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The Genetic Component of Discrete Disability Traits: An Analysis Using Liability Models with Age-Dependent Thresholds

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The presence of familial and genetic effects in the Activities-of-Daily-Life (ADL) data collected in the first wave of the 1995 Longitudinal Study of Aging of Danish Twins (LSADT) older than 75 is tested using multithreshold liability models of disability with age-dependent thresholds. These models are developed for discrete scores represented by five disability scales of male and female Danish twins. The presence of familial effects is revealed in all five scales of disability data for females and in three scales of data for males. Genetic effects are found to be significant in all four levels of aggregation of the Upper Limb-T (T = tiredness) disability scale for females and in the PADL-H (H = need for help) scale for males. Genetic effects are also pronounced in the Mobility-T scale for females and in the Lower Limb-T scale for males and females. For females, the genetic effects in the T-scale seem to be more pronounced than in the H-scale. For males, genetic effects are more pronounced in the H-scale. The estimates for MZ correlations in liability tend to be higher than the estimates for DZ correlations in almost all cases, which suggests that additional genetic effects may be revealed should the sample size of the ADL data be increased.

KEY WORDS: Contingency tables; cross-sectional data; disability; liability; elderly twins.

INTRODUCTION

Traditional methods of genetic analysis, applied by Cristensen *et al.* (1997a), to the activity of daily living (ADL) data taken from the Longitudinal Study of Aging in Danish Twins (LSADT) database reveal that there is a substantial genetic influence on physical ability among 80+-year-old Danish female twins. In their study Christensen *et al.* use a continuous approximation of the aggregated disability score. Such analysis may lose statistical efficiency because of the aggregation of several scales: the disability measured in different scales may experience different genetic influence. Disaggregated analysis requires models of discrete disability traits represented in several scales. Some ideas on the analysis of discrete censored survival times associated with the age-at-onset data are discussed by Pickles *et al.* (1994). In this paper methods of analysis of current status data are developed.

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Note that the ADL data correspond to more complicated processes than the survival data: the proportions of individuals in different disability states measured in cross-sectional studies are determined not only by the probability distribution of age at onset of disability but also by the distribution of age at death conditioned on disability state. In this article multithreshold liability models for disability traits are suggested and analyzed. Since disability is an age-dependent trait, the age dependence of the thresholds is assumed. The parameters of the thresholds and the heritability of liability are estimated directly from the joint likelihood of the data for monozygotic (MZ) and dizygotic (DZ) twins represented by discrete disability scores. The design of the study allows us to use five disability scales similar to the univariate studies of disability completed by Avlund *et al.* (1995, 1996). Our model was developed to evaluate relative magnitudes of genetic and environmental influence on liability to disability controlling for individual age by estimating correlations in liability for MZ and DZ twins. The hypotheses about the similarity of such correlations for MZ and DZ twins and about the significance of these correlations were tested using likelihood-ratio tests. The age dependence of the thresholds is estimated. The new approach is compared with the traditional analysis, which does not control for the age dependence of the thresholds. Our model was applied to all five disability scales, with four levels of aggregation for each scale. This method confirms that there is a substantial genetic influence on female disability measured in one of five scales. The genetic influence is less pronounced for male disability and for female disability measured in other scales. The results of an analysis show that the models with age-dependent thresholds fit the data better than the fixed-threshold models.

MATERIALS AND METHODS

The ADL Data for Danish Twins. For our research, we worked with the data collected for the Longitudinal Study of Aging Danish Twins (Christensen *et al.*, 1997b). This study included the population of all twins living in Denmark who were age 75 or older as of January 1995 (with or without a living cotwin). Altogether 3099 individuals were asked to participate in the main study as well as in pilot studies. Of those invited to participate, 2401 responded by filling out a questionnaire (including 213 responses by proxy). Disability information was collected, and disability scores are now available for 2254 individuals. Of these, 2031 individuals belong to the group of like-sex twins with known zygosity, which includes a total of 1618 twin pairs. Among them are 413 complete pairs (i.e., with disability scores available for both twins in the pair) which fall into the following categories: 51 male MZ twin pairs, 74 male DZ twin pairs, 117 female MZ pairs, and 171 female DZ pairs. Questionnaire data from single twins, defined as a twin whose cotwin was either deceased or not a participant in the study, were excluded from the analysis of familial and genetic effects. The mean age of female MZ twins in the sample is 79.8, with a standard deviation of 4.3. For male DZ twins it is 79.1, with a standard deviation of 3.9. For female DZ twins it is 79.6, with a standard deviation of 3.6.

Measures of Functional Ability. Functional ability was measured by accessing the ability of each individual in the study to perform a basic set of physical activities. In all, 16 activities were considered: (1) transfer (e.g., moving within a room), (2) walking indoors, (3) going outside, (4) walking outside in good weather conditions, (5) walking outside in poor weather conditions, (6) climbing up (or down) stairs, (7) going to the toilet, (8) dressing the lower part of the body, (9) putting/taking shoes/stockings on/off, (10) washing the lower part of the body, (11) cutting the toenails, (12) combing the hair, (13) washing the hair, (14) dressing the upper part of the body, (15) washing the upper part of the body, and (16) cutting the fingernails. An individual's performance of these activities was described relative to two additional dimensions: (a) the person was or was not tired afterward, and (b) the person could or could not manage without help. To make this study consistent with the previous studies, the five functional ability scales suggested by Avlund *et al.* (1995) were used. These consist of three tiredness scales, (i) Mobility T-scale (items 1–6), (ii) Lower Limb T-scale (items 7–11), and (iii) Upper Limb T-scale (items 12–16), and two dependency scales, (iv) Mobility H-scale (items 1–6) and (v) PADL H-scale (items 7–12 and 14–16). The activity performed in T-scales is characterized by additional information on whether or not the person is tired after competing the actions. The activities performed in H-scales are characterized by

additional information about whether the person uses somebody's help during the action (see Avlund *et al.*, 1995, 1996).

The Liability Model. The multi-thresholdliability model has been developed, tested, and applied to the Danish Twin ADL data. The model extends the standard approach to the genetic analysis of contingency tables by including the age dependence of the thresholds in the liability model of discrete traits. This approach permits us to use a wide variety of parametric functions to describe the dependence of the thresholds on the explanatory variable.

In this article a linear function of age is used to describe age dependence in the multithreshold model for the Danish Twin ADL data. All thresholds are assumed to have the same rate of change δ. Thus, just one additional parameter is introduced in comparison with the fixed-threshold model. This parameter is estimated, along with genetic parameters, using the maximum-likelihood method for combined MZ and DZ data (see the Appendix). In all, we tested three hypotheses about the presence of age effects, familial effects, and genetic effects on the disability traits of twins in the population of the intact twin pairs using the likelihood-ratio test. To detect the presence of age effects on disability traits, we tested the hypothesis which proposes a zero slope for threshold age functions. To detect the presence of a familial component on disability, we tested the hypothesis which proposes a zero association in the twin disability data for MZ and DZ twins combined. When the presence of a familial component in the scale is revealed, the genetic part of this component can then be evaluated by calculating the heritability estimates and testing the hypothesis about the significance of these estimates.

To investigate the sensitivity of our findings (when we found the presence of familial or genetic effects on disability) to the number of parameters included in the model (liability thresholds plus MZ and DZ correlations in the case of familial effects and liability thresholds plus the estimates of heritability and contribution of common and uncommon environmental factors in the case of genetic effects), we calculated four scores corresponding to the four levels of aggregation of disability indices for each of the five disability scales. The aggregated scores were calculated as follows: let Y_i be the disaggregated score, Y_i $\{0,1,2,\ldots, M\}$, i = 1,2,. . .n. Then the aggregated score X_i with the maximum value K was calculated using the formula

$$X_i = \left[\frac{K}{M} Y_i\right], \qquad i = 1, 2, \ldots, n$$

where the notation $[Z]$ means the integer part of Z. After this operation the values of X_i, i = 1,2,. . .,n are used to estimate the correlation liability. The four scores include (1) a dichotomous score, where the disability index is allowed to take only two values—either 0 or 1; (2) a score with three values for the disability index; (3) a score with four values for this index; and (4) a disaggregated score. For each scale and each score the data were summarized in 80 contigency tables (five scales, four aggregation scores, two sexes, and two zygosity groups). The GAUSS programming language with the respective library of subroutines was used for computation of the respective probabilities in the likelihood function. Parameter estimates and their standard errors were calculated using the GAUSS Maximum Likelihood Package. All p values were calculated using the likelihood-ratio test. The genetic analysis was performed using the narrow-sense heritability model. The likelihood-based confidence intervals (e.g., Neale and Miller, 1997) for the heritability of liability associated with different disability scales were calculated using models with age effects. The source code of the respective computer programs in GAUSS is available upon request.

RESULTS

The analyses of all four aggregated scores showed similar results. For this reason only the results related to disaggregated scores are presented. The female data showed the presence of a strong familial component in all five disability scales. The presence of genetic effects is manifested (p = .005), in the female disability data for the Upper Limb T-scale. Indications for the possible presence of genetic effects are also found in the Mobility T-scale for females (p = .041), in the PADL H-scale for males (p = .021), and in the Lower Limb T-scale for both males and females (p = .031 and p = .055, respectively).

The results of analysis are summarized in two tables. Table I deals with male disability data. Table II characterizes female disability. The structure

Table I. Results of the Analysis of Disability Scores: Male Twins

	ρ_{MZ}	ρ_{DZ}	h^2	c^2	$\rho_{MZ} = \rho_{DZ}$	$\delta = 0$	$\rho_{MZ} = 0$, $\rho_{DZ} = 0$
M T							
w/o age effects	0.33	0.09	0.28	0.00	0.151		
	(0.18)	(0.14)	(0.16)	(—)			
w. age effects	0.31	0.01	0.23	0.00	0.105	0.026	0.279
	(0.18)	(0.02)	(0.16)	(—)			
			[0.00–0.52]				
LL T							
w/o age effects	0.57	0.17	0.49	0.00	0.046		
	(0.15)	(0.14)	(0.15)	(-)			
w. age effects	0.55	0.13	0.47	0.00	0.031	0.051	0.016
	(0.15)	(0.14)	(0.15)	(—)			
			[0.13–0.72]				
UL T							
w/o age effects	0.37	0.29	0.15	0.22	0.408		
	(0.27)	(0.18)	(0.67)	(0.46)			
w. age effects	0.40	0.21	0.37	0.02	0.287	0.065	0.219
	(0.26)	(0.20)	(0.51)	(0.35)			
			[0.00–0.75]				
M H							
w/o age effects	0.15	−0.01	0.00	0.00	0.321		
	(0.29)	(0.08)	(—)	(—)			
w. age effects	0.11	−0.17	0.00	0.00	0.213	0.010	0.588
	(0.30)	(0.17)	(—)	(—)			
			[0.00–0.37]				
PADL H							
w/o age effects	0.58	0.16	0.51	0.00	0.042		
	(0.16)	(0.15)	(0.16)	(—)			
w. age effects	0.58	0.08	0.47	0.00	0.021	0.018	0.023
	(0.15)	(0.16)	(0.17)	(—)			
			[0.10–0.75]				

of these tables is as follows: the estimates of the correlation coefficients of liability calculated for MZ and DZ twins are shown in columns 2 and 3. The values for narrow-sense heritability, estimated directly from the liability models for combined data on MZ and DZ twins, are shown in the fourth column. The estimates of relative variance associated with common environmental factors are given in the fifth column. The sixth column contains the one-tailed p values (e.g., Chernoff, 1954) associated with testing hypothesis H_0, $\rho_{mz} = \rho_{dz}$, vs. the alternative H_1, $\rho_{mz} > \rho_{dz}$, i.e., the opposing hypothesis that there is no genetic influence on disability traits. The seventh column contains the p values for the likelihood-ratio statistic for testing the presence of age dependence (i.e., H_0, $\delta=0$, vs. H_1, $\delta\neq0$), where δ is the slope of the threshold-age function. The last column contains the p values for the likelihood-ratio statistic for testing the absence of a familial component in disability data, i.e., H_0, $\rho_{mz} = \rho_{dz} = \rho = 0$, vs. H_1, $\rho = 0$.

The first line, corresponding to each of the five disability scales represented in the tables, contains the results calculated under the fixed threshold model, i.e., without including age effects in the thresholds. The estimates in the second line of each scale are calculated using the age-dependent thresholds. The standard errors of the parameter estimates are shown in parentheses under the respective estimates. The absence of a number in the parentheses indicates that the standard error could not be calculated due to the parameter estimate location on the boundary of the parameter space (e.g., $c^2 = 0$). In these cases, all other parameters were reestimated with this parameter value taken at the boundary. The likelihood-based confidence intervals for heritability of liability [calculated using the method discussed by Neale and Miller (1997)] are

Table II. Results of the Analysis of Disability Scores: Female Twins

	ρ_{mz}	ρ_{dz}	h^2	c^2	$\rho_{mz} = \rho_{dz}$	$\delta = 0$	$\rho_{mz} = 0$, $\rho_{dz} = 0$
M T							
w/o age effects	0.34	0.18	0.31	0.03	0.065		
	(0.11)	(0.09)	(0.29)	(0.22)			
w. age effects	0.30	0.05	0.25	0.00	0.041	<0.001	0.027
	(0.11)	(0.10)	(0.10)	(—)			
			[0.05–0.43]				
LL T							
w/o age effects	0.42	0.23	0.38	0.04	0.090		
	(0.11)	(0.09)	(0.30)	(0.23)			
w. age effects	0.38	0.15	0.36	0.00	0.055	<0.001	0.002
	(0.11)	(0.10)	(0.10)	(—)			
			[0.15–0.54]				
UL T							
w/o age effects	0.51	0.08	0.42	0.00	0.008		
	(0.12)	(0.11)	(0.12)	(—)			
w. age effects	0.45	−0.05	0.29	0.00	0.005	<0.001	0.016
	(0.13)	(0.12)	(0.13)	(—)			
			[0.02–0.54]				
M H							
w/o age effects	0.25	0.31	0.00	0.29	0.354		
	(0.14)	(0.10)	(—)	(0.08)			
w. age effects	0.17	0.18	0.00	0.18	0.492	<0.001	0.141
	(0.14)	(0.11)	(—)	(0.09)			
			[0.00–0.44]				
PADL H							
w/o age effects	0.36	0.19	0.33	0.03	0.150		
	(0.12)	(0.10)	(0.19)	(0.12)			
w. age effects	0.33	0.12	0.30	0.00	0.102	<0.001	0.025
	(0.12)	(0.10)	(0.11)	(—)			
			[0.08–0.50]				

shown in brackets in the h^2 column under the standard errors (calculated by the GAUSS Maximum Likelihood Package).

Significance of Age Effects. The small p values in the seventh columns ($\delta = 0$) of both tables show that taking the age dependence of the thresholds into account significantly improves the fit of the model. The age effects are pronounced for all four levels of disability-scale aggregation (not shown in the tables). The estimated values of δ for males are about 0.06, with a standard error of about 0.02. For females these estimates are about 0.08, with a standard error of about 0.01, for all five scales.

Significance of Familial Effects. The small p values in the last columns of both tables indicate the presence of familial effects on disability in all scales except the M H-scale. The familial effects on disability for males are much less pronounced: only for the Lower Limb T-scale and the PADL H-scale are the respective p values small. The fact that the number of men participating in the study was half as large as the number of women may well be responsible for the male/female difference in p values. Consequently, one cannot expect reliable detection of genetic effects on the other disability scales for male data.

Significance of Genetic Effects. The small p values in columns 6 of both tables indicate the presence of genetic effects on respective scales. Despite the presence of familial effects on four scales of female data, the genetic effects are significantly pronounced only in the Upper Limb T-scale. The respective heritability estimate is about 0.3. Similar values for this estimate were calculated for all four levels of aggregation of this disability scale. The presence of genetic effects is also manifested in the PADL H-scale for males. The respective heritability estimate is about 0.5. In two scales we find rather small p values, which can be

used for testing the hypothesis that there is zero chance of inheritance of a disability. The first is the Mobility T-scale for females (0.041) with a heritability estimate of 0.25; the second is the Lower Limb T-scale for males and females, which have heritability estimates of 0.5 and 0.4, respectively. For all the male disability scales, estimates for MZ correlations in liability tend to be higher than for DZ correlations. The same result appears in the female disability scales, with the exception of the Mobility H-scale. The likelihood-based 95% confidence intervals confirm the presence of significant genetic effects measured in the Lower Limb T- and the PADL- T-scales for males and in all except the Mobility H-scale for females.

Remark. Note that the heritability estimates, calculated according to the formula $\hat{h}^2 = 2(\hat{\rho}_{mz} - \hat{\rho}_{dz})$ do not coincide with the estimates shown in the tables. The reason for this discrepancy is that the heritability estimates shown in columns 4 are calculated directly from the joint likelihood function of the integrated MZ and DZ data in the multithreshold heritability model. This method of estimation is preferable to the traditional two-step procedure (i.e., when correlations are calculated first), where, because of estimation errors in correlations, negative values of $\hat{c}^2$ can be obtained. Such a situation is also avoided in the structural equation approach (Neale and Cardon, 1992). One can see from Tables I and II that, for almost all scales, the genetic effects become more pronounced after the age dependence of the thresholds is introduced.

DISCUSSION

The results of recent genetic studies of human mortality and longevity show that genetic factors are responsible for about 50% of the variability in individual susceptibility to death (frailty) specified by the correlated frailty model for Danish twins (Yashin and Iachine, 1995a, b). This value exceeds the heritability estimate for human life span (about 25%) estimated from the same data (McGue *et al.*, 1993; Herskind *et al.*, 1996). If disability, as measured by some appropriate scale, can serve as a measure of frailty, one can expect that the genetic effects on such disability will be more pronounced than on life span. On the other hand, some disability indices used in this study may reflect a higher level of environmental influence and contain measurement errors.

The absence of reliable estimates of the familial effects for males and the genetic effects, as measured by the four disability scales, for females in Tables I and II may be the result of the small sample size of intact twin pairs. This conclusion is definitely relevant to males. Due to higher male mortality, the number of males in the sample is smaller than the number of females. Results shown in Tables I and II show that the broad-sense heritability model is more efficient in detection of genetic effects compared to the narrow-sense heritability model.

When using data on age-dependent trait prevalence, special care should be taken to exclude spurious familial and genetic effects. For example, the presence of age dependence in disability data may influence the estimates of familial and genetic effects when aggregated data are analyzed. Thus, by controlling for age dependence in disability studies, one can obtain more reliable estimates of genetic parameters. The traditional approach provides several methods of controlling for age dependence with most of them developed for studying continuous traits. For example, regression methods are often used to eliminate the effects of age variables for twins at the initial step of data analysis. The final step is focused on the genetic analysis of residuals (Neale and Cardon, 1992).

A more useful method allows for the one-step estimation of genetic parameters from regression equations (e.g., DeFries and Fulker, 1985; LaBuda *et al.*, 1986). This method gives its best results, however, when a trait is measured on a continuous scale. When disability traits are measured on traditional discrete scales (with 6–10 possible values) and the sample size of the data is large enough, age stratification may help control age dependence. This solution, however, is inappropriate in our case due to the relatively small sample size of the data on intact twin pairs presented in the first wave of the LSADT data.

In this article we develop an approach which allows us to fix the same age functions for the thresholds in the liability models for MZ and DZ twins. The hypotheses about the presence of age, familial, and genetic effects are tested by likelihood-ratio tests. The analysis shows that the use of different levels of aggregation for the scores gives us no reason to change our main conclusions about

either (1) the age dependence of the thresholds or (2) the presence of familial and genetic effects. Therefore only the results for the most informative (the disaggregated one) score are presented.

More detailed analysis shows that nonzero heritability estimates obtained in such cross-sectional studies of twins should be used with care, even if corrected for the age dependence of prevalence characteristics. It turns out that the dependence between mortality rates of related individuals with given health states may make a substantial contribution to the value of heritability estimates obtained in a genetic analysis of contingency tables corresponding to ADL data from a cross-sectional study. In some cases the nonzero heritability estimates in liability may be obtained in the absence of a direct genetic influence on the age at onset of disability or on the disability rate (Iachine *et al.*, 1997).

To take these effects into account, models which consider dependent health history processes for related individuals need to be developed. In addition to intact twin-pair data, used in traditional methods and their extensions, information on broken twin pairs can make a significant contribution to both the identifiability of a new model and the efficiency of its parameter estimates.

APPENDIX

The standard liability model uses $n - 1$ thresholds $\theta_1, \theta_2, \ldots, \theta_{n-1}$ to represent the distribution of individuals in accordance with n levels of their disability score function. We represent the age dependence of thresholds by linear functions $\theta_j + \delta x$, $j = 1,2,\ldots, n - 1$.

Thus, the theoretical proportions $P_{ij}(\theta_1,\ldots, \theta_{n-1}, \rho, \delta, x)$, $i,j = 1,2,\ldots, n - 1$, of twins corresponding to the $n \times n$ contingency table of cross-sectional data for age x may be represented in terms of the bivariate normal probability density function of liability:

$$P_{ij}(\theta_1, \theta_2, \ldots, \theta_{n-1}, \rho, \delta, x) = \int_{\theta_i+\delta x}^{\theta_{i-1}+\delta x} \int_{\theta_j+\delta x}^{\theta_{j-1}+\delta x} f(y_1, y_2; \rho)\, dy_1\, dy_2, \qquad i, j = 0, 1, \ldots, n - 1$$

where $\theta_0 = -\infty$, $\theta_n = +\infty$, and $f(y_1, y_2; \rho)$ is the bivariate normal probability density function of liability with correlation coefficient ρ and $N(0,1)$ marginals. Let i_k, j_k be the disability states of the two twins in a kth pair and let x_k be their age, registered in a cross-sectional study. Then the likelihood function of the data is

$$L(\theta_1, \theta_2, \ldots, \theta_{n-1}, \rho_{MZ}, \rho_{DZ}, \delta) = \prod_{k=1}^{N_{MZ}} P_{i_k j_k}(\theta_1, \ldots, \theta_{n-1}, \rho_{MZ}, \delta, x_k) \times \prod_{m=1}^{N_{DZ}} P_{i_m j_m}(\theta_1, \ldots, \theta_{n-1}, \rho_{DZ}, \delta, x_m)$$

Here N_{MZ} and N_{DZ} are the number of MZ and DZ twins pairs in the study.

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