Epidemiology and Genetics of Hypertension

RICHARD J. HAVLIK, M.D., AND MANNING FEINLEIB, M.D., DR.P.H.

SUMMARY The major decline in cardiovascular mortality during the last 20 years may be related to improved hypertension control, but a causal relationship has not been proven. Fundamental epidemiologic associations between age, sex, race, socioeconomic class, and blood pressure (BP) have been well characterized. Risk of coronary heart disease and stroke mortality and morbidity is linearly related to BP or to categorically defined hypertension. Weight is a major correlate of BP at all ages and in most populations. The relationships between hypertension and other nutritionally related factors are not so well defined. The Framingham Study (both cohort and offspring components) provides information about other BP correlates such as heart rate and clinical chemistry values as well as evidence suggesting a genetic influence on BP variability in families. Combined with observations from other studies, it appears that heredity plays a very important role in human hypertension.

(Hypertension 4 (supp III): III-121-III-127, 1982)

KEY WORDS • blood pressure • cardiovascular risk • heredity • environment • families • twins

To understand potential nutritional relationships with hypertension and put them in proper perspective, an appreciation of the basic epidemiology of blood pressure (BP) including population characteristics, known correlates, impact of genetics and family environment, natural history, and associated cardiovascular disease is desirable. At times, experiments of nature, such as the recent decline in coronary heart disease mortality, can help elucidate relationships and causal pathways.

Blood pressure change and hypertension control may be related to the major decline in cardiovascular disease mortality that has occurred especially during the past two decades. From 1968 to 1978, the death rate for coronary heart disease dropped over 25% and the stroke death rate decline accelerated (fig. 1). This decline occurred in all age-sex-race groups in the country. A conference was held at the National Institutes of Health to discuss the causes of the decline.1 There was strong sentiment favoring BP control as a key factor contributing to the decline; however, the data are not completely convincing for any identified factor having a consistent causal relationship with the decline.2 For example, using data taken from a random sample of the country, we find that the number of hypertensives identified and receiving adequate therapy has increased; but, the effect on the average BP level in the country has not changed markedly between the periods 1960–62 and 1971–74.3

Prevalence of definite hypertension defined by either systolic BP of 160 mm Hg or more or diastolic BP of 95 mm Hg or more was also similar in the two periods.3 More recent estimates suggest that there may have been some decrease in hypertension prevalence.4 In all age-sex groups, average weight, a major nutritional correlate of BP, was unchanged or slightly increased over 1960–62.5 Trends in salt disappearance data in the country over time are confounded by increased nonfood uses. Further population-based research relating the cardiovascular mortality decline to factors such as hypertension control or changes in BP correlates is urgently needed.

Epidemiologic Associations

As a fundamental epidemiologic observation it is well known that BP increases with age, at least in industrialized populations such as our own (fig. 2).6 Before the age of about 46 years, the mean systolic BPs are higher in men than women; but, after the age of 56 they are actually higher in women than men, cross-sectionally in the Framingham Study. It is possible that this observation represents relatively greater survival of women, since BP is a more powerful risk factor in men than women at younger ages. If a cohort of only survivors is followed, BPs continue to rise equally in both sexes. Since the number of individuals at older ages in this analysis is small and the trend lines represent a "synthetic" combination of separate BPs at different points in time, the absolute BP levels in

From the Epidemiology and Biometry Program, Division of Heart and Vascular Diseases, National Heart, Lung, and Blood Institute, Bethesda, Maryland.

This article was written by Drs. Havlik and Feinleib in their private capacity. No official support or endorsement by the National Institutes of Health is intended or should be inferred.

Address for reprints: Richard J. Havlik, M.D., NHLBI, Federal Building, Room 300, Bethesda, Maryland 20205.
It is well established that BP is higher in blacks than in whites. Interestingly, the racial difference in hypertension prevalence does not become evident until young adulthood. This suggests the possibility of delayed genetic expression or the accumulation of adverse environmental factors over the childhood years (table 1). Black-white differences have been an active area of research, but the reasons for the differences are still unknown. They are not due merely to lower socioeconomic class in blacks, although lower income and education are associated with higher BPs. By the age of 65 years over 40% of the population is hypertensive, and this figure does not include the borderline cases (table 1). As already indicated, the percentage is even higher in blacks.

Cardiovascular Risk

In the Framingham Study a population of men and women have been followed medically for 30 years. Figure 2 has already displayed cohort and cross-sectional data from this study. This study and almost all others have shown a positive, increasing relationship between baseline BP and subsequent risk of cardiovascular disease. The relationships are similar for fatal and nonfatal coronary heart disease and stroke, using single measurements of systolic or diastolic BP or an average of BPs to characterize an individual. If the same population is divided into normal, borderline, and hypertensive groups, coronary heart disease as well as other vascular disease rates increase respectively.
Table 2 shows the results of such an analysis for coronary incidence in a group of Framingham individuals 49 to 82 years of age. A common analysis strategy is to consider mathematically the relationship between BP and the probability of disease, taking into account the various factors that are related to BP as well as to coronary heart disease. The larger the regression coefficient, the more important the relationship. The coefficients are standardized into the same units, so they can be compared for relative independent strength of association. In this older population high density lipoprotein cholesterol (HDL) and low density lipoprotein (LDL) cholesterol play major roles, but systolic BP and left ventricular hypertrophy continue to contribute independently to risk.

The same statistical approach can be used with stroke (table 3). In this case, BP is the major factor associated with subsequent stroke; cholesterol is not a significant predictor. It should be emphasized that the decline in mortality has been greater for stroke than coronary heart disease. Interestingly, for both heart attack and stroke the decline has occurred mostly in black females, who as a group have received relatively more attention as new recipients of antihypertensive therapy.

Weight and Nutritional Relationships

For etiological research purposes, epidemiologists use cross-cultural studies to gain insights into possible reasons for BP variations between populations. For example, there are important and continuing studies comparing BP between Japanese in Japan and Japanese-Americans in Hawaii and San Francisco. The stroke mortality rates decrease dramatically when one compares Japan to California, but the coronary rates go up. When comparing BP among the three locations, the difference is not very great, but BP does seem to be higher among the San Francisco group. It should be recognized that these measurements in three locations were not rigorously standardized. Another study has examined island natives moving from non-Westernized and unacculturated areas to cities in New Zealand. Generally the BPs are higher in the migrants. When evaluating what factors might be involved in such relationships with BP, weight must be considered. As has already been discussed in this Symposium, it appears that weight or some measure of obesity is associated with BP at all ages almost everywhere. Weights are greater among the San Francisco group. In the Framingham Study, when natural increases or decreases in weight over time are observed in the same population, there is a corresponding increase or decrease in BP. Such changes are more supportive of a causal relationship than are cross-sectional associations.
Obviously, weight is integrally related to general nutrition not only because those who are overweight, assuming similar physical activity, usually consume more calories, but as discussed in another presentation, possibly more sodium. Data on salt intake in the Framingham Study were only based on food frequency of salty foods and use of table salt as well as a single 24-hour collection of urine for sodium analysis on a subsample. As might have been anticipated with these inadequate methods, no definite relationship was found with BP. Also, subgroup data from a Framingham dietary evaluation failed to show any consistent relationship between mean daily intake of total calories, proteins, fat, or cholesterol and quartile of BP.

**Correlates in Framingham Offspring Study**

Much of our risk and correlational data has come from the original Framingham Study. At the present time there is being completed a follow-up examination of the children of the original cohort, who themselves are adults of approximately the age of their parents when they first entered the study. This follow-up will provide an opportunity to compare BPs at two points in time, evaluate new potential correlates and familial relationships, and, of course, determine cardiovascular risk relationships.

During 1971–75, a baseline examination of the available offspring, following a protocol similar to that used with their parents, was completed with a good participation rate. Many of the same factors, such as weight, heart rate, and alcohol were found to correlate with BP in both generations. In an attempt to identify new correlates of BP, these same factors along with a number of other ones including clinical chemistries such as serum calcium, LDH, and SGOT were mathematically compared for their relationship, if any, with BP. In table 4, the final results of the analysis are displayed. Those factors, with the larger standardized regression coefficients such as weight and pulse rate, are known from previous studies to be associated with BP as are glucose, hematocrit, and alcohol. Interestingly, serum proteins, triglycerides, and phosphorus are related to BP. The latter is an inverse relationship — the higher the phosphorus the lower the BP. Even with these factors one can explain only a small fraction of the differences among BPs in individuals. The proportion of variance for which the data account ($R^2$) is about 25% in men but more in women.

**Familial Associations**

The Framingham Cohort experience coupled with the Framingham Offspring Study provides a unique opportunity to evaluate the potential influence of genetics on hypertension. The strategy of understanding the influence of heredity on the population distribution of BP or the variation among individuals in the population is heavily dependent on the selected "model." We may assume that Mendel must have done a fair amount of observing in his monastery setting before deducing the segregation of characteristics in pea plants. Families of various types including parents, offspring, siblings, spouses, twins (both identical and fraternal) and adopted individuals provide the opportunity to understand the impact of genetics on hypertension.

In table 4, the separate effects of paternal and maternal BP determined some 20 years earlier, when the parents were of a similar age to their offspring, are shown. Over and above the effects of the BP correlates, many of which are known to aggregate in families, there is a statistically significant effect of parental BP except for paternal BP in women.

Table 5 illustrates the relationship between parents and adult offspring. These correlations of about 0.15 are remarkably similar to those done concurrently in the usual family study, when BP of parents and children are evaluated at the same point in time. In the latter case, there is no question that current home environment is being shared. In the former case, the families have been separated for some years, although the effect of learned behavior carried to the new home situation cannot be minimized.

Siblings share on the average about one-half of their genes, just as do parents and offspring. This theoretical "model" would predict a correlation of about 0.5 between siblings, if BP has polygenetic inheritance. Indeed, the correlations are comparable between siblings and parent-offspring, but not to that level (table 6). The age-adjusted sibling correlations may be slightly higher than parent-offspring ones. This has been reported by other studies. The reason that this disparity

---

**Table 4. Multiple Regression Analysis for Systolic Blood Pressure in Men and Women Aged 20–49 Years (Framingham Offspring)**

<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Standardized Regression Coeff.</th>
<th>$F^*$</th>
<th>Standardized Regression Coeff.</th>
<th>$F^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>0.231</td>
<td>39.9</td>
<td>0.260</td>
<td>55.3</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>0.196</td>
<td>26.2</td>
<td>0.249</td>
<td>51.5</td>
</tr>
<tr>
<td>Total serum proteins</td>
<td>0.186</td>
<td>24.2</td>
<td>0.090</td>
<td>7.2</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.107</td>
<td>8.6</td>
<td>0.063</td>
<td>3.9</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.097</td>
<td>6.9</td>
<td>0.121</td>
<td>13.1</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>-0.084</td>
<td>5.0</td>
<td>-0.108</td>
<td>9.0</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>0.094</td>
<td>6.5</td>
<td>0.062</td>
<td>3.0</td>
</tr>
<tr>
<td>Plasma triglycerides</td>
<td>0.057</td>
<td>2.3</td>
<td>0.081</td>
<td>5.1</td>
</tr>
<tr>
<td>Maternal SBP</td>
<td>0.097</td>
<td>5.7</td>
<td>0.129</td>
<td>13.8</td>
</tr>
<tr>
<td>Paternal SBP</td>
<td>0.071</td>
<td>3.8</td>
<td>0.048</td>
<td>2.1</td>
</tr>
<tr>
<td>Multiple $R^2$</td>
<td>0.278</td>
<td></td>
<td>0.404</td>
<td></td>
</tr>
</tbody>
</table>

*Significant at $p < 0.05$.

may be important for understanding the model is that such a difference between siblings and parent-offspring suggests "dominance" or the likelihood that an offspring is more like one or the other parent because a certain trait is segregating to one or the other offspring. The classic example is brown eyes being dominant over blue. Normally, since an offspring receives 50% of genes from one parent and 50% from the other, the midparent value, which is an average of the two, should explain or predict BP completely in the offspring. When it does not, this is another hint that dominance may be a factor. Dominance is not synonymous with single gene inheritance. Certain genes in a polygenic setting can be dominant. In a population sense, blood pressure is thought to be polygenic, as forcefully presented by the late Sir George Pickering. There are, of course, some single gene problems that may be related to BP, such as certain enzyme deficiencies leading to endocrine abnormalities and resulting hypertension.

The sibling data also introduce another aspect of understanding the interplay of other correlates and familial aggregation. If the relationships are adjusted statistically for some of the other factors, such as weight, that are correlated with BP and also aggregate in families, the correlation coefficients change some-

TABLE 5. Age-Adjusted Correlation Coefficients* for Parents and Offspring for Systolic and Diastolic Blood Pressure in Framingham Study

<table>
<thead>
<tr>
<th>Relationship</th>
<th>No. of families</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father-son</td>
<td>729</td>
<td>0.171</td>
<td>0.160</td>
</tr>
<tr>
<td>Father-daughter</td>
<td>766</td>
<td>0.103</td>
<td>0.146</td>
</tr>
<tr>
<td>Mother-son</td>
<td>729</td>
<td>0.144</td>
<td>0.131</td>
</tr>
<tr>
<td>Mother-daughter</td>
<td>766</td>
<td>0.168</td>
<td>0.152</td>
</tr>
</tbody>
</table>

*Pairwise computation.

what. Similar changes occur when the parent-offspring correlations are adjusted. This aspect becomes important when we evaluate the relationships in systolic BP between spouses.

It should be emphasized that familial aggregation is not synonymous with heredity. Shared environment is a potent force in confounding the effect of genes and complicating the analysis. Although there are statistical approaches that have been used in an attempt to adjust for the effect of common environment, one strategy is to compare the relationships between related and nonrelated individuals in the same families. In the Framingham Study, we have analyzed data mainly from the perspective of spouse relationships, although there are some adoption data available as well. Since the spouses share the same home environment to a major degree, one could expect to understand the potential influence of common environment by evaluating spouse relationships. Table 7 presents data from two different spouse groups, the parents and the offspring. Although with unadjusted correlation analysis it might appear that both parent and offspring spouses have rather similar BPs, with adjustment for cofactors the apparent correlational relationship is decreased substantially. This is the phenomenon described as assortative mating or marriage. Individuals of the same age, appearance, and habits tend to marry more often. This is the more likely explanation for the original correlation than common environment. Some attempts have been made to determine if those couples who are married for a longer time and thus are theoretically exposed to common environment for a greater period have increasing correlations. This does not seem to be the case.

This type of observational analysis suggests that genetic factors are the most likely reason for familial aggregation of BP. The Framingham Study has the potential for considering more complicated interrelationships. For example, observations can be obtained from second-degree relatives such as an uncle or aunt and niece and nephew. On the average, these relatives share only about 25% of genes, so the expected BP correlations should be lower.

TABLE 6. Simple Correlation Coefficients for Systolic Blood Pressure Residuals* in Framingham Offspring Aged 20-49 Years

<table>
<thead>
<tr>
<th>Relationship</th>
<th>No. of families</th>
<th>Age adjustment</th>
<th>Full adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brothers</td>
<td>256</td>
<td>0.143</td>
<td>0.119</td>
</tr>
<tr>
<td>Sisters</td>
<td>283</td>
<td>0.207</td>
<td>0.080</td>
</tr>
<tr>
<td>Brother-sister</td>
<td>414</td>
<td>0.193</td>
<td>0.199</td>
</tr>
</tbody>
</table>

*Residuals are obtained by regressing blood pressure (BP) on age alone or with weight, pulse, and alcohol consumption (covariates) for parents and offspring separately and applying the coefficient(s) so obtained to each individual's covariate(s). The amount this "expected" BP differs from the actual BP is the residual.

TABLE 7. Simple Correlation Coefficients for Spouses in the Framingham Heart Study Cohort and in the Offspring for Systolic Blood Pressure and Systolic Blood Pressure Residuals*

<table>
<thead>
<tr>
<th>Spouse pairs</th>
<th>No. of families</th>
<th>No adjustment</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>1202</td>
<td>0.152</td>
<td>0.045</td>
</tr>
<tr>
<td>Offspring</td>
<td>1194</td>
<td>0.089</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Residuals are obtained by regressing blood pressure (BP) on age, weight, pulse, and alcohol consumption (covariates) for parents and offspring separately and applying the coefficients so obtained to each individual's covariate(s). The amount this "expected" BP differs from the actual BP is the residual.
Studies of Twins

Another approach used by the National Heart, Lung, and Blood Institute over the past few years has been the twin model.22 This is a powerful strategy that has been improved somewhat to minimize the impact of common environment, which is a constant concern when evaluating risk factor data in twins. The strategy involves a statistical comparison of the similarity of identical vs fraternal twins. The simplest approach is to compare the intraclass correlation coefficients. For systolic BP and diastolic BP, the correlations for middle-aged veteran twins are much higher for monozygotic (MZ) than dizygotic (DZ) twins (0.55 and 0.58 vs 0.25 and 0.27).22 This relationship can be translated mathematically into a heritability estimate or the percent of the total variance that can be attributed to genetics. Using the relationship of twice the difference of the monozygotic and dizygotic twin correlations for BP, we find that approximately 60% of the variability is attributed to heredity. This statistical analysis does not, however, avoid the possibility that the environment of the MZ twin pairs is differentially more alike than that for DZ pairs. One approach to minimizing the potential effect of common environment is to evaluate twins at young ages, when the cumulative effects of factors such as weight. In the 7-year-old twins, there are other approaches to family investigations, and a number of different models have been used. Most have given similar estimates of the genetic influence on BP for 7-year-old23 and newborn twins have been found.24 Also, there is the potential interrelationship with other potentially inherited or environmentally influenced factors such as weight. In the 7-year-old twins, there was essentially no change in the heritability estimate after correction for weight.23 A further investigative approach, using college-aged twins, involved a sodium-loading and depletion protocol.25 Following sodium loading, evidence was found for a genetic influence on factors that help regulate BP, such as natriuretic response, renin activity, plasma aldosterone, and norepinephrine, in this young adult population.

Genetic Implications

There are other approaches to family investigations, and a number of different models have been used. Most have given similar estimates of the genetic influence on BP variability. Table 8 provides a summary synthesizing data from the Framingham and twin studies.21 These are approximate intrafamily correlation coefficients. The additive or linearly related polygenic inherited variability can be estimated as twice the first degree (on the average, half the genes in common) or four times the second degree (on the average, one-quarter the genes in common) relatives’ correlation coefficient. The dominance component has been theoretically estimated to be approximated by subtracting one-half the additive component from the sibling correlation and multiplying by four. Since the twin correlations are higher than expected, this excess may be a good estimate or indicator of shared environment. The nonshared environment or the sum of other factors influencing BP variability could be as high as 45% (the difference between 100% and the sum of the identified variances). As is well recognized, there is a great deal of intraindividual variability in blood pressure from day to day and between longer periods as well as measurement error. From moment to moment, the correlation may only be about 0.8. A squaring of the correlation or 64% is an estimate of the intraindividual consistency over time, leaving almost a 40% error estimate. This error estimate is very close to that for the estimated environmental variation. Undoubtedly, some of the difference between the additive component and the total variance must be related to identified and unknown environmental factors.

Ideally, we would like to identify a specific set of genes that influences BP. Hopefully, in the future we will have genetic markers that could pinpoint those at higher risk for hypertension. The current interests in cellular ion fluxes and HLA typing are examples of such efforts. Early and precise identification of high risk individuals would give a major preventive and therapeutic advantage. It is important to emphasize that no matter what the underlying genes, the specific environment is critical as well. Depending on the available diet, certain diseases, such as phenylketonuria, can have a heritability of 100% or 0%. Thus, heritability estimates will vary depending on the environment in which individuals with specific genes are found. The strategy of migration studies involves holding genes constant and changing environment. Obviously, we do not yet have either a precise statistical or molecular view of the BP controlling genome or completely accurate estimates of the environment; but we are reasonably certain that genetics play a very important role in human hypertension.

### Table 8. Summary of Correlation Coefficients and Resulting Sources of Variation Estimates for Family Studies of Blood Pressure

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>Estimated Sources of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent-offspring</td>
<td>0.15</td>
</tr>
<tr>
<td>Uncle-nephew</td>
<td>0.075</td>
</tr>
<tr>
<td>Siblings</td>
<td>0.20</td>
</tr>
<tr>
<td>Identical twins</td>
<td>0.55</td>
</tr>
<tr>
<td>Fraternal twins</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*VA = additive genetic variance.
†VD = dominance effect in genetic variance.
‡VST = shared environment unique to twins.
§VNS = nonshared environment.

(Source: Adapted from Feinleib M, Garrison RJ: The contribution of family studies to the partitioning of population variation of blood pressure. In Genetic Analysis of Common Diseases: Applications to Predictive Factors in Coronary Disease, edited by Sing CF, Skolnick M. New York: Alan R. Liss, 1979, p 653.)
References


Epidemiology and genetics of hypertension.
R J Havlik and M Feinleib

*Hypertension*. 1982;4:III121
doi: 10.1161/01.HYP.4.5_Pt_2.III121

*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/4/5_Pt_2/III121

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Hypertension* is online at:
http://hyper.ahajournals.org//subscriptions/