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Familial and Individual Influences on Blood Pressure

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Abstract. Although familial aggregation of blood pressure is well documented, few studies have considered the changing contribution of genetic and environmental influences during adulthood. Applying maximum likelihood model fitting to blood pressure covariation in balanced pedigrees including both parents and their young adult twin offsprings (25 MZ, 32 DZ, aged between 16 and 24 years), it is shown that the increased variation in parents is explained by such developmental changes. For DBP, an apparent reduction in heritability from 68% to 38% from young adulthood to middle age results from the increasing impact of individual environmental experience (E_1), with little or no influence from shared family environmental (E_2). For SBP, shared environmental effects may play a part. Given the relatively small size of the present sample, the conclusions are to be seen as tentative. An augmented family study, incorporating middle aged twins and their young adult offspring, will clarify the causation of these developmental changes.

Key words: Blood pressure, Family study, Familial aggregation, Age, Model fitting, Hypertension

INTRODUCTION

Epidemiological evidence has implicated family history as a significant risk factor in

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essential hypertension. Blood pressure levels show marked familial aggregation [1,8, 14,15,22,35]. Offspring of hypertensive parents are more likely to develop essential hypertension as adults than are the children of normotensives [26,27].

Of course, not all those with a positive family history will become hypertensive, and other risk factors, such as weight, race and personality, have been implicated [13]. For example, it has been hypothesized that transient elevations of blood pressure due to experience of stressful life events, eg, social and occupational stress, may, in time, lead to the development of essential hypertension [25].

Manuck suggested that heart rate reactivity could be used to determine a predisposition to hypertension by virtue of its covariation with resting blood pressure [21]. Other workers have shown a link between heart rate reactivity and a parental history of hypertension [3,7,10,12] in young normotensive adults. However, initial blood pressure levels are the strongest single predictors of future hypertension [17,28]. For most people, the BP in early adulthood is a reliable index of that which will be seen over the adult years [4,19].

The objective of this paper is to illustrate various plausible models to account for variations in blood pressure in young and middle-aged adults. It is hoped that these will usefully supplement the information from simple models of heritability by discerning not the genetic but also the environmental contributions to the development of future hypertension. Such alternative models may blind us nearer to identifying highly susceptible individuals, so that early intervention can be carried out to control hypertension development.

By using a twin study technique, the relative importance of genetic and environmental factors could be determined. Twin studies have been widely used to investigate psychological and biomedical phenotypes [16,23,24]. Although twin studies have their limitations [6,18], they do provide an opportunity to separate some of the constitutional and environmental factors in the etiology of disorders such as hypertension. Importantly, in the current study we were able to assess developmental changes by recording blood pressures in both parents and their offspring. Using this augmented family study technique, comparison could be made across generations.

Genetic and Environmental Models for Blood Pressure

DBP. For any particular individual, the DBP, the lowest arterial pressure during the cardiac cycle, will be influenced by the period of the cardiac cycle (pulse or heart rate), the speed of transfer of arterial blood to the veins, which will be affected by vascular resistance, and the plasma volume. The relative influence of these factors may change so that, while heart rate may be an important determinant of short-term changes in young adults, increased vascular resistance and alterations in renal fluid retention mechanisms may be of greater importance in middle age [25].

SBP. The systolic blood pressure equates to the period of peak ejection in the cardiac cycle. Two main factors can influence the systolic blood pressure level, vascular resistance and myocardial contractility. As with DBP, vascular resistance acts in a like manner – the higher the resistance, the higher the SBP. Myocardial contractility effects the SBP via the mediation of extrinsic and intrinsic neurohumoral mechanisms upon myocardial performance. The volume of blood pumped per unit time and its interaction with vascular resistance and cardiac contractility determines the pressure reached for

both systolic and diastolic pressure.

Our dependent measure, BP, is an index of the interactions between these interrelated mechanisms. It is highly unlikely, a priori, that variation in such an index will be accounted for by a simple determinant such as a major Mendelian gene or a straightforward environmental variable involving only diet or life style. Nevertheless, by fitting genetic and environmental models to the observed variation between individuals, we can determine the relative importance of different types of causes and we can eliminate some hypotheses as being inadequate. Equally important in the prevention of pathological outcomes is a consideration of the patterns and degree of relationship between BP variation in young adults and the apparently greater variation (some of it pathological) in middle age. With our data structure we can begin to investigate this.

METHOD

Subjects

Initially 40 pairs of monozygotic and 40 pairs of dizygotic healthy male twins were obtained from the population-based Birmingham Family Study Register. From these, 57 complete families were interviewed (father and mother both available for testing) comprising 25 MZ twin families and 32 DZ twin families. All the twins were aged between 16 and 24 years (mean age 19.3 ± 2.5 years) and their parents were middle aged (mothers' mean age = 49.7 ± 5.9 years; fathers' mean age = 51.9 ± 6.2 years). All lived in the West Midlands area.

Procedure and Apparatus

Blood pressure readings were taken as part of the overall testing session. The details of the psychophysiological testing have been reported elsewhere [3]. The testing protocol required the subjects to refrain from smoking, physical exercise and drinking tea, coffee or alcohol for one hour preceding the session, as such factors are know to influence heart rate and blood pressure.

An initial BP measurement, based on the average of two readings, was recorded for each twin by a trained observer. A standard sphygmomanometer and stethoscope were used. The cuff was placed on the left arm over the brachial artery with the subject in a seated position.

One twin then completed questionnaires to provide information about his general health and lifestyle. Meanwhile, his brother underwent psychophysiological testing. Order of testing had previously been decided by a flip of a coin.

After both twins had completed the questionnaires and psychophysiological testing, a final blood pressure measure was recorded in the same manner as above.

Home Visits

Wherever possible, a researcher (JS) visited the twins' parents in their homes. On each visit, blood pressure measurements were taken initially and at the conclusion of the visit. Blood pressure was measured in both the twins and their parents by the same researcher (JS). The parents completed the same questionnaires as those given to the

twins. Details of drug treatment were taken; where individuals were currently receiving hypertensive medication, they were classified as having a blood pressure of 150/90 mmHg for the purposes of analysis. (This was applicable for one mother of MZ twins and 4 mothers and 2 fathers of DZ twins). This procedure was carried out because the medication could possibly have lowered actual blood pressure readings.

RESULTS

Analytical Discussion

Analysing individual differences in blood pressure

Diastolic and systolic pressures are continuous variables which are distributed unimodally for a given age, race and sex and for which the categories of "hypertensive" and "normotensive" designate values above and below arbitrary thresholds [8,33]. Although therapeutic intervention to lower the BP is often consequent on exceeding these thresholds (which themselves may depend on age, sex and race), the risk of mortality or of nonfatal cardiovascular disease is positively and linearly related to BP across a wide range of values for every age group [13,20,31]. It is thus more appropriate and efficient to consider individual differences in the continuous variation, than it is to use categorical data based on medical diagnoses of hypertension.

Our basic data are direct individual assessments of BP in young adult MZ and DZ twins and both of their middle aged parents. We can take as our starting point for the analyses of these balanced pedigrees the variance-covariance matrix for each family type [6]. These are given in Tables 1 and 2 along with the correlations between the different relationships within the pedigrees. It is clear from the considerably greater variances in the parents, that attempts to explain only the standardised correlations between relatives may lead to an unrealistically oversimplified description of the determinants of variation in BP, one which does not take account of intergenerational

Table 1. Covariance and Correlation Matrices* for Diastolic Pressure

	First born twin	Second born twin	Mother	Father
MZ Twins	(N = 25 families)			
First born twin	90.9350	0.8520	0.0990	0.1100
Second born twin	77.8617	91.8733	0.1980	0.2390
Mother	9.4888	19.0963	100.7567	-0.0770
Father	10.7413	23.5992	-7.9092	105.7975
DZ Twins	(N = 32 families)			
First born twin	44.0796	0.3810	0.2120	0.3690
Second born twin	13.1477	26.9695	0.0210	0.4270
Mother	13.0948	1.0050	86.3508	0.0250
Father	26.7117	24.1522	2.5121	118.8347

* Variances are given on the leading diagonal of each of the two 4 × 4 matrices, covariances in the lower triangle, and correlations in the upper off-diagonal entries.

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Table 2. Covariance and Correlation Matrices* for Systolic Blood Pressure

	First born twin	Second born twin	Mother	Father
MZ Twins	(N = 25 families)			
First born twin	98.9150	0.6590	0.2120	0.1230
Second born twin	66.6592	103.3100	0.2550	0.0430
Mother	36.5233	44.8238	299.5275	-0.0160
Father	18.4871	6.6554	4.1317	229.4858
DZ Twins	(N = 32 families)			
First born twin	134.2760	0.2910	0.1200	0.2530
Second born twin	33.6951	99.7732	0.3040	0.3630
Mother	24.9695	54.1305	317.0985	0.1300
Father	59.5819	74.1739	47.4771	418.1368

* Variances are given on the leading diagonal of each of the two 4 × 4 matrices, covariances in the lower triangle, and correlations in the upper off-diagonal entries.

or developmental changes in the genetic and environmental influences on BP.

The variability between the parents is markedly greater than that of the offspring in our samples. Variances in the parents are 1.6 and 2.9 times those for the offspring for DBP and SBP, respectively. However, the mean BPs given in Table 3 show that this

Table 3. Mean Systolic and Diastolic Blood Pressures in MZ and DZ Twins and Their Parents

	MZ twins (N=25)		DZ twins (N=32)		Total sample (N=57)	
Variable	Mean SBP	Mean DBP	Mean SBP	Mean DBP	Mean SBP	Mean DBP
First born twin	121.46	78.82	124,92	80.47	123.40	79.75
Second born twin	118.82	77.54	121.72	78.58	120.45	78.12
Mother	123.82	83.84	121.55	81.31	122.55	82.42
Father	130.44	86.62	133.80	87.42	132.33	87.07

increase in variability is not a simple scalar effect associated with the higher BPs of the parents as the mean maternal BPs are similar to their sons' and the elevation in the fathers mean is only about 10%. Such a marked and nonscalar increase in population variation is overlooked by traditional correlational analyses even though it may provide important information about developmental changes [32].

Although usually hidden by an armoury of data standardisation techniques, where unstandardised data have been published, similar age related trends in population variance are found. For example, Harburg et al [11] report SBP population variance

increasing from 121, at age 25-29 years, to 388 at age 50-59 years in males, and from 172 to 449 in females. For DBP, the increases are smaller: from 77 to 119 in males and from 77 to 135 for females. De Faire et al [5] report a variance of 148 at mean age of 26.9 years, compared with 484 in females of $\bar{X}$ 54.6 years and males 412 at $\bar{X}$ 56.6 years. (Again, the increases are smaller for DBP).

In the Blood Pressure Study [31], variance does not appear to increase with age but this is probably because these data exclude those rejected by life insurance schemes due to the presence of high blood pressure. The inclusion of such individuals would considerably increase the variance of the older age groups. This is confirmed by the HANES study [29] data, which used a representative sample of individuals aged 18-74 years.

Our approach to these data is to consider a series of alternative hypotheses to account for the patterns of variation and covariation between relatives. We proceed from the most parsimonious hypotheses through to more complex hypotheses, rejecting the more parsimonious hypotheses when they are shown to be statistically inadequate to account for our observations. As we consider models with 3 or more parameters, the variety of plausible models which are equally parsimonious increases considerably, and we are inevitably left with a set of alternative explanations. This is especially so when the data are limited, both in structure and in number. Nevertheless, specifying these explanations helps to identify the additional data needed to discriminate more clearly between the alternatives.

For each measure of BP we have 10 statistics (4 variances and 6 covariances) for each of the two family types. These 20 observed statistics may be written into the two observation matrices $S_i (i = 1,2)$, corresponding to Tables 1 and 2. Each matrix is associated with N_i degrees of freedom depending on the number of families contributing to the data. For any particular hypothesis or model, to account for the observations we will derive two matrices of expected variances and covariances i $(i = 1,2)$. Following the procedures outlined by Eaves et al [6] we may arrive at maximum likelihood estimates of the parameters in our model by maximising:

$$L = -\frac{1}{2} \sum_{i=1}^{i=2} N_i \left[\ln|\Sigma_i| + t\mu(S_i \Sigma_i^{-1})\right] + \text{constant}$$

The programme was developed for this purpose by L. Eaves & P. Young and updated for the use of subroutine E04 UAF from the Numerical Algorithms Group (NAG, 1984) by K. Kelly & P. Raynor, which allows for constrained and nonlinear minimization. Standard errors for the parameter estimates are derived numerically and the adequacy of any particular model, involving P parameters and with likelihood L_1, may be tested by a chi-square test:

$$\chi^2 = 2(L_0 - L_1) \text{ for 20-p degrees of freedom,}$$

where

$$L_0 = -\frac{1}{2} \sum_{i=1}^{i=2} N_i \left[\ln|S_i| + V_i\right] = \text{constant}$$

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(V_i is the order of the ith matrix which is 4 for each in our case). The simplified summary output from this procedure will comprise the estimates of the parameters in the model together with their standard errors, the χ^2 goodness of fit statistics for the model, the degrees of freedom and the probability of observing the data given the model and parameter estimates.

Analysis of Models

A. Is there familial aggregation of BP?

DBP. Although familial aggregation is well documented, for any particular set of data we ought to examine our ability to reject a null hypothesis. In Table 4, the simplest possible null hypothesis is given in Model I. Here, all variation is attributed to idiosyncratic individual environmental effects (E_1). These are not shared by family members either as offspring during development (E_2, developmental) or culturally by the family as a whole (E_2, family) as, for example, might be the case for a method of food preparation associated with the transmitted values of a social class or of a religion. There is no assortative mating and no genetic influence. Furthermore, in Model I the population variance is assumed to be equivalent for offspring and for parents. In Model V, also

Table 4. Specification of One and Two Parameter Models for Twins and Their Parents

Model	df		Variance-covariance expectations*			
			Twin 1	Twin 2	Mother	Father
I. E_1	19	Twin 1	E_1	0	0	0
		Twin 2	0	E_1	0	0
		Mother	0	0	E_1	0
		Father	0	0	0	E_1
II. E_1,D_R	18	Twin 1	$E_1+1/2D_R$	$1/2D_R$	$1/4D_R$	$1/4D_R$
		Twin 2	$1/4D_R$	$E_1+1/2D_R$	$1/4D_R$	$1/4D_R$
		Mother	$1/4D_R$	$1/4D_R$	$E_1+1/2D_R$	0
		Father	$1/4D_R$	$1/4D_R$	0	$E_1+1/2D_R$
III. E_1,E_2 (developmental)	18	Twin 1	E_1+E_2	E_2	0	0
		Twin 2	E_2	E_1+E_2	0	0
		Mother	0	0	E_1+E_2	0
		Father	0	0	0	E_1+E_2
IV. E_1,E_2 (family)	18	Twin 1	E_1+E_2	E_2	E_2	E_2
		Twin 2	E_2	E_1+E_2	E_2	E_2
		Mother	E_2	E_2	E_1+E_2	E_2
		Father	E_2	E_2	E_2	E_1+E_2
V. E_1 (twins), E_1 (parents)	18	Twin 1	E_{1t}	0	0	0
		Twin 2	0	E_{1t}	0	0
		Mother	0	0	E_{1p}	0
		Father	0	0	0	E_{1p}

* Upper triangles give specifications for MZ twins, lower triangles for DZ twins. Definitions of parameters are given in the text.

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Table 5. Specification of Three Parameter Models for Twins and Their Parents

Model	df		Variance-covariance expectations*			
			Twin 1	Twin 2	Mother	Father
VI. E_1(twins), E_1(parents), D_R	17	Twin 1	$E_{1t}+1/2D_R$	$1/2D_R$	$1/4D_R$	$1/4D_R$
		Twin 2	$1/4D_R$	$E_{1t}+1/2D_R$	$1/4D_R$	$1/4D_R$
		Mother	$1/4D_R$	$1/4D_R$	$E_{1p}+1/2D_R$	0
		Father	$1/4D_R$	$1/4D_R$	0	$E_{1p}+1/2D_R$
VII. E_1(twins), E_1(parents) E_2(developmental)	17	Twin 1	$E_{1t}+E_2$	E_2	0	0
		Twin 2	E_2	$E_{1t}+E_2$	0	0
		Mother	0	0	$E_{1p}+E_2$	0
		Father	0	0	0	$E_{1p}+E_2$
VIII. E_1(twins), E_1(parents) E_2(family)	17	Twin 1	$E_{1t}+E_2$	E_2	E_2	E_2
		Twin 2	E_2	$E_{1t}+E_2$	E_2	E_2
		Mother	E_2	E_2	$E_{1p}+E_2$	E_2
		Father	E_2	E_2	E_2	$E_{1p}+E_2$
IX. E_1, D_R(twins), D_R(parents), D_R(tp covariance)	16	Twin 1	$E_1+1/2D_{Rt}$	$1/2D_{Rt}$	$1/4D_{Rtp}$	$1/4D_{Rtp}$
		Twin 2	$1/4D_{Rt}$	$E_1+1/2D_{Rt}$	$1/4D_{Rtp}$	$1/4D_{Rtp}$
		Mother	$1/4D_{Rtp}$	$1/4D_{Rtp}$	$E_1+1/2D_{Rp}$	0
		Father	$1/4D_{Rtp}$	$1/4D_{Rtp}$	0	$E_1+1/2D_{Rp}$

* Upper triangles give specifications for MZ twins, lower triangles for DZ twins. Definitions of parameters are given in the text.

given in Table 4, this last assumption is relaxed to allow offspring and parents to take different values for the population variance.

In Table 6 we see the results of attempting to fit these models to our observed data. In each case the fit is poor and such simple assumptions are clearly inadequate ($P < 0.001$). We therefore have evidence in our data for genetic influences, or shared family environmental influences or phenotypic assortation among spouses.

B. Can a simple genetic or a shared environmental effect model account for the data?

The second model (II) shown in Table 4, the simple additive genetic effects and within-family environmental effects model, is traditionally invoked as an account of family resemblance. In the model matrix we see the greater covariance for MZ twins in the upper triangle ($1/2D_R$) than for DZ twins in the lower triangle ($1/4D_R$). This is the only difference between the model matrices for MZ and DZ twin families, and although this difference may be significant when tested separately – clearly implicating genetic variation given the usual assumptions – its contribution to the overall likelihood statistic for these data is considerably less important than it would be were the parents of these twins not included in the data set. With our data set, the differences between the MZ and DZ families may be less important than the pattern of variances and covariances

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Table 6. The Results of Fitting Genetic and Environmental Models to DBP

Model		θ	se	df	χ^2	P
I.	E_1	81.46	7.63	19	75.42	0.0001
II.	E_1	22.97	5.04			
	D_R	141.35	26.80	18	37.77	0.0056
III.	E_1	19.33	3.78			
	E_2(developmental)	67.10	9.75	18	36.27	0.0065
IV.	E_1	64.21	6.94			
	E_2(family)	17.26	6.48	18	62.75	0.0001
V.	E_1(twins)	58.68	7.52			
	E_1(parents)	92.03	13.22	18	67.70	0.0001
VI.	E_1(twins)	18.88	3.57			
	E_1(parents)	66.41	14.35			
	D_R	80.43	18.37	17	24.63	0.1034
VII.	E_1(twins)	18.50	3.47			
	E_1(parents)	61.36	16.71			
	E_2(developmental)	41.53	9.67	17	30.12	0.0255
VIII.	E_1(twins)	22.84	4.96			
	E_1(parents)	99.27	14.44			
	E_2(family)	30.91	8.22	17	36.53	0.0039
IX.	E_1	11.91	2.95			
	D_R(twins)	85.51	16.16			
	D_R(parents)	181.47	27.78			
	D_R(tp cov)	62.60	24.05	16	20.48	0.1994

within the families irrespective of zygosity of the offspring.

We can see from the result in Table 6 that Model II is clearly inadequate ($P<0.01$) as are the alternative environmental Models III ($P < 0.01$) and IV ($P < 0.001$). The first of these assumes that in addition to individual environmental effects there are environmental influences shared by offspring, but that these shared influences are not necessarily common to the parents as well and do not themselves give rise to parent-offspring covariance. This would correspond to a shared influence on DBP whose critical period ended with adulthood; the shared environment of spouses or of offspring and parent would not then give rise to resemblance in DBP. For example, the development of human measured intelligence is sometimes assumed to be subject to such educational or developmental influences.

The alternative in Model IV is of an environmental influence whose continuing impact is on the whole family. If dietary salt had continuing impact on BP, say, and if variation in salt intake was shared for environmental reasons by whole families, then this would be such an influence. Both Models III and IV represent extreme assumptions which would only be approximated in reality, and for our data both these models are rejected ($P < 0.0001$).

Thus no simple genetic or environmental model, of the kind traditionally invoked, is adequate for our data. There is an indication of greater MZ total variance than DZ

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total variance for DBP ($F_{63,49} = 2.46$, $P < 0.01$). However, this does not lead to overall failure of models once age is accounted for. While the possibility of a sibling competition or cooperation model might be considered [6], we prefer to await independent verification of this difference in variance before giving it undue attention. It is more plausible that the real reason for this inadequacy lies in the increased population variance in the middle aged parents compared to adult offspring. The usual procedure of standardising to Z scores for each age and sex group [8,32] hides this inadequacy and leads to heritability estimates which are some sort of unspecified average figure and, since the increase in variance may be either environmental or genetic in origin, are not necessarily applicable to any particular group.

C. How do genetic and environmental influences change with age?

Since no simple 2 parameter model is adequate to explain our data, and since the most likely source of this inadequacy is in the failure to account for the changing population variance between young adulthood and middle age, we next consider a variety of models which make allowance for this feature of the data. In Table 5 four such models are specified.

In the first of these, Model VI, a heritable influence (D_R) is supposed to affect offspring and parents equally and to give rise to the covariance between parents and offspring measured at different ages. However, the individual environmental influences are allowed to exert different, and for our data, increasing influence with age. This is a plausible model in which heritable constitutional differences result in a more or less fixed underlying variation between individuals, while the pattern of exposure to, or protection from, environmental risk factors during the adult life span has an increasing impact on individual differences in DBP. In Table 6 we can see that this model is fully adequate for our data ($P < 0.10$) while the two environmental models (VII & VIII) which allow similar changes in the impact of individual experience but include shared environmental effects can be rejected ($P < 0.05$).Adopting Model VI, then, suggests a threefold increase in the impact of individual environmental factors affecting variance in DBP from young adulthood to middle age. But the heritability, calculated as $1/2D_R/(1/2D_R + E_1)$, falls from 68% to 38% during this period. De Faire et al [5] have recently demonstrated a similar low heritability when using middle aged twins. Data from the Framingham study [8] show that sibling correlations are essentially stable from about 30 onwards. Thus, if our model were correct, it would suggest that the major environmental risk period was from the late teens to early thirties, when individual adult lifestyles are being adopted. Such a result, if substantiated, would have important implications for targetting preventative health education.

However, we should note that the statistical adequacy of a simple model for our data will in part be a function of the power of the study, which in our case of 57 balanced pedigrees involving 228 individuals is inevitably limited. Given this, the alternative genetic and environmental model which holds the environmental impact constant while the expression of genetic influences is amplified (Model IX), although fitting the data very well indeed ($P < 0.20$), need not be invoked. Were this model appropriate, the genetic correlation between older and younger adults' DBPs would be $r = D_{Rtpcov}/D_{Rt}D_{Rp} = 0.50$. But this alternative model is of necessity more complex since the additive genetic parameters for the offspring, the parents and for the parent-

offspring covariation (DRtpcov) have to be specified separately. Thus, our principle of parsimony precludes its adoption at this stage. However, while our data structure permits discrimination of genetic and environmental influences in the offspring, without different degrees of genetic relationship in the parental groups (eg, twins), it is not as suitable for doing this in the parents. An extended data structure is now required to resolve these alternative accounts of how genetic and environmental influences change with age. In order to be efficient, the family study should be constructed to include adult twins and their offspring as well as young twins and their parents.

SBP. For the purpose of exposition, we have decribed the model fitting process in detail for DBP. The rationale is similar for SBP. The results of the model fitting for SBP are given in Table 7. As for DBP, the simple 2 parameter Models I to IV are inadequate for our data. However, in the case of SBP, we have no evidence for rejecting the influence of common environmental effects, in particular those of the kind shared culturally by a whole family. When a changing population variance with age is taken into account all the Models V to IX give an adequate fit. The implications will be discussed below.

Table 7. The Results of Fitting Genetic and Environmental Models to SBP

Model		θ	se	df	χ^2	P
I.	E_1	216.22	20.25	19	61.14	0.0001
II.	E_1	91.63	22.34			
	D_R	299.76	85.87	18	43.17	0.0008
III.	E_1	69.06	14.60			
	E_2(developmental)	168.50	29.46	18	42.74	0.0009
IV.	E_1	178.11	19.26			
	E_2(family)	38.11	16.21	18	52.18	0.0000
V.	E_1(twins)	110.45	14.54			
	E_1(parents)	288.87	41.33	18	27.95	0.0628
VI.	E_1(twins)	60.02	10.75			
	E_1(parents)	263.28	42.43			
	D_R	102.80	30.98	17	11.68	0.8189
VII.	E_1(twins)	61.89	11.59			
	E_1(parents)	274.24	45.57			
	E_2(developmental)	48.15	15.91	17	17.57	0.4163
VIII.	E_1(twins)	64.10	11.53			
	E_1(parents)	286.78	40.17			
	E_2(family)	44.06	13.84	17	10.96	0.8585
IX.	E_1	36.60	10.18			
	D_R(twins)	149.27	37.68			
	D_R(parents)	573.11	88.43			
	D_R(tp cov)	151.13	58.12	16	5.85	0.9896

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Summary of Results

We may now summarise our conclusions for the analysis of familial influence on DBP and SBP.

(1) As with most published studies we find highly significant evidence of familial aggregation for DBP and SBP.

(2) However, no simple genetic or environmental model of the kind usually adopted is adequate for our data.

(3) The reason for the inadequacy is that the population variance increases from our young adult offspring to our middle aged parents. This is particularly apparent for SBP. This increase in variance might reflect genetic or environmental influences differentially. Traditional correlational analyses overlook or hide these effects thereby losing information of considerable importance in lifespan developmental changes in blood pressure.

(4) With or without allowing for age related changes in impact, none of a variety of environmental models which we considered adequately accounted for our data with respect to DBP. For SBP, Model V gives a description of the data which might be taken at face value to be statistically adequate ($P = 0.06$). However, this would ignore the welter of studies demonstrating familial aggregation and our own observed MZ correlation of 0.66, so this environmental model too is, in practice, implausible.

(5) Whilst a simple genetic and environmental model does not account for individual differences in DBP and SBP, allowing for age-related changes in individual environmental influence gives highly significant improvements in fit to the data. A model with simple additive genetic effects, no assortative mating and neither shared developmental or cultural environmental influences was adequate to account for our data (Model VI).

This model would give a fall in heritability from 68% to 38% (DBP) from young adulthood to middle age as the impact of individual lifestyle variation accumulates while the genetic effects themselves would be expressed in the same way in young and older adults. The changing impact would most likely occur in relatively young adulthood when individual adult lifestyles are being established.

(6) All the models VI to IX which allow for some familial aggregation as well as this age-related increase in variance gave highly significant improvements in fit to the data for SBP but not DBP. Discriminations between these models is not possible on formal statistical criteria alone since they each account for the data set well. However, given the MZ twin correlation of 0.66 compared to the DZ twin correlation of 0.29, we must allow for some genetic influences, whilst at the same time we have no evidence for rejecting the influences upon SBP of common environmental effects, in particular those of the kind shared culturally by a whole family.

(7) It is conceded that our data structure cannot resolve all these matters. For example, were we to allow for both different genetic and different environmental effects in parents and offspring, E_{1P} and D_{RP} become confounded. A more complex alternative model which postulates such a change in the expression of the genes with age may yet be necessary. Having highlighted the need to take account of the important developmental information contained in the age-related changes in genetic and environmental expression, we need to collect an extended data set including adult twins to resolve these various alternative models. Such work may also enable us to account for the different patterns for SBP and DBP within the context of physiological control

mechanisms.

DISCUSSION

The genetic contribution to arterial pressure is well established, but until now it has been difficult to separate genetic and environmental covariance. Previous workers have suggested that for blood pressure anything between 34% and 64% of the variance between individuals may be due to hereditary factors [9].

Concordance for blood pressure is high in twins; we found correlations of 0.66 for SBP and 0.85 for DBP in MZ twins. The figures for DZ twins were 0.29 and 0.38, respectively. These figures compare well with those of other workers [2,30]. Concordance in sibs (about 0.2-0.3) is also suggestive of genetic influences or possibly early family-shared environmental influence at work [35].

Studies on adopted children show no correlation between them and their adoptive parents, strengthening the argument for heredity [1].

Several longitudinal studies, such as the Framingham and Utah studies, have shown distinct familial aggregation of hypertension. These are not to be discussed here, but have been recently reviewed by Williams [34]. 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 analyses. It would appear from our results that the influence of an individuals' environment varies according to their age, hence the separation of E_1 into different variances for parents and offspring gives a more adequate model, while simpler models which do not allow for developmental differences are seen to fail.

An augumented family study using middle age twins and their offspring should help to resolve further the different contribution to these changes in BP. For these analyses, it is necessary to consider the variances and covariances rather than simple correlations, if important information about the process of development is not to be lost.

It is likely that essential hypertension often represents the end result of a genetically determined differential response to various environmental factors. It is important to remember that factors inducing its onset are not necessarily the same as the factors which maintain hypertension once it is established. Hence, the usefulness of looking at both middle-aged parents and their young adult offspring.

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