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Heritability and Stability of Resting Blood Pressure in Australian Twins

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In Australian twins participating in three different studies (1979–1996), the contribution of genetic and environmental influences to variation in resting systolic (SBP) and diastolic blood pressure (DBP) was studied. The sample consisted of 368 monozygotic and 335 dizygotic twin pairs with measurements for both individuals. Blood pressure measurements in two studies were available for 115 complete twin pairs, and 49 twin pairs had measurements in three studies. This allowed assessment of blood pressure tracking over an average period of 12 years in the age range of 23 to 45 years. Multivariate analyses showed significant heritability (h^2) of blood pressure in all studies (SBP $h^2 = 19\%$ – 56% , DBP $h^2 = 37\%$ – 52%). In addition, the analyses showed that the blood pressure tracking was explained by the same set of genetic factors. These results replicate an earlier finding in Dutch twins that also showed stability of the contribution of genetic factors to blood pressure tracking.

Research has shown a significant contribution of genes to the individual variation in resting blood pressure with mean heritability estimates of around 50%, for both systolic (SBP) and diastolic blood pressure (DBP; Evans et al., 2003). In addition, although there is an increase in means and variance of blood pressure (BP) with age, longitudinal studies also suggest a substantial stability in individual BP differences (Burton et al., 2005; Eisenmann et al., 2004). This stability (tracking) can be caused by the influence of both genetic and environmental factors. Knowledge about the contribution of these factors to BP tracking is important. If different genes are expressed across the lifespan, the pooling of study data with different ages will not achieve the usual gain in Quantitative Trait Locus (QTL) detection power (Lalouel, 2003).

Population studies have shown that there is significant tracking of BP and twin studies have analyzed whether factors contributing to it are genetic or environmental (Colletto et al., 1993; Hottenga et al., 2005; Iliadou et al., 2002; Snieder et al., 1995). A general finding is that the genetic factors influencing BP remain largely the same over time with no consistent evidence of new genetic factors emerging.

Recently we have shown in a Dutch twin sample that stable genetic factors influence BP in the first part of life, while environmental factors change (Hottenga et al., 2005). In the current study we aimed to replicate this in an independent sample of Australian twins. We combined BP data from three different studies of the Australian Twin Registry, carried out in 1979–1980, 1990–1992 and 1992–1996, in which part of the sample was measured repeatedly (Heath et al., 1997; Martin et al., 1985; Whitfield et al., 1996). These data were analyzed using the same longitudinal structural equation modeling approach as previously used in the Dutch twin sample.

Subjects and Methods

Subjects

The Australian data used in the present article are derived from three studies on twins who were recruited from the Australian Twin Registry. Study 1 (Alcohol Challenge Twin Study, ACTS) was conducted 1979 to 1980, and was mainly directed towards testing for the genetic effects on intoxication and alcohol metabolism after a test dose of alcohol under controlled conditions (Martin et al., 1985). Prealcohol resting BP readings were obtained for 412 young twins (206 pairs, born 1944–1963) who completed the alcohol challenge protocol. Subjects were asked to lie quietly for 2 minutes after which manual readings of blood pressure were taken. The same nurse took all readings.

A follow-up study (Study 2) on these twins was conducted 1990 to 1992 (Whitfield et al., 1996). Data on blood pressure were available for a total of 258 out of the original 412 twins (108 complete pairs). Subjects provided information about alcohol use and alcohol use disorders, and blood was collected for isolation of DNA and for measurement of alcohol markers and cardiovascular risk factors. SBP

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Table 1

Tracking of Systolic and Diastolic Blood Pressure Within Individuals Across Three Australian Twin Studies

Blood Pressure		<i>N</i>	Age (range)	Study 1	Study 2
SBP	Study 1	412	23.1 (18–40)		
	Study 2	258	33.9 (27–45)	.44 (.33–.54)	
	Study 3	1662	45.1 (30–86)	.35 (.14–.51)	.60 (.45–.70)
DBP	Study 1	412	23.1 (18–40)		
	Study 2	258	33.9 (27–45)	.33 (.21–.44)	
	Study 3	1662	45.1 (30–86)	.25 (.06–.41)	.63 (.51–.72)

Note: *N* = the number of subjects in the study. Age = mean age at measurement (range). Correlations were calculated after adjusting BP measurements for age at time of measurement and sex. The 95% confidence interval is given between brackets.

and DBP were measured with subjects sitting quietly for around 2 minutes, using an automated blood pressure recorder (Dynamap 845 Vital Signs Monitor; Critikon Inc.). The means of two results taken at 1-minute intervals were calculated.

Many of the subjects from the ACTS also participated in a 1992–1993 twin study of genetic influences on alcohol use disorders and associated psychopathology (Study 3; Heath et al., 1997). In 1993 to 1996, blood was collected from 1134 men and 2241 women for a study of alcohol biomarkers and to obtain DNA for genetic association studies (Whitfield et al., 1998a, 1998b). SBP and DBP were measured at that time on 605 of the men and 1057 of the women, including 563 twin pairs, using the same equipment and conditions as in Study 2.

In the three studies BP measurements were available for 1895 subjects (368 complete monozygotic [MZ] pairs and 335 dizygotic [DZ] pairs) with 159 subjects having measurements in two studies and 139 subjects having measurements in three. BP measurements were available for 115 complete twin pairs in two studies, and 49 complete twin pairs had measurements in three. For each of the studies, informed consent was obtained from participants and appropriate ethics committees approved the studies. In studies 2 and 3 a correction was made for people using anti-hypertensive medication as reported in the survey of 1993. Constant values of 14 mmHg for SBP, and 10 mmHg for DBP, were added to the measured BP values (Cui et al., 2003; Hottenga et al., 2005; Palmer et al., 2003). The number of subjects using medication was two and 158 for studies 2 and 3, respectively.

Statistical Analysis

The contribution of genetic and environmental factors to the longitudinal phenotype was evaluated with a multivariate approach and was analyzed separately for SBP and DBP. Individuals with values in one study only were retained in the analysis, as they contributed to the estimation of heritability, variances and the effects of sex and age at time of measurement. The means, total variance and regression of age and sex on BP were allowed to differ between studies. Models using a full Cholesky (triangular) decomposition for the variance and covari-

ance components were fitted to the data (Neale & Cardon, 1992). The total variance of blood pressure was divided into additive genetic variance (A), common familial environmental variance (C) and unique environmental variance (E). The covariance between twin pairs was modeled by setting the correlations for the additive genetic factors to 1 for MZ twin pairs and .5 for DZ twin pairs. Correlations were set to unity for the shared environmental factors. A series of nested AE, CE and E models were then fitted to the data. Equal heritability was determined by equating the relative contribution of the A and E components between studies. Tracking of environmental factors was tested by removing the environmental covariance in individuals between studies. Afterwards, a single factor model for the A component was tested to study whether there is a common set of genetic factors underlying the BP variation in the three studies. In the final model the relative contribution of these factors was equated over studies. All models in the multivariate analyses, parameters and their 95% confidence intervals were estimated by raw-data maximum likelihood with the Mx computer program (Neale, 2004). Comparison of models was performed with the likelihood ratio test, or the Akaike information criterion (AIC) in case there was no difference in number of free parameters between the tested models. An α level of .01 was employed.

Results

Linear regression of age with blood pressure shows that SBP and DBP increase with age in all studies, but this effect was only significant for Study 3, which is by far the largest, and has the widest age range (30 to 86 years). Males had higher SBP and DBP than females in each of the studies (p values < .005). For studies 1 to 3 the mean (*SD*) SBP levels were 117.2 (14.8), 127.3 (10.5) and 132.4 (15.4) in males, while in females they were 110.7 (11.5), 114.1 (11.6) and 126.6 (18.4). For DBP the mean levels were 72.8 (12.0), 77.2 (9.0), and 81.4 (11.5) for males and 69.3 (10.5), 70.5 (9.6), and 76.8 (11.6) for females. Age at measurement and sex were modeled as covariates on the means in the subsequent models.

Table 2

Product Moment Twin Correlations for Resting Blood Pressure in the Three Australian Twin Studies

Blood Pressure	Zygoty	<i>N</i>	Study 1	<i>N</i>	Study 2	<i>N</i>	Study 3
SBP	MZ	88	.38 (.18–.53)	48	.23 (–.02–.45)	310	.57 (.49–.63)
	DZ	118	.13 (–.04–.30)	60	.26 (–.02–.47)	253	.23 (.11–.35)
DBP	MZ	88	.46 (.29–.59)	48	.34 (.09–.53)	310	.53 (.46–.60)
	DZ	118	.28 (.10–.44)	60	.18 (–.10–.43)	253	.33 (.21–.43)

Note: SBP systolic blood pressure, DBP Diastolic blood pressure, MZ monozygotic twins, DZ dizygotic twins, *N* number of pairs. Correlations were calculated after adjusting BP measurements for age at time of measurement and sex. 95% confidence interval around estimate is given in brackets.

Table 1 shows the tracking of BP after correction of age at measurement and sex in 298 individuals who were measured in at least two studies. The correlations range from .35 to .60 for SBP and from .25 to .63 for DBP indicating reasonable tracking of BP. The tracking from Study 2 to Study 3 is higher than tracking from Study 1 to Study 2 for both SBP and DBP. This reflects the shorter time span of 2 to 3 years between Study 2 and Study 3 compared to the average of 12 years between Study 1 and Study 2.

In Table 2 the product moment correlations are presented for the MZ and DZ twin pairs for each study. No sex differences were found between male and female correlations within zygosity, nor between same-sex and opposite-sex DZ pairs, so only the pooled MZ and DZ correlations are shown. For SBP the MZ correlation is greater than (Study 1 and Study 3), or similar to (Study 2), the correlation of DZ twins pairs indicating the influence of genetic effects and possible common environmental effects. For DBP the MZ correlations are higher than the DZ correlations in all instances, indicating mainly the influence of genetic effects.

Assumptions of equal means and variances between twins, and equal effects of age and sex, were formally tested for the individual studies. All held for SBP and DBP. The results of the subsequent ACE model fitting are shown in Table 3 for SBP. The effect of common environmental influences was not significant ($p = .996$), but models without genetic (A)

influences ($p < .001$) or unique environmental influences ($p < .0001$) were rejected.

For the repeated measures, a single genetic factor model that left the contribution of unique environmental factors in full Cholesky gave the best fit to the data. Although time-specific unique environmental factors were found, unique environmental factors contributing to tracking over all three studies and to tracking from Study 2 to Study 3 were found as well.

For DBP the results of the multivariate structural equation modeling are presented in Table 4. The common environment component of the model could be removed from the model without a significant reduction of fit ($p = .903$). However, this was also true for the model without additive genetic factors ($p = .039$). A model with only unique environment did not fit to the data ($p < .001$). Based on the lowest AIC, AE = -4.8 and CE = 7.3 , the AE model was chosen. For the repeated measures, again a single genetic factor model that left the contribution of unique environmental factors in full Cholesky gave the best fit to the data. As for SBP, tracking of DBP across studies was due to a set of common genetic factors and unique environmental factors. The influence of these factors on the total DBP variation, differs across studies (Study 1 A = 39%, Study 2 A = 37%, Study 3 A = 52%; $p = .0097$).

Figure 1 summarizes the most parsimonious models for DBP and SBP.

Table 3

Multivariate Analysis Goodness-of-Fit Parameters of Sex and Age at Time of Measurement Adjusted Systolic Blood Pressure

Models SBP	–2LL	<i>df</i>	$\Delta\chi^2$	Δdf	<i>p</i>
ACE Cholesky	14,666.1	1816			
AE Cholesky	14,666.8	1822	0.6	6	.996
CE Cholesky	14,699.7	1822	33.5	6	.000
E Cholesky	14,832.9	1828	166.8	12	.000
A Cholesky equal heritability, E Cholesky	14,674.7	1824	7.9	2	.019 ^a
A Cholesky, E no environmental covariance across time	14,694.2	1825	27.4	3	.000 ^a
A one common factor, E Cholesky	14,673.6	1825	6.9	3	.076^a
A one common factor with equal variance proportions, E Cholesky	14,687.3	1827	20.6	5	.001 ^a

Note: –2LL – 2 times maximum likelihood, *df* degrees of freedom. ^aLikelihood ratio test against the AE model. Most parsimonious model is given in bold. Level of significance $\alpha = .01$.

Table 4

Multivariate Analysis Goodness-of-Fit Parameters of Sex and Age at Time of Measurement Adjusted Diastolic Blood Pressure

Models DBP	-2LL	df	$\Delta\chi^2$	Δdf	p
ACE Cholesky	13,741.2	1816			
AE Cholesky	13,743.4	1822	2.2	6	.903
CE Cholesky	13,754.4	1822	13.3	6	.039
E Cholesky	13,921.6	1828	180.4	12	.000
A Cholesky equal heritability, E Cholesky	13,746.4	1824	3.0	2	.223 ^a
A Cholesky, E no environmental covariance across time	13,755.9	1825	12.5	3	.006 ^a
A one common factor, E Cholesky	13,753.8	1825	10.5	3	.015a
A one common factor with equal variance proportions, E Cholesky	13,758.5	1827	15.2	5	.0097 ^a

Note: -2LL -2 times maximum likelihood, df degrees of freedom. ^a Likelihood ratio test against the AE model. Most parsimonious model is given in bold. Level of significance $\alpha = .01$.

Discussion

For resting SBP measured in three different studies of Australian twins we obtained heritability estimates ranging between 19% and 56%. For DBP the heritability ranges from 37% to 52%. Unique environmental and additive genetic factors sufficed to explain the individual variance in BP, which is in agreement with previous studies (Evans et al., 2003; Hottenga et al., 2005; Snieder, 2004). In a subset of twins who were repeatedly measured across the three studies reasonable tracking of BP was found. Retest correlation across on average a 12-year period was .35 for SBP and .25 for DBP. Using a multivariate approach, the genetic and environmental contribution to tracking of SBP and DBP was studied. Both additive genetic and unique environmental factors contribute to the stability in BP. The relative contribution of the genetic factor to the total variance seems to change

over time, but a major contribution to this apparent change in heritability may be the low MZ correlation obtained in Study 2 (19%). This correlation strongly deviates from what the MZ correlation found in much larger samples (Evans et al., 2003) including that in Study 3. In view of the low sample size of this study, sampling variation may explain the low heritability rather than a true change in genetic architecture over time.

Together with a comparable study of Dutch twins on the genetics of BP tracking (Hottenga et al., 2005), this study of Australian twins suggests that stable genetic factors influence BP across the first part of the adult life span, with no evidence for new genetic factors emerging. In contrast to the Netherlands, where it was shown that there was no contribution of unique environmental factors to tracking, these factors appear to contribute to BP stability in the Australian sample. We conclude that longitudinal BP data from

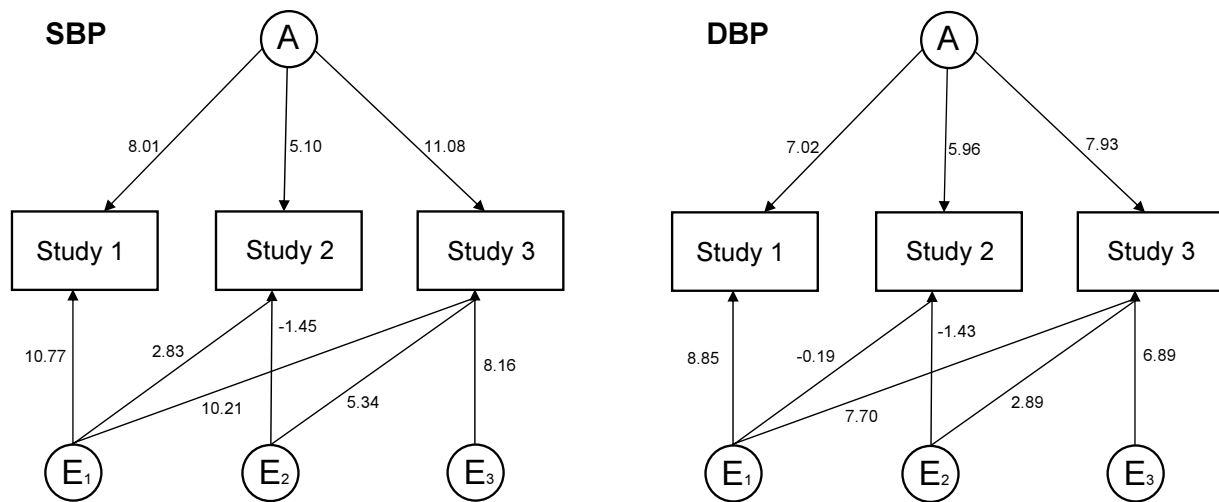


Figure 1

Pathway models showing latent and environmental influences on the measured mean systolic and diastolic blood pressure corrected for sex and age at measurement.

Note: A represents the additive genetic factors common to the three measurements. E₁₋₃ shows the unique environmental influences for individuals at each time point/study. Path coefficients are shown.

repeated measurements can be used for QTL mapping with a model that assumes that the same genes influence BP at various ages. However, for the environmental influences a model should be specified that allows for both general and age-specific factors.

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