The Heritability of Mortality Due to Heart Diseases: A Correlated Frailty Model Applied to Danish Twins

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Data of the Danish Twin Registry on monozygotic and dizygotic twins are used to analyse genetic and environmental influences on susceptibility to heart diseases for males and females, respectively. The sample includes 7955 like-sexed twin pairs born between 1870 and 1930. Follow-up was from 1 January 1943 to 31 December 1993 which results in truncation (twin pairs were included in the study if both individuals were still alive at the beginning of the follow-up) and censoring (nearly 40% of the study population was still alive at the end of the follow-up). We use the correlated gamma-frailty model for the genetic analysis of frailty to account for this censoring and truncation. During the follow-up 9370 deaths occurred, 3393 deaths were due to heart diseases in general, including 2476 deaths due to coronary heart disease (CHD). Proportions of variance of frailty attributable to genetic and environmental factors were analyzed using the structural equation model approach. Different standard biometric models are fitted to the data to evaluate the magnitude and nature of genetic and environmental factors on mortality. Using the best fitting model heritability of frailty (liability to death) was found to be 0.55 (0.07) and 0.53 (0.11) with respect to heart diseases and CHD, respectively, for males and 0.52 (0.10) and 0.58 (0.14) for females in a parametric analysis. A semi-parametric analysis shows very similar results. These analyses may indicate the existence of a strong genetic influence on individual frailty associated with mortality caused by heart diseases and CHD in both, males and females. The nature of genetic influences on frailty with respect to heart diseases and CHD is probably additive. No evidence for dominance and shared environment was found.

Genetic and environmental influences on heart diseases (and here especially on CHD as the most important subgroup among heart diseases, covering around three quarter of all deaths caused by heart diseases) has been widely discussed in the literature, because heart diseases are the main cause of death in the developed world today. Most interest has been focused on environmental factors, since these can be modified and controlled. The role of family history in heart diseases has been well established. Twin studies may be the most appropriate way for quantitating the relative role of the extent to which the familial occurrence of heart diseases is due to genetic mechanisms. Furthermore, questions about the nature of the genetic effect (additive versus non-additive) can be addressed. Former studies from the Danish (Harvald & Hauge, 1970) and Swedish (de Faire et al., 1975; Marenberg et al., 1994) twin registries found a genetic component in the risk of death from coronary heart disease. All of these studies, however, used traditional approaches of analysis of concordance rates. But especially in the presence of truncated and censored lifetime data (or more general duration data) concordance analysis is of limited value. Approaches from survival analysis are needed to account for truncation and censoring. Such kinds of methods have to be combined with methods of genetic epidemiology. Furthermore, heterogeneity of individuals in susceptibility to heart diseases should be included in the model. For such a combined analysis we apply the correlated gamma-frailty model (Yashin et al., 1995; Yashin & Iachine, 1995a) in the present paper, which takes into account the dependence of life spans of relatives (here twins) and allows us to estimate the effect of genetic factors in frailty on mortality due to heart diseases.

This approach enables us to combine information about cause of death with data on age at death and to include truncated and censored observations. This substantially raises the number of twin pairs used in our study and consequently the statistical power of the analysis. For each individual we assume two competing risks of latent times (lifetime with respect to death due heart diseases or CHD and lifetime with respect to death due to all other diseases (including censoring)). Furthermore, we assume that these competing risks are independent. An extension of the model to more than two competing risks or to the multivariate case in family studies is straightforward. We empirically demonstrate the advantages of the model in the statistical analysis of lifetime data from Danish twins, which were partially used in McGue et al. (1993) and Herskind et al. (1996), but now with special focus on mortality caused by heart diseases and CHD. The data set was expanded to include 7955 like-sex twin pairs from the birth cohorts 1870–1930, which were followed up from 1 January 1943 until 31 December 1993.

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Material and Methods

Survival times of identical (MZ) and fraternal (DZ) male and female twins were ascertained from the Danish Twin Registry. This was founded in 1954 as the world's first nation-wide twin registry and has been developed ever since. This population-based registry includes all twins born in Denmark during the period 1870–1910 and all like-sex pairs born between 1911 and 1930. The birth registers from all 2200 parishes of the relevant time period were manually scrutinised to identify all multiple births. A search was then carried out for twins, or if the twin was not still alive, their closest relatives in regional population registers (in operation since 1924) or other public sources, especially the archives of probate courts and censuses. As soon as a twin was traced, a questionnaire was sent to the twin or to the closest relatives.

Questions about phenotypic similarities included in the questionnaires were used to assess the zygosity. This zygosity classification was compared with laboratory methods (serological markers). The misclassification rate was found to be below 5% (Holm, 1983; Lykken, 1978). The follow-up procedure traced nearly all twins who did not die or emigrate before the age of 15. Death status, age at death and cause of death were obtained from the Central Person Register, the Danish Cause-of-Death Register, the Danish Cancer Registry (founded in 1942), and other public registries in Denmark. The validity of the twin register was checked on the basis of a comparison of information about year of death with the nation-wide Danish Cancer Registry. There was 99% agreement, although both registries were independent (Holm, 1983). Further data corrections increased this level of agreement to almost 100%. For further, detailed information about the Danish Twin Registry see Hauge (1968).

The data set provided by the Danish Twin Register contains records of 14051 twin pairs born between 1 January 1870 and 31 December 1930. In 9528 twin pairs both partners were still alive on 1 January 1943. Only these pairs could be used for analysis, because cause of death is available for individuals in Denmark since 1943 (Juel & Helweg-Larsen, 1999). Consequently, lifetimes are bivariate left truncated. Pairs with unknown zygosity (1327 pairs) or incomplete information on cause of death (246 pairs) were excluded, leaving a study population of 7955 twin pairs. Individuals were followed from up 1 January 1943 to 31 December 1993, and those identified as deceased after that date have been classified here as 'living'. At the end of follow-up, around 40% of the twins are still alive, resulting in right censored data. Altogether, we have 1344 male monozygotic twin pairs and 2411 dizygotic twin pairs, 1470 female monozygotic twin pairs and 2730 dizygotic twin pairs. As a consequence of the selection criteria used in our study population, in addition to the lifetimes, there is also information on cause of death for all non-censored lifetimes, that is, for all individuals in the study population who died during the follow-up. For this study, only the underlying cause of death was considered. For more detailed information about death status, gender, and zygosity of the study population see Table 1.

Table 1

Study Population* by Gender, Zygosity and Status

status	males		females	
	MZ twins	DZ twins	MZ twins	DZ twins
both twins dead	731	1257	622	1072
one twin alive, cotwin dead	284	617	332	773
both twins alive	329	537	516	885
all pairs together	1344	2411	1470	2730

*number of pairs

Mortality

After the age of 6, death rates for Danish twins born between 1870 and 1900 are almost the same as those for the same cohorts of the Danish population. The distributions of age at death for monozygotic twins are close to those of dizygotic twins for both sexes (Christensen et al., 1995). This similarity enables us to generalise genetic results from survival models for twins to the whole population with respect to all-cause mortality. Additionally, for our purposes it is necessary to compare the death rates of twins related to heart diseases with the respective rates for the general population. For the present report heart diseases and CHD are grouped as ICD 400–468 (CHD 420) in the sixth and seventh revision and as ICD 390–429 and 440–459 (CHD 410–414) in the eighth ICD revision.

We wished to compare the pattern of death from heart diseases for twins with that of the general population. Aggregated cause-specific mortality data in five-year mutually exclusive age groups (20–24, 25–29, 30–34, …, 80–84) is available for the general population going back to 1952 from the WHO Mortality Data Base. Death rates for heart diseases and CHD for males and females, respectively, are shown in Figure 1–4. The bars for twin mortality rates include 95 % confidence intervals. Confidence intervals were calculated using the normal approximation of the binomial distribution.

Standardised Mortality Ratios (SMR) were calculated (Taeger et al., 2000) to compare the mortality pattern of the twin sample with that of the respective general population. The mortality among twins of the study population is slightly lower than mortality among the general population with significant differences for males (Table 2).

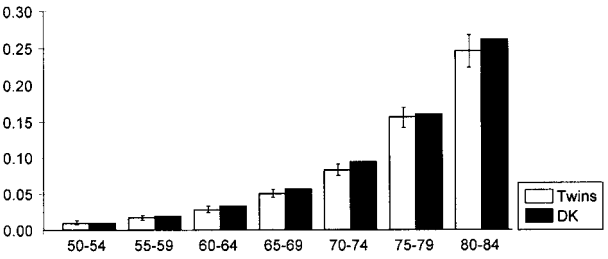

Figure 1

Mortality rates heart diseases (males).

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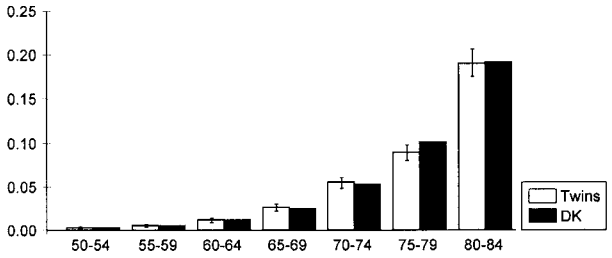

Figure 2

Mortality rates heart diseases (females).

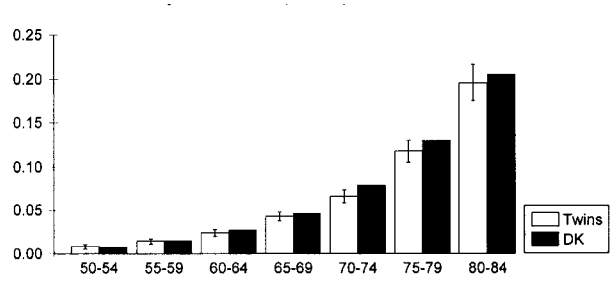

Figure 3

Mortality rates CHD (males).

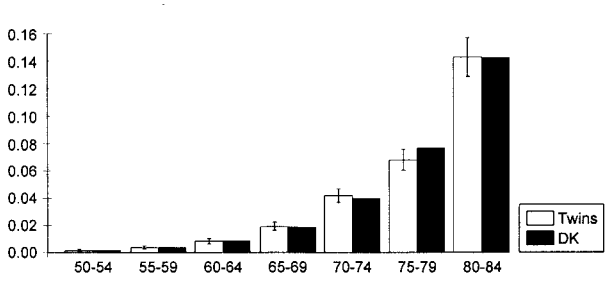

Figure 4

Mortality rates CHD (females).

This was expected because pairs with unknown zygosity and twin individuals with incomplete lifetime information about the partner can not be used in genetic analysis and were excluded from the study population. Pairs with unknown zygosity show a higher mortality compared with other twin pairs because a reason for being without a known zygosity could be early death. Furthermore, the reason for twin individuals without information about their partner is often early death of the partner, which implies an unfavorable prognosis for this group of individuals. Because of the bivariate truncation the study population forms a selected group of twins, which shows slightly lower mortality than in the general twin population. Including twin pairs of unknown zygosity and twins without information about the partner into the analysis leads to slightly increased mortality among twins.

To take advantage of the more detailed mortality information available in twins rather than for the total population we performed the log rank test to compare the cause specific mortality pattern of monozygotic and dizygotic twins. The log rank test did not detect any differences between monozygotic and dizygotic twins in mortality with respect to heart diseases (p = 0.09 for males and p = 0.25 for females) and with respect to CHD (p = 0.14 for males and p = 0.09 for females). The similarities between the mortality pattern of Danish Twins and the Danish population with respect to heart diseases and CHD are fundamental and allow us to generalise the results of genetic analysis of twin mortality due to heart diseases and CHD to the general population.

Statistical Methods

For a first rough analysis, concordance rates, a widely used and accepted indicator of similarities in twins, were calculated to facilitate comparisons with other twin studies and with the results of the following analysis combining elements of life time analysis and methods of quantitative genetic. The probandwise concordance rate was computed as the probability that a twin is affected given that his/her co-twin is affected (McGue, 1992), that means

$$\frac{2C}{2C + D},$$

where C stands for the number of concordant pairs and D for the number of discordant pairs. The influence of

Table 2

Standardised Mortality Ratios with Respect to Heart Diseases and CHD

	No. of expected deaths	No. of observed deaths	SMR	confidence interval
heart diseases				
Males	1535.98	1385	90	85–95
Females	1108.94	1072	97	91–103
CHD				
Males	1890.17	1746	97	88–97
Females	1508.06	1485	98	94–104

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genetic factors is indicated by greater within-pair similarity among monozygotic twins than among dizygotic twins.

For a more powerful approach it is more appropriate to use methods of survival analysis. However, univariate life time models cannot capture the association between the life spans of related individuals like twins. Consequently, bivariate distributions of dependent lifetimes are necessary. For genetic analysis of time-to-event data correlations between durations are needed. In this paper we want to analyze genetic and environmental factors acting on frailty (susceptibility) to mortality due to heart diseases instead of lifetimes directly. The correlated gamma-frailty model can be used to fit bivariate lifetime data and provide a specific parameter for correlation of frailty to death. The interesting point here is that individual frailties in twin pairs could not be observed, but their correlation can be estimated by application of the correlated gamma-frailty model.

Now we want to make more detailed assumptions about the structure of the lifetimes. To include heterogeneity in our model, we assume a correlated gamma-frailty model (Yashin & Iachine, 1994; 1995b; Wienke et al., 2000). For more detailed information about the frailty concept in the univariate case see Vaupel et al. (1979). Let Z_i (i = 1,2) be the frailties of the two individuals of a twin pair. Assume that their individual hazards are represented by the proportional hazards model $\mu(x,Z_i) = Z_i \mu_0(x)(i$ = 1,2) with a baseline hazard function $\mu_0(x)$ describing the risk of dying as a function of age. Let the lifetimes of the two twin partners be conditionally independent given their frailties Z_1 and Z_2, and furthermore a decomposition $Z_1 = Y_0+Y_1$ and $Z_2 = Y_0+Y_2$, where Y_0, Y_1, and Y_2 are independent gamma-distributed random variables with $Y_0 \sim \Gamma(k_0, \lambda)$, $Y_1 \sim \Gamma(k_1, \lambda)$ and $Y_2 \sim \Gamma(k_2, \lambda)$. Here k_0, k_1, k_2, λ are non-negative parameters and $\Gamma(k, \lambda)$ denotes a Gamma distribution with parameters k and λ. Obviously, Z_1 and Z_2 are correlated in view of the shared part of frailty Y_0 in both Z_1 and Z_2. To force Z_1 and Z_2 to have the same distribution we assume that shape parameters k_1 and k_2 for the distributions of Y_1 and Y_2 are the same, $k_1 = k_2$. This condition makes sense for twins, because there is no reason to assume different distributions of frailty in twin partners. Furthermore, we employ the standard assumption that the mean frailty of individuals is one (at the beginning of the follow-up), which means that

$$EZ_i = \frac{k_o + k_i}{\lambda} = 1 \ (i = 1,2).$$

The common variance is given by $\sigma^2 = 1/\lambda$. Let ρ be the correlation coefficient of Z_1 and Z_2, which is given simply by

$$\rho(Z_1,Z_2) = \frac{k_o}{k_o + k_1}.$$

Because frailties Z_i (i = 1,2) are usually unobservable their correlation coefficient used in the methods of quantitative genetics cannot be estimated from the empirical data directly. So a bivariate lifetime model is needed that allows indirect calculation of the parameters. The bivariate gamma distributed frailty with the above-mentioned properties was constructed in Yashin and Iachine (1995b). The unconditional bivariate survival function now is given by

$$S(x_1,x_2) = S(x_1)^{1-\rho} S(x_2)^{1-\rho} \left(S(x_1)^{-\sigma^2} + S(x_2)^{-\sigma^2} - 1\right)^{-\frac{\rho}{\sigma^2}}, \quad (1)$$

where $S(x)$ denotes the marginal univariate survival function, assumed to be equal for both partners in a twin pair. We used a parametric approach by fitting a Gamma-Gompertz model to the data, e.g.,

$$S(x) = \left(1 + s^2 \frac{\alpha}{\beta} (e^{\beta x} - 1)\right)^{-\frac{1}{s^2}},$$

where α, β, s^2, σ^2, ρ are parameters to be estimated. In an additional analysis we dropped the assumption about the parametric form of the marginal survival function. In this semi-parametric analysis the marginal survival function (which is needed for the evaluation of the likelihood function) is estimated from univariate survival data by using the Kaplan-Meier estimator (Kaplan & Meier, 1958).

Let $(X_{11},X_{12}),\ldots,(X_{n1},X_{n2})$ be independent and identically distributed (i.i.d.) non-negative two-dimensional random vectors (pairs of lifetimes). The lifetimes (X_{i1},X_{i2}) are assumed to be independently censored from the right by i.i.d. pairs of non-negative random variables $(C_{11},C_{12}),\ldots,(C_{n1},C_{n2})$, which are independent of the (X_{i1},X_{i2}). Thus, instead of (X_{i1},X_{i2}) we only observe

$$(T_{i1}, T_{i2}, \Delta_{i1}, \Delta_{i2}) \quad (2)$$

with $T_{ij} = \min\{X_{ij},C_{ij}\}, \Delta_{ij} = 1(X_{ij} \le C_{ij})(i = 1,\ldots,n; j = 1,2)$, where 1(.) denotes the indicator function of the event in the brackets. Let us assume that the lifetimes follow a distribution given by the bivariate survival function $S(x_1,x_2) = P(X_{i1}>x_1, X_{i2}>x_2)$ and denote by $C(c_1,c_2) = P(C_{i1}>c_1, C_{i2}> c_2)$ the survival function of censoring times. Hence, the survival function of the four-dimensional latent times is of the form

$$S(x_1,c_1,x_2,c_2) = S(x_1,x_2)C(c_1,c_2). \quad (3)$$

Starting from this model we are able to derive the likelihood function of the data in (2):

$$L(t_1,t_2,\delta_1,\delta_2) = \delta_1\delta_2 S_{t_1t_2}(t_1,t_2) - \delta_1(1-\delta_2)S_{t_1}(t_1,t_2) - (1-\delta_1)\delta_2 S_{t_2}(t_1,t_2) + (1-\delta_1)(1-\delta_2)S(t_1,t_2) \quad (4)$$

with partial derivatives

$$S_{t_1}(t_1,t_2) = \frac{\partial S(t_1,t_2)}{\partial t_i} \ (i = 1,2)$$

and $$S_{t_1t_2}(t_1,t_2) = \frac{\partial S(t_1,t_2)}{\partial t_1 \partial t_2}.$$

Here $(t_1, t_2, \delta_1, \delta_2)$ denotes a realisation of the random vector $(T_1, T_2, \Delta_1, \Delta_2)$. Because of the independence assumption between lifetimes (X_{i1}, X_{i2}) and censoring times (C_{i1}, C_{i2}) the distribution of the censoring times does not enter the likelihood function.

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As mentioned above, the twin pair data set used is not a randomly selected from the total twin population. Since both members of a twin pair had to be still alive on 1 January 1943, the survival times in the data set are sampled from specific conditional distributions. If a twin pair was born in year y (where y = 1870, …, 1930), the condition of survival of both twins until the year 1943 implies that both twins had to survive until the age of 1943-y in order to be included in the sample. If the survival times are denoted by X_1 and X_2 with survival function $S(x_1, x_2)$, then the conditional survival function for a twin pair born in year y is:

$$S(x_1,x_2 \mid X_1>1943-y,\, X_2>1943-y) = \frac{S(x_1,x_2)}{S(1943-y,1943-y)}$$

Consequently, the likelihood function of independently left truncated an right censored lifetime data is given by

$$\begin{aligned} &L(t_1,t_2,\delta_1,\delta_2,y) \\ &= \big(\delta_1\delta_2 S_{t_1t_2}(t_1,t_2) - \delta_1(1-\delta_2)S_{t_1}(t_1,t_2) \\ &-(1-\delta_1)\delta_2 S_{t_2}(t_1,t_2) + (1-\delta_1)(1-\delta_2)S(t_1,t_2)\big) \\ &/S(1943-y,1943-y) \end{aligned} \quad (5)$$

For a combined analysis of monozygotic and dizygotic twins we include two correlation coefficients, ρ_{MZ} and ρ_{DZ}, respectively. These correlations between monozygotic and dizygotic twins provide information about genetic and environmental influences on frailty within individuals.

Quantitative Genetics of Frailty

In twin studies the intrapair-correlations of the trait of interest in monozygotic and dizygotic twin pairs play the key role for analysis of genetic and environmental factors. Using these coefficients, we want to fit five standard genetic models of frailty that corresponds to five different assumptions about its structure. We use the notation of Yashin and Iachine (1995a) and McGue et al. (1993) for such models. Resemblance in twins is (completely for monozygotic twins and partly for dizygotic twins) caused by three factors: additive genetic factors (A), genetic factors due to dominance (D) and shared environmental factors (C). Non- shared environment is (completely for monozygotic twins and partly for dizygotic twins) responsible for intrapair differences in twins. From the estimation point of view, only three parameters could be included into the model simultaneously, because there are only data about two different groups of relatives (monozygotic and dizygotic twins). More complex models need data about additional groups of relatives like parents or offspring. Each additional group of relatives in the study allow for an additional parameter in the model, but this point is beyond the scope of the present paper. The following biometric models were fitted to the data: AE, DE, ACE, ADE and CE. Shared environmental factors and dominance factors cannot be estimated simultaneously, because they are completely confounded in the classical study where twins reared together (Heath et al., 1989). In these notations an ACE model refers to the decomposition of frailty Z = A+C+E and a CE model refers to the decomposition Z = C+E. ADE, AE and DE models are defined similarly. We use the small letters a^2, d^2, c^2, e^2 to refer to the respective proportions of variance. For example, the relation $1 = a^2+c^2+e^2$ corresponds to the decomposition of variance in the ACE model of frailty. Standard assumptions about of the quantitative genetics yields in the following relations:

$$\begin{aligned} \rho_{MZ} &= a^2 + d^2 + c^2 \\ \rho_{DZ} &= 0.5a^2 + 0.25d^2 + c^2 \\ 1 &= a^2 + d^2 + c^2 + e^2 \end{aligned} \quad (6)$$

To combine the approach of quantitative genetics with the methods of survival analysis we used the correlated gamma-frailty model with genetic and environmental components of frailty. In this approach the genetic and environmental parameters of frailty decomposition are estimated directly by the maximum likelihood method. Analysis was made with standard statistical software packages SPSS and GAUSS.

Results

The number of concordant and discordant twin pairs with respect to death caused by heart diseases and CHD is given in Table 3.

Table 3

Probandwise Concordances for Heart Diseases and CHD

	males			females		
	concordant pairs	discordant pairs	concordance rate	concordant pairs	discordant pairs	concordance rate
heart diseases						
MZ twins	137	392	0.41	116	316	0.42
DZ twins	215	750	0.36	170	659	0.34
CHD						
MZ twins	84	338	0.33	57	255	0.31
DZ twins	126	645	0.28	80	544	0.23

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Table 4

Results of Genetic Analysis of Frailty to Mortality from Heart Disease

	σ	a^2	d^2	c^2	e^2	Log-L	AIC
males							
ACE	2.14 (0.31)	0.47 (0.14)		0.08 (0.11)	0.45 (0.08)	2.45796	18471.2796
AE	2.19 (0.31)	0.56 (0.07)			0.44 (0.07)	2.45802	18469.7302
ADE	2.19 (—)	0.56 (—)	0.00 (—)		0.44 (—)	2.45802	18471.7302
DE	2.40 (0.34)		0.55 (0.07)		0.45 (0.07)	2.45957	18481.3707
CE	1.98 (0.31)			0.43 (0.07)	0.57 (0.07)	2.45930	18479.3430
females							
ACE	2.02 (—)	0.52 (—)		0.00 (—)	0.48 (—)	1.83446	15421.4640
AE	2.02 (0.40)	0.52 (0.10)			0.48 (0.10)	1.83446	15419.4640
ADE	2.06 (0.41)	0.41 (0.26)	0.11 (0.26)		0.48 (0.10)	1.83444	15421.2960
DE	2.20 (0.47)		0.53 (0.10)		0.47 (0.10)	1.83482	15422.4880
CE	1.93 (0.39)			0.36 (0.08)	0.64 (0.08)	1.83579	15430.6360

Table 5

Results of Genetic Analysis of Frailty to Mortality from CHD

	σ	a^2	d^2	c^2	e^2	Log-L	AIC
males							
ACE	2.27 (—)	0.53 (—)		0.00 (—)	0.47 (—)	1.97478	14842.5978
AE	2.27 (0.48)	0.53 (0.11)			0.47 (0.11)	1.97478	14840.5978
ADE	2.32 (0.49)	0.43 (0.25)	0.11 (0.24)		0.46 (0.11)	1.97475	14842.3725
DE	2.53 (0.48)		0.54 (0.09)		0.46 (0.09)	1.97524	14844.0524
CE	2.04 (0.53)			0.40 (0.11)	0.60 (0.11)	1.97638	14852.6138
females							
ACE	1.87 (—)	0.58 (—)		0.00 (—)	0.42 (—)	1.35874	11425.4160
AE	1.87 (0.41)	0.58 (0.14)			0.42 (0.14)	1.35874	11423.4160
ADE	1.91 (0.40)	0.30 (0.32)	0.32 (0.35)		0.38 (0.14)	1.35864	11424.5760
DE	1.94 (0.41)		0.63 (0.14)		0.37 (0.14)	1.35875	11423.5000
CE	1.87 (0.46)			0.38 (0.11)	0.62 (0.11)	1.35985	11432.7400

Using the classic twin study design we calculate proband-wise concordance rates of monozygotic and dizygotic twins for a preliminary analysis. Concordance rates with respect to heart diseases are 0.41 and 0.36 for male and 0.42 and 0.34 for female monozygotic and dizygotic twins, respectively. The figures with respect to CHD are 0.33 and 0.28 for males and 0.31 and 0.23 for females, respectively.

Applying the correlated frailty model to heart diseases in males the likelihood ratio test prefers the ACE model compared with the CE model and the ADE model compared with the DE model (Table 4). Furthermore, the AE model is preferred by the likelihood ratio test compared with the ADE and ACE model. Consequently, the AE model is the best fitting model with a heritability estimate of 0.56 (0.07). For females the ACE model shows a better fit than the CE model, whereas the DE model is better than the ADE model using the likelihood ratio test. Otherwise the ACE model is not supported compared with the AE model. Finally, the AE and DE model are not nested and cannot compared by the likelihood ratio test. With respect to the Akaike Information Criterion (AIC) the AE model shows a better fit with heritability estimate 0.52 (0.10). The same argumentation leads to the AE model as best fitting model for CHD with heritability estimates 0.53 (0.11) and 0.58 (0.14) in males and females, respectively (Table 5). The results of the semi-parametric analysis are similar (Table 6–7). Standard errors are not shown in cases with zero estimates of c^2 or d^2 since zero is the boundary of the parameter space.

Discussion

In the traditional twin study, a comparison is made between monozygotic and dizygotic twins. If genes are

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Table 6

Results of Genetic Analysis of Frailty to Mortality from Heart Diseases (semi-parametric analysis)

	σ	a^2	d^2	c^2	e^2	Log-L	AIC
males							
ACE	2.20 (0.32)	0.45 (0.14)		0.08 (0.11)	0.47 (0.07)	0.320801	2415.21551
AE	2.25 (0.31)	0.54 (0.07)			0.46 (0.07)	0.320863	2413.68113
ADE	2.25 (—)	0.54 (—)	0.00 (—)		0.46 (—)	0.320863	2415.68113
DE	2.46 (0.34)		0.54 (0.07)		0.46 (0.07)	0.322360	2424.92360
CE	2.05 (0.31)			0.42 (0.07)	0.58 (0.07)	0.322097	2422.94847
females							
ACE	2.03 (—)	0.52 (—)		0.00 (—)	0.48 (—)	0.249624	2102.84160
AE	2.03 (0.38)	0.52 (0.10)			0.48 (0.10)	0.249624	2100.84160
ADE	2.05 (0.39)	0.41 (0.25)	0.11 (0.26)		0.48 (0.10)	0.249601	2102.64840
DE	2.18 (0.44)		0.53 (0.10)		0.47 (0.10)	0.249988	2103.89920
CE	1.94 (0.38)			0.36 (0.08)	0.64 (0.08)	0.250946	2111.94640

Table 7

Results of Genetic Analysis of Frailty to Mortality from CHD (semi-parametric analysis)

	σ	a^2	d^2	c^2	e^2	Log-L	AIC
males							
ACE	2.39 (—)	0.50 (—)		0.00 (—)	0.50 (—)	0.273444	2059.56444
AE	2.39 (0.48)	0.50 (0.10)			0.50 (0.10)	0.273444	2057.56444
ADE	2.43 (0.49)	0.40 (0.23)	0.11 (0.23)		0.49 (0.10)	0.273418	2059.36918
DE	2.62 (0.48)		0.52 (0.09)		0.48 (0.09)	0.273897	2060.96647
CE	2.21 (0.53)		0.36 (0.09)	0.36 (0.09)	0.64 (0.09)	0.274975	2069.06225
females							
ACE	1.96 (—)	0.56 (—)		0.00 (—)	0.44 (0.13)	0.197019	1660.95960
AE	1.96 (0.42)	0.56 (0.13)			0.44 (0.13)	0.197019	1658.95960
ADE	2.00 (0.41)	0.28 (0.31)	0.32 (0.34)		0.40 (0.13)	0.196912	1660.06080
DE	2.02 (0.41)		0.62 (0.13)		0.38 (0.13)	0.197015	1658.92600
CE	1.97 (0.48)			0.36 (0.10)	0.64 (0.10)	0.198151	1668.46840

involved in mortality due to heart diseases, there should be a greater concordance rate for death due to heart diseases among monozygotic twin pairs than dizygotic pairs. Several assumptions are made in applying the twin method, including similar environment and similarities between types of twins (dizygotic twins tend to be more frequently associated with older mothers and previous siblings). Theses issues have not had a significant influence on previous twin studies and, similarly, are not expected to significantly influence our conclusions, see Kendler and Holm (1985). For example, mortality rates with respect to heart diseases and CHD of monozygotic and dizygotic twins show no significant difference as mentioned above. Published work with twins and heart diseases is limited to a few reports on CHD, which is responsible for around three quarter of all deaths due to heart diseases. A Danish study (Harvald & Hauge, 1970) detect that concordance was higher among monozygotic than among dizygotic twins with respect to mortality due to CHD. Concordance rates were found to be 0.39 vs. 0.26 in males and 0.44 vs. 0.14 in females. An early investigation of Swedish twins (de Faire et al., 1975) with 11 years follow-up found higher concordance rate for monozygotic twins than for dizygotic twins with respect to death due to CHD for both, males (0.16 vs. 0.08) and females (0.11 vs. 0.07). An extended 26 years follow-up of the same cohort (Marenberg et al., 1994) shows again higher concordance rates for death due to CHD of monozygotic compared with dizygotic twins, 0.40 vs. 0.32 in males and 0.33 vs. 0.24 in females, respectively. For adoptees a significantly increased mortality rate from heart diseases was found among adoptees whose biologic parents died early on these causes (Sørensen et al., 1988). All these

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results are in line with the major finding in this study of a strong genetic effect in frailty to death due to heart diseases (and more specific, to CHD, results are in brackets), based on concordance rates of 0.41 and 0.36 (0.33 and 0.28) for male and 0.42 and 0.34 (0.31 and 0.23) for female monozygotic and dizygotic twins, respectively.

However, concordance rates are of limited value in the case of truncated and censored lifetimes. Despite the long follow-up period from 1943 through 1993 truncation and censoring is important for the data used in the present paper. To overcome these limitations in concordance analysis, to include information about lifetime and allow for heterogeneity in individual susceptibility to death caused by heart diseases and CHD we suggest a genetic analysis of frailty. This analysis assesses the importance of genetic and environmental factors, allows the calculation of heritability estimates and evaluates the nature of the genetic influence on mortality due to heart diseases and CHD (or other diseases). Our analysis of frailty presented here is based on a relatively large twin population. The major findings of this study are the profound genetic effects revealed in frailty to mortality due to heart diseases in general and more specifically in CHD. The analysis prefers the AE model for both sexes, which means the nature of genetic effects is additive. No evidence for genetic effects caused by dominance and shared environment was found. Heritability estimates of frailty to heart diseases and CHD are always in the range 0.5–0.6 for males and females, respectively.

An additional semi-parametric analysis without any assumptions about the distributional form of the marginal survival times shows very similar results and supports the choice of Gamma-Gompertz parameterisation.

This and above cited results contradict the findings of significant higher concordances of dizygotic twins compared with monozygotic twins for all cardiovascular diseases and slightly increased concordance of dizygotic twins for ischemic heart disease in a twin study of army veterans by Reed and coworkers (Reed et al., 1991). It seems to be that selection in connection with enlistment into the armed service as well as volunteering for the twin study resulted in a decline in the number of concordant monozygotic pairs. Furthermore, the mentioned study suffers from small numbers of deaths due to heart diseases.

Cause-of-death statistics are taken at face value although there are limitations in time trend comparability with respect to validity and reliability of cause of death certification and coding and with respect to revisions in the ICD. By describing mortality for relatively broad diagnostic groups, effects of this limitation are lessened. There is one inherent difficulty in this kind of study caused by the fact that cause of death is available for Danish individuals after 1943 only. Thus, about 45% of all twin pairs included in the Danish Twin Registry (especially twins from the older birthcohorts who died at early ages) are lost to the analysis because unknown cause of death (or unknown zygosity). If genetic factors have a stronger effect at younger ages, as found by several authors (de Faire et al., 1975; Marenberg et al., 1994; Sørensen et al., 1988), this loss may lead to an underestimation of genetic effects. Despite this limitation the present study is one of the largest twin studies in this area with a reasonable number of deaths according to the long follow-up period.

A second limitation of this study is the lack of information about risk factors such as smoking, alcohol intake, diet, exercises etc. In interpreting our results, we cannot rule out the possibility that monozygotic twins shared more environmental risk factors than the dizygotic twins. For example, monozygotic twins are more concordant with respect to their smoking behavior than dizygotic twins (Carmelli et al., 1992). This greater similarity of experience could be important because smoking is a strong risk factor for heart diseases and could inflate estimates of genetic variance. However, in the Swedish twin study about coronary heart disease inclusion of risk factors (hypertension, diabetes, smoking, birth cohort, body mass index, marital status and education) in the analysis does not change the results substantially (Marenberg et al., 1994).

The present approach is relevant for multiple loci models as well as for a single locus with a high level of polymorphism. For models describing loci with small numbers of alleles see Begun et al. (2000). Our study suggests substantial genetic influence to susceptibility to death from heart diseases modeled by frailty. Further research is needed to determine the molecular mechanisms that underlie genetic susceptibility to death from heart diseases and how these mechanisms may vary with age. The suggested model gives a clear illustration of how survival analysis and genetic epidemiology could be merged for genetic analysis of time-to-event data.

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