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A Developmental Hypothesis for Adult Blood Pressure

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Abstract. Observed increases in phenotypic variance for blood pressure during adulthood are a predictable consequence of an *a priori* model for developmental change and continuity previously applied to cognitive development. The implications of this model for genetic and environmental covariances depend on the mechanism which maintains developmental continuity. Using data from young adult twins and their parents, it is shown how traditionally estimated genetic and environmental parameters may be reinterpreted in the light of the developmental model. Illustrative data suggest a hypothesis that genetic effects on blood pressure are largely temporally pleiotropic, acting consistently but not cumulatively throughout adulthood, while environmental influences act haphazardly but their effects are transmitted forward with high fidelity.

Key words: Development, Blood pressure, Genetic factors, Environmental factors

Sims et al [16,17] drew attention to the importance of age changes in the population variance for blood pressure; there is a large increase for systolic blood pressure (SBP) and a smaller increase for diastolic blood pressure (DBP) from young adulthood ($<$ 30 years) to middle age ($>$ 50 years) [3,7,16,17]. Such an increase is a predictable consequence of the general theory of developmental change outlined by Eaves et al [4]. Using their model, or a restricted form of it [9], it is possible to reinterpret traditionally estimated genetic and environmental parameters to give a parsimonious hypothesis about the mechanism of developmental change in blood pressure. In this paper we illustrate this approach using data reported by Sims et al [17].

THE MODEL

A general model for development is outlined in Fig. 1. Here a phenotype, P, is measured on occasions 0,1...,m. On each occasion the phenotype is a function of the genetic effect, G'_i, and the environmental effect, E'_i.

The genetic effect, G'_i, is in turn a linear function of pleiotropic genes, G_C, which influence all occasions directly, genetic effects specific to the occasion, G_S, and the transmitted influence of the genetic effect from the previous occasion. The environmental effect is similarly determined. Important parameters in this model are the extent to which genetic or environmental influences are common throughout development (g_c or e_c large) as opposed to being transient or age or occasion specific (g_s or e_s large), and the extent to which genetic influences (switching on or off of genes) or environmental influences (eg, habits, disease) are transmitted and accumulate from occasion to occasion. These latter two developmental transmission paths are represented by j and z in our model. Phenotype to phenotype transmission without regard to the provenance of the variation is the special case when $j = z$.

In the absence of developmental transmission ($j = z = 0$), we assume that contemporary genetic and environmental influences are constant in their contributed variance from occasion to occasion. If we now introduce developmental transmission, Eaves et al [4] show that the phenotypic variance, V_p, will increase towards an asymptotic equilibrium value. In general:

$$(1)\quad V_{pm} = h^2 (g_c^2 a_{k,k} + g_s^2 b_{k,k}) + e^2 (e_c^2 c_{k,k} + e_s^2 d_{k,k}), \text{ where } k = m + 1,$$

for occasion 0,1,...,m, and with random mating and additive gene action the genetic covariance between relatives measured at occasion k-1 and L-1 respectively, $L \leqslant k$, will be:

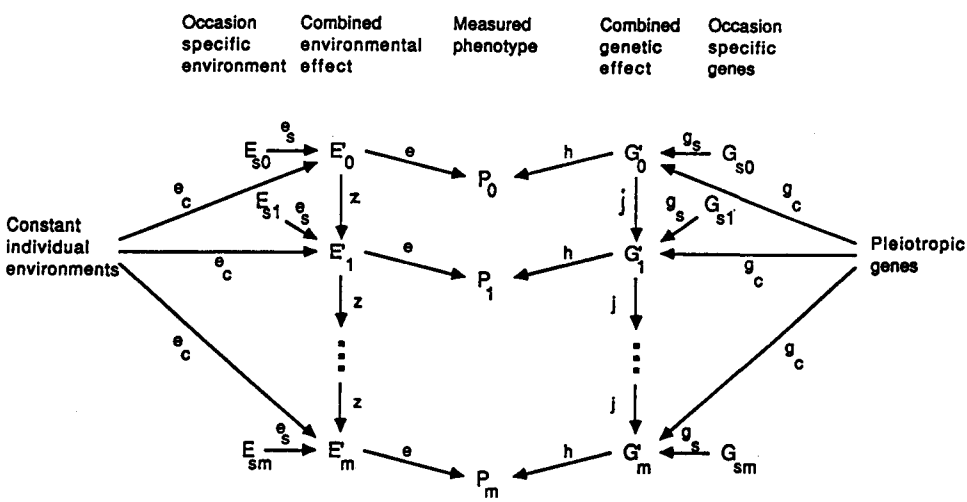

Fig. 1 - A general model for development of quantitative phenotypes

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(2) $\mathrm{Cov}_{P_k,P_L} = rh^2\,[g_c^2 a_{k,L} + g_s^2 b_{k,L}]$ where

$$a_{k,L} = \frac{(1-j^k)(1-j^L)}{(1-j)^2} \qquad b_{k,L} = \frac{j^{k-L}\,(1-j^{2L})}{1-j^2}$$

$$c_{k,L} = \frac{(1-z^k)(1-z^L)}{(1-z)^2} \qquad d_{k,L} = \frac{z^{k-L}\,(1-z^{2L})}{1-z^2}$$

and r is the coefficient of relationship.

A considerable further simplification is achieved if we consider two occasions, the first (P_0) prior to the onset of developmental transmission and the second near to equilibrium (P_∞).

Then we have:

$$V_{P_0} = h^2\,(g_c^2 + g_s^2) + e^2\,(e_c^2 + e_s^2)$$

$$V_{P_\infty} = h^2\left[g_c^2\left(\frac{1}{1-j}\right)^2 + g_s^2\left(\frac{1}{1-j^2}\right)\right] + e^2\left[e_c^2\left(\frac{1}{1-z}\right)^2 + e_s^2\left(\frac{1}{1-z^2}\right)\right]$$

$$\text{and } \mathrm{Cov}_{P_\infty,P_0} = rh^2 g_c^2\,\frac{1}{1-j}$$

These expectations are derived by letting k and L become large in equations (1) and (2). This formulation provides a preliminary *a priori* account of the patterns of variation and genetic covariation for relatives of different ages. In particular it provides a hypothesis to account for observed increased in phenotypic variance and changes in heritability with age.

ILLUSTRATIVE DATA

To illustrate the application of this model we consider a data set which has been subjected to traditional biometrical analyses by Sims et al [17] and comes from 85 balanced pedigrees, each consisting of a pair of healthy male twins obtained from the population based Birmingham Family Study Register and both of their parents. The 40 MZ pairs and 45 DZ pairs were between 16 and 24 years (mean age = 19.1 ± 3.0 years) and their parents were middle aged (mothers' mean age = 49.1 ± 6.0; fathers' mean age = = 51.5 ± 6.0 years). Details of BP measurement and other procedures are given in Sims et al [16].

Our initial analyses followed the procedure described by Sims et al [16,17] with, as would be expected, the same outcome. Models were fitted using the maximum likelihood

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routines of Lisrel VI [10]. No models which ignored developmental change from young adulthood to middle age fitted the DBP or SBP data and neither did any model which did not allow for familial aggregation. In Table 1 we present the two sets of expectations for the variance-covariance matrix for models which both fit the data adequately and specified some genetic variation. Model A allows individual environmental influences affecting the young adult offspring twins (E_{1t}) to differ from those affecting the middle aged parents (E_{1p}), while additive genetic influences (V_A) are constant. Model B allows both environmental and genetic influences to differ between parents (V_{Ap}) and offspring (V_{At}) and so the genetic covariance between parents and offspring also may take its own value (V_{Atp}).

Table 2 summarizes the results of fitting these two models along with a model without developmental changes (E_1, V_A) and one without genetic effects (E_{1t}, E_{1p}) for comparison. Clearly Model A provides a completely adequate account of the data ($\chi^2(17) < 17$, $P > 0.5$) while Model B does not give a significant improvement in fit for either SBP or DBP ($\chi^2(1) < 2$, ns). Since Model A is more parsimonious and gives an equally good fit to the data we adopt Model A.

THE DEVELOPMENTAL INTERPRETATION

Our best model (A) assumes that $V_{At} = V_{Ap} = V_{Atp}$. If we consider the twins to have been measured at or before the onset of developmental transmission and the parents to have been measured close to equilibrium, then this implies that:

$$V_{At} = h^2 (g_c^2 + g_s^2)$$

$$V_{Ap} = h^2 \left[g_c^2 \left(\frac{1}{1-j} \right)^2 + g_s^2 \left(\frac{1}{1-j^2} \right) \right]$$

$$V_{Atp} = h^2 g_c^2 \left(\frac{1}{1-j} \right)$$

The equality contraints of Model A are only satisfied reasonably ($j \geqslant 0$) when $j = 0$ and $g_s^2 = 0$. That is, the model implies both that all genetic effects are directly temporally pleiotropic across different ages without additional developmental accumulation through switching on or off of genes or some other process.

For the environmental influences however, we have:

$$E_{1t} = e^2 (e_c^2 + e_s^2)$$

$$E_{1p} = e^2 \left[e_c^2 \left(\frac{1}{1-z} \right)^2 + e_s^2 \left(\frac{1}{1-z^2} \right) \right]$$

Without longitudinal data we cannot distinguish between constant and occasion

Table 1 - Specifications of alternative traditional developmental-genetic models

Model	df	Variance-covariance expectations* Twin 1	Twin 2	Mother	Father
Model A: $E1_t$, $E1_p$, V_A	17	$E_{1t} + V_A$	$1/2\ V_A$	$1/2\ V_A$	$1/2\ V_A$
		V_A	$E_{1t} + V_A$	$1/2\ V_A$	$1/2\ V_A$
		$1/2\ V_A$	$1/2\ V_A$	$E_{1p} + V_A$	0
		$1/2\ V_A$	$1/2\ V_A$	0	$E_{1p} + V_A$
Model B: $E1_t$, V_{At}, V_{Atp}, $E1_p + V_{Ap}$	16	$E_{1t} + V_{At}$	$1/2\ V_{At}$	$1/2\ V_{Atp}$	$1/2\ V_{Atp}$
		V_{At}	$E_{1t} + V_{At}$	$1/2\ V_{Atp}$	$1/2\ V_{Atp}$
		$1/2\ V_{Atp}$	$1/2\ V_{Atp}$	$E_{1p} + V_{Ap}$	0
		$1/2\ V_{Atp}$	$1/2\ V_{Atp}$	0	$E_{1p} + V_{Ap}$

* Upper triangles give specifications for DZ twins, lower triangles for MZ twins. See text for parameter definitions.

Table 2 - Summary of traditional genetic model fitting

Model	Systolic Blood Pressure: Goodness of fit df	χ^2	P	Parameter estimates for adequate models: Parameter Estimate (± se)	Diastolic Blood Pressure: Goodness of fit df	χ^2	P	Parameter estimates for adequate models: Parameter Estimate (± se)
No development E_1, V_A	18	54.2	< 0.001		18	49.7	< 0.001	
No familial transmission E_1 (twins) E_1 (parent)	18	52.8	< 0.001		18	82.3	< 0.001	
Model A	17	8.2	0.963	E_1(twins) 35.81 ± 7.48 E_1(parents) 222.82 ± 33.04 V_A 76.98 ± 14.66	17	16.0	0.523	E_1(twins) 12.78 ± 2.74 E_1(parents) 71.79 ± 12.01 V_A 42.09 ± 7.02
Model B	16	6.7	0.979	E_1(twins) 38.18 ± 8.14 V_A(twins) 71.59 ± 14.74 V_A(tp cov) 192.96 ± 73.38 V_A(parents) 255.07 ± 33.28 + E_1(parents)	16	14.1	0.592	E_1(twins) 12.19 ± 2.68 V_A(twins) 43.86 ± 7.36 V_A(tpcov) 62.39 ± 36.76 V_A(parents) 94.71 ± 33.12 + E_1(parents)
Improvement of B over A	1	1.5	ns		1	1.9	ns	

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specific environmental effects. However our simulations have shown that in the absence of genetic transmission and the presence of even moderate environmental transmission ($z \approx 0.4$) anything other than low zero values for e_c results in phenotypes which show both increasing occasion to occasion reliabilities and decreasing MZ correlations to an extent incompatible with data for most known phenotypes with the possible exception of handedness. The plausible hypothesis is that environmental influences are transient in their occurrence ($e_c^2 = 0$) but that their impact is transmitted across occasions. On these assumptions we have:

$$\left(\frac{1}{1 - z^2}\right) = E_{1p} / E_{1t}$$

giving $z > 0.9$ for both DBP and SBP. Thus our best consistent hypothesis for the developmental changes between young adulthood and middle age has $j = 0, g_s = 0, e_c = 0$ and $z \approx 0.9$. This hypothesis is summarized in Fig. 2.

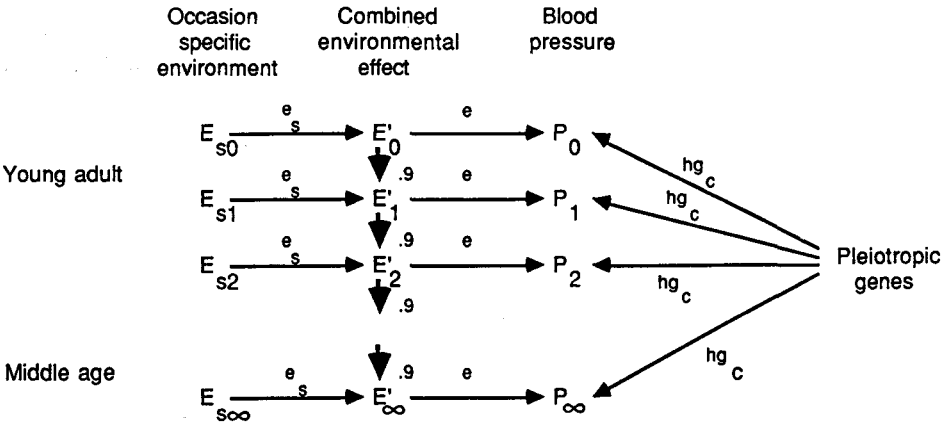

Fig. 2 - A developmental genetic model for adult blood pressure

DISCUSSION

Our main purpose has been to draw attention to the existence of a formalized quantitative description of development which may be useful in making sense of blood pressure and other clinical data. Not only have Sims et al [16,17] and Province and Rao [13] reported lower heritabilities for older than for younger adults, but declining heritabilities for bilirubin, blood urea nitrogen, glucose and uric acid measures over a 10 year period have been recently reported in the National Heart, Lung and Blood Institute Twin Study [11]. For plasma glucose concentration there is a marked increase in population variance

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from younger to older adults [6]. These kinds of observations may be explained within the framework of the model discussed here, although longitudinal, genetically informative data are necessary for proper resolution of the model [9]. The particular hypothesis for adult BP we have presented in this paper would have a number of implications.

For a disease process such as hypertension, which is associated with extreme scores on an underlying continuum, failure to reject a common factor (ie, nondevelopmental) account of continuity or tracking during adulthood would suggest that changes in lifestyle that are made from time to time during adulthood, in exercise habits or diet for example have little or no implication for risk; at most the effects would be transient. Furthermore, rejection of the common factor account in favor of developmental transmission implicates changing exposure to environmental risk during adulthood as etiologically important only if the transmission is shown to be not solely through genetic influences. The data we have analyzed are consistent with a model which suggests precisely this: developmental transmission is both required and predominantly or completely environmental.

The model makes a variety of testable predictions. First, at some point between young adulthood and middle age the accumulation of developmentally transmitted environmental influences on blood pressure must begin, and with this must begin the increase of phenotypic variance. Epidemiological data confirm this; for example the U.S. Health and Nutrition Examination Survey [14], based on a total of 17,854 individuals aged 6-74 years reports the variance for white adults shown in Fig. 3. Given the linear relationship between BP and mortality, variances for the older age groups will be attenuated. Also, the variances in the U.S. population are higher than ours at all ages as a consequence of the sampling strategy, the populations sampled and the measurement procedure. Nevertheless the pattern of variance is not out of line with the model and points to the onset of transmitted environmental effects somewhere around age 30.

Secondly, the correlations between relatives, eg, twins or siblings, should decline with age but the covariances should not. Data on this are not readily available as twin and family studies usually span a wide age band and published reports are often based on age

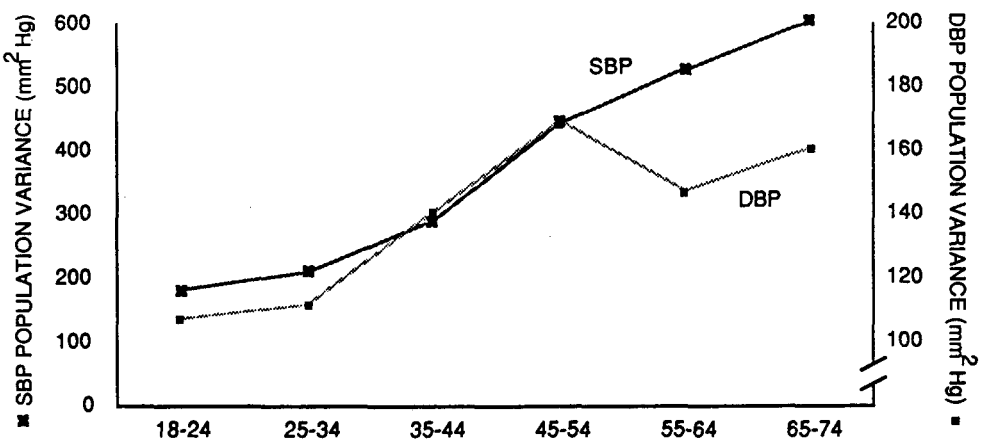

Fig. 3 - Age changes in population variance for systolic and diastolic blood pressure amond adult white Americans based on data in Robert and Mauree (1977).

standardized scores [8,15]. Interestingly, however, a recent analysis of family data for systolic blood pressure using arbitrary functions for temporal changes in familial aggregation parameters [13] is compatible with a steady decline in sib correlations between early adulthood and age 50 with no change thereafter. Against this, data from the Framingham study [5] suggested little attenuation of the sibling correlation over an 18 year period for adults who spanned 30 to 60 years of age. More systematic data are now needed to resolve this.

Thirdly the parent-offspring covariance should be constant whether it is based on measurements from a longitudinal study taken when both were young, both were old, or as is more usual in a cross-sectional study when parents are old and offspring young. However, the correlation coefficients should give the pattern $r_{young,young} > r_{old,young} > r_{old,old}$. It would follow also that parental BP observed as a young adult would be a better predictor of offspring BP and hypertension in middle age than parental BP taken in middle age. This is because young adult measurements are more reliable indexes of the genotype, and the same genes that affect young adult BP pleiotropically affect middle aged BP. We hope that such predictions will pique researchers in the field sufficiently to cause them to give greater attention to developmental effects on adult BP and to present their own data in a form more suitable for developmental analysis.

Corey et al [2] have done this for pedigree data on BP and reported no evidence of developmental effects. However, the validity of their conclusions is compromised by two aspects of their analysis: First, they included subjects as young as 3 months, and secondly they adopted the "simplifying assumption" of no transmission of environmental effects ($z = 0$). BP rises from birth to adolescence as body size increases, then it levels off, and then begins to rise again in adulthood for reasons that cannot be ascribed wholly to body weight increases [12]; it is very likely that lifespan analyses throw together at least two different developmental phases which are controlled quite differently. This view is consistent with the emergence of race differences in BP during the second phase and not the first (see Baron et al [1]). Thus assuming that preadolescent and adult BP can be modeled by the same process seems unlikely to lead to a proper understanding of either developmental phase. Secondly, by assuming no transmission of environmental effects, Corey et al precluded detecting the major developmental feature of our hypothesis. For these reasons we suspect that a reanalysis of Corey et al's larger data set might yet provide confirmation of the hypothesis presented here.

Irrespective of the fate of our particular developmental model, the general approach is useful in that it provides parsimonious *a priori* expectations for developmental trends. We are exploring a number of issues including the role of measurement unreliability, the inclusion of covariates, most obviously those related to body size, and what are the best experimental designs for resolving the causes of developmental change or tracking.

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