.082</td>
</tr>
<tr>
<td>( P_M, f_C )</td>
<td>0.190</td>
<td>0.148</td>
</tr>
<tr>
<td>( f_M, f_C )</td>
<td>0.001</td>
<td>-0.059</td>
</tr>
<tr>
<td>( f_M, f_C )</td>
<td>0.242</td>
<td>0.242</td>
</tr>
<tr>
<td>( f_M, f_C )</td>
<td>0.131</td>
<td>0.094</td>
</tr>
<tr>
<td>( f_M, f_C )</td>
<td>0.135</td>
<td>0.008</td>
</tr>
</tbody>
</table>

For abbreviations, see table 1.
hypothesis. The general model fits the data well both for systolic and for diastolic pressure ($\chi^2 = 6.95$ and $\chi^2 = 9.23$ respectively). The results are similar for the two traits. The genetic heritability was notably small (0.181 and 0.127 for systolic and diastolic pressure respectively) with no evidence of intergenerational differences. The cultural heritability was small in children (0.015 and 0.005) but significantly larger for adults (0.188 and 0.076 for the two variables). The environmental marital correlation was significant for both traits. A maternal effect was evident for systolic blood pressure, but not for diastolic pressure.

Discussion

Our finding of an effect of age, sex, and obesity on blood pressure is in agreement with similar studies in Hawaii; but, in contrast, we could not find any significant effects of smoking and alcohol consumption on blood pressure levels.

The genetic heritabilities were low for both systolic (0.18) and diastolic (0.13) pressures. Published studies, reviewed by Iselius et al., support our findings; they found a genetic heritability of 0.23 for systolic pressure and 0.12 for diastolic pressure. There is no evidence that the genetic heritability is due to a major locus. Based mainly upon twin studies, larger estimates of genetic heritability have been proposed. Family studies have shown heritabilities that are closer to our findings. It has been suggested that the reason for this discrepancy is dominance effects; however, a more likely reason is that monozygous twins tend to share their environment more than ordinary siblings. This is supported by previous observations of Iselius et al. that recognized an environmental variance component unique to MZ twins of 0.16 for systolic pressure and 0.27 for diastolic pressure.

The cultural heritability was very low for children and significantly higher for adults. The environmental marital correlation was also high in adults, possibly due to similarities in diet (e.g., salt intake) and common psychosocial effects. The maternal effect found for systolic pressure is also likely to be due to dietary factors and propinquity. The finding of a maternal environmental effect on blood pressure is of special interest and could have an implication on the planning of primary prevention.

It is evident that the variation of blood pressure in this population was not primarily due to genetic factors. Future research for genetic effects should be more productive if concentrated on particular causes for blood pressure variation and not on the complex final result.

References

1. Iselius L, Morton NE, Rao DR: Family resemblance for blood pressure. Hum Hered. In press