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How heritable is individual susceptibility to death? The results of an analysis of survival data on Danish, Swedish and Finnish twins

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Molecular epidemiological studies confirm a substantial contribution of individual genes to variability in susceptibility to disease and death for humans. To evaluate the contribution of all genes to susceptibility and to estimate individual survival characteristics, survival data on related individuals (eg twins or other relatives) are needed. Correlated gamma-frailty models of bivariate survival are used in a joint analysis of survival data on more than 31 000 pairs of Danish, Swedish and Finnish male and female twins using the maximum likelihood method. Additive decomposition of frailty into genetic and environmental components is used to estimate heritability in frailty. The estimate of the standard deviation of frailty from the pooled data is about 1.5. The hypothesis that variance in frailty and correlations of frailty for twins are similar in the data from all three countries is accepted. The estimate of narrow-sense heritability in frailty is about 0.5. The age trajectories of individual hazards are evaluated for all three populations of twins and both sexes. The results of our analysis confirm the presence of genetic influences on individual frailty and longevity. They also suggest that the mechanism of these genetic influences may be similar for the three Scandinavian countries. Furthermore, results indicate that the increase in individual hazard with age is more rapid than predicted by traditional demographic life tables.

Keywords: aging, frailty, heritability, bivariate model, related individuals

Introduction

Recent studies in the field of molecular epidemiology show that susceptibility to disease and death exhibits a high degree of variation among individuals in human populations.[1] Direct measurement of the specific genetic and environmental contributions to such variability is complicated: numerous genes may be involved and many of them are unknown. Collecting information on a large number of genes is costly. Fortunately, information about susceptibility to disease and death may often be obtained indirectly from the analysis of population data on age at onset of disease or on life spans of related individuals using the concept of 'unobserved susceptibility'. Models based on this concept may be developed using the notions of liability[2–4] or frailty.[5–16] Such models are used to study genetic influence on specific durations (age at onset of disease, life span, etc).

Genetic influences on human life span were found in the analyses of survival data on adopted children[17] and twins.[18] Recent genetic studies of longevity using survival data on Danish twins show that variation in human life span is moderately heritable. The heritability of human life span was estimated by McGue et al[19] to be about 25% in a study based on the analysis of a cohort of Danish twins born 1870–1880. This estimate was confirmed by Herskind et al[20] using survival data on Danish twins born 1870–1900. Yashin and Iachine[15,16] estimated the role of genes in susceptibility to death using frailty models applied to the same data set used by Herskind et al.[20] They showed that the estimates of heritability in gamma-distributed frailty are about

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50% for both sexes. This result confirmed the importance of studying susceptibility to death in analysing genetics of aging and longevity. In this paper we apply a correlated gamma-frailty model to the genetic analysis of frailty in a population-based sample of Danish, Swedish and Finnish like-sexed twins. In particular, we estimate the variances and correlations of the frailty distributions for all three populations of twins for both sexes and investigate the hypothesis that frailty variance and correlations of frailty for MZ and DZ twins are common for all three countries. The parameters of genetic models of frailty are estimated and relative fits of the different models to the data are compared. Finally, we obtain semiparametric estimates of the underlying (individual) hazards and compare them with the marginal mortality rates.

Data

The structure of the available data from three Scandinavian registers is shown in Figure 1 in which the twin cohorts whose data are included in Danish, Swedish and Finnish Twin Registers are shown on a plane with time and age as coordinate axes. This method of data representation, known as a 'Lexis diagram', was proposed by the German demographer William Lexis in 1875. Such diagrams are widely used in demography and biostatistics where data are often taken from different birth cohorts subjected to various truncation and censoring conditions.[21] Thin lines in Figure 1 outline data available in the registers. Thick lines outline data used in our study. They include all twins who both survived to age 30. A

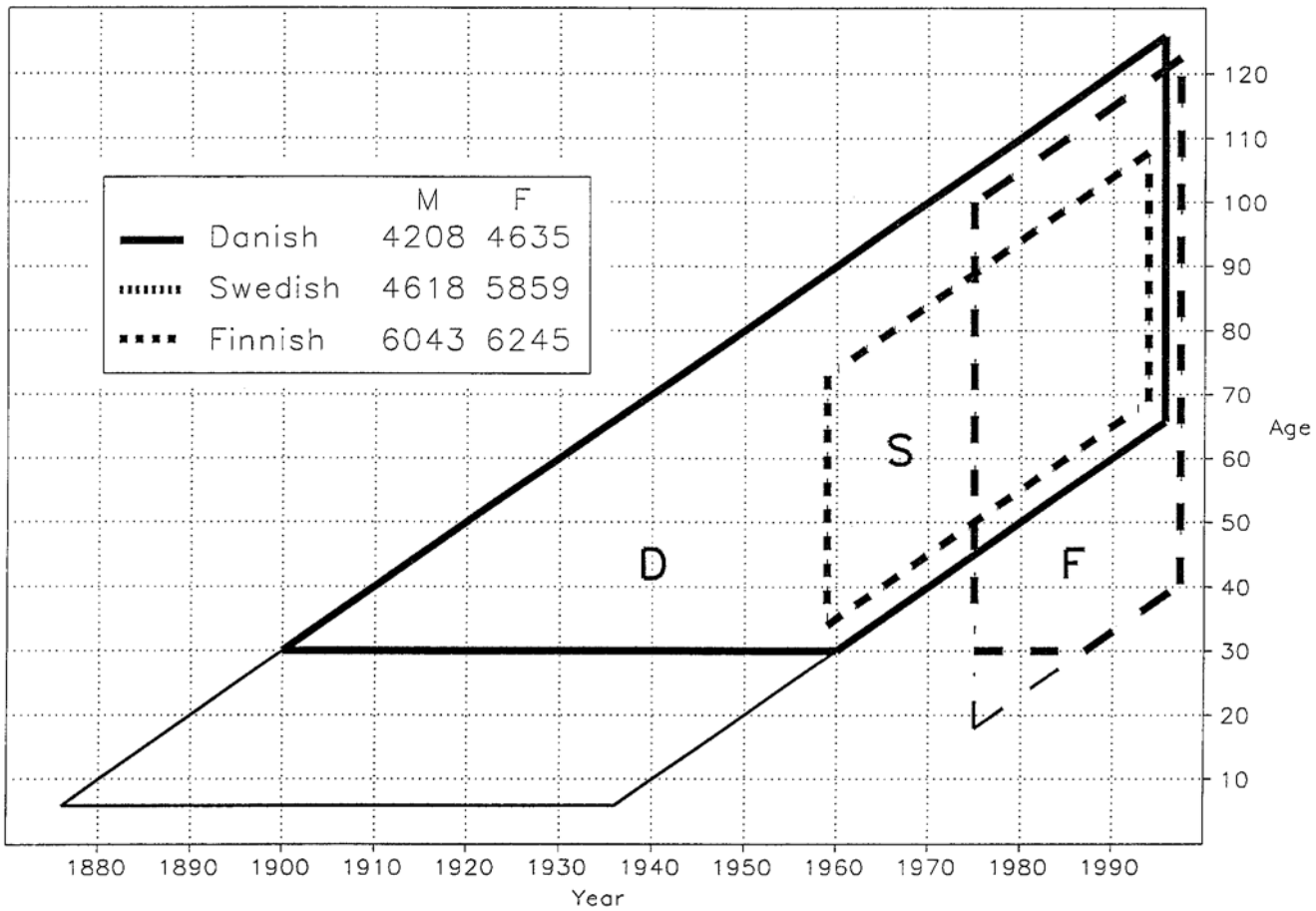

Figure 1 Lexis diagram illustrating the sample structure in the three Twin Registers. The thick solid line outlines the part of the Danish cohort of twins born 1870–1930 which includes twins when both survived to age 30. Survival data from this part were used in the analyses here. The short-dashed line defines the cohorts of Swedish twins used in this study, and the thick long-dashed line defines the cohorts of Finnish twins when both survived to age 30. The thin lines (solid for Danish and long-dashed for Finnish twins) outline the data available in respective registers which were not used in this study. The key gives the number of twin pairs from the respective registers by sex used in the analysis.

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description of the data with respect to sex, zygosity and censoring status is given in Table 1.

Danish twins

The older part of the Danish Twin Register contains survival data on all twins born in Denmark between 1870 and 1910 and all same-sexed twin pairs born between 1911 and 1930 where both individuals survived to age 6.[22,23] The twins were ascertained through a manual search of all birth registers kept locally by the parishes in Denmark. Public registers were used to identify twins, or when necessary, their closest relatives. As soon as a twin was traced a questionnaire was mailed to him or her. If neither of the twin partners were alive, a questionnaire was sent to the closest relative. The zygosity diagnosis was based on items in the main questionnaire regarding physical similarity. The reliability of this method was validated by comparison with zygosity classification based on blood, serum and enzyme group determination, and was found to be very high with fewer than 5% of the pairs misclassified. To make Danish data comparable with Swedish and Finnish data we used the data on same-sex twins with known zygosity born in 1870–1930, where both twins survived to age 30. These data include 1495 male MZ twin pairs, 2713 male DZ twin pairs, 1613 female MZ twin pairs, and 3022 female DZ twin pairs.

Swedish twins

The survival data from the Swedish Twin Registry used in our analysis are represented by the twin sample originally referred to as the 'old' cohort.[24] This cohort consists of all same-sexed twin pairs born between 1886 and 1925 where both members of the pair were living in Sweden in 1959. Altogether 12 889 of the 41 017 pairs born from 1886 to 1925 were located and mailed a questionnaire in 1959. Responses were received from both members of 10 945 pairs. Only pairs for whom zygosity could be established (using questionnaire methodology) and who had not emigrated were used in the current analyses. A total of 468 pairs were excluded from the analysis because of missing information. The remaining sample consisted of 1645 male MZ pairs, 2973 male DZ pairs, 2002 female MZ pairs and 3857 female DZ pairs whose data were used in this study.

Finnish twins

The older part of the Finnish Twin Cohort consists of all same-sexed Finnish twin pairs born between 1875 and 1957 and where both co-twins were alive in 1975.[25] These twin pairs were selected from the Central Population Registry of Finland in 1974. A questionnaire was mailed to all pairs in August–October 1975. Zygosity was determined by examining the responses of both members of each twin pair to two questions on physical similarity during school age. A set of decision rules were used to classify the twin pairs as monozygotic (MZ), dizygotic (DZ) or of undetermined zygosity. The validity of of the questionnaire method for determining zygosity was studied in a sub-sample in whom eleven blood markers were analysed.[26] About 93% of all respondent pairs could be classified as monozygotic or dizygotic with only a slight probability of misclassification (1.7%). Only data from intact pairs (ie pairs with information on both twins) with known zygosity who had not emigrated and where both twins survived to age 30 were included here. Altogether there were 1817 male MZ pairs, 4226 male DZ pairs, 2043 female MZ pairs and 4202 female DZ twin pairs. The dates of birth and

Table 1 Composition of the Scandinavian twins survival data by country, sex, zygosity and censoring status. The numbers in columns denote pairs of individuals

Country	Sex	Zygosity	None censored	One censored	Both censored	Total
Denmark	Males	MZ	921	290	284	1 495
Denmark	Males	DZ	1 610	647	456	2 713
Denmark	Females	MZ	807	350	456	1 613
Denmark	Females	DZ	1 462	775	785	3 022
Sweden	Males	MZ	804	425	416	1 645
Sweden	Males	DZ	1 337	903	733	2 973
Sweden	Females	MZ	738	482	782	2 002
Sweden	Females	DZ	1 374	1 105	1 378	3 857
Finland	Males	MZ	194	281	1 342	1 817
Finland	Males	DZ	360	794	3 072	4 226
Finland	Females	MZ	156	227	1 660	2 043
Finland	Females	DZ	292	525	3 385	4 202
All	All	All	10 055	6 804	14 749	31 608

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death were taken from the official birth and death registers of the respective countries.

Method

The data were analysed using the correlated gamma-frailty model of bivariate survival by applying the maximum likelihood method. Each data set is characterised by a certain truncation condition that originates from the procedure used to sample the twin pairs. Specifically, the criteria for inclusion required that both members of the twin pair had to survive until age 30 in the Danish sample. In the case of the Swedish data, both twins in a pair had to survive until the year 1959, and in the case of the Finnish data, both twins had to survive until the year 1975 (or until the age 30, whichever occurred first) to be included in the sample. Thus, the survival times in the data are sampled from certain conditional distributions.

For example, if a twin pair was born in the year y, where y = (1886,...,1925) for Swedish twins, the condition for survival of both twins until the year 1959 implies that both twins had to survive until the age of 1959–y in order to be included in the sample. If the survival times are denoted T_1 and T_2 with survival function $S(x_1, x_2)$, then the conditional survival function for a twin pair born in year y is:

$$S_y(x_1,x_2)=P(T_1>x_1,T_2>x_2 \mid T_1>1959-y,T_2>1959-y)=\frac{S(x_1,x_2)}{S(1959-y,1959-y)} \quad (1)$$

where x_1 and x_2 are censoring times for two related individuals.

For Finnish twins this survival function is:

$$S_y(x_1,x_2)=P(T_1>x_1,T_2>x_2 \mid T_1>x,T_2>x)=\frac{S(x_1,x_2)}{S(x,x)} \quad (2)$$

where x = max(30, 1975 – y). The likelihood function for the different censoring modes of the individuals in a twin pair was constructed from such conditional survival functions and their partial derivatives with respect to x_1 or x_2 or both. The derivation of the correlated gamma-frailty model is presented in Appendix 1.

To evaluate the relative magnitude of genetic and environmental effects on susceptibility to death, six genetic models were analysed (see Appendix 1). The additive structure of frailty yields a linear decomposition of variance and of the correlation coefficients of frailty between members of MZ and DZ pairs. The parameters of this decomposition are estimated from combined bivariate survival data, ie data on the life spans of twin 1 and twin 2 for MZ and DZ twin pairs. For this purpose we use an inclusive survival model, in which the parameters of the marginal survival functions and variances of the frailty distributions are assumed to be the same for MZ and DZ twins. This permits us to perform a simultaneous analysis of MZ and DZ survival data using one likelihood function. The estimates of narrow sense heritability are based on the AE model of frailty, which provides the best fit to all available bivariate data. Likelihood based confidence intervals have been computed for the narrow sense heritability estimate following the procedure described by Neale and Miller.[27] The nested models are compared using likelihood ratio tests. The Akaike Information Criterion (AIC) is used to compare non-nested models. This type of analysis is described in detail by Yashin and Iachine.[16]

To assess the similarity of frailty distribution for Danish, Swedish and Finnish twins we performed a joint analysis of the survival data from the three countries by sex. In this analysis the likelihood function of the data is calculated on the assumption that frailty variances and correlations of frailty for MZ and DZ have common values σ^2, ρ_{MZ}, ρ_{DZ} for all three countries, and that the parameters of the marginal univariate survival function (a, b, c, s) are country-specific. This model is nested within the model specifying that all parameters are country-specific, and a likelihood ratio test can be used to test the hypothesis of the similarity of frailty parameters. If this hypothesis is not rejected the combined model can be used to improve the precision of parameter estimates. Another likelihood ratio test is conducted to investigate whether or not the data may be further aggregated by using common parameters associated with marginal univariate survival function for all three countries.

Results

The results of the statistical analysis of survival data on Danish, Swedish and Finnish twins are shown in Tables 2 and 3 for males and females, respectively. As seen in Table 2 the estimates of the standard deviation of individual frailty are almost the same for the Danish and Swedish male twins (about 1.24 and 1.36) and is greater (about 2.24) for the Finnish male twins. In all three samples of twins the correlation coefficients of frailty differ significantly for MZ and DZ twins, as expected. A comparison of the univariate survival distributions and frailty

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variances for MZ and DZ twins using the likelihood ratio test confirms the hypothesis that they are similar. The P-values of the respective likelihood ratio tests are shown in the column headed UMZ = UDZ for Danish, Swedish and Finnish twins. The P-values for testing the similarity of correlations in frailty among MZ and DZ twins are shown in the column headed $\rho_{MZ} = \rho_{DZ}$.

The last column in Table2 gives narrow sense heritability in frailty estimated from an AE-model (see Appendix 1). It can be seen that these estimates range from $h^2 = 0.60$ for Swedish twins to $h^2 = 0.36$ for Finnish twins, with $h^2 = 0.59$ for Danish twins. The estimates based on analysis of pooled data from the three registers are 1.36 for the standard deviation of frailty and 0.57 for the narrow-sense heritability (last row in Table2). A likelihood ratio test confirms the hypothesis that frailty variance and correlations of frailty for MZ and DZ twins are equal for all three countries (P = 0.34). An additional likelihood ratio test rejects the hypothesis that univariate survival distributions in the three twin male populations are similar (P-value < 0.001, not shown).

For the female twins, the estimates of the standard deviation of frailty are similar for the Swedish and Finnish samples (about 2.31 and 2.36); and are about twice that of the standard deviation of frailty for Danish female twins (about 1.32). A comparison of the univariate lifetime distributions and frailty variances for MZ and DZ twins reveal that they are probably less similar than in the case of males. However, the respective P-values (0.06, 0.07 and 0.15) are not significant at the 5% level. Again, the estimates of correlation coefficients of frailty are significantly different for MZ and DZ twins in all three samples. The heritability estimate is greatest for Danish females (about 0.54) and somewhat lower for Finnish and Swedish twins (0.41 and 0.37). The

Table 2 The results of analysis of survival data on Danish, Swedish and Finnish male twins using correlated gamma-frailty model

Data	σ	UMZ=UDZ	ρ_{MZ}	ρ_{DZ}	$\rho_{MZ}=\rho_{DZ}$	h^2
Danish (1870–1930)	1.24 (0.18)	0.12	0.59 (0.08)	0.32 (0.05)	<0.001	0.59 (0.46–0.75)
Swedish (1886–1925)	1.36 (0.13)	0.36	0.61 (0.06)	0.26 (0.04)	<0.001	0.60 (0.48–0.74)
Finnish (1875–1957)	2.24 (0.46)	0.73	0.38 (0.08)	0.15 (0.05)	<0.001	0.36 (0.23–0.62)
Joint analysis	1.36 (0.12)	0.34[a]	0.58 (0.05)	0.27 (0.03)	<0.001	0.57 (0.49–0.67)

[a]P-value is for the null-hypothesis of common frailty parameters.
The numbers in the Data column refer to the birth cohorts included. Columns headed σ, ρ_{MZ} and ρ_{DZ} contain the estimates of respective parameters. Their standard errors are placed in parentheses under the estimates. Column UMZ=UDZ lists the P-values for tests of the null-hypothesis that univariate survival functions and frailty variances of MZ and DZ twins are equal for Denmark, Sweden and Finland respectively. In the case of joint analysis this column contains the P-value for testing the null-hypothesis that common values of σ, ρ_{MZ} and ρ_{DZ} may be used for all three countries. The column headed $\rho_{MZ}=\rho_{DZ}$ contains P-values for testing the null-hypothesis that $\rho_{MZ}=\rho_{DZ}$. Estimates of narrow-sense heritability in individual frailty together with their 95% likelihood-based confidence intervals (in parentheses) are used in the last column.

Table 3 The results of analysis of survival data on Danish, Swedish and Finnish female twins using correlated gamma-frailty model

Data	σ	UMZ=UDZ	ρ_{MZ}	ρ_{DZ}	$\rho_{MZ}=\rho_{DZ}$	h^2
Danish (1870–1930)	1.32 (0.19)	0.06	0.53 (0.08)	0.29 (0.05)	<0.001	0.54 (0.41–0.70)
Swedish (1886–1925)	2.31 (1.03)	0.07	0.39 (0.11)	0.15 (0.08)	<0.001	0.41 (0.29–0.67)
Finnish (1875–1957)	2.36 (2.28)	0.15	0.38 (0.27)	0.16 (0.13)	0.006	0.37 (0.18–0.73)
Joint analysis	1.46 (0.24)	0.50[a]	0.51 (0.07)	0.25 (0.05)	<0.001	0.51 (0.41–0.63)

[a]P-value is for the null-hypothesis of common frailty parameters.
The numbers in the Data column refer to the birth cohorts included. Columns headed σ, ρ_{MZ} and ρ_{DZ} contain the estimates of respective parameters. Their standard errors are placed in parentheses under the estimates. Column UMZ=UDZ lists the P-values for tests of the null-hypothesis that univariate survival functions and frailty variances of MZ and DZ twins are equal for Denmark, Sweden and Finland respectively. In the case of joint analysis this column contains the P-value for testing the null-hypothesis that common values of σ, ρ_{MZ} and ρ_{DZ} may be used for all three countries. The column headed $\rho_{MZ}=\rho_{DZ}$ contains P-values for testing the null-hypothesis that $\rho_{MZ}=\rho_{DZ}$. Estimates of narrow-sense heritability in individual frailty together with their 95% likelihood-based confidence intervals (in parentheses) are used in the last column.

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estimates based on the analysis of pooled data from the three registers are 1.46 for the standard deviation of frailty and 0.51 for the narrow-sense heritability (last row in Table 3). Also for the female data the likelihood ratio test confirms the hypothesis that frailty variance and correlations for MZ and DZ twins are equal for all three countries (P = 0.50). The hypothesis that univariate survival distributions in the three twin populations are similar is rejected for female data (P-value < 0.001, not shown).

Figure 2 shows the empirical mortality rate (thin solid line), the mortality rate calculated from the correlated frailty model (dashed line) and the underlying hazard $\mu_0(x)$ (thick solid line) as functions of age on a logarithmic scale for Danish, Swedish and Finnish twins by sex.

It will be seen from these graphs that the correlated frailty model provides a good fit to the empirical data for all six populations of twins (three countries times two sexes). In all cases the estimates of the underlying hazards increase with age faster than the estimates of marginal hazards: the slope of individual hazards is greater than the slope of the Gompertz (exponential) curve.

Figure 3 allows us to compare the marginal and underlying hazards calculated with the correlated frailty model for Danish (dashed line), Swedish (thin solid line) and Finnish twins (thick solid line). The marginal mortality rates for Danish and Finnish male twins (top-left panel) are the highest for all ages. The top-right panel in Figure 3 shows that Danish mortality rate is the highest for female twins. The Swedish male mortality is the lowest until age 80, after which all three graphs virtually converge. The mortality rate for Swedish females is the lowest until age 50. Between ages 50 and 85 it coincides with the mortality rate for Finnish females and becomes lowest again after age 85.

Among the males, the estimates of the individual mortality rate (underlying hazard) are highest for the Finnish twins, and lowest for Swedish twins until age 85 (bottom-left panel in Figure 3). After age 85 the individual hazard rate for Danish male twins is the lowest. For females (bottom-right panel in Figure 3) the individual hazard for Danish twins is the highest until age 65 and is lowest after age 70. The individual hazards for Swedish and Finnish female twins are almost equivalent, with a slightly lower hazard for Swedish twins around 85–100 years of age.

Discussion

Traditional genetic analyses of susceptibility to disease and death are based on the notion of liability. According to Falconer,[28] liability, Z, is a standard normally distributed random variable that is related to the discontinuous trait Y by a threshold. Later this definition was extended to describe more sophisticated liability-trait relationships.[2,29] Models of more complicated quantitative traits, including durations, have also been suggested and analysed using multivariate survival data.[2–4]

Liability models provide a convenient methodological framework for studying the genetic and environmental aspects of survival. However, to use these models the parametric specification of the univariate conditional survival functions' given liability is needed. Such parametrisation is often difficult to justify biologically. In the case of bivariate frailty models, such specification is not needed: this function can be estimated semi-parametrically[15,16] from bivariate survival data. Thus, by using frailty – rather than liability – models in bivariate survival studies, one poorly justifiable technical assumption is avoided.

Furthermore, in the case of traditional liability models the likelihood function of survival data is not represented in a closed analytical form, because averaging with respect to unobserved liability often cannot be done analytically and has to be replaced by numerical approximations. Consequently, the maximum likelihood procedure may require substantial computational efforts which may be accompanied by undesirable complications, such as convergence failure and numerical instability. Such efforts are not required in the case of the frailty models discussed here because the likelihood functions of the data can be written in analytical form, which simplifies further calculations.

Finally, frailty models provide a fairly 'natural' approximation to non-linear hazard functions. Indeed, the linear approximation of hazard $\mu(x,Z)$ (eg by means of Taylor series expansion), where Z represents the susceptibility variable, yields the frailty (proportional hazard) model $\mu(x,Z) \approx Z\mu_0(x)$, because $\mu(x,0) = 0$, ie the hazard is equal to zero when the frailty is zero. The proportionality of hazards also facilitates other applications of genetic analysis of survival data. For example, the additive decomposition of individual frailty, which is used in genetic models, generates a competing risks structure in the survival models, where respective risks are associated with the genetic and environmental influence on mortality. The survival function associated with the genetic component can also be used to evaluate the biological limits of human longevity.[15]

The results of the genetic analysis of Danish, Swedish and Finnish twin data confirm the hypothesis that genetic effects influence individual frailty and hence, life span in all these populations for both sexes. The underlying hazards for all three samples

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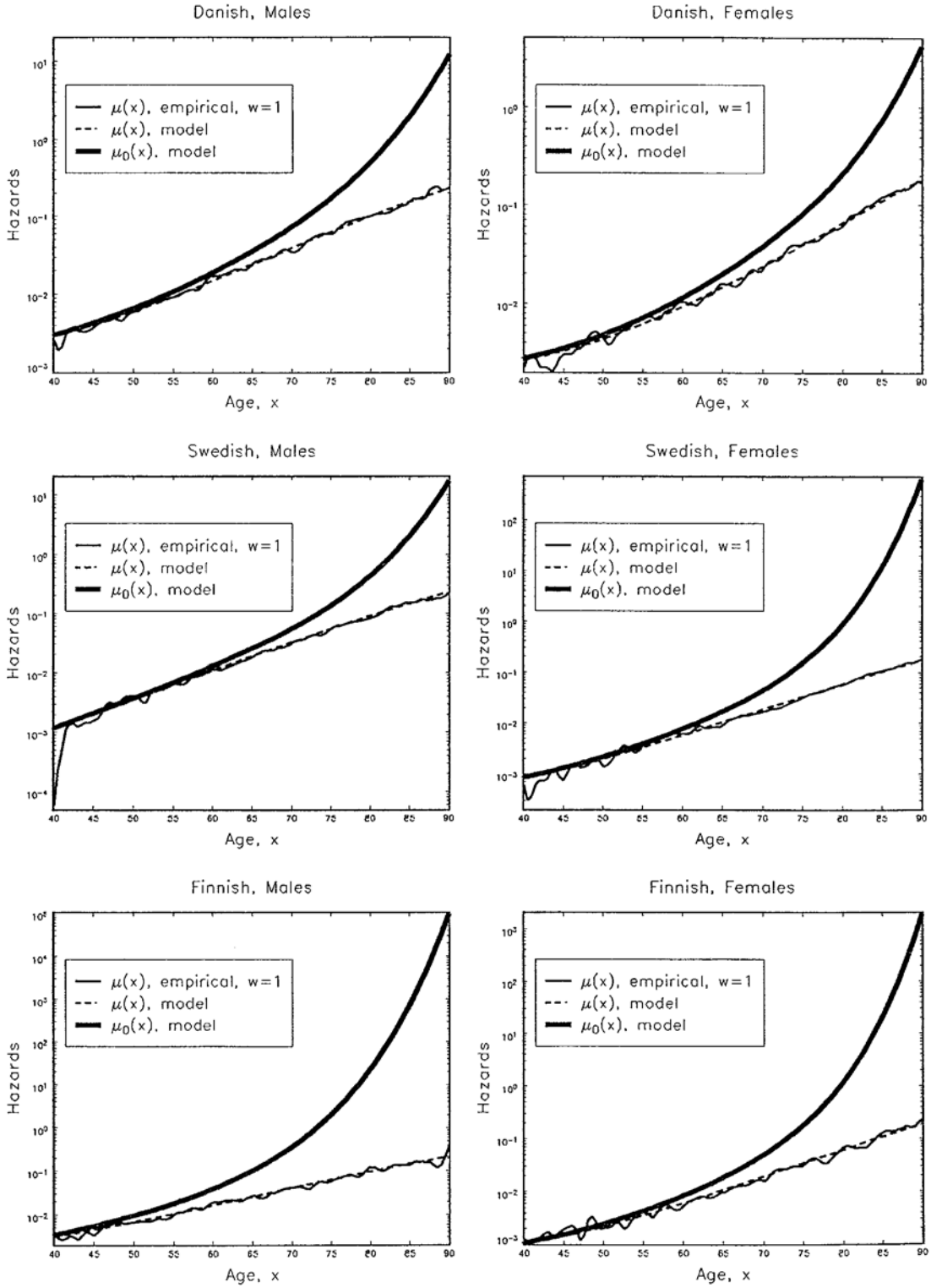

Figure 2 The age-trajectories of the empirical total mortality (thin solid line), total mortality estimated from the univariate subset of bivariate data (dashed line) and the underlying hazard estimated from the bivariate data using the correlated gamma-frailty model (thick solid line) for Danish (top panels), Swedish (middle panels) and Finnish (bottom panels) twins, male (left panels) and female (right panels).

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and for both sexes increases faster than the Gompertz hazard. The steeper slope of the individual hazard compared with the marginal hazard suggests that the estimates of changes in individual survival with age calculated from standard demographic life tables may be misleading: the increase of individual hazard with age occurs faster than traditional demographic methods predict. This result is important for the calculation of individual chances of survival.

The Lexis diagram in Figure 1 shows the difference in birth cohorts and follow up times for twins from different Twin Registers. This difference in selection/truncation conditions may create difficulties in the analysis of mortality data when traditional methods are applied.[30] The use of the correlated frailty models, however, allows us to take all such conditions into account. As a result the differences in the structure of the data from different sources do not create additional problems in the joint analysis of these data. This makes the correlated gamma-frailty model a convenient tool for performing such combined analysis where the sampling conditions (eg survival until a certain year or age) vary from one data set to another. The use of this model to study various aspects of life-span dependence is discussed by Yashin and Iachine.[31]

That frailty distributions for the Danish, Swedish and Finnish twin populations are similar, as confirmed by the likelihood ratio test, is an important finding. First, it permits us to improve the quality of parameter estimates by combining survival data in a single likelihood function. The quality may be measured by the width of the respective confidence intervals defined as the difference between the upper and the lower confidence interval boundaries. Note that the width of the confidence intervals for the heritability estimate reduce from 0.29, 0.26 and 0.39 for Danish, Swedish and Finnish male twins respectively to 0.18 in the joint male twins analysis. The respective reduction in the confidence interval width for female twins is from 0.29, 0.38 and 0.55 in the stratified by country analysis to 0.22 in the joint analysis. The analyses also reveal remarkable similarity between bivariate frailty distributions for

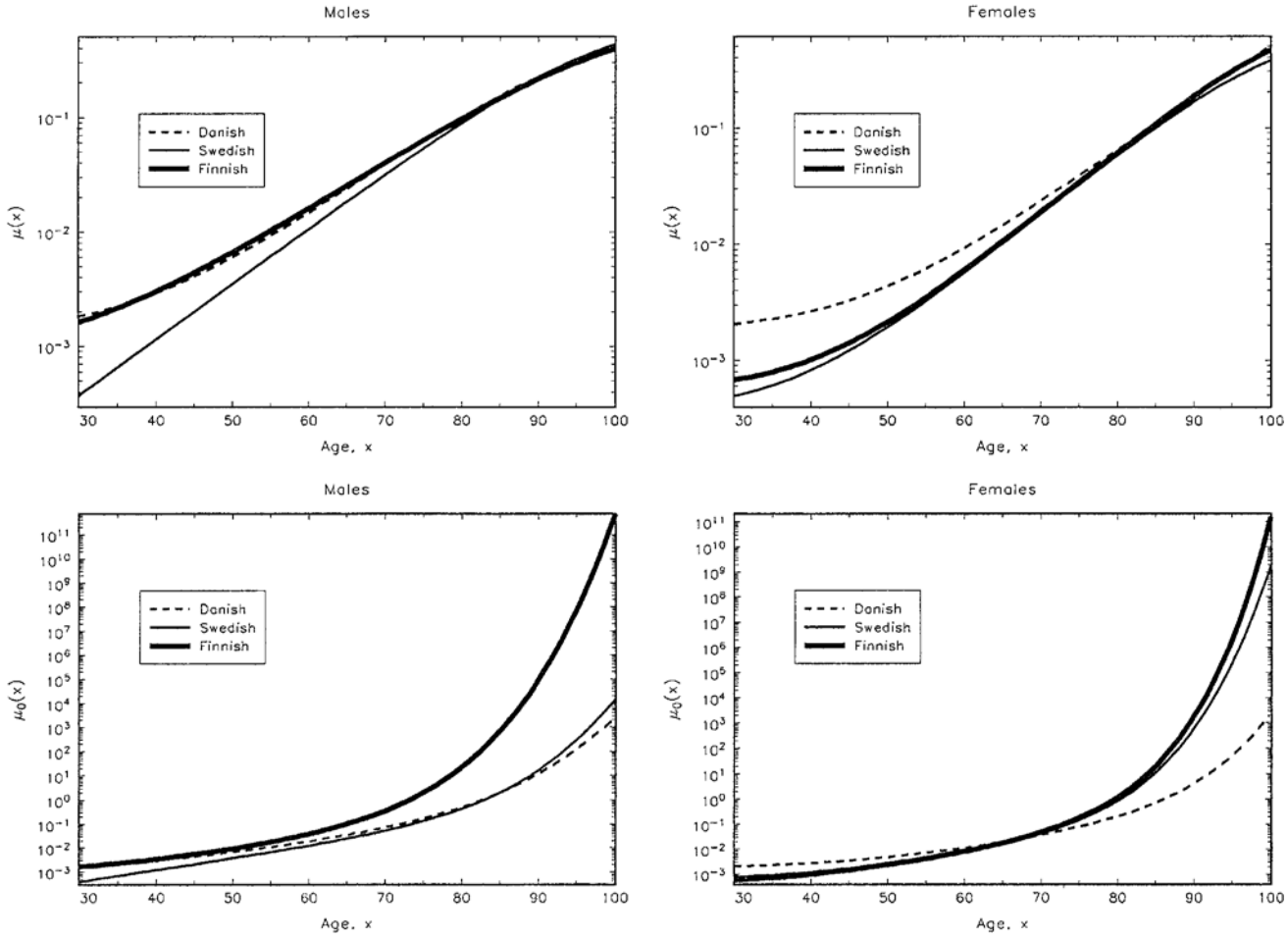

Figure 3 The age-trajectories of the empirical total mortality (top panels) and the underlying hazards (bottom panels) for Danish (dashed line), Swedish (thin solid line) and Finnish (thick solid line) male (left panels) and female (right panels) twins.

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male and female twins (see the last lines in Tables 2 and 3). Such similarity opens an opportunity for the joint analysis of male and female data. One can see, however, that such an analysis would not add anything new to our findings. The sample sizes of the data used in separate analyses are large enough to make reliable conclusions about parameter estimates. In both cases (male and female data) the estimates of heritability in frailty are about 0.5, and these estimates are significantly different from zero.

Second, similarity in the frailty distributions themselves is important for understanding the role of genes and environment in mortality and longevity. Our analysis reveal that countries with quite different patterns of survival show this similarity in the mechanism of life-span association for related individuals. Is this similarity a fundamental property for all twin populations? Answers to these questions require further investigation using more detailed data on aging processes in twins.

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Appendix 1

Correlated gamma-frailty models

Let T_i, i = 1,2 be the life spans of the two related individuals and $\mu_i(Z_i, x) = Z_i\mu_{0i}(x)$ be their conditional individual hazards with the individual frailties Z_i, i = 1,2 and the underlying hazards $\mu_{0i}(x)$, i = 1,2. We assume that the frailties are gamma-distributed with means 1 and variances σ_1^2 and σ_2^2 and that they are correlated with the correlation coefficient ρ_z. This assumption can be satisfied when Z_1 and Z_2 have the representations $Z_1 = Y_0 + Y_1$ and $Z_2 = \alpha(Y_0 + Y_1)$, $\alpha > 0$ with variables Y_0, Y_1, Y_2 being independent and gamma-distributed, with different shape parameters and the same scale parameters. The life spans T_1 and T_2 are assumed to be conditionally independent given frailties Z_1, Z_2. The marginal bivariate survival function in this case is:

$$S(x_1,x_2)=\left(1+\sigma_1^2H_1(x_1)+\sigma_2^2H_2(x_2)\right)^{\frac{\rho_z}{\sigma_1\sigma_2}}$$
$$\times\left(1+\sigma_1^2H_1(x_1)\right)^{\frac{1}{\sigma_1^2}+\frac{\rho_z}{\sigma_1\sigma_2}}\left(1+\sigma_2^2H_2(x_2)\right)^{\frac{1}{\sigma_2^2}+\frac{\rho_z}{\sigma_1\sigma_2}}$$

where $H_i(x)=\int_0^x\mu_{0i}(u)du, i=1,2.$

In our study we assume that $\sigma_1 = \sigma_2 = \sigma$, $H_1(x) = H_2(x) = H(x)$. We also assume that the marginal univariate survival function can be represented as

$$\bar{S}(x)=\left(1+s^2\left[\frac{a}{b}(e^{bx}-1)+cx\right]\right)^{-\frac{1}{s^2}}$$

where a, b, c, s are unknown parameters. This representation is called the 'gamma-Makeham model'. The underlying cumulative hazard function can be expressed as:

$$H(x)=\frac{\bar{S}(x)^{-\sigma^2}-1}{\sigma^2}$$

The bivariate correlated frailty model defined in this way contains seven unknown parameters: a, b, c, s, σ, ρ_{MZ}, ρ_{DZ}, where σ, ρ_{MZ}, ρ_{DZ} characterise the bivariate frailty distributions for MZ and DZ survival data. Estimates of the parameters were obtained by maximising the respective likelihood functions for twin survival data. Note that parametrisation of the likelihood of bivariate data differs from that used in the univariate analysis of frailty models without observed covariates, where the parametric structure of the underlying hazards was used.

Genetic models of frailty

Let A, D, I, C, E, and H refer to additive genetic effects, dominant genetic effects, epistatic genetic effects, shared environmental effects, non-shared environmental effects, and total genetic effects, respectively, in the decomposition of individual frailty. Accordingly, an ACE model refers to the decomposition of frailty Z = A + C + E. We use lower case a^2, d^2, i^2, c^2, e^2 to denote the respective proportions of variance. For example, the equations

$$1 = a^2 + c^2 + e^2$$

and

$$\rho = \rho_1a^2 + \rho_4c^2 + \rho_5e^2$$

describe the decomposition of standardised variance and correlation coefficient of frailty. Here ρ_1, ρ_4, ρ_5, are correlations between respective components within a twin pair. (Similarly, ρ_2 and ρ_3 are correlations between dominant genetic and epistatic genetic components of frailty).

Standard assumptions of quantitative genetic models (Neale and Cardon, 1992) specify values of ρ_i, i = 1, 2,...5 and R for MZ and DZ twins. For example, in the case of MZ twins ρ_i = 1, i = 1,2,3,4; ρ_5 = 0; R = 1. For DZ twins ρ_1 = 0.5; ρ_2 = 0.25; ρ_3 = m; ρ_4 = 1; ρ_5 = 0; R = k. Here $0 \le m \le 0.25$, $0 \le k \le 0.5$ are unknown parameters. Note that these decompositions in the statistical analysis of the data are based on the assumption of equal variances of the frailty distributions for MZ and DZ twins.

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