The Genetics of Coronary Heart Disease: The Contribution of Twin Studies

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Despite the decline in coronary heart disease in many European countries, the disease remains an enormous public health problem. Although we know a great deal about environmental risk factors for coronary heart disease, a heritable component was recognized a long time ago. The earliest and best known examples of how our genetic constitution may determine cardiovascular risk relate to lipoprotein(a), familial hypercholesterolaemia and apolipoprotein E. In the past 20 years a fair number of polymorphisms assessed singly have shown strong associations with the disease but most are subject to poor repeatability. Twins constitute a compelling natural experiment to establish the genetic contribution to coronary heart disease and its risk factors. GenomEUtwin, a recently funded Framework 5 Programme of the European Community, affords the opportunity of comparing the heritability of risk factors in different European Twin Registries. As an illustration we present the heritabilities of systolic and diastolic blood pressure, based on data from over 4000 twin pairs from six different European countries and Australia. Heritabilities for systolic blood pressure are between 52 and 66% and for diastolic blood pressure between 44 and 66%. There is no evidence of sex differences in heritability estimates and very little to no evidence for a significant contribution of shared family environment. A non-twin based prospective case/cohort study of coronary heart disease and stroke (MORGAM) will allow hypotheses relating to cardiovascular disease, generated in the twin cohorts, to be tested prospectively in adult populations. Twin studies have also contributed to our understanding of the life course hypothesis, and GenomEUtwin has the potential to add to this.

As early as 1819, Samuel Black (Evans, 1995) the Irish physician, in reviewing angina pectoris, noted:

> We have seen that the disease appears to be connected with a plethoric state of the system and with obesity: that the great majority of the subjects of it have belonged to the better ranks of society, who were in the habit of sitting down everyday to a plentiful table, in the pleasures of which they may have indulged to a greater extent than was suitable to the tendency of their constitution …

He plainly recognized a genetic contribution to coronary heart disease (CHD).

The Genetics of Lipid Metabolism

The best examples of the genetic contribution to cardiovascular risk relate to lipid metabolism. Much has been learnt concerning the genetics of cholesterol, its sub-fractions and its lipoproteins. The story began with the report (Berg, 1963) that lipoprotein(a) is a heritable risk factor for cardiovascular disease. This is an altered form of low density lipoprotein cholesterol (LDL) with a large glycoprotein bonded to the apolipoprotein B100 moiety of low density lipoprotein cholesterol; the protein bears a striking resemblance to plasminogen, and there appears to be cross reactivity between them.

One well known and serious defect in cholesterol metabolism is familial hypercholesterolaemia (Brown & Goldstein, 1986). The heterozygous state of this autosomal dominant condition, present in around 1 in 500 of most western populations, is associated with elevated cholesterol and premature CHD. The homozygous state leads to accelerated vascular disease and, without treatment, survival into the teenage years is unusual. The unravelling of receptor mediated endocyclasis is a fascinating story. The underlying problem is a deficiency in LDL cholesterol receptors and so cholesterol accumulates in inappropriate places, e.g., the walls of arteries. Similarly, if there is a mutation in the codon for the amino acid 3500 in apolipoprotein B100, hypercholesterolaemia results (Farese et al., 1992). Thankfully, however, this "Familial Defective Apo B" is even rarer than familial hypercholesterolaemia.

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By convention when these genetic variations are common we refer to them as polymorphisms. Examples include single nucleotide polymorphism or SNPs. Such SNPs may occur at sites which have no effect on gene function or they may occur in coding regions (resulting in an altered function of the gene product) or in gene regulatory elements (resulting in altered quantities of the gene product being produced). It is this combination of 30–40 small differences in each of 30–40,000 genes which makes us different from one another — and different from anyone who has ever lived or will live (Payne & Montgomery, 2002).

One of the best known and well-elucidated of these polymorphisms affects apolipoprotein E. In the ECTIM study (a case control study of myocardial infarction) which was mounted between the WHO-MONICA (MONItoring in CArdiovascular disease) project centers in Belfast, Lille, Strasbourg and Toulouse, male patients aged 25–64 years were recruited (Luc et al., 1994). Despite a three-fold higher level of CHD in Northern Ireland than in France, classical risk factor levels were very similar. A total of 574 cases and 722 controls were available for a comparison of apolipoprotein E phenotype and genotype. Competition by Apo B and Apo E for the LDL receptor (the avidity of the receptor being determined genetically) explained the different atherogenic potentials, with the $\varepsilon 4$ allele being associated with higher levels of LDL cholesterol and consequently a greater susceptibility to atherosclerosis. The $\varepsilon 2$ allele favors peripheral LDL catabolism. The relative risks associated with the $\varepsilon 2$ and $\varepsilon 4$ alleles were 0.73 and 1.33, respectively, suggesting that 12% of myocardial infarction might be attributable to this polymorphism. The $\varepsilon 4$ allele frequency was 14.3%, 14%, 10.8% and 5.2% in Belfast, Lille, Strasbourg and Toulouse, respectively (similarly, the prevalence of $\varepsilon 2$ was 10.3%, 11.9%, 8.5% and 5.6%). There is even greater variation around the world with an $\varepsilon 4$ allele frequency ranging from over 30% in Nigeria to less than 5% in Japan (Cambien, 1994). It has also been shown (Amouyel et al., 1994) that $\varepsilon 4$ allele carriers have a several-fold risk of developing Alzheimer's disease and a lesser risk of developing Creutzfeldt-Jakob disease.

An alternative strategy to studying people who become ill and die prematurely is to study those who survive into extreme old age. In the United Kingdom reaching 100 years of age attracts a message from Royalty; not so in France where such prodigious age will attract a researcher, complete with needle and syringe, to acquire white cells for the extraction of DNA. A total of 338 Centenarians were assembled (Schächter et al., 1994) in this way, 294 (87%) of whom were women. The $\varepsilon 4$ allele was less common than expected whereas the $\varepsilon 2$ allele was more common, indicating selective survival/mortality in the presence of these two alleles.

The better understanding of such gene–environment interactions in relation to CHD and factors such as diet may greatly refine treatment in the future, and explain why the classic risk factors are often imprecise in defining an individual's risk. Rare mutations with big effects are disastrous for the individual but have small population impact, whereas common polymorphisms with small effects may together produce common diseases and carry a large population impact.

This may sound plausible enough, but when one considers that there might be several hundred polymorphisms involved in various systems and pathways which may affect atherosclerosis, the prospect is daunting. An editorial in *The Lancet* drew attention to concerns about association studies (Anon, 2003). "In the post-human genome era it is no longer acceptable for *The Lancet* to publish manuscripts that imply a genetic association with disease yet fail to identify the causative genetic variant". The size and validity of the positive studies which that Journal has published have also been questioned. Hirschhorn and colleagues looked at over 600 positive associations and found that although 92 associations were replicated at least once, only 6 of 166 associations that had been repeatedly studied were replicated in more than 75% of subsequent studies (Hirschhorn et al., 2002). This is all part of the "problems of reporting genetic associations with complex outcomes" (Colhoun et al., 2003). Then there is the bind of positive publication bias and the pitfalls of meta-analysis. In addition, it may be that it is haplotypic combinations of polymorphisms which contribute most to risk and so analyses are required which take multiple polymorphisms into account (Hirschhorn et al., 2002). Similarly in a review of 55 meta-analyses, it was shown (Ionannidis et al., 2003) that: "Typically, large studies and subsequent research suggested weak associations or no association at all, compared to strong associations proposed by smaller studies and first research". This could be due to bias or heterogeneity. To compound this complexity it is known that the expression of some genes affecting lipid metabolism is age dependent (Snieder et al., 1997). As a preliminary strategy to actual gene finding, it might be helpful to first establish the (joint) genetic architecture of the coronary risk factors in twin studies.

Twin Studies

Familial clustering of disease in families is well recognized; for example, Osler (1910) described a family in which three generations had been afflicted with angina pectoris (he actually reported the family's surname!). Twins represent a very special resource to investigate the causes of this clustering: twins share intrauterine environment and age; monozygotic (MZ) twins nearly always share all their genes and dizygotic (DZ) twins share, on average, 50% of their segregating genes. As Boomsma et al. (2002) stated, "By facilitating comparisons between MZ and DZ twins, twin registers represent some of the best resources for evaluating the importance of genetic variation in the susceptibility to disease." They are also an excellent resource for studying the significance of genotype × environment interactions. Allied to this are the recent advances in statistical modelling which allow the simultaneous analysis of many variables.

In the Swedish Twin Registry, 21,004 twins or pairs were investigated for the risk of death from CHD (Marenberg et al., 1994). Relative hazard estimates were obtained in a multivariate survival analysis. The study assessed the relative hazard of a twin's death from CHD when the other twin had died of CHD before the age of 55 years, as compared with the hazard when the twin survived beyond the age of 55

years. The relative hazard in MZ twins was roughly double that of DZ twins and, although the effect was attenuated by age, it persisted into old age. A more recent report (Lichtenstein et al., 2002) from the same registry has extolled it as a unique resource for clinical, epidemiological and genetic studies. Further follow-up of this cohort, in an attempt to quantify more accurately the genetic and environmental components of CHD death, confirmed the genetic contribution and also found that these genetic effects were less likely to diminish with age than previously reported (Zdravkovic et al., 2002). The next step should be the incorporation of environmental exposure data to permit more accurate quantification of the genetic and environmental risks. Perhaps the most powerful "natural experiment" design of all is that of "twin adoption" in MZ pairs. Here the twins are separated early in life and the effects of different environments can be uniquely studied (De Faire et al., 1975). A variant of this is when MZ twins are discordant for a certain "environmental" factor. Haapanen et al. (1989) studied 50 pairs of MZ twins who were discordant for smoking, a major risk factor for CHD. Carotid artery atherosclerotic plaques were significantly larger in the smokers. Similarly, Jartti et al. (2002) in The Finnish Twin Cohort, compared pairs who were discordant for remaining in Finland or migrating to Sweden at least 20 years before. Although there was no difference in carotid intima-media thickness, in MZ twins who migrated to Sweden endothelial function was significantly better, and this difference was independent of the classic risk factors. This suggests that lifestyle influences were at work, but the effect of other unknown factors cannot be excluded. Studying MZ and DZ twins under different conditions (e.g., laboratory stress) seems to reveal that the influence of genetic factors increases during stress, which constitutes evidence for genotype × environment interaction (Boomsma et al, 1998). In both Dutch and Australian twins, an effect of the alpha-1-antitrypsin gene was found for blood pressure assessed during stress, but not during rest (Boomsma et al., 1991).

Heritability of Risk Factors in Twin Studies

Comparing the resemblance of MZ twins for a trait with the resemblance of DZ twins offers an estimate of the extent to which genetic and environmental variation determines phenotypic variation of that trait (Boomsma et al., 2002). These estimates may vary across sex, age or country, although the latter possibility has seldom been addressed. The participation of several large twin cohorts in GenomEUtwin affords the unique opportunity to compare the heritability of various cardiovascular risk factors in different twin populations. This is demonstrated for resting arm cuff systolic (SBP) and diastolic blood pressure (DBP) in Table 1. These heritabilities summarize blood pressure data from more than 4000 twin pairs from six different countries.

The striking result immediately apparent is the congruence of the results across the 6 participating countries. Heritabilities of resting blood pressure are between 44 and 66% across samples for DBP. For SBP, the range of estimates is even narrower at between 52 and 66%. Given the huge number of twin pairs (see Appendix for details) used in these analyses we may confidently assert that 50% of the amount of variance in blood pressure is due to genetic factors. Shared environmental factors do not seem to play an important role, except possibly in Finland.

Twin studies have also yielded evidence for the heritability of many other CHD risk factors. For many lipid factors, particularly lipoprotein(a), the heritability is substantial (Snieder et al., 1999). In a UK heritability study of haemostatic factor levels, de Lange et al., showed (2001) that genetic factors accounted for about 41–75% of the variation. Another related phenotype to blood pressure is pulse wave velocity or augmentation, a measure of vascular resistance and this too was found to be strongly heritable (Snieder et al., 2000). Similarly, it has been calculated (Boomsma et al., 1994) in Dutch twin pairs that smoking initiation was influenced by genetic factors (39%) and shared environmental influences (54%). In smokers, genetic factors determined a staggering 86% of the amount smoked (Koopmans et al., 1999). In male British doctors aged under 45 years who

Table 1

Maximum Likelihood Estimates of Twin Correlations (r) and Heritability (h^2) with 95% Confidence Intervals (CI), Based on Age and Sex Adjusted Data

	MZM			DZM			MZF			DZF			DOS			h^2		
	r	95% CIs		r	95% CIs		r	95% CIs		r	95% CIs		r	95% CIs		95% CIs		
SBP																		
Australia	0.47	0.29	0.64	0.15	–0.25	0.49	0.55	0.45	0.63	0.28	0.08	0.43	0.17	–0.05	0.37	0.52	0.44	0.59
Denmark	0.60	0.49	0.70	0.32	0.17	0.46	0.70	0.61	0.77	0.46	0.33	0.57				0.66	0.60	0.71
Finland	0.45	0.31	0.57	0.33	0.21	0.44	0.50	0.36	0.62	0.43	0.29	0.55				0.53	0.46	0.60
Netherlands	0.50	0.34	0.63	0.25	0.03	0.45	0.47	0.33	0.60	0.36	0.18	0.52	0.26	0.05	0.45	0.54	0.44	0.62
Sweden	0.51	0.27	0.70	0.28	0.05	0.47	0.51	0.30	0.67	0.28	0.11	0.44				0.54	0.41	0.65
UK							0.56	0.50	0.62	0.27	0.22	0.33				0.53	0.48	0.58
DBP																		
Australia	0.47	0.30	0.60	0.23	–0.10	0.50	0.53	0.43	0.61	0.39	0.21	0.54	0.20	0.00	0.38	0.51	0.44	0.58
Denmark	0.63	0.52	0.71	0.31	0.15	0.45	0.71	0.62	0.78	0.43	0.30	0.54				0.66	0.60	0.71
Finland	0.40	0.26	0.53	0.29	0.17	0.40	0.50	0.35	0.62	0.38	0.24	0.51				0.47	0.39	0.54
Netherlands	0.51	0.35	0.64	0.28	0.06	0.47	0.46	0.31	0.59	0.30	0.11	0.47	0.22	0.01	0.41	0.53	0.44	0.61
Sweden	0.24	–0.05	0.49	0.31	0.09	0.50	0.50	0.30	0.67	0.16	–0.02	0.33				0.44	0.29	0.56
UK							0.49	0.42	0.55	0.23	0.18	0.29				0.48	0.42	0.53

smoked heavily, coronary mortality was 15 times greater than in non-smokers (Doll & Peto, 1976), which suggests that a genetic predisposition of smokers to tobacco addiction, making it nearly impossible for them to quit, could be a major determinant of premature CHD fatality.

Addressing the Life Course Events Hypothesis in Twin Studies

It has been observed, "that hypotheses based on multiple observed associations, such as that pertaining to life course events" (Elford et al., 1992) should be rigorously tested and several advocates of the hypothesis have recently accepted that genetic studies give scope to assess the interactive effects of genes and environment over the life course (Kuh et al., 2003). Twin studies provide an elegant means to realize this objective. The accumulating evidence that CHD begins in early life has moved some of the focus of the research from factors acting in middle age to exposures at other periods of life. This approach has now developed into the "life course" epidemiological perspective, which recognizes that lifelong experiences, extending from the antenatal period through childhood, adolescence and adulthood, constitute a longitudinal and dynamic exposure within which the risk of chronic disease evolves (Kuh & Ben Shlomo, 1997).

The life course perspective pertaining to CHD thus recognizes three hypotheses:

1. CHD and coronary risk factors have their origins in early life exposures. Barker (1998) has demonstrated the importance of the fetal development — "programming" — for later risk, and factors acting throughout childhood up to early adulthood also independently influence later risk (McCarron & Davey Smith, 1998).
2. CHD disease risk evolves over the life course and the influence of specific factors is often conditioned by the presence of other (later) exposures (Frankel et al., 1996).
3. Genetic and environmental factors (including social and behavioural exposures) interact to cause disease.

The GenomEUtwin population-based twin cohorts facilitate the identification of disease alleles, enabling testing of the effect of any identified variant at the population level, as well as investigating the effect of life course events. The well-documented advantages of these cohorts, including tight matching on age and early life environment, point to the potential of this research.

Early concerns that twins were unsuitable candidates for studying the role of fetal development and, therefore, a poor model for studying health have been largely proven unfounded. The hypothesis that because of the special intrauterine experiences and conditions of twinning, the causal pathways of a number of diseases could be different from that of singletons, and the additional belief that twins would be more vulnerable to adult chronic diseases were refuted by the observation that similar rates of all-cause and cardiovascular disease mortality occur in singletons and twins (Christensen et al., 2001; Vagero & Leon, 1994).

An important component of the life course perspective is investigation of the early life period — often understood to denote fetal life. Twin studies will be important for evaluating the programming hypothesis by (Barker, 1998) investigating a range of variables in relation to fetal growth. To date, the characteristic that has been most studied is blood pressure. Until recently the data pointed to the conclusion that low birthweight is a risk factor for high blood pressure in later life, but more recent rigorous assessment of the earlier studies has led to the suggestion that the earlier findings stemmed from the impact of random error, selective emphasis of particular results, and inappropriate adjustment for current weight and confounding factors (Huxley et al., 2002). In view of the ongoing debate on the role of birthweight in determining adult blood pressure it is of interest that the findings from twin studies have been conflicting (Poulter et al., 1999; Christensen et al., 2001). Ijzerman et al. (2000) showed in Dutch adolescent twins whose mothers had reported their birthweight, that the association of low birthweight and high blood pressure was due to common genetic influences. While small sample sizes and maternally-reported birthweight could have been responsible for some of the inconsistencies, the possibility remains that a combination of genetic, maternal, and environmental factors during childhood and adolescence, associated with fetal growth may have influenced the previously reported associations. Similarly, the twin-pair design can also be used to investigate whether low birthweight is associated with increased risk of CHD. Such a study has been carried out in Sweden (Hubinette et al., 2001) where, in a case-control design of 132 same-sex twin pairs discordant for myocardial infarction and 118 individually matched control twin pairs, there was no within-pair association between birth characteristics and risk of myocardial infarction. Clearly, further research is required to improve understanding of the causal pathways and, therefore, investigation of these hypotheses using the much larger numbers of twins in GenomEUtwin should help to elucidate the associations between birth characteristics and subsequent risk of CHD.

Extension of such an investigation to the consideration of the impact of 'catch-up' growth in childhood would be a significant advance in unravelling early life antecedents of CHD. While it has been hypothesized that different paths of early growth may explain the heterogeneity among individuals to coronary risk, there are few empirical data and, as with the study of fetal growth, twin cohorts which have collected growth data are ideally placed to contribute to this debate. CHD, which usually manifests itself in later life can be defined as an age-specific trait. Characterizing such traits requires information on factors, not just early in life, but over long periods (e.g., many decades). Risk factor profiles change throughout an individual's life span, necessitating knowledge of the status of these characteristics at multiple time points. Longitudinal data, when used in analyses of a twin cohort — and ultimately, combined with genotypic information — could provide valuable opportunities to learn how traits are affected by age-genotype and gene × environment interactions over time. Large samples, as available in GenomEUtwin, are needed because of the requirement to distinguish among age groups and because of the genetic complexity of many disease traits. Moreover, the availability of data from cohorts dating back to the late 19th

century will allow assessment of how trends in environmental exposures have contributed to genetic expression.

More complex yet, but likely to provide a truer assessment of the role of life course exposures will involve investigation of the genetic and environmental contribution to QTL expression or rate-of-change traits (NIA Aging and Genetic Epidemiology Working Group, 2000) over the lifespan. A small number of twin studies which have broached this issue have yielded evidence that genetic factors significantly affect rates of change with age in several physiological measures, including lipids (Snieder et al., 1997) adiposity and lipid profile (Korkeila et al., 1995; Austin et al., 1997), and change and stability of body mass index (Fabsitz et al., 1992; Friedlander et al., 1997).

Conclusions

There is now overwhelming evidence for genetic predisposition to CHD. We have long been aware that the trends in incidence and mortality from CHD vary greatly, not only just by country but also over time, suggesting that although genotype may determine risk in susceptible individuals under specific exposures, it is the broader environmental factors which drive these trends. Twin studies have contributed a great deal to our knowledge in establishing the heritable nature of various CHD risk factors. The findings on the heritability of blood pressure in the present study from twin registries in several countries, add to those of previous reports (Hong et al., 1994; Iliadou et al., 2002; Snieder et al., 2003). Indeed, the present results from these registries demonstrate a remarkable degree of coherence, although this may reflect a similarity between these northern European populations, and could differ in other populations. The finding of similar heritabilities in African-Americans (Snieder et al., 2003) suggests that this is unlikely.

Genetic factors may influence not only physiological functions at one point in time but also their rates of change over time (period and/or cohort), which may in turn influence whether and when disease occurs. In addition to environmental factors, which clearly are operating, the effect of various "variability genes" may be acting independently of the genetic influences on the absolute levels of these risk factors.

Several other related research questions which, if answered, will improve our understanding of the complex and changing factors that determine coronary health, will be investigated in GenomEUtwin. Examples include:

- Are genetic effects fixed regardless of changing environment over an individual's lifetime and over generations, or is there a dynamic interplay between genes and environment?
- Can a dynamic concept of heritability (e.g., blood pressure at several time points) elucidate how genetic factors contribute to evolving health states?
- Which environmental factors, if any, act to switch genes on and off, and how does this depend on when the exposure occurred?

One of the GenomEUtwin cohorts is not twin-based: MORGAM(MOnica, Risk, Genetics, Archiving and Monograph) is a large prospective cohort study of classic risk and genetic factors in the development of cardiovascular disease (Evans, 2000). Genotypes identified in the twin cohorts as conferring cardiovascular risk will be investigated in MORGAM. Exploitation of the GenomEUtwin cohorts in this manner should improve our understanding of the life course paradigm and CHD, and ultimately provide better epidemiological and genetic methods of tackling this important problem.

Acknowledgments

A part of these data originates from the GenomEUtwin project which is supported by the European Union Contract No. QLG2-CT-2002-01254. The data from the Swedish cohort were supported by National Institutes of Aging grants AG 04563 and AG 10175.

The blood pressure data collection from the Netherlands Twin Register was funded by the Netherlands Heart Foundation (86.083, 88.042 and 90.313; and by the Human Frontiers of Science Program (RG0154/1998-B). Blood pressure data from the Finnish Twin Cohort were collected in four separate clinical investigations conducted under the aegis of Dr Taina Rantanen, Prof Tapani Ronnemaa, Prof Jaakko Tuomilehto and Tapio Videman. Collection of blood pressure data from the UK was supported by grants from the BHF and CDRF and was overseen by Harold Snieder.

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Appendix

Genetic Analyses of Blood Pressure Data

Quantitative genetic analyses were carried out to identify and quantify genetic and environmental influences on variation in blood pressure. Structural equation modeling was used to partition the variances in SBP and DBP into genetic and environmental components. These models are widely used and described in detail elsewhere (e.g., Neale & Cardon, 1992) and in this special issue by Posthuma et al. (2003). Each model comprised a set of simultaneous linear equations specifying the expectations for the degree to which additive genetic (A), dominant genetic (D), shared-environment (C) and non-shared environment (E) contribute to the phenotypic variation. Covariances between MZ and DZ male and female twins were modeled as a function of additive genetic influences (since the twin correlations did not indicate the presence of genetic dominance) and of a common environment shared by family members. The model for the means included a linear regression of age and sex, and was simultaneously modeled with the partitioning of the variance in all countries. Before conducting the genetic modeling, maximum likelihood correlations were computed to estimate the degree of similarity in blood pressure between members of MZ and DZ twin pairs. These correlations were stratified by country and zygosity and data were corrected for age and sex. Correlations were used to guide model selection (ACE, ADE) for the biometric analyses. An ACE model was always chosen. Sex-differences in the variance components were explored through a series of hierarchical procedures. Two types of sex differences were analyzed: sex-differences in the magnitude of the genetic and environmental variance components and sex differences in the set of genes which influence variation in blood pressure in males and females. This last test was only possible for countries that supplied data on opposite-sex twin pairs. Results (not reported in the Tables) indicated that the same genes are expressed in males and females. Throughout, the significance of specific parameters is assessed using Chi-square difference testing and comparing nested models. All models are nested under the full ACE model which allowed means and covariances to be different for all zygosity by sex by country groups. Models were fitted to the raw data. This allowed the data from incomplete twin pairs to be analyzed as well. Although incomplete pairs do not provide information on twin covariances, they are still informative for some of the parameter estimates (e.g., the regression of blood pressure on age and sex, and to obtain estimates of blood pressure variances). Table A gives an overview of the number of participants in all countries and their average ages. Tables B and C provide the main fit statistics for systolic and diastolic blood pressure. These tables clearly show the absence of sex differences in the relative contributions of genetic and environmental factors to blood pressure variance. Also, they indicate the absence of a significant effect of shared family environment (with the exception of the Finnish data). The absence of an effect of shared family environment is demonstrated even more clearly in Table D. This table shows the estimates of the variance components and the standardized genetic component (i.e., heritability) for the ACE and AE model. The point estimates for the variance of shared environment is small, or even zero. The small decrease in goodness-of-fit when this component is removed from the model indicates its non-significant contribution to the total variance in blood pressure. Table D also shows the large differences in the absolute sizes of the genetic and environmental variance components. There is a clear trend that variances are larger in the older samples. However, there is an increase in both the genetic and environmental variance components so that heritability estimates remain very similar.

Table A

Number of Twins and Complete Twin Pairs by Country

Number of twin pairs (twin 1, twin 2, complete pairs)

	MZM	DZM	MZF	DZF	DOS (Female, Male)	age (range)
SBP						
Australia	143 / 127 / 89	79 / 67 / 40	294 / 280 / 222	160 / 142 / 106	182 / 191 / 106	
Denmark	153 / 153 / 153	146 / 146 / 146	158 / 158 / 158	167 / 167 / 167		
Finland	151 / 151 / 151	236 / 236 / 236	122 / 122 / 122	155 / 155 / 155		
Netherlands	100 / 99 / 99	78 / 78 / 78	125 / 126 / 124	100 / 100 / 98	87 / 84 / 84	
Sweden	46 / 45 / 45	73 / 73 / 73	63 / 63 / 63	121 / 121 / 121		
UK			529 / 532 / 498	1175 / 1189 / 1078		
DBP						
Australia	143 / 127 / 89	79 / 67 / 40	294 / 280 / 222	160 / 142 / 106	182 / 191 / 106	45.5 (30–86) yr
Denmark	153 / 153 / 153	146 / 146 / 146	158 / 158 / 158	167 / 167 / 167		37.8 (18–66) yr
Finland	151 / 151 / 151	236 / 236 / 236	122 / 122 / 122	155 / 155 / 155		58.6 (37–76) yr
Netherlands	100 / 99 / 99	78 / 78 / 78	125 / 126 / 124	100 / 100 / 98	87 / 84 / 84	32.2 (13–71) yr
Sweden	46 / 45 / 45	73 / 73 / 73	63 / 63 / 63	120 / 119 / 118		65.2 (43–86) yr
UK			529 / 532 / 498	1175 / 1189 / 1078		46.6 (18–79) yr

Table B

Model Fit Statistics for Systolic Blood Pressure: ACE, AE, CE and E with or without Sex Differences in Parameter Estimates for Variance Components

SBP	minus 2 times LL	*df*	$\Delta\chi^2$	*df*	*p*	AIC
Australia						
full model	13394.003	1656				
ACE no sex	13397.045	1659	3.042	3	0.385	–2.958
AE no sex	13397.045	1660	3.042	4	0.551	–4.958
CE no sex	13417.300	1660	23.297	4	0.000	15.297
E no sex	13503.750	1661	109.747	5	0.000	99.747
Denmark						
full model	9782.949	1239				
ACE no sex	9788.642	1242	5.693	3	0.128	–0.307
AE no sex	9790.032	1243	7.083	4	0.132	–0.917
CE no sex	9815.555	1243	32.606	4	0.000	24.606
E no sex	10010.852	1244	227.903	5	0.000	217.903
Finland						
full model	11681.327	1319				
ACE no sex	11683.199	1322	1.872	3	0.599	–4.128
AE no sex	11690.144	1323	8.817	4	0.066	0.817
CE no sex	11687.506	1323	6.179	4	0.186	–1.821
E no sex	11816.971	1324	135.644	5	0.000	125.644
Netherlands						
full model	7280.963	968				
ACE no sex	7283.365	971	2.402	3	0.493	–3.598
AE no sex	7283.365	972	2.402	4	0.662	–5.598
CE no sex	7297.825	972	16.862	4	0.002	8.862
E no sex	7366.911	973	85.947	5	0.000	75.947
Sweden						
full model	5343.547	596				
ACE no sex	5343.910	599	0.363	3	0.948	–5.637
AE no sex	5343.926	600	0.379	4	0.984	–7.621
CE no sex	5351.243	600	7.696	4	0.103	–0.304
E no sex	5392.705	601	49.158	5	0.000	39.158
UK (females only)						
ACE	28754.707	3420				
AE	28755.361	3421	0.654	1	0.419	–1.346
CE	28785.747	3421	31.04	1	0.000	29.040
E	29007.962	3422	253.255	2	0.000	249.255

Note: Full model is ACE model with sex differences in variance components, this is the model against which other models are compared (except for UK where only women participated); "no sex" means models without sex differences in variance components (see methods).

Table C

Model Fit Statistics for Diastolic Blood Pressure: ACE, AE, CE and E with or Without Sex Differences in Parameter Estimates for Variance Components

DBP	minus 2 times LL	*df*	$\Delta\chi^2$	*df*	*p*	AIC
Australia						
full model	12360.137	1656				
ACE no sex	12365.459	1659	5.321	3	0.149	–0.679
AE no sex	12365.861	1660	5.724	4	0.221	–2.276
CE no sex	12376.096	1660	15.959	4	0.003	7.959
E no sex	12485.663	1661	125.526	5	0.000	115.526
Denmark						
full model	8972.207	1239				
ACE no sex	8976.159	1242	3.952	3	0.267	–2.048
AE no sex	8977.320	1243	5.113	4	0.276	–2.887
CE no sex	9004.827	1243	32.620	4	0.000	24.620
E no sex	9205.194	1244	232.988	5	0.000	222.988
Finland						
full model	10156.516	1319				
ACE no sex	10180.340	1322	23.825	3	0.000	17.825
AE no sex	10185.493	1323	28.978	4	0.000	20.978
CE no sex	10182.871	1323	26.356	4	0.000	26.356
E no sex	10280.938	1324	124.423	5	0.000	114.423
Netherlands						
full model	6846.121	968				
ACE no sex	6846.404	971	0.283	3	0.963	–5.717
AE no sex	6846.404	972	0.283	4	0.991	–7.717
CE no sex	6860.294	972	14.173	4	0.006	6.173
E no sex	6934.803	973	88.682	5	0.000	78.682
Sweden						
full model	4459.590	593				
ACE no sex	4460.672	596	1.083	3	0.781	–4.917
AE no sex	4460.672	597	1.083	4	0.897	–6.917
CE no sex	4465.166	597	5.576	4	0.233	–2.424
E no sex	4490.507	598	30.917	5	0.000	20.917
UK (females only)						
ACE	26061.370	3422				
AE	26061.370	3423	0.000	1	1.000	–2.000
CE	26090.231	3423	28.862	1	0.000	26.862
E	26249.152	3424	187.783	2	0.000	183.783

Note: Full model is ACE model with sex differences in variance components. This is the model against which other models are compared (except for UK where only women participated); "no sex" means models without sex differences in variance components (see methods).

Table D

Estimates for Genetic, Shared and Non-shared Environmental Variance Components for Age-corrected Diastolic and Systolic Blood Pressure

	SBP						DBP					
	Model	*Va*	*Vc*	*Ve*	h^2	$\Delta \chi^2_1$	Model	*Va*	*Vc*	*Ve*	h^2	$\Delta \chi^2_1$
Australia						0.000						0.403
	ACE	101.08	0.00	94.66	52.0%		ACE	45.32	8.29	51.85	43.0%	
	AE	101.08		94.66	52.0%		AE	54.18		51.12	51.0%	
Denmark						1.390						1.163
	ACE	94.72	20.86	62.43	53.0%		ACE	50.90	10.09	32.12	55.0%	
	AE	115.99		60.87	66.0%		AE	61.11		31.40	66.0%	
Finland						6.945*						5.153*
	ACE	104.54	108.26	216.46	24.0%		ACE	27.17	30.81	76.84	20.0%	
	AE	228.05		198.59	53.0%		AE	62.91		71.32	47.0%	
Netherlands						0.000						0.000
	ACE	60.21	0.00	51.45	54.0%		ACE	37.60	0.00	33.49	53.0%	
	AE	60.21		51.45	54.0%		AE	37.60		33.49	53.0%	
Sweden						0.016						0.000
	ACE	228.12	7.68	202.09	53.0%		ACE	44.42	0.00	57.59	44.0%	
	AE	237.23		200.50	54.0%		AE	44.42		57.59	44.0%	
UK						0.654						0.000
	ACE	130.94	14.60	133.47	47.0%		ACE	59.10	0.00	65.21	48.0%	
	AE	147.70		130.74	53.0%		AE	59.10		65.21	48.0%	

Note: * $p < .05$

Variance components estimates are given for the ACE and AE Model (without Sex Differences). The Chi-squared statistic gives the difference in goodness-of-fit between the ACE and AE Model and indicates that C can nearly always be omitted from the model as an explanation for familial resemblance.