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ARTICLE

Genetic influences on angina pectoris and its impact on coronary heart disease

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As functional properties of the coronaries may differ between coronary heart disease (CHD) patients with or without angina pectoris (AP), it is possible that different genetic mechanisms could be involved in the various CHD phenotypes. The primary aim of this study was, therefore, to determine the relative importance of genetic factors for AP as well as the impact of AP on CHD death in general. All same-sexed twins born between 1886 and 1958 included in the Swedish Twin Registry served as a base for this study. Information from the Swedish Cause of Death Register was used for diagnosing CHD death. Standard methods applied in twin research such as survival and quantitative genetic models were used. The impact of AP on CHD death was significant among both sexes, with larger estimates for males (hazard ratio and 95% CI 2.0 (1.8–2.3)) than females (1.6 (1.4–1.8)). Probandwise concordances and intraclass correlations for AP and CHD death were in general greater in monozygotic than dizygotic twins among both sexes. Heritability analyses resulted in moderate heritability estimates for AP in both sexes (0.39 (0.29–0.49) for males and 0.43 (0.08–0.51) for females). The correlation between AP and CHD was exclusively explained by the influence of familial factors in both sexes. In conclusion, our data imply genetic influences for AP and CHD death among both sexes and that AP is important as a risk factor for CHD death in both males and females, due in part to shared genetic pathways.
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Introduction

An accumulated body of evidence clearly indicates the existence of a genetic predisposition to coronary heart disease (CHD). Long-term follow-up studies on population-based twin registries like those in Denmark and Sweden have shown that death from CHD is influenced by genetic factors,[1,2] particularly at early ages.[3–5] For practical and statistical (power) reasons, most previous studies have focused on CHD at large without trying to subdivide the CHD phenotype into various components such as angina pectoris (AP) and myocardial infarction (MI). Considering that functional properties of the coronaries may differ between CHD-patients with or without AP, it is possible that different genetic mechanisms could be involved in the different CHD-phenotypes. So far, however, little is known about the role of genetic factors in AP. Early studies on the Swedish Twin Registry (STR) by Cederlof *et al*[6] estimating concordance rates for symptoms of AP by using a slightly modified Rose questionnaire[7] indicated that genetic factors may be involved in AP. Therefore, our primary aim was to explore further the possible impact of genetic influences on AP. Second, we were interested in assessing the impact

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of AP on CHD death as well as the genetic contribution to the correlation between these two phenotypes. The main analyses were performed on same-sexed twins born in Sweden between 1886 and 1945.

Materials and methods

The Swedish Twin Registry

The STR was established in the late 1950s[8,9] primarily for studying the effect of smoking on health. The registry has since then been a valuable resource and is regularly matched with the Swedish Cause of Death Register. The STR consists of three different cohorts, those born between 1886 and 1925 (cohort I), twins born between 1926 and 1958 (cohort II), and twins born from 1959 and later. The same-sexed twins from the first two cohorts, born between 1886 and 1958, were used in the present study. Twins born between 1886 and 1925 received three mail-out questionnaires (in 1961, 1963, and 1967) and some selected pairs in 1970 due to non-response to the 1967 questionnaire. Twins born between 1926 and 1958 received a questionnaire in 1972/1973. Twin similarity in the STR was determined by asking twins whether they and their twin partner were similar as two peas in a pod during childhood or not more than siblings in general. If both twins answered yes to this question they were classified as monozygotic (MZ). Twin pairs where both twins answered that they were not more similar than siblings in general were classified as dizygotic (DZ). Those who answered differently were classified as not determined zygosity. This method of determining twin similarity has been proven as adequate, and in total 95% of all diagnoses has been shown to be correct.

AP and CHD

Information on AP for these cohorts was obtained from self-reports.[10] The questionnaires included a set of questions regarding chest pain elaborated by Rose[7] that the World Health Organisation in 1963 recommended for use in epidemiological studies.[11] With the exception of the 1963 questionnaire, diagnoses of AP were further divided in three groups, atypical, effort, and emotional angina. For the present study, only effort and emotional angina were considered as AP. Information regarding CHD death was obtained by merging the STR with the Swedish Cause of Death Registry. CHD death was defined by four different revisions of the ICD during the follow-up period from 1961 to 2001: ICD7 (420, 422.1), ICD8 (410–414), ICD9 (410–414), and ICD10 (I20–I25).

All twins born after 1945 were excluded from the main analyses (AP) as they were too young to be considered for the diagnosis of AP when the questionnaires were sent out. The final sample included in the analyses consisted of 38 924 twins.

Survival analyses

The proportional hazards model or the Cox model is considered as the standard model in basic survival analysis.[12] This model is useful when the aim is to determine hazard ratios (HR) for various risk factors. In the present study, this model was used in order to evaluate the impact of AP on death from CHD.

The classical twin approach

The classical twin approach[13] compares phenotypic resemblance of MZ and DZ twins in order to determine the contribution of environmental and genetic effects on a phenotype. Identical or MZ twins share all their genes in common as compared to fraternal or DZ twins who share on average half of their segregating genes.

Probandwise concordances

Probandwise concordance rates[14] are calculated separately for MZ and DZ twins and if higher rates are observed among MZ than DZ twins, the difference is interpreted to indicate the influence of genetic factors on the trait of interest. Concordant pairs are pairs where both twin-partners experienced the event under study. Discordant pairs are pairs where one twin-partner experienced the event under study. Probandwise concordance is calculated as two times the number of concordant pairs (C) divided by the sum of two times the number of concordant and the number of discordant pairs (D) ($2C/(2C+D)$).

Intraclass correlation and heritability

Liability (susceptibility to an event under study) is considered as an underlying unknown trait influenced by both genetic and environmental factors.[15] This approach utilises threshold models, where the threshold is a point reflecting prevalence on a latent distribution of liability. The prevalence for the present study was calculated from all twins included in the analyses. Individuals above the threshold were assumed to develop the disease and individuals below this point were assumed not to develop the disease. Structural equation modelling techniques implemented in the software Mx[16] were adapted to calculate intraclass correlations as well as to evaluate heritability based on the liability threshold model. All analyses were performed separately for males and females. Intraclass correlations estimate the within-pair correlations in disease liability under the assumption of bivariate normal distribution. In order to evaluate heritability, both contingency tables and raw data can be used. For the present study, raw data were used to estimate heritability in the univariate (single phenotype) as well as in the bivariate (two phenotype) case. Univariate heritability analyses were adjusted for age at followup or death by adjusting the threshold based on the regression coefficient for age on prevalence. A bivariate model was used to analyse genetic contributions to the variation for both phenotypes as well

as the genetic contributions to the correlation between the two phenotypes. Both models rely on several assumptions such as: equal influences of environment for both zygosity groups, absence of epistatic effects, absence of gene × environment interaction as well as absence of assortative mating for the phenotype. Liability is further assumed to consist of additive (*A*) and non-additive (*D*) genetic factors as well as shared (*C*) and non-shared (*E*) environmental factors. Four models were run to obtain estimates of variance components representing these factors. The models are ACE, ADE, AE, and CE, where the ACE model consists of an additive genetic component, a shared and a non-shared environmental component. The other three models are similarly defined. Estimation of variance components for shared environment and dominant genetic factors at the same time (in one model) was not possible as these two components are negatively confounded.[17] In order to determine which full (non-nested) model is the most suitable, the correlation estimates, based on gender and zygosity were compared. A model with additive genetic variance is preferred when the correlation among MZ twins is around two times larger than the correlation among DZ twins. If the DZ correlation is less than half the MZ correlation, the dominant genetic model is preferred. If the DZ correlation is greater than half the MZ correlation, shared environmental influences are indicated. Likelihood ratio test was used in order to compare nested models by comparing 2 log-likelihood – statistic for the full and the reduced models. If the difference (following a χ^2 distribution with one degree of freedom in the univariate case) is observed to be significant the conclusion is that the full model fits the data better than the reduced. In order to determine the best fitting non-nested model, we used the Akaike Information Criterion (AIC).[18] The software used for the present study were Stata,[19] SPSS,[20] and Mx.[16]

Results

In total we observed 2225 cases of AP (835 among males, and 1390 among females).

Proportional hazards model

The impact of self-reported AP on CHD death was significant both among males and females. HR for CHD death obtained by the proportional hazards model (Table 1) yielded ratios of 2.0 (95% CI, 1.8–2.3) among males, and 1.6 (1.4–1.8) among females. Analysing males and females together resulted in an HR of 1.6 (1.5–1.8). Including sex in the model increased the AP estimate to HR 1.8 (1.6–2.0). Men had a significantly greater risk of CHD death than women (HR 2.2 (2.0–2.3)). Including an interaction term for AP and sex indicated that the impact of AP on CHD death was significantly higher among males as well.

Probandwise concordances and intraclass correlations

Probandwise concordances and intraclass correlations (Table 2) were greater for MZ twins as compared to DZ twins for both AP and CHD. Concordances for AP were slightly larger in MZ females than MZ males. Similarly, intraclass correlations for AP were larger in MZ pairs than in DZ pairs, and greater for MZ females than MZ males. These patterns suggest that genetic influences are of importance for both sexes, and that familial environmental influences may be of importance for males. The concordances and intraclass correlations for CHD suggest fewer gender differences than for AP.

Table 2 Concordant and discordant pairs, probandwise concordances, and tetrachoric (intraclass) correlations, by sex and zygosity

	Males		*Females*	
	MZ twins	*DZ twins*	*MZ twins*	*DZ twins*
AP				
Concordant pairs	30	32	63	49
Discordant pairs	249	420	362	750
Probandwise concordance	0.19	0.13	0.26	0.12
Tetrachoric correlation	0.39	0.27	0.46	0.15
CHD				
Concordant pairs	180	288	118	191
Discordant pairs	586	1188	529	1038
Probandwise concordance	0.38	0.33	0.31	0.27
Tetrachoric correlation	0.50	0.38	0.48	0.39
AP and CHD				
AP–CHD correlation	0.32	0.28	0.24	0.17

Table 1 Hazard ratios with 95% confidence intervals

Explanatory variables	*Model I*	*Model II*	*Model III*	*Males only*	*Females only*
AP	1.6** (1.5–1.8)	1.8** (1.6–2.0)	1.6** (1.4–1.8)	2.0** (1.8–2.3)	1.6** (1.4–1.8)
Sex		2.2** (2.0–2.3)	2.1** (2.0–2.2)		
AP × sex			1.2* (1.0–1.5)		

Model I includes AP, Model II includes AP and sex (woman as the reference group), Model III includes AP, sex, and AP × sex (an interaction term), *$P = 0.017$, **$P = 0.000$.

Heritabilities

The univariate model The pattern of correlations for MZ and DZ twins suggested that the full model with shared environment should be used among males. Comparing the AE and CE model with the ACE model by the likelihood ratio test (ACE *vs* AE, difference of 0.95, 1_{df}) and (ACE *vs* CE, 2.6, 1_{df}) indicated that both nested models give a better fit than the full model. Comparison of AIC values indicated that the AE model was the better fitting model for AP in males. In females, the large difference in correlations preferred a full model including dominant genetic effects instead of the ACE model. The likelihood ratio test comparing AE with the ADE model resulted in a significant difference (5.7, 1_{df}) indicating that there was a significant non-additive effect (D) (Table 3). The heritability for AP (Table 3) in males was 0.39 (0.29–0.49) and in females 0.43 (0.08–0.51). The pattern of twin correlations for CHD indicated that a full model including shared environment (ACE) was most appropriate in both males and females. The best fitting model in both sexes was the AE model. Heritability of CHD (Table 4) from the AE model was 0.45 (0.39–0.50) in males and 0.39 (0.33–0.45) in females.

The bivariate model

The ACE model was the better fitting model in the bivariate model of AP and CHD (Table 5). Depicting the correlation between AP and CHD into components *A*, *C*, and *E* resulted in moderate familial influence on the correlation among both sexes. The phenotypic correlation was almost completely explained by familial factors, that is, both genetic (*A*) and shared environmental (*C*) correlations were positive. The genetic proportion of the correlation was 0.44 among males and 0.55 among females. The contribution of the shared environmental part to the total phenotypic correlation was 0.67 for males and 0.39 for females. The proportion of the non-shared (unique) environmental factors to the correlation was smaller for both males and females.

Discussion

Our data clearly indicate that AP diagnosed by responses to a questionnaire increases the hazard of dying from CHD for both sexes with a slightly higher impact for males compared with females. The association between the two phenotypes is moderately large and almost entirely explained by familial factors (shared environment and genetic factors). The influence of genetic factors plays a moderate role for the occurrence of AP as well as for death from CHD among both sexes.

In addition, our findings confirm and extend previous findings concerning the existence of a genetic predisposition for the development of AP based on substantially smaller samples from the STR.[6] Later studies focusing on

Table 4 Heritability estimates for CHD death, by sex

CHD	a^2	c^2,d^2	e^2	*−2 log-l*	*Difference in 2 log-l*[l]	*Probability*
Males						
ACE	0.32	0.10	0.58	15392.23		
AE[a]	0.45		**0.55**	15395.00	2.770[b]	0.096
CE		0.32	0.68	15407.94	15.703[b]	0.000
ADE	0.45	0.00	0.55	15395.00		
Females						
ACE	0.25	0.10	0.64	13508.10		
AE[a]	0.39		0.61	13510.61	2.513[b]	0.113
CE		0.28	0.72	13515.76	7.660[b]	0.006
ADE	0.39	0.00	0.61	13510.61		

All results adjusted for age.
[a]Best fitting model.
[b]Comparison of the ACE model with the AE and the CE model.
[l]One degree of freedom.

Table 3 Heritability estimates for AP, by sex

Angina pectoris	a^2	c^2,d^2	e^2	*−2 log-l*	*Difference in 2 log-l*[a]	*Probability*
Males						
ACE	0.25	0.12	0.63	6442.195		
AE[b]	**0.39**		**0.61**	6443.141	0.947[c]	0.331
CE		0.29	0.71	6444.795	2.600[c]	0.107
ADE	0.39	0.00	0.61	6443.141		
Females						
ADE[b]	0.00	0.43	0.57	9734.299		
AE	0.38		0.62	9739.974	5.675[d]	0.017
ACE	0.38	0.00	0.62	9739.974		
CE		0.24	0.76	9761.745		

All results adjusted for age.
[a]One degree of freedom.
[b]Best fitting model.
[c]Comparison of the ACE model with the AE and the CE model.
[d]Comparison of the ADE model with the AE model.

Table 5 Heritability and proportions of AP–CHD correlation obtained by the bivariate model (ACE), by sex

	ACE model			*Model comparison*				
	a^2	c^2	e^2	*Model*	*−2 log-l*	*Difference in 2 log-l*[a]	*Probability*	*AIC*
Males				ACE[b]	20968.98			−46091.019
AP	0.24	0.16	0.60	AE	20995.49	26.513	0.000[c]	−46070.506
CHD	0.25	0.26	0.49	CE	20983.17	14.186	0.003[c]	−46082.833
Proportion of correlation	0.44	0.67	−0.11	ADE	20995.39			−46064.607
Females				ACE[b]	23505.82			−58070.176
AP	0.38	0.03	0.59	AE	23530.62	24.799	0.000[c]	−58051.378
CHD	0.16	0.32	0.53	CE	23528.75	22.929	0.000[c]	−58053.247
Proportion of correlation	0.55	0.39	0.06	ADE	23526.96			−58049.036

[a]Three degrees of freedom.
[b]Best fitting model.
[c]Comparison of the ACE model with the AE and the CE model.

CHD in general both on Swedish and Danish twins suggested that death from CHD was moderately influenced by genetic factors.[1–5] Our current data (with longer follow-up than previously published data) indicated heritability estimates for CHD death similar to those previously reported for both Swedish and Danish twins.[1,2,5] Our data also suggest that AP as a single factor has a significant impact on CHD death in both sexes, although somewhat more apparent in males. The association between AP and CHD is entirely explained by familial factors, more so due to shared genetic factors among women than men.

Follow-up studies of the Framingham population have shown that CHD manifestations differ between sexes. MI was more likely unrecognised in women as compared to men, and AP in women more often seemed uncomplicated whereas AP in men was also more often related to MI.[21] A merging of AP and MI into one end point (CHD) may therefore, be more suitable in males.[22] Causes other than coronary artery disease for chest discomfort could be more common in women.[23]

The Rose questionnaire, slightly modified, served as the basis for evaluating AP in twins included in STR. The main results and conclusions were, therefore, based on self-reported symptoms and not on physical examination. The results were, however, partly confirmed by use of information from the Swedish Hospital Discharge Register (SHDR), covering AP diagnoses on all in-patient care at Swedish Hospitals from the period 1987 to 2003. As this register reflects only the more severe forms of AP the number of observed AP cases was much lower than the self-reports, 614 (329 males and 285 females). Although the SHDR-probandwise concordance rates for AP were somewhat lower (0.12 for MZ and 0.05 for DZ twins) than the corresponding rates based on the self-reports, the patterns overall were quite similar. Despite weaknesses, the Rose questionnaire as elaborated in the beginning of 1960s predicts future cardiovascular disease fairly well.[24] During the years, a number of papers have been published concerning the validity/reliability of the Rose questionnaire.[10,23,25] A study based on Swedish twins compared the questionnaire diagnosis with clinical diagnosis where the examination was based on detailed medical history together with results from an exercise test.[10] The clinical diagnosis required also a pathologic post exercise electrocardiogram reaction. The study was, however, based on a small sample of 170 twin pairs with few AP cases (eight men and 11 women). Out of eight male AP cases according to the questionnaire, four were confirmed at the clinic as manifest cases. This comparison showed an association among males but not among females. Lundman *et al*,[25] study of the validity of the Rose questionnaire included in the STR, showed a high frequency of false-positives, and suggested that this questionnaire is useful only for screening of potential CHD cases. Furthermore, Harris and Weissfeld[23] showed that the reliability of reporting AP (standardised Rose questionnaire) in The Lipid Research Clinics Prevalence Study was somewhat lower among women than men. The overall age-adjusted kappa was 0.65 (0.60–0.78) for males and 0.51 (0.42–0.60) for females. Despite the poorer accuracy of reporting AP in women, self-reported AP in the present study increases the hazard of CHD death both in women as well as in men.

It is important, though, to note that self-reported information regarding chest pain based on this questionnaire could have resulted in a number of false-positive AP cases. However, concordances for AP obtained by SHDR confirmed the genetic findings on self-reported AP. Information regarding CHD death was obtained from the Swedish Cause of Death Registry for which the validity of coding CHD deaths has been shown to be fairly good.[26]

The classical twin approach,[13] as applied in this particular study, relies on several crucial assumptions.[27] One of the key assumptions is that of 'equal environments'. There is no reason to believe that there are any cases in which greater imposed similarities in the environment result in differential similarities for MZ than DZ twins for cardio-

vascular outcomes. Perinatal differences in implantation patterns, intrauterine position as well delivery events may underestimate concordances among MZ twins and, therefore, underestimate the impact of genetic effects. In addition, assuming an absence of gene × environment interactions may underestimate familial factors. Assortative mating, if not included, underestimates the genetic component and overestimates the impact of the shared environment. It is difficult to imagine that mates select for AP or a specific cause of death. Furthermore, the twin model is underpowered to evaluate the relative importance of non-additive genetic influences such as epigenetic effects.

In conclusion, self-reported AP influences the hazard of dying from CHD among both sexes, although to a higher degree among males. Genetic factors are of importance for the occurrence of both AP and CHD death among both sexes. Finally, familial factors almost exclusively explain the correlation between these two phenotypes.

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