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Genetic Influences on CHD-death and the Impact of Known Risk Factors: Comparison of Two Frailty Models

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The importance of some recognized risk factors on genetic influences for coronary heart disease (CHD) needs further clarification. The aim of the present study was therefore to study the impact of known risk factors on genetic influences for CHD-death. Both twin (correlated gamma-frailty) and non-twin models (univariate gamma-frailty) were utilized and compared regarding their suitability for genetic analyses. The study population consisted of twins born in Sweden between 1886 and 1925. As expected, our findings indicate that genetic influences are important for CHD-death. Inclusion of risk factors in the twin-model increased heritability estimates, primarily due to a substantial reduction in non-shared environmental variances. The genetic influences for CHD-death are only marginally mediated through the risk factors among males, but more so among females. Although the outcome phenotype used in the present study is not behavioral, the analyses demonstrate the potential of frailty models for quantitative genetic analyses of categorical phenotypes.

KEY WORDS: Coronary heart disease; frailty; heritability; risk factors; twins.

INTRODUCTION

Various studies have suggested that coronary heart disease (CHD) is influenced by genetic factors (Li *et al*., 2000; Wienke *et al*., 2001; Zdravkovic *et al*., 2002). One way of determining the impact of genetic influences as well as other risk factors on CHD risk has been to compare relative hazards (risks) for a CHD event among relatives of different degrees with adjustment for confounding. This approach was used by Marenberg and colleagues who studied CHD-mortality and the effect of some known risk factors among Swedish twins (Marenberg *et al*., 1994). They found CHD-mortality to be influenced by genetic factors for both sexes (particularly at younger ages), and that the relative hazards for monozygotic (MZ) and dizygotic (DZ) twins were only slightly influenced by risk factors for CHD.

During the last several decades different approaches for analyzing the relative importance of genetic factors have been introduced. These approaches can be separated into two groups, the liability (Falconer, 1965) and the frailty approaches (Clayton, 1978; Hougaard, 2000; Yashin *et al*., 1995). The liability approach is based on threshold models, where the threshold is a point reflecting prevalence on a latent distribution of liability. Individuals above

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this point are assumed to have the disease under study and individuals below this point are assumed not to have the disease. Structural equation modeling techniques, like the ones implemented in the frequently used software Mx (Neale, 1997), have been adapted to evaluate heritability based on the liability threshold model. The multivariate frailty approach may be considered in two ways: shared and correlated frailty. In general, frailty is also modelled as a latent trait, however these models are analogous to hazards models in that they focus on times to events. Furthermore, frailties are not *a priori* considered to be normally distributed. Rather, the latent distribution is frequently considered to follow the gamma distribution. Shared frailty models assume that members within a twin pair share the frailty. Correlated frailty models assume that twins in a pair have different but correlated frailties. In general, correlated frailty approach deals with more complex models, and hence requires larger data sets than the liability approaches.

In order to determine the relative influence of genetic and environmental factors in general on CHD-death, we recently applied a frailty approach to data on CHD-death (Wienke *et al.*, 2001; Zdravkovic *et al.*, 2002). The influence of genetic factors on CHD-death was moderate. However, the question of how much of the influence was due to genetic influences mediated through related risk factors remains to be studied. Therefore, the main focus of the present study was to determine to what extent genetic influences for CHD-death in the Swedish Twin Registry are affected by genetic effects for cardiovascular risk factors (genetic confounding). Thus, the aim of this paper is to determine how much of the genetic risk for CHD is mediated by the risk factors for CHD that are themselves in part genetically influenced. Furthermore, we demonstrate differences and similarities in results that can be obtained from two frailty models, a univariate gamma-frailty model that we call the non-twin model and a correlated gamma-frailty model that we call the twin model.

MATERIAL

The Swedish Twin Registry

The Swedish Twin Registry (Lichtenstein *et al.*, 2002; Pedersen *et al.*, 2002) is currently the largest population-based twin registry in the world. The registry adequately represents the Swedish population regarding cardiovascular morbidity and mortality and it includes information on all twins born in Sweden between 1886 and 2001. The present study is based on the oldest cohort from the registry, that is, all like-sexed pairs born between 1886 and 1925, who still lived within the country as unbroken pairs and responded to two questionnaires in 1961 and 1963. The cohort is regularly matched with the Swedish Cause of Death Registry to obtain international classification of death codes (ICD) for information from death certificates, with a follow-up from 1961 through 1996. Information on known CHD-related risk factors was obtained from two questionnaires mailed to all like-sexed twins in 1961 and 1963. The response rate for the first questionnaire (sent out in 1961) represented 84.9% of the pairs. The second questionnaire (sent out in 1963) was sent to all twins who responded to the first questionnaire. The rate of response for the second questionnaire was 92% of those responded to the first questionnaire (Cederlof *et al.*, 1977). The average age of the twins responding to the first questionnaire was approximately 50 years. All twins with undetermined zygosity ($N = 878$) were excluded from the analyses as well as another 20 pairs because of missing information in the Cause of Death Registry. Individuals with height recorded as below 140 cm were excluded from the analyses ($N = 13$) as well as individuals reporting a weight below 40 kg or above 150 kg ($N = 30$). In order to facilitate the comparison between models, only twin-pairs with complete information on the study variables were considered. This was done for three reasons. Firstly, the twin model as analyzed requires complete information on all variables for both twins within a pair. Secondly, for comparability between the twin and the non-twin model we decided to apply both models on same data set. Thirdly, the analysis of heritability is the primary focus of this paper. The final sample, therefore, contained 14,170 twins where of 2,270 MZ and 4,074 DZ males and 2,750 MZ and 5,076 DZ females, respectively.

Study Variables

Information on CHD-death and life span were our primary variables as well as information on risk factors (presented in Table I). In order to adjust for year at birth, a variable for different birth periods was created, based on the intervals 1886–1895, 1896–1905, 1906–1915, and 1916–1925. The period between 1886 and 1895 served as the reference category. Smoking status was determined by asking the subjects whether they have ever smoked, if they were

Table I. Distribution of Risk Factors by Sex

Risk factors		Males (number of twins)	Females (number of twins)
Smoking	Current smokers	3138 (49.5%)	1333 (17.0%)
	Former smokers	1061 (16.7%)	313 (4.0%)
	Non smokers*	2145 (33.8%)	6180 (79.0%)
BMI	$\geq$28 kg/m^2	694 (10.9%)	1110 (14.2%)
	24 $\leq$ BMI $<$ 28 kg/m^2	3001 (47.3%)	2839 (36.3%)
	$<$24 kg/m^2*	2649 (41.8%)	3877 (49.5%)
Level of education	Above grade school	2083 (32.8%)	2003 (25.6%)
	Grade school*	4261 (67.2%)	5823 (74.4%)
Hypertension	Yes	246 (3.9%)	817 (10.4%)
	No*	6098 (96.1%)	7009 (89.6%)
Diabetes	Yes	73 (1.2%)	128 (1.6%)
	No*	6271 (98.8%)	7698 (98.4%)
Marital status	Married	5084 (80.1%)	5857 (74.8%)
	Divorced	316 (5.0%)	798 (10.2%)
	Unmarried*	944 (14.9%)	1171 (15.0%)

* Represents the reference group in the multivariate analysis.

currently smoking or if they have stopped smoking. The non-smoker category served as the reference category. By dividing each subject's weight in kilograms (kg) with the square of the height in meters (m^2) a variable for body mass index (BMI) was created where values below 24 kg/m^2 served as the reference category and the other two groups were 24 $\leq$ BMI$<$ 28 kg/m^2 and equal to or greater than 28 kg/m^2. Self reported hypertension and diabetes were treated as dichotomous variables where the reference group was free from hypertension and free from diabetes, respectively. Marital status was classified in three groups: married, not married, and divorced. The unmarried group served as the reference group. Educational level was divided into two categories, grade school (reference group), and above grade school. Zygosity was included in the non-twin model with monozygosity as the reference group.

METHODS

Frailty Models

The key idea behind the concept of frailty is that individuals have different "frailties" (in the present study susceptibility to CHD-death), and that those who are most frail have an increased risk to die earlier than others (Vaupel *et al.*, 1979). A frailty model is an extension of the Cox model (Cox 1972), the main feature of which is to include an unobserved random variable (frailty) for unobserved heterogeneity. Different distributions can be chosen for the frailty. In this paper frailty is assumed to be gamma distributed. It is not possible that frailty takes a negative form, and the gamma distribution is frequently used as a distribution on positive numbers (Abbring and van den Berg, 2003). Arguments in favor of this distribution are based on mathematical and computational aspects. We have applied two gamma frailty models in this paper, a univariate gamma-frailty model that we chose to call the non-twin model and a correlated gamma-frailty model that we chose to call the twin model.

The Univariate Gamma-Frailty Model

The univariate gamma-frailty model (the non-twin model) is applied in order to assess the potential importance of genetic risk in terms of hazards for CHD-death treating related individuals as independent observations. This is a parametric approach which needs specification for the baseline hazard function (Gompertz in the present study) and for the distribution of the frailty (gamma in the present study). Relative hazards of CHD-death given that one's twin-partner died from CHD were calculated for MZ and for DZ-twins and the ratio between the hazards was then computed. If higher relative hazards are observed among MZ-twins than DZ-twins (relative hazard ratio above one) the difference reflects the influence of genetic factors. As the model includes an unobserved random variable for

hidden heterogeneity, it is not possible to interpret the estimates as relative hazard rates on a group level but rather on an individual level (conditional hazard rates). The statistical software package Stata (StataCorp. 2001) was used for the analyses by the non-twin model.

The Correlated Gamma-Frailty Model

The correlated gamma-frailty model (the twin model) is particularly useful when dependent lifetime analyses are applied (Yashin and Iachine 1995; Yashin *et al.*, 1995; Yashin *et al.*, 1996). The relationship between susceptibility to death and longevity is modeled by the notion of random hazard. Susceptibility is represented by an unobserved random variable called frailty when the random variable acts multiplicatively on the baseline hazard. The correlated frailty approach deals with individual frailties. Therefore, frailties do not necessarily have to be the same for both twins within a pair. Consider the frailty of the first twin in a pair to consist of $Y_0 + Y_1$, and the frailty of the second twin to consist of Y_0+Y_2, where Y_0, Y_1, and Y_2 are independent gamma distributed random variables. The frailties of the two twins are evidently correlated by the shared part of the frailty Y_0. The correlated gamma-frailty is a bivariate lifetime model that deals with censored and truncated observations, and permits a combination of survival analysis with the methods of quantitative genetics. As the correlated gamma-frailty model stems from the frailty model introduced by Vaupel and colleagues, it is feasible to evaluate the impact of genetic influences mediated through risk factors, their impact on CHD-death as well as to quantify to what extent susceptibility to CHD-death is genetically influenced. Observed covariates (risk factors) are modeled in the correlated gamma-frailty model in a fashion similar to modeling in the univariate gamma frailty and the Cox model, (Cox, 1972). When applying the correlated gamma-frailty model, estimates of variance attributable to genetic as well as to environmental factors are obtained at the same time as the risk factors are modelled. The genetic analysis makes use of the correlation calculated between relatives (in the present study MZ and DZ-twins) for partitioning the correlation into components attributable to shared genes and environments from which heritability could be calculated. The correlation coefficients ρ_{MZ} and ρ_{DZ} calculated for MZ and DZ-twins provide information about both genetic and environmental influences. For example, under the assumption of equal environments for both MZ and DZ-twins, differences in the two correlation coefficients reflect the influence of genetic factors. Five models based on different assumptions about genetic structure were fit to variance estimates produced by the gamma-frailty model. These models are based on genetic (additive (A), non-additive (D)) and environmental components (shared (C), non-shared (E)). The AE-model refers to the decomposition of variation in frailty $P_z = A + E$, and ADE, ACE, DE, and CE-models are similarly defined. From the estimation point of view no more than three components can be simultaneously represented in a model based on MZ and DZ-twins. The components D and C cannot be estimated in the same model. Selection of the best fitting nested model was based on the likelihood ratio test and selection of the best fitting non-nested model was based on Akaike information criterion (AIC) (Akaike, 1987). The statistical software Gauss, (Aptech Systems, 1996) was used for these analyses.

RESULTS

From the period 1961–1996, there were 2499 CHD-deaths (1437 male and 1062 female). Risk factor estimates obtained by the twin and the non-twin model are similar. In general, estimates obtained by the twin model are larger, particularly for risk factors with a low number of cases such as diabetes and hypertension. Independently of gender, the health-related risk factors hypertension, diabetes, and high BMI as well as life-style habits such as smoking contributed significantly to an increase in the risk of dying from CHD (presented in Table II). The relative hazard of CHD-death was significantly lower for twins with a level of education above grade school (among males) and among married compared to unmarried twins (among both males and females). The adjusted relative hazards (Figure 1) indicate an apparent difference in the influence of genetic factors on CHD-death. The relative hazard for MZ-twins whose partner died from CHD was significantly larger than the relative hazard for DZ-twins among both sexes.

The best fitting genetic model for both sexes was the AE-model, indicating that the nature of genetic factors influencing CHD-death is additive and the nature of environmental effects is non-shared or individual specific (presented in Table III). Furthermore, the purely environmental model (CE) did not fit the data, and hence

Table II. Parameter Estimates and 95% Confidence Intervals of Relative Hazards for Risk Factors by Sex and Model

Risk factors	Males		Females	
	Univariate gamma-frailty model (the non-twin model)	Correlated gamma-frailty model (the twin model)	Univariate gamma-frailty model (the non-twin model)	Correlated gamma- frailty model (the twin model)
Current smokers	1.8 (1.5–2.1)	2.1 (1.6–2.7)	2.4 (1.9–3.0)	2.6 (1.9–3.4)
Former smokers	0.9 (0.8–1.2)	1.0 (0.8–1.3)	1.2 (0.7–1.9)	1.2 (0.7–2.1)
Hypertension	2.8 (2.0–4.0)	3.4 (2.2–5.4)	2.8 (2.2–3.6)	3.0 (2.2–4.1)
Diabetes	3.7 (2.0–7.1)	4.9 (2.1–11.3)	9.1 (4.5–18.2)	12.7 (5.4–29.5)
$24 \leq$ BMI < 28 kg/m^2	1.3 (1.1–1.5)	1.4 (1.2–1. 7)	1.3 (1.1–1.6)	1.4 (1.1–1.7)
BMI ≥ 28 kg/m^2	1.5 (1.2–1.9)	1.6 (1.2–2.1)	1.7 (1.4–2.2)	1.9 (1.4–2.5)
Education	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.7–1.0)	0.8 (0.6–1.0)
Married	0.7 (0.6–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.9)	0.7 (0.5–0.9)
Divorced	1.2 (0.8–1.6)	1.3 (0.9–2.0)	0.7 (0.5–1.0)	0.7 (0.5–1.0)

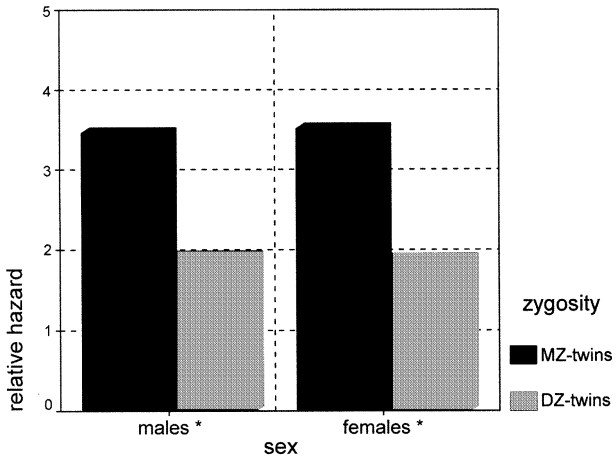

Fig. 1. Adjusted relative hazards of CHD-death for MZ and DZ twins whose partner died from CHD by sex. *denotes that the adjusted relative hazard for MZ-twins is significantly different from the adjusted relative hazard for DZ-twins. * p-value < 0.01.

CHD-death is not influenced solely by environmental factors. The heritability estimate obtained in the crude analysis (not considering risk factors) was 0.40 (0.26–0.54) among females and 0.59 (0.41–0.76) among males. When including risk factors in the analysis, we observed a slight decrease of the genetic variance, more apparent among females, and a substantial decrease of the non-shared environmental variance among both sexes. Thus, a very slight portion of the genetic variance among males, and a moderate portion of the genetic variance among females is accounted for by the genetic variance for these risk factors. On the other hand, the risk factors do account for a substantial part of the individual specific environmental variance.

DISCUSSION

Our findings suggest that death from CHD is moderately influenced by additive genetic factors.

Table III. Estimates of the Components of Variance in Frailty to Mortality from Coronary Heart Diseases Obtained by the Twin Model: AE-Model With and Without Risk Factors

Genetic model AE:	Males				Females			
	Crude		Adjusted*		Crude		Adjusted*	
	S^2	S^2/σ^2	S^2	S^2/σ^2	S^2	S^2/σ^2	S^2	S^2/σ^2
Additive genetic Component (A)	2.97	0.59 (0.41–0.76)	2.26	0.74 (0.55–0.92)	4.66	0.40 (0.26–0.54)	2.07	0.55 (0.36–0.73)
Non-shared environmental Component (E)	2.09	0.41 (0.24–0.59)	0.80	0.26 (0.08–0.44)	6.95	0.60 (0.46–0.74)	1.72	0.45 (0.27–0.64)

*Adjusted for smoking, BMI, hypertension, diabetes, marital status, level of education, and birth periods. 95 % confidence intervals are presented in brackets. The total variance for the AE-model is as follows:$\mathrm{Var}(P_z) = \sigma^2 = S_A^2 + S_E^2$, where P_z = frailty, σ^2 is the variation of frailty, S^2 is the variation due to additive genetic factors (A) or due to non-shared environmental factors (E). The heritability estimate is calculated by S_A^2/σ^2.

Although measured risk factors for CHD-death are important, these risk factors account marginally for genetic influences for CHD-death among males but more so among females. The CHD-related risk factors explained a substantial portion of the individual specific (non-shared) environmental variance. Apparent increases in heritability after inclusion of these risk factors were not due to genetic effects but rather due to individual specific environmental variance attributable to these measured risk factors.

Results presented in this study suggest that the risk factors together have a greater environmental than genetic impact on CHD-death. Earlier studies on CHD-death have shown that the influence of genetic factors seems to be moderate (Marenberg *et al*., 1994; Wienke *et al*., 2001; Winkelmann *et al*., 2000; Zdravkovic *et al*., 2002). Earlier studies have also suggested genetic influences for CHD-related risk factors such as BMI (Allison *et al*., 1996; Bouchard 1997; Coady *et al*., 2002; Herskind *et al*., 1996a; Pausova *et al*., 2001), smoking (Carmelli *et al*., 1992; Osler *et al*., 2001), educational attainment (Lichtenstein *et al*., 1992), marital status, personality and divorce (Jockin *et al*., 1996), blood pressure (Hong *et al*., 1994) and diabetes (Kaprio *et al*., 1992; Kyvik et al., 1995; Mayer *et al*., 1996). Furthermore, Nelson *et al*. found that the influence due to genetic factors on body fat, insulin, and cardiovascular disease (CVD) differed among sexes, and that heritability estimates were higher for females in general. They suggested that there were shared genetic and environmental effects among all variables except CVD (Nelson *et al*., 2000). Another study examining several phenotypes and common genetic factors is the study by Herskind and colleagues who showed that only a small fraction of genetic influences on longevity is mediated by genetic factors in common to smoking and BMI (Herskind *et al*., 1996b). Despite the role of genetic factors for these risk factors, their impact is not reflected to any great extent in the genetic variance for CHD-death.

In the present study the best fitting genetic model was the AE-model for both sexes. By including risk factors in the twin-model we observed a slight increase of heritability. This may seem a bit strange, although use of the heritability coefficient when computed as a proportion of variance may be misleading. One does not know whether the heritability increases due to an increase in the genetic variance or due to a decrease in the environmental variance. In the present case, the increase was largely due to the influences of the latter. By including CHD-related risk factors in the analysis we mainly reduced the environmental heterogeneity in frailty, as this variability was attributable to observed environmental factors. Thus, the focus should not be on the apparent increase in heritability but rather on the relatively large decrease in the environmental variance. These results help us to understand that the risk factors studied represent primarily environmental sources of variation for CHD-death, despite the role that genetic influences may play for the specific risk factors.

A secondary purpose of this paper was to contrast the types of interpretations that can be drawn from two types of models applied. The estimates obtained by the two models are similar. Both models stem from the Cox model, which is considered standard in survival analysis. The twin model stems from the non-twin model introduced by Vaupel and colleagues. For both models, observed covariates (risk factors) are modelled in a fashion parallel to modelling in the Cox models. Thus, it is not surprising that the estimates obtained by both the twin and the non-twin model for the observed risk factors were similar in pattern if not in absolute values. In general, risk factor estimates were larger for the twin model. Nonetheless, the principal statistical difference between the non-twin and the twin model is the handling of the correlation between twins within a pair. In the non-twin models this correlation is not captured, resulting in independent observation analysis and in incorrect standard errors for the estimates. An important difference between the non-twin and the twin model is that estimation of the impact of risk factors on the trait under study is possible, but the question of its nature, genetic or environmental, remains unanswered in the non-twin model. In contrast, by applying the twin model, estimation of the impact of risk factors as well as genetic and environmental influences is possible, which speaks in favor of the twin model. However, a disadvantage of these models (parametric approach) in general, is the need for specifying the baseline hazard function (Gompertz in the present study) and the distribution of the frailty (gamma in the present study).

In frailty models all calculations are based on the assumption of mutually independent covariates. If both observed and unobserved covariates are dependent, then frailty (considering frailty as a combination of all unobserved covariates) and

observed covariates are not independent. Such dependence is not included in standard frailty models like correlated gamma-frailty model and can cause strange results. It is, however possible to extend the model by including such dependence. For example, we observed a surprisingly high estimate regarding diabetes, particularly among females. However, this was not due to possible dependence between frailty and diabetes as we did not find any evidence for an interaction, but rather due to the small number of cases and consequently a large variability of the estimate. In standard models the assumption of homogeneity is frequently used and the estimates are interpreted on a group level. There are many risk factors (both known, such as lipids, and yet unknown factors) that are related to CHD and which would have been of interest to include in the analyses. However lack of information on such risk factors, observable as well as unobservable, leads to heterogeneity (Hougaard, 2000). The standard approach has been to ignore such factors unless it is possible to find the necessary information for each individual. In such approaches heterogeneity is included in the error term, which leads to an increase in variability of the response compared to the case and risk estimates become smaller and result in an underestimation of relative risks. In survival analysis this increase of variability affects the hazard function. This, in turn, influences both the assumption of proportional hazards as well as the hazard ratios. Therefore, frailty models are preferable compared to standard approaches in analyses of this type of data.

Data for the present study consist of information from twins drawn from the largest and one of the oldest population-based twin registries in the world, with a follow-up from 1961 through 1996. In total, we observed a large number of CHD-deaths, 1437 males and 1062 females. The strength of the present study is, therefore, its statistical power, the large number of cases, the long length of the follow-up as well as the reliability of coding CHD-deaths (de Faire *et al*., 1976). In contrast, the limitations of the study were left truncation of the data (although this has been corrected for), and that the information on risk factors was obtained from self-reported questionnaires in 1961 and 1963. It was not possible to study gene environment interaction, which requires information about other relatives such as offspring. Thus, this is a limitation due to the data and not due to the choice of models. Finally, no information on lipid levels was available for the twins at that time. Therefore, our conclusions regarding the impact of risk factors on genetic influences for CHD-death do not take potential genetic influences mediated through lipoproteins into account.

We conclude that the genetic influences on CHD-death are moderate among both sexes. These influences are marginally mediated among males and moderately among females through genetic factors in common with a number of risk factors. The impact of the studied risk factors is mainly environmental.

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