# Familial Patterns of Covariation for Cardiovascular Risk Factors in Adults

## The Victorian Family Heart Study

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The Victorian Family Heart Study was established to address the causes of familial patterns in cardiovascular risk factors. From 1990 to 1996, a representative population sample of 783 adult families (2,959 individuals), each comprising both parents (40–70 years) and at least one natural adult offspring (18–30 years), was recruited in Melbourne, Australia. Included in both generations were 461 monozygotic and dizygotic twins as pairs or singletons. A multivariate normal model was used for pedigree analysis of height, weight, body mass index, diastolic and systolic blood pressure, pulse rate, and total and high density lipoprotein cholesterol. All traits showed evidence for additive genetic variation, explaining from 55% (height) to 26% (pulse) of age- and sex-adjusted variance. An effect persisting into adulthood of shared family environment during cohabitation explained from 39% (body mass index) to 13% (systolic blood pressure) of variance (not nominally significant for diastolic blood pressure). These shared environmental effects were strongest within twin pairs, less so for sibling pairs, and least for parent-offspring pairs (in which an effect was not observed for weight, diastolic and systolic blood pressure, and total cholesterol). On a background of genetic influences, there are periods in early life during which the family environment cements long-term correlations between adult relatives in cardiovascular risk factors. *Am J Epidemiol* 2000;152:704–15.

blood pressure; body mass index; cholesterol; family characteristics; genes; twins

Cardiovascular disease is familial, in that individuals with a close relative with the disease are themselves at increased risk (1). It is possible that at least part of the reason for this is that nongenetic risk factors for the disease are themselves correlated within families (2). This issue has also been addressed from a theoretical perspective, using mathematical models (3). Established cardiovascular risk factors that have consistently been demonstrated to be correlated between relatives include height (4, 5), weight, body mass index (6–8), blood pressure, and cholesterol (9–11).

Familial correlations in risk factors can result from shared genetic predisposition or shared family environment. Correlations are most likely a consequence of, and even interaction between, both types of familial factors. The relative contribution of genetic and nongenetic factors in explaining variation in cardiovascular risk factors is not necessarily uniform. Certain factors may be influenced to a greater extent by lifestyle and behavior (12) than by genetic variation. Understanding the relative magnitudes of these two components of variation is of potential importance for directing gene searches (to traits with substantial "heritability"; i.e., for which the genetic component explains a relatively large proportion of variance) or for identifying environmental or lifestyles factors that are or have been shared within families while cohabiting, even if the family members are no longer living together.

There are several methods for determining the genetic and environmental components of variance in physiologic quantitative traits. Each involves families to greater or lesser extents and utilizes a variety of sampling and analytical approaches. Genetic inferences are made from analyses of relatives with different degrees of genetic similarity. These range from none or low similarity in the case of spouses (13) or adoptees (14) to genetic identity in monozygotic twin pairs (15, 16). The sampling frameworks and ascertainment schemes for biometric analyses of cardiovascular risk factors vary from those targeting families who meet special criteria regarding health (such as preexisting cardiovascular disease (17)) or specific family composition (such as those including adoptees as children (18) or adults (19) or monozygotic or dizygotic twin pairs (15, 20)) to recruitment from the general population (6). The last approach is likely to provide information that may be applicable to the population, but it offers smaller proportions of families that are especially informative for disentangling the effects of shared genes from those of shared environments. In reality, however, obtaining a high

response rate from a random sample of families is difficult. In the case of screening through medical clinics, it is more difficult to make inferences to the population (21), despite the existence of various mathematical methods for making so-called "corrections" for theoretical modes of family ascertainment that in practice rarely apply.

The Victorian Family Heart Study was established in 1990 to address the causes of familial patterns in cardiovascular risk factors. The study was designed to measure a number of simple and well-recognized risk factors in a large number of volunteer families of adults selected from the general population and to *enrich* the sample with families comprising dizygotic and monozygotic twin pairs. In this way, we hoped to derive a population sample that was both representative and informative. The aim of this analysis was to examine the familial patterns of covariation of risk factors so as to quantify the contribution of genetic and environmental effects in explaining variation.

## MATERIALS AND METHODS

### Recruitment

For this study the aim was to recruit families that comprised, at a minimum, a mother and father with at least one natural child. A family was eligible if both parents were aged between 40 and 70 years and if at least one offspring was aged between 18 and 30 years, inclusive. Other offspring were included if they were aged between 18 and 30 years. The lower age for offspring was set to minimize the potential confounding effect of growth on the phenotypes under study. Recruitment was limited to Caucasian families to reduce the possible confounding effect of racially determined genetic differences. A family history of heart disease was not relevant to recruitment, the aim being to enroll a representative sample of families exhibiting a broad cross-section of cardiovascular risk factor levels.

Potential participating families were identified through a variety of community-based sources. These included the Australian Twin Registry, the Melbourne Collaborative Cohort Study (Health 2000), general practitioners, and work sites (Common Scientific and Industrial Research Organization). We asked a total of 8,060 individuals by letter or telephone to indicate whether their families would be willing to participate in the Victorian Family Heart Study and received 2,946 (37 percent) responses from 2,711 families. Of these, 1,108 (41 percent) families were excluded because they were ineligible (key family member unavailable, no natural children, ethnic origin), and 820 (30 percent) declined, leaving a total of 783 families. Recruitment was undertaken between 1991 and 1996.

Figure 1 displays the different types and numbers of families grouped according to the presence or absence of twins, their zygosity, and whether they occur at the parental or offspring generation.

### Phenotype measurement

These studies were approved by the Ethics Review Committee of the Alfred Hospital, Melbourne, and informed consent was obtained from all participants. Participants attended one of our research clinics. Trained research nurses enrolled subjects, obtained relevant details, measured cardiovascular risk factors according to standardized measurement techniques, and took blood for DNA analysis. Detailed information was obtained regarding treatment with oral contraceptives, hormone replacement therapy, antihypertensive medications, and lipid-lowering therapy. Participants were asked to categorize their smoking habits as never smoked, exsmoker, current smoker with less than or equal to 20 cigarettes (or equivalent) per day, or currrent smoker with more than 20 cigarettes per day.

After removing heavy clothing and shoes, subjects were measured to the nearest 0.5 cm for height with the use of a wall-mounted ruler. Weight was measured to the nearest 0.5 kg with scales that were calibrated regularly. Subjects then rested supine for 10 minutes, during which time a suitably sized sphygmomanometer cuff was applied to the right arm. Blood pressure was measured using a standard mercury sphygmomanometer. Systolic blood pressure was taken as the return of arterial sounds (Korotkoff phase I) and diastolic blood pressure as the disappearance of sounds (Korotkoff phase V). Blood pressure measurements were made to the nearest 2 mmHg. Three measurements of systolic blood pressure and diastolic blood pressure were taken, the last two of which were recorded. The pulse rate was measured for 60 seconds. Subjects then stood for 2 minutes, and systolic blood pressure, diastolic blood pressure, and the pulse rate were measured again. In this analysis lying and standing readings were averaged to provide estimates of systolic blood pressure, diastolic blood pressure, and pulse rate.

### Biochemical measurements

Following phenotypic measurements, venous blood was collected for biochemical analysis and DNA extraction. After insertion of a butterfly needle, the tourniquet was released before collection of 7 ml of blood into lithium heparin anticoagulant for cholesterol and 14 ml of blood into ethylenediaminetetraacetic acid (EDTA) anticoagulant for DNA. Total cholesterol and high density lipoprotein cholesterol were measured by automated biochemical analysis systems and were subject to quality assurance testing every 3 months.

### Statistical methods

The familial patterns in cardiovascular risk factors were analyzed using a multivariate normal model for pedigree analysis (22–26), fitted using the FISHER statistical package (27). The method allows for estimation of the correlations or covariances between relatives and for fitting various genetic and environmental models of variation, while concurrently adjusting the mean for measured factors. In each of the analyses below, a separate quadratic was fitted to the mean for males and females, and the residual variance was relatively stable with age and independent of sex. Families were presumed to be independent, so the log likelihood of
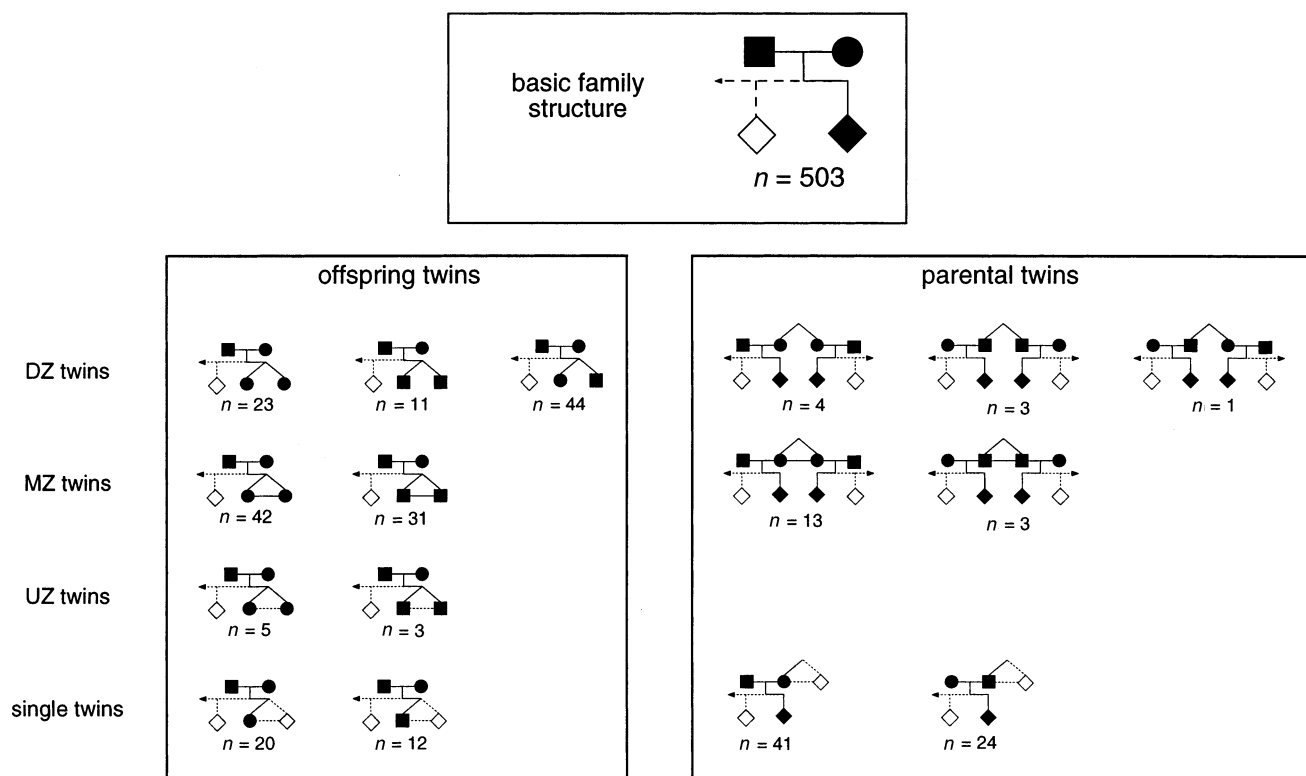
**FIGURE 1.** Diagrammatic representation of family structures, Victorian Family Heart Study, 1990–1996. There were 503 families without twins and 280 families with at least one twin. Twins were monozygotic (MZ), dizygotic (DZ), or of unknown zygosity (UZ) and occurred in the offspring or parental generation as pairs or singletons.

the total sample was the sum of log likelihoods over all families.

The model assumes that, for a family of size $n$, the distribution of the vector of trait values, $\underline{Y} = (Y_1, ..., Y_n)'$, has an $n$-variate normal distribution with mean $\mu = (\mu_1, ..., \mu_n)'$ and covariance $\Omega = (\omega_{ij})$. The covariances were initially parameterized as $\omega_{ij} = \rho_{ij}\sigma^2$, where $\rho_{ij} = \rho_{MZ}$ for monozygotic twin pairs, $\rho_{DZ}$ for dizygotic twin pairs, $\rho_{sib}$ for nontwin sibling pairs, $\rho_{po}$ for parent-offspring pairs, $\rho_{sp}$ for spouse pairs, and so on, ..., and $\sigma^2 = (\sigma_i^2\sigma_j^2)^{1/2}$, where $\sigma_i^2$ and $\sigma_j^2$ are the variances of individuals $i$ and $j$, respectively. The correlations were also broken down by sex (e.g., sister-sister, brother-brother, sister-brother, mother-daughter, father-son, mother-child, and so on) in some analyses.

Following Fisher (28), the genetic and environmental model of variation assumes that $\sigma^2 = \sigma_a^2 + \sigma_{se}^2 + \sigma_e^2$, where $\sigma_a^2$ is the additive genetic variance component, $\sigma_{se}^2$ is the shared environment variance component, and $\sigma_e^2$ is the individual environment variance component (29). For two individuals $i$ and $j$ within the same family, the covariance between the residuals, $\text{cov}((Y_i - \mu_i)(Y_j - \mu_j))$, is given by $\sigma_a^2 + \gamma_{tw}\sigma_{se}^2$ for monozygotic twin pairs, $1/2\sigma_a^2 + \gamma_{tw}\sigma_{se}^2$ for dizygotic twin pairs, $1/2\sigma_a^2 + \gamma_{sib}\sigma_{se}^2$ for nontwin sibling pairs, and $1/2\sigma_a^2 + \gamma_{po}\sigma_{se}^2$ for parent-offspring pairs. For spouse pairs, the covariance was estimated as $\rho_{sp}\sigma^2$. In all analyses, $\gamma_{tw} = 1$, and for each of the nontwin relationships

the shared environment coefficient, $\gamma$, has been either estimated or fixed to be in the interval [0, 1]. That is, we have assumed that the persisting effect of shared environment during cohabitation is the same within monozygotic pairs as it is within dizygotic pairs; this is the critical assumption of the classic twin model (30). Within all other relationships, the effect of shared environment is assumed to be less than or equal to that within twin pairs.

In subsequent analyses, we interpreted any correlation between spouses in terms of 1) the effects of spouses having shared their environment since marriage or 2) the consequence of spouses being correlated for the trait at the time of their marriage. The latter effect is known as "assortative mating." It is not possible from the data we have collected to determine which of the two scenarios is more appropriate. Nevertheless, for height (which is fully attained by adulthood and varies little within an individual over the age range of the subjects in this study), one must presume that the spouse correlation was due to assortative mating. In fitting the assortative mating model, the only change to the covariance modeling above was that the additive genetic component in the covariance between siblings and dizygotic pairs is given instead by $1/2(1 + \rho_{sp})\sigma_a^2$; see Fisher (28).

A range of models was fitted, starting with the "simplest model" in which a correlation between spouses, $\rho_{sp}$, was estimated, along with all covariance components. It was also

assumed that only the shared environment coefficient for twin pairs, $\gamma_{tw} = 1$, was non-0. This is equivalent to fitting the classic twin model. (Should any of the estimated variance components have not been significant at the 0.05 level, that component was deleted and the model refitted.) Following this, different sets of shared environment coefficients were fitted for the nontwin relatives. In the "full model," all three variance components and all shared environment coefficients were fitted together. The choice of the "best model" was made by use of the likelihood ratio criterion. If a variance component estimate (in particular, $\sigma_{se}^2$) was not significant at the 0.05 level, it was set to zero and the model refitted.

## RESULTS

A total of 783 families, comprising 2,959 individuals, were recruited into the study. The study sample comprised 1,549 parents and 1,410 offspring with a total of 1,517 females and 1,442 males. Families with one or two participating offspring were most common. There were 320, 323, 112, 23, and 3 families with one, two, three, four, and five participating offspring, respectively. In 15 families only one parent took part. One of these families comprised the mother only, who was included as one of a pair of twins in the parental generation (figure 1). Figure

1 also provides details of the number and nature of families involving twins. A total of 89 monozygotic and 86 dizygotic twin pairs participated. Most twin pairs were in the offspring generation, but 16 monozygotic and eight dizygotic twin pairs were included as parents of separate families.

The summary data in table 1 show that males and females were of comparable age in both generations. In general, males were taller and heavier and had a higher body mass index, systolic blood pressure, and diastolic blood pressure. The pulse rate and high density lipoprotein cholesterol were higher in females. On average, parents had a higher weight, body mass index, blood pressure, and total cholesterol level but a lower pulse rate and height than did offspring. The means for these variables are consistently close (on average, differing by 0.6 percent) to the mean values recorded in other previous Australian population-based studies of cardiovascular risk factors (31).

Figures 2–4 show the estimated correlation coefficients for the age- and sex-adjusted risk factors. For none of these traits was there a difference in the correlation by sex within the categories of monozygotic, dizygotic, nontwin sibling, or parent-offspring pairs.

Tables 2–4 show the parameter estimates for fitted models to the age- and sex-adjusted risk factors.

**TABLE 1. Descriptive statistics of measured phenotypes according to generation and by sex, Victorian Family Heart Study, 1990–1996**

| | No. | Age (years) | | | Height (cm) | | | Weight (kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Median | IQR* | Mean | Median | IQR | Mean | Median | IQR |
| Offspring | | | | | | | | | | |
| Male | 674 | 24.1 (3.78)† | 24 | 21–27 | 177.8 (6.64) | 178 | 173–182 | 76.7 (12.34) | 76 | 68–84 |
| Female | 736 | 24.0 (3.63) | 24 | 21–27 | 164.8 (6.59) | 165 | 160–169 | 61.7 (10.58) | 61 | 55–66 |
| Parents | | | | | | | | | | |
| Male | 768 | 55.2 (6.38) | 55 | 50–60 | 173.8 (7.04) | 174 | 169–179 | 81.6 (11.92) | 81 | 74–89 |
| Female | 781 | 52.5 (5.9) | 52 | 48–56 | 161.6 (6.33) | 161 | 157–166 | 67.9 (11.88) | 66 | 60–74 |

| | Body mass index (kg/m²) | | | Systolic blood pressure (mmHg) | | | Diastolic blood pressure (mmHg) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | IQR | Mean | Median | IQR | Mean | Median | IQR |
| Offspring | | | | | | | | | |
| Male | 24.2 (3.62) | 23.8 | 21.7–26.1 | 122.4 (10.53) | 122 | 115–129 | 72.0 (9.38) | 72 | 65.5–78 |
| Female | 22.7 (3.58) | 22.1 | 20.3–24.4 | 113.1 (9.87) | 112.5 | 107–119.3 | 68.2 (8.59) | 68 | 62.5–73.5 |
| Parents | | | | | | | | | |
| Male | 27.0 (3.40) | 26.6 | 24.6–29.0 | 130.0 (15.14) | 127.5 | 120–137.5 | 82.2 (8.80) | 82 | 76–87.5 |
| Female | 26.0 (4.49) | 25.2 | 22.9–28.6 | 124.5 (14.87) | 122.5 | 113.5–133.5 | 78.2 (8.59) | 78 | 72–84 |

| | Pulse rate (per minute) | | | Total cholesterol (mmol/liter) | | | High density lipoprotein cholesterol (mmol/liter) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | IQR | Mean | Median | IQR | Mean | Median | IQR |
| Offspring | | | | | | | | | |
| Male | 71.4 (10.1) | 71 | 64.5–77.5 | 4.7 (0.97) | 4.6 | 4.0–5.2 | 1.19 (0.32) | 1.2 | 1.0–1.3 |
| Female | 74.5 (10.0) | 74 | 67.3–81 | 4.7 (0.84) | 4.6 | 4.1–5.3 | 1.48 (0.39) | 1.4 | 1.2–1.7 |
| Parents | | | | | | | | | |
| Male | 69.6 (9.9) | 69 | 62.5–76 | 5.8 (0.99) | 5.8 | 5.1–6.4 | 1.20 (0.49) | 1.1 | 0.9–1.4 |
| Female | 71.8 (9.3) | 71 | 65–77.5 | 5.8 (1.01) | 5.7 | 5.1–6.4 | 1.58 (0.49) | 1.5 | 1.3–1.8 |

\* IQR, interquartile range.
† Numbers in parentheses, standard deviation.

## Anthropometric risk factors

For height, figure 2 shows that the correlation was highest for monozygotic pairs, where it was about 0.9. The correlations for the different categories of first-degree relatives were similar and, although clearly less than the correlation for monozygotic pairs, they were generally in excess of half the monozygotic correlation. There was also a moderate correlation within spouse pairs of about 0.4.

The greater monozygotic versus dizygotic correlation is consistent with a genetic component of variance, under the critical assumption of the classic twin model. The congruity of the correlation within different types of first-degree relatives is also consistent with a genetic cause of variation. The excess when compared with one-half the monozygotic correlation is consistent with the existence of environmental determinants that are common to members of the same family. As noted in Materials and Methods, Statistical methods, the spouse correlation is likely to be a consequence of assortative mating.

Table 2 shows that the best-fitting model included both a genetic and a shared environment component. Furthermore, the effect of the shared environment was estimated to have been the same, irrespective of type of relationship within a pair. That is, it was the same for twin pairs, irrespective of their zygosity, as it was for nontwin sibling pairs and parent-offspring pairs.

When the assortative mating model was fitted, the estimate for $\sigma_a^2$ was 23.63 (standard error, 1.39), while the estimates for $\sigma_{se}^2$ and the shared environment coefficients remained unchanged. That is, 55 percent of variance was attributable to additive genetic factors, 15 percent to the effects of a shared family environment, and the remaining 30 percent to individual-specific environmental factors.

For weight and body mass index, figure 2 shows that the monozygotic correlations were again high (around 0.8), but a different pattern to height was apparent across the other relationships. The correlations decreased in going from monozygotic to dizygotic to nontwin sibling to parent-offspring to spouse pairs. The best-fitting model for weight (table 3) included a genetic and shared environment component, but in this case the latter effect was limited to twin pairs. The correlation within twin pairs due to this effect was $1.0 \times 29.47 / (83.70 + 29.47 + 21.52) = 0.22$, similar to the correlation between spouse pairs of 0.24. If all of the spouse correlation is presumed to be due to nongenetic factors, it was estimated that 62 percent of the variance was attributable to additive genetic factors, 22 percent to the shared twin environment, and the remaining 16 percent to individual environment. When the assortative model was fitted instead, presuming that all of the spouse correlation was evident at marriage, the genetic component of variance became 67.6 or 50 percent of variance.

For body mass index, the best-fitting model included a genetic and a shared environment component. The latter effect explained 35 percent of variance and was greatest in twin pairs, about one half as strong within nontwin sibling pairs, and half as strong again within parent-offspring pairs. The correlation within twin pairs attributed to this effect was 0.39, and that within nontwin siblings was 0.18. The correlation between spouse pairs was 0.26. If all the spouse correlation was attributed to nongenetic factors, the genetic component explained 40 percent of variance. When the assortative mating model was fitted, this was reduced to 32 percent.

## Hemodynamic risk factors

Figure 3 shows that the general pattern observed for weight and body mass index, a decline in correlation from monozygotic pairs through to spouse pairs, was generally evident for systolic blood pressure and diastolic blood pressure. The monozygotic correlations were still highest but now in the 0.5–0.6 range. The best-fitting model for systolic blood pressure included both a genetic and a shared environmental component but, for diastolic blood pressure, it included only a genetic component.

For systolic blood pressure, the effect of the shared environment explained 13 percent of variance and was estimated to be the same within twin pairs as it was within nontwin sibling pairs, but it was not evident within parent-offspring pairs (table 3). That is, it was restricted to the one generation. The
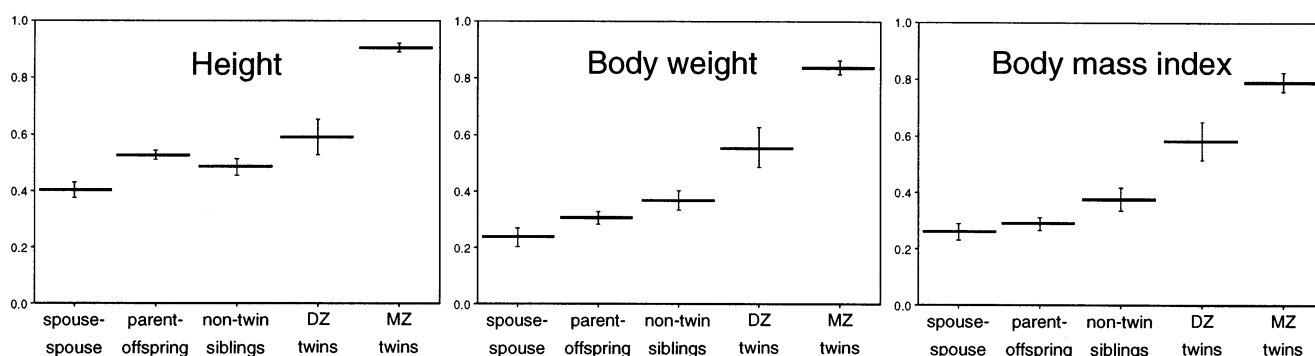


**FIGURE 2.** Correlation coefficients and their standard errors for the following pairs of family members: spouse-spouse, parent-offspring, nontwin siblings, dizygotic (DZ) twins, and monozygotic (MZ) twins for height (left), weight (middle), and body mass index (right), Victorian Family Heart Study, 1990–1996.

**TABLE 2. Statistical modeling of genetic and environmental components of variance of height, weight, and body mass index, Victorian Family Heart Study, 1990–1996\***

| Model | $\sigma_a^2$ | $\sigma_{ae}^2$ | $\rho_{sp}$ | $\gamma_{po}$ | $\gamma_{tw}$ | $\gamma_{sib}$ | $\sigma_e^2$ | Log likelihood |
|---|---|---|---|---|---|---|---|---|
| | | | | *Height* | | | | |
| Simplest | 37.410 (1.213)† | 0.000 (0.000) | 0.341 (0.028) | 0.000 | 1.000 | 0.000 | 3.321 (0.405) | −6,729.07 |
| Full‡ | 27.440 (5.432) | 11.730 (5.460) | 0.402 (0.029) | 0.774 (0.129) | 1.000 | 0.634 (0.118) | 4.006 (0.606) | −6,718.93 |
| Best fit | 32.990 (1.713) | 6.232 (1.534) | 0.396 (0.029) | 1.000 | 1.000 | 1.000 | 4.002 (0.604) | −6,720.62 |
| Assortative mating | 23.630 (1.385) | 6.232 (1.534) | 0.396 (0.029) | 1.000 | 1.000 | 1.000 | 13.370 (0.597) | −6,720.62 |
| | | | | *Weight* | | | | |
| Simplest | 83.700 (6.569) | 29.470 (5.528) | 0.239 (0.032) | 0.000 | 1.000 | 0.000 | 21.520 (3.120) | −8,728.70 |
| Full | 76.710 (20.400) | 36.520 (19.920) | 0.232 (0.033) | 0.078 (0.259) | 1.000 | 0.308 (0.183) | 21.800 (3.327) | −8,725.24 |
| Best fit | 83.700 (6.569) | 29.470 (5.528) | 0.239 (0.032) | 0.000 | 1.000 | 0.000 | 21.520 (3.120) | −8,728.70 |
| | | | | *Body mass index* | | | | |
| Simplest | 8.316 (0.710) | 3.195 (0.648) | 0.262 (0.030) | 0.000 | 1.000 | 0.000 | 2.862 (0.402) | −5,361.69 |
| Full | 5.817 (2.111) | 5.649 (1.990) | 0.259 (0.031) | 0.225 (0.129) | 1.000 | 0.448 (0.111) | 3.026 (0.468) | −5,358.62 |
| Best fit | 5.817 (2.111) | 5.649 (1.990) | 0.259 (0.031) | 0.225 (0.129) | 1.000 | 0.448 (0.111) | 3.026 (0.468) | −5,358.62 |

\* Variance components and the log likelihoods are provided for the simplest, full, and most parsimonious model for each phenotype.
† Numbers in parentheses, standard error. Any estimate without a standard error has been fixed at the designated value.
‡ The full model takes into account the following components: additive genetic ($\sigma_a^2$), shared environment ($\sigma_{se}^2$) and error ($\sigma_e^2$) effects, correlation coefficient between spouse pairs ($\rho_{sp}$), and shared environment coefficients for parent-offspring pairs ($\gamma_{po}$), twin pairs ($\gamma_{tw}$), and nontwin sibling pairs ($\gamma_{sib}$).

**TABLE 3. Statistical modeling of genetic and environmental components of variance of systolic and diastolic blood pressure and pulse rate, Victorian Family Heart Study, 1990–1996\***

| Model | $\sigma_a^2$ | $\sigma_{ae}^2$ | $\rho_{sp}$ | $\gamma_{po}$ | $\gamma_{tw}$ | $\gamma_{sib}$ | $\sigma_e^2$ | Log likelihood |
|---|---|---|---|---|---|---|---|---|
| | | | | *Systolic blood pressure* | | | | |
| Simplest | 70.990 (8.001)† | 12.540 (12.860) | 0.128 (0.028) | 0.000 | 1.000 | 0.000 | 81.780 (11.970) | −9,161.41 |
| Full‡ | 62.460 (29.650) | 26.810 (20.900) | 0.123 (0.029) | 0.142 (0.486) | 1.000 | 1.000 | 77.850 (12.780) | −9,158.35 |
| Best fit | 69.370 (8.081) | 22.080 (8.188) | 0.123 (0.029) | 0.000 | 1.000 | 1.000 | 75.500 (7.855) | −9,158.38 |
| | | | | *Diastolic blood pressure* | | | | |
| Simplest | 32.560 (3.327) | 6.910 (4.136) | 0.149 (0.035) | 0.000 | 1.000 | 0.000 | 35.820 (3.802) | −7,966.87 |
| Full | 23.540 (15.090) | 14.370 (12.400) | 0.147 (0.036) | 0.304 (1.307) | 1.000 | 0.496 (0.260) | 37.470 (5.029) | −7,966.24 |
| Best fit | 34.430 (3.238) | 0.000 | 0.157 (0.035) | 0.000 | 0.000 | 0.000 | 41.030 (2.630) | −7,968.18 |
| | | | | *Pulse rate* | | | | |
| Simplest | 24.500 (3.930) | 18.300 (5.896) | 0.086 (0.038) | 0.000 | 1.000 | 0.000 | 52.620 (5.478) | −8,373.97 |
| Full | 14.230 (21.560) | 26.140 (17.110) | 0.089 (0.038) | 0.215 (0.293) | 1.000 | 0.132 (0.366) | 55.050 (7.651) | −8,373.70 |
| Best fit | 24.500 (3.930) | 18.300 (5.896) | 0.086 (0.038) | 0.000 | 1.000 | 0.000 | 52.620 (5.478) | −8,373.97 |

\* Variance components and the log likelihoods are provided for the simplest, full, and most parsimonious model for each phenotype.
† Numbers in parentheses, standard error. Any estimate without a standard error has been fixed at the designated value.
‡ The full model takes into account the following components: additive genetic ($\sigma_a^2$), shared environment ($\sigma_{se}^2$) and error ($\sigma_e^2$) effects, correlation coefficient between spouse pairs ($\rho_{sp}$), and shared environment coefficients for parent-offspring pairs ($\gamma_{po}$), twin pairs ($\gamma_{tw}$), and nontwin sibling pairs ($\gamma_{sib}$).
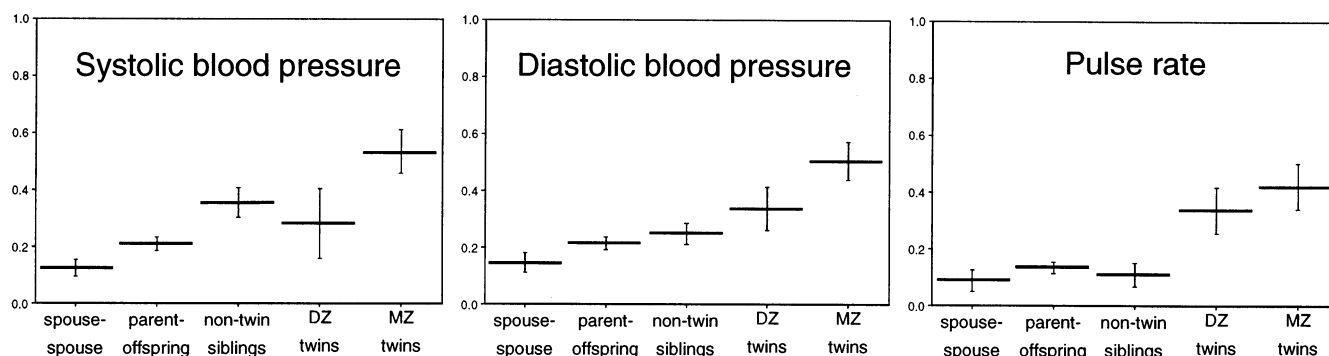
**FIGURE 3.** Correlation coefficients and their standard errors for the following pairs of family members: spouse-spouse, parent-offspring, non-twin siblings, dizygotic (DZ) twins, and monozygotic (MZ) twins for systolic blood pressure (left), diastolic blood pressure (middle), and pulse rate (right), Victorian Family Heart Study, 1990–1996.

spouse correlation was 0.12. If this was all attributed to the within-generation shared environment effect, the genetic component explained 41 percent of variance. If all of the spouse correlation was attributed to assortative mating, the genetic component explained 37 percent of variance.

For diastolic blood pressure, the full model attributed 19 percent of variance to a shared environment effect, which was about half or less within nontwin sibling and parent-offspring pairs than it was within twin pairs, but this effect was not nominally significant. The spouse correlation was 0.16. When the shared environment effect was ignored and the spouse correlation attributed to nongenetic factors, the additive genetic component explained 46 percent of variance. When the spouse correlation was all attributed to assortative mating, this became 42 percent.

For pulse, figure 3 shows that the twin correlations were modest and similar, and there were only weak correlations within nontwin pairs. Table 3 shows that the best-fitting model allowed for a genetic and shared environment component. The latter explained 19 percent of variance but was evident only within twin pairs. The spouse correlation was 0.09. When it was attributed to nongenetic factors, 26 percent of variance

was attributable to additive genetic factors. When it was attributed to assortative mating, this dropped to 24 percent.

**Biochemical risk factors**

Figure 4 shows a pattern in correlations for total cholesterol that is similar to that seen in figure 2 for weight and body mass index. The pattern for high density lipoprotein cholesterol was similar in that monozygotic pairs were highly correlated for both lipid measures. However, there was a clear difference between total and high density lipoprotein cholesterol in the correlation within spouse pairs, being low for total cholesterol but as strong as in first-degree relatives for high density lipoprotein cholesterol.

For total cholesterol, the best-fitting model included both a genetic and shared environment component, the latter being evident only within twin pairs and explaining 15 percent of variance (table 4). The spouse correlation was 0.07; when attributed to nongenetic factors, the genetic variance explained 49 percent of variance, otherwise 46 percent.

For high density lipoprotein cholesterol, the best-fitting model included both a genetic and shared environment com-
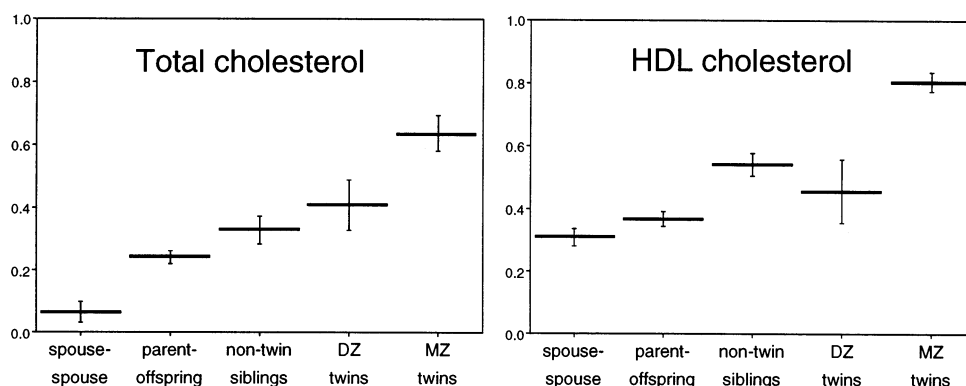


**FIGURE 4.** Correlation coefficients and their standard errors for the following pairs of family members: spouse-spouse, parent-offspring, non-twin siblings, dizygotic (DZ) twins, and monozygotic (MZ) twins for total cholesterol (left) and high density lipoprotein (HDL) cholesterol (right) levels, Victorian Family Heart Study, 1990–1996.

**TABLE 4. Statistical modeling of genetic and environmental components of variance of total and high density lipoprotein cholesterol levels, Victorian Family Heart Study, 1990–1996***

| Model | $\sigma_a^2$ | $\sigma_{ae}^2$ | $\rho_{sp}$ | $\gamma_{po}$ | $\gamma_{tw}$ | $\gamma_{sib}$ | $\sigma_e^2$ | Log likelihood |
|---|---|---|---|---|---|---|---|---|
| *Total cholesterol* | | | | | | | | |
| Simplest | 0.426 (0.040)† | 0.130 (0.047) | 0.070 (0.032) | 0.000 | 1.000 | 0.000 | 0.317 (0.041) | −1,192.74 |
| Full‡ | 0.415 (0.171) | 0.144 (0.150) | 0.064 (0.033) | 0.019 (0.597) | 1.000 | 0.527 (0.310) | 0.318 (0.049) | −1,191.02 |
| Best fit | 0.426 (0.040) | 0.130 (0.047) | 0.070 (0.032) | 0.000 | 1.000 | 0.000 | 0.317 (0.041) | −1,192.74 |
| *High density lipoprotein cholesterol* | | | | | | | | |
| Simplest | 0.143 (0.011) | 0.010 (0.009) | 0.320 (0.026) | 0.000 | 1.000 | 0.000 | 0.037 (0.006) | 1,262.67 |
| Full | 0.110 (0.018) | 0.046 (0.016) | 0.312 (0.027) | 0.349 (0.136) | 1.000 | 1.000 | 0.037 (0.006) | 1,269.26 |
| Best fit | 0.110 (0.018) | 0.046 (0.016) | 0.312 (0.027) | 0.349 (0.136) | 1.000 | 1.000 | 0.037 (0.006) | 1,269.26 |

* Variance components and the log likelihoods are provided for the simplest, full, and most parsimonious model for each phenotype.

† Numbers in parentheses, standard error. Any estimate without a standard error has been fixed at the designated value.

‡ The full model takes into account the following components: additive genetic ($\sigma_a^2$), shared environment ($\sigma_{se}^2$) and error ($\sigma_e^2$) effects, correlation coefficient between spouse pairs ($\rho_{sp}$), and shared environment coefficients for parent-offspring pairs ($\gamma_{po}$), twin pairs ($\gamma_{tw}$), and nontwin sibling pairs ($\gamma_{sib}$).

ponent. The latter effect explained 24 percent of variance and was the same within sibling pairs, whether or not they were twins, and about one third as strong within parent-offspring pairs. The spouse correlation was 0.31; when attributed to nongenetic factors, the genetic variance explained 57 percent of variance, otherwise 43 percent.

## DISCUSSION

The Victorian Family Heart Study provides an opportunity for informative analyses of the genetic and environmental components of variance of major cardiovascular risk factors in the general adult population. Certain features of the research design are noteworthy. Unlike many other family studies of cardiovascular risk, both parents and offspring were adult. As a result, we avoided the effects of normal growth and maturation on the ranking of the anthropometric, hemodynamic, and biochemical variables under consideration. Furthermore, most offspring were living independently of their parents, and of one another, at the time of the study. As such, the effects attributed to environmental factors shared by family members must reflect behaviors and lifestyles that occurred when parents and children cohabited. That we found evidence for these effects during independent adult life suggests that there must have been periods in early life during which the family environment cemented long-term correlations between relatives in cardiovascular risk factors. Therefore, although our study as yet contains no longitudinal follow-up, it allows certain inferences to be made about the persistent effects of early family environment.

The study families were volunteers and not randomly selected. However, we made special efforts to attract a representative sample of families by avoiding oversampling of families with heart disease. In brochures and correspondence given to potential families, we wrote, "Even if you come from a family where heart disease is virtually unknown, your help is just as important." The fact that the distribution and mean values for the eight phenotypes were similar to those found by other recent regional population surveys, such as the 1990 National Heart Foundation Risk Factor Prevalence Survey (31), suggests that analyses of our study sample will not yield biased estimates.

The Victorian Family Heart Study is unusual in the way in which twins were included. The Australian Twin Registry was used not to select twin pairs per se but to ascertain families. As such, twins are included as single individuals or as pairs, together with any studied relatives, whether they were in the preceding, same, or succeeding generation; see figure 1. The multivariate normal model is able to handle such nonregular data. On average, twins showed minor differences from the remainder of the participants (data not shown). They were more often female, but the analyses used data adjusted for sex differences. In the offspring generation, twins were of slightly smaller physical build. In both generations, twins showed no differences in total cholesterol, high density lipoprotein cholesterol, or pulse rate. Twins in the offspring generation had blood pressures on average 2 mmHg less than did nontwin offspring. These comparisons suggest that selection of twins in this study has

not been associated with substantial bias, and their inclusion in the general population sample has not created important distortion of phenotype distributions.

The informativeness of the Victorian Family Heart Study for disentangling the effects of shared genes from those of shared environment during cohabitation has been enhanced by including families containing monozygotic or dizygotic twins, either as parents or as offspring. Figure 1 shows that, in families where there are twin pairs and nontwin siblings in the offspring generation, combinations include twin-twin pairs (which may differ by zygosity), twin-sibling pairs, and sibling-sibling pairs. Although exposed to the same family environment, the sibling-sibling pairs are not subject to any within-twin pair environmental effects. In those where there are twin pairs in the parental generation, their offspring are genetically related as first or second degree relatives, depending on whether the twin pair is monozygotic or dizygotic, yet presumably they have not been raised in the same familial environment. The method of statistical analysis that we have used is capable of maximizing the information contained in all these contrasts.

Statistical analyses showed that, for all of the phenotypes examined in this study, there was evidence of both genetic and shared environmental components of variance. However, the balance of these two components differed between phenotypes. Furthermore, the design permitted analysis of the relative importance of shared environment between different types of relative pairs within families. These environmental patterns within families differed between phenotypes. The cardiovascular risk factors also differed in the proportion of variance that could be ascribed to individual variation, which included measurement error. Consistent with the hemodynamic variables being inherently unstable, these showed the greatest individual-specific variance.

The anthropometric variables showed interesting and contrasting patterns. For height, the correlations in figure 2 across the different categories of first-degree relatives were similar, consistent with the classic description dating back more than 80 years (28) of familial covariation in height being mostly due to genetic factors. For weight and body mass index, however, correlations between first-degree relatives varied considerably. This immediately suggests a role for shared environmental factors that determine body size, such as diet and exercise. Our study suggests that such factors have an effect during childhood and adolescence and that their legacy persists in adulthood, at least to age 30. The same pattern of correlations across first-degree pairs is more or less evident for all of the other risk factors considered here. Modeling suggested that the variance attributed to those past shared family environmental effects varied from almost 40 percent for body mass index to being small and not nominally significant for diastolic blood pressure. Most phenotypes had a variance component for shared environment that explained in the range of 10 percent to just over 20 percent of age- and sex-adjusted variance.

Although derived from weight and height, body mass index showed a smaller proportion of variance attributed to additive genetic factors. This is consistent with at least one

other study (32). It is likely that the high genetic component of variance for weight is the result of its covariation with height, an influence lost when adjusting for height in the calculation of body mass index.

It was also consistently observed that the correlation within monozygotic pairs was greater than within dizygotic pairs and other first-degree relatives. This is compatible with a role for genetic factors, under the assumption that the effect within twin pairs of shared environmental factors specific to the trait in question is independent of zygosity. We have not been able to make a formal test of this critical assumption. We have, however, been able to consider how the environmental effect shared within nontwin pairs and parent-offspring pairs compared with that within twin pairs. For some traits, such as height, systolic blood pressure, and high density lipoprotein cholesterol, all sibling pairs appear to have shared such environmental effects to the same extent while, for the others, the effects within nontwin sibling pairs were greatly reduced or nonexistent. An effect of shared environment within parent-offspring pairs was usually nonexistent or weak compared with that within sibling pairs.

The evidence for a substantial genetic contribution to variance of systolic and diastolic blood pressure is consistent with previous analyses (33–39). However, the apparent absence of an influence of a persisting effect of shared environmental factors on diastolic blood pressure contrasted with the findings for systolic blood pressure and with other published data regarding diastolic blood pressure. The reason for this discrepancy is unclear and may be a consequence of lack of power to detect a small effect. Using the standard error of $\sigma_{se}^2$ in the full model, we estimate that we had 80 percent power at $\alpha = 0.05$ to detect an effect of shared environment of 40 percent or more for diastolic pressure. However, it is consistent with one other study that also found no evidence for an effect of shared environment on diastolic blood pressure in a Greece-Australia migrant and nonmigrant family study (40). Different patterns for systolic and diastolic pressure may reflect physiologic differences in the determination of the two pressures and their differences in natural history (41) and effects on cardiovascular risk (42).

For all cardiovascular risk factors, spouse pairs were correlated, although this varied from about 0.1 for pulse and total cholesterol up to about 0.3 for high density lipoprotein cholesterol and 0.4 for height. As spouse pairing usually takes place after linear growth has ceased, the strong correlation for height almost surely represents the result of assortative mating (i.e., people tend to marry someone of a similar height, even within a population). The spouse correlation for age- and sex-adjusted height was almost as high as the correlation between first-degree relatives. In contrast, it is not as biologically plausible that the moderate spouse correlations in covert phenotypes such as high density lipoprotein cholesterol, for example, could be attributed to assortative mating. The spouse correlation for high density lipoprotein cholesterol should, therefore, be more appropriately attributed to the shared marital environment. Further support for this comes from the modeling of first-degree relatives, which suggested a role for the shared environment that

explained almost one quarter of variance and was as high in nontwin sibling pairs as in twin pairs and was also evident in parent-offspring pairs.

The contrast between total and high density lipoprotein cholesterol is interesting. Previously reported estimates of "heritability" (i.e., the percentage of total variance attributed to the genetic component of variance (43)) for total cholesterol and high density lipoprotein cholesterol have generally been about 40–60 percent, with no consistent difference (44–50). The cultural and environmental influences, however, have consistently been higher for high density lipoprotein cholesterol than for total cholesterol (36, 45, 47–50). Our observation, that for total cholesterol the spouse correlation was weaker and the shared environment explained less variance and was restricted to twin pairs only, is consistent with a greater role for family environmental and lifestyle factors for high density lipoprotein cholesterol than for total cholesterol. It had been suggested that the rearing environment has persistent effects on total but not on high density lipoprotein cholesterol (51), consistent with a short-term effect of environment on high density lipoprotein cholesterol. However, our data suggest that early environmental effects on high density lipoprotein cholesterol may persist. Furthermore, the moderate spouse correlation could be due to current and recent cohabitation. High density lipoprotein cholesterol is known to be modified by lifestyle factors (52–54), such as alcohol, cigarette smoking, and exercise, and the continued sharing of these activities in the parental environment may explain the spouse correlation for couples aged 40 and 70 years. Nevertheless, the responses in high density lipoprotein cholesterol to environmental factors may vary between individuals, and this may be due to genetic factors (55, 56).

If a trait has genetic variance and there is also assortative mating, the offspring will be genetically more similar to one another than if there is no assortative mating. The effect will depend on the amount of variance attributed to genetic factors and the observed correlation between spouse pairs. Because we have data only on spouse pairs who have presumably known each other for two decades or more, it is difficult to assign a cause to an observed spouse correlation. Previous longitudinal studies of cardiovascular risk factors have found inconsistent trends in the spouse correlation in relation to the duration of marriage (13, 57). Over time, correlations appeared to weaken for blood pressure and body mass index but strengthened for total cholesterol. However, in those studies, the small magnitude of changes in spouse correlations would favor assortative mating, rather than cohabitation, as the more plausible explanation. Nevertheless, in our analyses we found (other than for height) that there was little change in the estimates of genetic variance, irrespective of whether spouse correlation was attributed to assortative mating or not.

In summary, the genetic and environmental architecture of cardiovascular risk factors is apparently not uniform across traits, even those physiologically related such as the blood pressure and cholesterol measures. Although genetic factors have a substantial impact, we also found that the environment shared during upbringing can have persistent effects into early adulthood. It should be noted that our results were derived from a relatively homogeneous population and, therefore, cannot be extrapolated without verification to other racial or geographic groups.

These analyses were of individual traits, however, and did not systematically examine the intercorrelation between individual phenotypes and its impact on trait-specific and trait-shared variance components. Because certain cardiovascular risk factors are known to aggregate, future analyses of these data will consider multiples of risk factors together, in order to establish if there are substantial genetic or shared environmental components that influence and, hence, help to define clusters of risk factors (32, 58).

## REFERENCES

1. Brand FN, Kiely DK, Kannel WB, et al. Family patterns of coronary heart disease mortality: the Framingham Longevity Study. J Clin Epidemiol 1992;45:169–74.
2. Snowden CB, McNamara PM, Garrison RJ, et al. Predicting coronary heart disease in siblings—a multivariate assessment: the Framingham Heart Study. Am J Epidemiol 1982;115: 217–22.
3. Hopper JL, Carlin JB. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. Am J Epidemiol 1992;136: 1138–47.
4. Hebert PR, Rich-Edwards JW, Manson JE, et al. Height and incidence of cardiovascular disease in male physicians. Circulation 1993;88:1437–43.
5. Rich-Edwards JW, Manson JE, Stampfer MJ, et al. Height and the risk of cardiovascular disease in women. Am J Epidemiol 1995;142:909–17.
6. Longini IM Jr, Higgins MW, Hinton PC, et al. Genetic and environmental sources of familial aggregation of body mass in Tecumseh, Michigan. Hum Biol 1984;56:733–57.
7. Moll PP, Burns TL, Lauer RM. The genetic and environmental sources of body mass index variability: the Muscatine Ponderosity Family Study. Am J Hum Genet 1991;49:1243–55.

8. Friedlander Y, Kark JD, Kaufmann NA, et al. Familial aggregation of body mass index in ethnically diverse families in Jerusalem. The Jerusalem Lipid Research Clinic. Int J Obes 1988;12:237–47.
9. Wilson PW, Abbott RD, Castelli WP. High density lipoprotein cholesterol and mortality. The Framingham Heart Study. Arteriosclerosis 1988;8:737–41.
10. Sosenko JM, Breslow JL, Ellison RC, et al. Familial aggregation of total cholesterol, high density lipoprotein cholesterol, and total triglyceride levels in plasma. Am J Epidemiol 1980;112:656–60.
11. Beaty TH, Self SG, Chase GA, et al. Assessment of variance components models on pedigrees using cholesterol, low-density, and high-density lipoprotein measurements. Am J Med Genet 1983;16:117–29.
12. Wannamethee SG, Whincup PH, Shaper G, et al. Influence of fathers' social class on cardiovascular disease in middle-aged men. Lancet 1996;348:1259–63.
13. Knuiman MW, Divitini ML, Welborn TA, et al. Familial correlations, cohabitation effects, and heritability for cardiovascular risk factors. Ann Epidemiol 1996;6:188–94.
14. Annest JL, Sing CF, Biron P, et al. Familial aggregation of blood pressure and weight in adoptive families. I. Comparisons of blood pressure and weight statistics among families with adopted, natural, or both natural and adopted children. Am J Epidemiol 1979;110:479–91.
15. Feinleib M, Garrison RJ, Fabsitz R, et al. The NHLBI twin study of cardiovascular disease risk factors: methodology and summary of results. Am J Epidemiol 1977;106:284–5.
16. Austin MA, King MC, Bawol RD, et al. Risk factors for coronary heart disease in adult female twins. Genetic heritability and shared environmental influences. Am J Epidemiol 1987;125:308–18.
17. Williams RR, Hunt SC. Recruitment of members of high-risk Utah pedigrees. Control Clin Trials 1987;8:105s–14s.
18. Mongeau JG, Biron P, Sing CF. The influence of genetics and household environment upon the variability of normal blood pressure: the Montreal Adoption Survey. Clin Exp Hypertens A 1986;8:653–60.
19. Sorensen TI, Price RA, Stunkard AJ, et al. Genetics of obesity in adult adoptees and their biological siblings. BMJ 1989;298:87–90.
20. Stunkard AJ, Harris JR, Pedersen NL, et al. The body-mass index of twins who have been reared apart. N Engl J Med 1990;322:1483–7.
21. Hanis CL, Chakraborty R. Nonrandom sampling in human genetics: familial correlations. IMA J Math Appl Med Biol 1984;1:193–213.
22. Lange HJ, Reiter R. Data reduction in the evaluation of multivariate epidemiological studies. Methods Inf Med 1972;11:253–7.
23. Hopper JL, Mathews JD. Extensions to multivariate normal models for pedigree analysis. Ann Hum Genet 1982;46:373–83.
24. Hopper JL, Green RM, Nowson CA, et al. Genetic, common environment, and individual specific components of variance for bone mineral density in 10- to 26-year-old females: a twin study. Am J Epidemiol 1998;147:17–29.
25. Hopper JL, Mathews JD. Extensions to multivariate normal models for pedigree analysis. II. Modeling the effects of shared environment on the analysis of variation of blood lead levels. Am J Epidemiol 1983;117:344–55.
26. Hopper JL, Mathews JD. A multivariate normal model for pedigree and longitudinal data and the software "FISHER." Aust J Statist 1994;36:153–76.
27. Lange K, Boehnke M, Weeks D. Programs for pedigree analysis. Los Angeles, CA: Department of Biomathematics, University of California, 1987.
28. Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance. Trans R Soc Edin 1918;52:399–433.
29. Hopper JL. Genetic correlations and covariance. In: Encyclopedia of biostatistics. London, UK: John Wiley & Sons, 1998:1669–76.
30. Hopper JL. Twin concordance. In: Encyclopedia of biostatistics. London, UK: John Wiley & Sons, 1998:4626–9.
31. Committee RFPSM. Risk Factor Prevalence Study: survey no. 3 1989. Canberra, Australia: National Heart Foundation of Australia and Australian Institute of Health, 1990.
32. Annest JL, Sing CF, Biron P, et al. Familial aggregation of blood pressure and weight in adoptive families. III. Analysis of the role of shared genes and shared household environment in explaining family resemblance for height, weight, and selected weight/height indices. Am J Epidemiol 1983;117:492–506.
33. Tambs K, Moum T, Holmen J, et al. Genetic and environmental effects on blood pressure in a Norwegian sample. Genet Epidemiol 1992;9:11–26.
34. Annest JL, Sing CF, Biron P, et al. Familial aggregation of blood pressure and weight in adoptive families. II. Estimation of the relative contributions of genetic and common environmental factors to blood pressure correlations between family members. Am J Epidemiol 1979;110:492–503.
35. Havlik RJ, Garrison RJ, Feinleib M, et al. Blood pressure aggregation in families. Am J Epidemiol 1979;110:304–12.
36. Hunt SC, Hasstedt SJ, Kuida H, et al. Genetic heritability and common environmental components of resting and stressed blood pressures, lipids, and body mass index in Utah pedigrees and twins. Am J Epidemiol 1989;129:625–38.
37. Longini IM Jr, Higgins MW, Hinton PC, et al. Environmental and genetic sources of familial aggregation of blood pressure in Tecumseh, Michigan. Am J Epidemiol 1984;120:131–44.
38. Moll PP, Harburg E, Burns TL, et al. Heredity, stress and blood pressure, a family set approach: the Detroit Project revisited. J Chronic Dis 1983;36:317–28.
39. Mongeau JG. Heredity and blood pressure. Semin Nephrol 1989;9:208–16.
40. Hopper JL, Macaskill G, Powles JG, et al. Pedigree analysis of blood pressure in subjects from rural Greece and relatives who migrated to Melbourne, Australia. Genet Epidemiol 1992;9:225–38.
41. Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96:308–15.
42. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. Arch Intern Med 1993;153:598–615.
43. Hopper JL. Heritability. In: Encyclopedia of biostatistics. London, UK: John Wiley & Sons, 1998:1905–6.
44. Perusse L, Rice T, Despres JP, et al. Familial resemblance of plasma lipids, lipoproteins and postheparin lipoprotein and hepatic lipases in the HERITAGE Family Study. Arterioscler Thromb Vasc Biol 1997;17:3263–9.
45. Brenn T. Genetic and environmental effects on coronary heart disease risk factors in northern Norway. The cardiovascular disease study in Finnmark. Ann Hum Genet 1994;58:369–79.
46. Steinmetz J, Boerwinkle E, Gueguen R, et al. Multivariate genetic analysis of high density lipoprotein particles. Atherosclerosis 1992;92:219–27.
47. Rice T, Vogler GP, Perry TS, et al. Familial aggregation of lipids and lipoproteins in families ascertained through random and nonrandom probands in the Iowa Lipid Research Clinics family study. Hum Hered 1991;41:107–21.
48. Bucher KD, Friedlander Y, Kaplan EB, et al. Biological and cultural sources of familial resemblance in plasma lipids: a comparison between North America and Israel—the Lipid Research Clinics Program. Genet Epidemiol 1988;5:17–33.
49. Namboodiri KK, Kaplan EB, Heuch I, et al. The Collaborative Lipid Research Clinics Family Study: biological and cultural determinants of familial resemblance for plasma lipids and lipoproteins. Genet Epidemiol 1985;2:227–54.
50. Dahlen G, Ericson C, de Faire U, et al. Genetic and environmental determinants of cholesterol and high density lipoprotein cholesterol concentrations in blood. Int J Epidemiol 1983;12:32–5.
51. Kervinen K, Kaprio J, Koskenvuo M, et al. Serum lipids and apolipoprotein E phenotypes in identical twins reared apart. Clin Genet 1998;53:191–9.

52. Gartside PS, Khoury P, Glueck CJ. Determinants of high-density lipoprotein cholesterol in Blacks and Whites: the Second National Health and Nutrition Examination Survey. Am Heart J 1984;108:641–53.

53. Haertel U, Heiss G, Filipiak B, et al. Cross-sectional and longitudinal associations between high density lipoprotein cholesterol and women's employment. Am J Epidemiol 1992;135:68–78.

54. Verdery RB, Walford RL. Changes in plasma lipids and lipoproteins in humans during a 2-year period of dietary restriction in biosphere 2. Arch Intern Med 1998;158:900–6.

55. Fumeron F, Betoulle D, Luc G, et al. Alcohol intake modulates the effect of a polymorphism of the cholesteryl ester transfer protein gene on plasma high density lipoprotein and the risk of myocardial infarction. J Clin Invest 1995;96:1664–71.

56. Sigurdsson G Jr, Gudnason V, Sigurdsson G, et al. Interaction between a polymorphism of the apo A-I promoter region and smoking determines plasma levels of HDL and apo A-I. Arterioscler Thromb 1992;12:1017–22.

57. Knuiman MW, Divitini ML, Bartholomew HC, et al. Spouse correlations in cardiovascular risk factors and the effect of marriage duration. Am J Epidemiol 1996;143:48–53.

58. Perusse L, Rice T, Despres JP, et al. Cross-trait familial resemblance for body fat and blood lipids: familial correlations in the Quebec Family Study. Arterioscler Thromb Vasc Biol 1997;17:3270–7.