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The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870–1900

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Abstract The aim of this study was to explore, in a large and non-censored twin cohort, the nature (i.e., additive versus non-additive) and magnitude (i.e., heritability) of genetic influences on inter-individual differences in human longevity. The sample comprised all identified and traced non-emigrant like-sex twin pairs born in Denmark during the period 1870–1900 with a zygosity diagnosis and both members of the pairs surviving the age of 15 years. A total of 2872 pairs were included. Age at death was obtained from the Danish Central Person Register, the Danish Cause-of-Death Register and various other registers. The sample was almost non-censored on the date of the last follow-up (May 1, 1994), all but 0.6% had died, leaving a total of 2872 pairs for analysis. Proportions of variance attributable to genetic and environmental factors were assessed from variance-covariance matrices using the structural equation model approach. The most parsimonious explanation of the data was provided by a model that included genetic dominance (non-additive genetic effects caused by interaction within gene loci) and non-shared environmental factors (environmental factors that are individual-specific and not shared in a family). The heritability of longevity was estimated to be 0.26 for males and 0.23 for females. The small sex-difference was caused by a greater impact of non-shared environmental factors in the females. Heritability was found to be constant over the three 10-year birth cohorts included. Thus, longevity seems to be only moderately heritable. The nature of genetic influences on longevity is probably non-additive and environmental influences non-shared. There is no evidence for an impact of shared (family) environment.

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Introduction

An increased emphasis has recently been placed on the search for specific genes that influence longevity. Among others, the epsilon 4 allele of apo E (Kervinen et al. 1994; Schächter et al. 1994), the R allele of apo B (Kervinen et al. 1994), and the Lp(a) lipoprotein gene (Berg 1994) have all been associated with human longevity. The inheritance of longevity is however probably complex (Schächter et al. 1993), and the importance of many genes, especially those that each explain a minor proportion of the variance, may remain as yet unrecognized (Gerdes U, Olsen H, Andersen-Ranberg K, Vaupel J, Jeune B (in preparation)).

A number of studies have attempted to assess the overall genetic influence on the variation in human lifespan. Family studies have generally shown weak correlations in length of life between parents and offspring (0.01–0.15; Pearl 1931; Cohen 1964; Wyshak 1978), whereas correlations between siblings tend to be higher (0.15–0.35) (Cohen 1964; Wyshak 1978). Genetic factors contributing to sibling resemblance may be additive or non-additive, whereas those contributing to parent-offspring resemblance can be only additive. Non-additive genetic effects are the result of gene interactions among gene effects either within (dominance) or between (epistasis) gene loci and are therefore not transmitted from generation to generation. The higher correlation found among siblings than among parents-offspring suggests that non-additivity is present, although it may also reflect a higher degree of shared environment among siblings than among parents and offspring.

In twin and adoption studies, a separation of the impact of genetic factors and the effect of family environment is possible. However, in the majority of previous twin studies (e.g., Jarvik et al. 1960; Hrubec and Neel 1981) and in the only adoption study (Sørensen et al. 1988) conducted on the heritability of longevity, length of life has been censored, and therefore only a partial assessment of the importance of genetic influences on human life span could be provided. In addition, in some of the studies, the populations were heavily truncated, e.g., subjects were included only if they were Second World War veterans (Hrubec and Neel 1981) or had passed the age of 60 (Jarvik et al. 1960). Only one study has been conducted in which a genetically informative cohort has been followed throughout their adult lifespan. The study, comprising 600 Danish twin pairs born during the period 1870–1880, showed that longevity was moderately heritable (0.22) and that non-additive genetic factors (genetic intra-locus interaction) were important (McGue et al. 1993).

We have explored, in a large and nearly non-censored twin cohort, the nature (i.e., additive versus non-additive) and magnitude (i.e., heritability) of genetic influences on individual differences in human longevity. The population studied is that of the Danish twins as used by McGue et al. (1993) but here it has been expanded to include 2872 pairs followed up for more than 94 years, allowing a much more detailed and powerful analysis.

Materials and methods

Subjects

The Danish Twin Register

The study was based on The Danish Twin Register, which is a population-based register established in 1954 by Bent Harvald and Mogens Hauge. The register includes all twins born in Denmark during the period 1870–1910 and all like-sex pairs born from 1911 to 1930. The procedures used have been described in detail previously (Hauge et al. 1968; Hauge 1981). The birth registers of the pertinent calendar years from all 2200 parishes were manually scrutinized for twin births. A search was carried out for twins, or whenever needed, their closest relatives in regional population registers (in operation since 1924) and from other public sources, especially the archives of probate courts and censuses. The follow-up procedure traced nearly all twins surviving the age of 15. Almost every untraced twin died or emigrated in childhood.

Zygosity was determined by self-reported similarities. The probability of misclassification using this method compared with serological markers has repeatedly been estimated to be below 5% (Hauge 1981; Lykken 1978).

Death status was obtained from the Central Person Register, the Danish Cause-of-Death Register, and various other public registries in Denmark. The last follow-up was completed on May 1, 1994.

The numbers reported in the present paper differ slightly from those of previous papers based on the Danish Twin Register (McGue et al. 1993; Christensen et al. 1995) because of the longer follow-up time, the identification of additional twins, the establishment of zygosity diagnoses, etc.

The validity of the Danish twin panel of like-sex cohorts born 1881–1920 has been investigated by comparing information on death status with the nationwide Danish Cancer Registry (compiled in 1942). The two registries were ascertained independently but showed 99% agreement on year of death (Holm 1983). Further data correction increased this percentage to almost 100%.

Death rates for twins and the general Danish population have been shown not to differ significantly after the age of 6 years, except for a modest excess in female twin mortality in the 60–89 year age-range (1.14 times higher than the standard population; Christensen et al. 1995). A substantial difference in death rate between twins and singletons would have indicated that results from twin studies are not valid for the general population.

Study population

In this study, all traced non-emigrant like-sex twins born in Denmark in the period 1870–1900 (inclusive) with a zygosity diagnosis and both members of the pairs surviving the age of 15 were included. The cohorts 1870–1900 were chosen to avoid censoring. Only 36 (0.6%) out of 5810 twin individuals were alive at the 1994 follow-up. Pairs in which one or both cotwins were still alive (33) were excluded leaving a total of 2872 pairs for analysis. The material was divided into an 11-year and two 10-year birth cohorts. Table 1 briefly describes the sample.

The mean age at death for monozygotic (MZ) twins exceeded that of dizygotic (DZ) twins by around 2 years. In the paper by Christensen et al. (1995), which involved the same twin population as the present study, an unexplained tendency for middle aged (30–59 years) MZ twins to have a reduced mortality compared with DZ twins was found; however, the difference was only significant for females. Otherwise, the mortality for MZ and DZ twins did not differ consistently after the age of 6.

The difference in mean age at death of about two years between males and females in the present twin study is comparable to the pattern of the general Scandinavian population born 1870–1900. The small gender difference for these cohorts might be a result of increased female mortality associated with pregnancies and child deliveries.

Statistical methods

The effect of sex, zygosity, and the year of birth on longevity was analyzed using analysis of variance. Because the longevity data were

Table 1 Study population by gender, zygosity and birth cohorts

Sex	Zygosity	1870–1880			1881–1890			1891–1900		
		n[a]	Mean age at death (SD)	*r*	*n*	Mean age at death (SD)	*r*	*n*	Mean age at death (SD)	*r*
Males	MZ	113	71.45 (15.85)	0.251	168	70.14 (16.05)	0.223	232	70.86 (16.64)	0.189
	DZ	186	70.11 (17.06)	0.081	306	68.43 (18.10)	0.111	403	69.30 (17.76)	0.088
Females	MZ	126	73.11 (16.32)	0.313	184	72.90 (17.75)	0.226	210	73.88 (17.84)	0.183
	DZ	215	70.65 (17.84)	0.019	329	70.70 (19.13)	0.130	400	72.26 (18.35)	0.066

[a] Number of pairs

negatively skewed they were then normalized using a quadratic transformation. The proportions of variance attributable to genetic and environmental factors were assessed from variance-covariance matrices using the structural equation model approach (Neale and Cardon 1992) with Mx as statistical software (Neale 1994).

Under the assumption of no epistasis and no gene-environment interaction or correlation, resemblance in twins is the result of three sets of latent factors (Fig. 1). (1) Additive genetic factors (A) contribute twice as much to the correlation in MZ twins as in DZ twins. MZ twins share all their genes by descent, whereas DZ twins, like ordinary siblings, share on average only half of their (additive) genetic effects. (2) Genetic dominance factors (D) caused by intra-locus interaction are shared by MZ twins but are only shared by a factor of 0.25 by DZ twins. (3) Shared environmental factors (C), i.e., those environmental factors, such as the rearing environment, that make members of a twin pair resemble each other, are assumed to contribute equally to the correlation in MZ and DZ twins. In addition to the latter, the model also includes non-shared environment (individual-specific environment; E), which, together with measurement error, is a measure of the impact of those environmental experiences that may make members of a twin pair different.

Six biometric models with different combinations of the four above latent factors viz., the ADE, AE, DE, ACE, CE, and E models, were fitted to the twin data. Shared environmental effects and effects caused by dominance cannot be assessed simultaneously as they are completely confounded in the classical study of twins reared together (Heath et al. 1988). To check for heterogeneity across sex and cohorts, models with different constraints on parameters across sex and/or cohort were fitted to the data.

Model fitting was by maximum likelihood, and the selection of the best fitting model was based on the following criteria: (1) a non-significant P-value in the Chi-square goodness of fit test; (2) minimizing the Akaike information criterion (AIC = χ^2 minus twice the degrees of freedom); (3) no parameter could be eliminated from the model without a significant increase in the Chi-square goodness of fit statistic. This approach reflects a balance between goodness of fit and parsimony.

Heritability was computed as genetic variance divided by total phenotypic variance. Genetic and environmental variances were derived from the best fitting model.

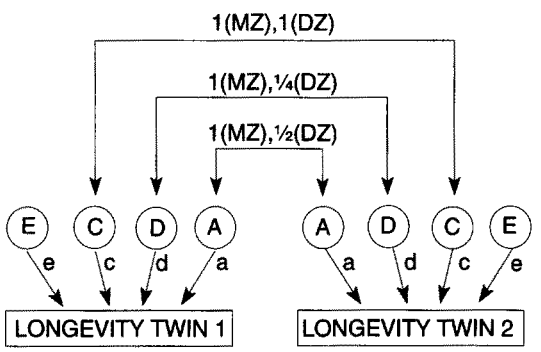

Fig. 1 Path model. The figure illustrates a model for causes of longevity. Latent etiologic factors are divided into additive genetic factors (*A*), genetic dominance factors (*D*), shared (*C*) and non-shared (*E*) environment. Additive genetic factors and genetic dominance factors are both perfectly correlated in MZ twins, whereas in DZ twins, the correlation between additive genetic factors equals 1/2 and the correlation between genetic dominance factors equals 1/4. Shared environment is assumed to contribute equally to the correlation in MZ and DZ twins. Non-shared environment is responsible for twin differences in longevity and is not correlated in MZ or DZ twins. The proportions of variance attributable to the latent factors are the square of the respective standardized path coefficients (e.g., the proportion of additive genetic variance equals a^2), which are estimated through maximum likelihood procedures. Heritability equals genetic variance divided by total phenotypic variance

Results

Analysis of variance showed a small, but statistically significant, impact of sex and zygosity on longevity, but together they explained less than 1% of the longevity variance. The year of birth had no significant impact. The phenotypic variance was consistently higher for females than for males in all groups.

Intraclass correlations

Intraclass correlations for MZ twins were consistently greater than for DZs in all subgroups, although the difference was only significant at the 5% level for females born 1870–1880 (Table 1). This pattern implicates genetic influences on individual differences in length of life. MZ correlations exceeded twice the DZ correlation for the cohorts 1870–1880 and 1891–1900, thereby suggesting a non-additive model. For the 1881–1890 cohort, DZ correlations were about half the MZ correlation.

Model fitting

To find the most parsimonious explanation for the observed pattern of resemblance for age at death, six biometric (Table 2) models were fitted to the normalized data (age-at-death squared). The DE model gave the best fit by AIC, but the AE model gave only a slightly worse fit. The model that included both additive and non-additive genetic factors (ADE) did not give as good a fit by AIC as either the AE or DE models. Pure environmental models (E and CE) did not fit the data well.

In order to identify which variance components varied significantly across sex and cohorts, DE submodels with different combinations of D and E fixed to be equal across sex and/or cohorts were fitted to the data (Table 3). All submodels gave a good fit to the data ($P > 0.05$), but the model with D and E fixed across cohorts and D fixed but E free to vary across sex gave the best fit to the data

Table 2 Biometric models for longevity allowing for sex and cohort differences in all variance components (*A* additive genetic effects, *D* genetic effects attributable to dominance, *C* shared environment, *E* non-shared environment)

Model	Model fit index			
	χ^2	*df*	*P*	AIC
DE[a]	19.36	24	0.73	−28.64
AE	20.41	24	0.67	−27.60
ADE	16.73	18	0.54	−19.27
ACE	20.40	18	0.31	−15.60
CE	34.26	24	0.08	−13.74
E	85.05	30	<0.001	25.05

[a] Best fitting model according to Akaike information criterion (AIC = $\chi^2 - 2 \times df$)

Table 3 DE-submodels for longevity with different combinations of genetic and environmental variance components fixed over sex and/or birth cohort. All models gave a good fit to the data ($P > 0.05$); the figures for the model giving the best fit by AIC ($\chi^2 - 2 \times df$) are in bold type (*D* genetic dominance effects, *E* non-shared environment)

			Cohort			
			D fixed E fixed	D fixed E free	D free E fixed	D free E free
Sex	D fixed	χ^2	39.07	36.84	36.43	34.67
	E fixed	*df*	34	32	32	30
		AIC	−28.58	−27.16	−27.57	−25.34
	D fixed	χ^2	**24.58**	22.07	22.26	19.96
	E free	*df*	**33**	29	31	27
		AIC	**−41.42**	−35.93	−39.74	−34.04
	D free	χ^2	27.07	24.95	24.57	22.80
	E fixed	*df*	33	31	29	27
		AIC	−38.93	−37.05	−33.42	−31.20
	D free	χ^2	24.09	21.57	21.53	19.36
	E free	*df*	32	28	28	24
		AIC	−39.91	−34.43	−34.48	−28.64

by AIC ($\chi^2 = 24.58$, $df = 33$, $P = 0.86$, AIC = −41.42). This result suggests the presence of sex differences in environmental variance components (E), but no significant cohort differences in either genetic or environmental variance components.

Heritability

Heritability estimates computed from genetic and environmental variances derived from the best fitting submodel (the model that included D and E, with sex differences in variance components resulting from non-shared environment and no cohort differences) were 0.26 for males and 0.23 for females (Table 4). Heritability computed on the basis of the best AE submodel gave similar results.

Discussion

Our analysis of longevity is based on the largest population of twins reported so far. The population is also the least truncated and the least censored population yet studied. The findings substantially strengthen the previous analysis of mortality in Danish twins born 1870–1880 (approximately 20% of the present sample; McGue et al. 1993); longevity is only moderately heritable. The nature of genetic influences is most consistent with non-additive genetic effects, and the environmental influences with non-shared (individual-specific) environmental factors. There is no evidence for an impact of shared (family) environment. The heritability estimate is robust; thus, there are only small sex differences and no cohort differences in heritability for the birth cohorts 1870–1900. Furthermore, heritability estimates derived from the best fitting additive and non-additive model are nearly identical.

The low heritability found is consistent with previous theoretical (Fisher 1930) and animal studies (Roff and Mousseau 1987) that show low heritability for fertility and longevity and other life history traits that are directly tied to the evolutionary fitness of the organism. The low inter-individual genetic variation is a result of the strong selection pressure on these fitness traits. Higher heritability is found for behavioral, morphologic, and physiologic traits.

The slightly smaller heritability for females in the present study is the result of a relatively higher non-shared environmental variance in females; this also explains the consistently higher phenotypic variance for age at death for the females. No cohort effects were found, in agreement with Mayer's family study (Mayer 1991), which showed heritability of longevity to be constant over several centuries. A heritability estimate is always population and time specific, since it describes the variance pattern of the population under study. The stability of the heritability estimate over sex and cohorts is, however, remarkable given the large changes in living conditions that occurred around the turn of the century.

A few twin studies in non-Danish populations have considered the genetics of longevity, but none of them provides estimates of heritability by using path analysis. Based on the National Academy of Sciences-National Research Council Twin Registry (a large sample of male twin veterans), Hrubec and Neel (1981) found a heritability of liability to death of 0.5. In order to avoid censoring problems in the veteran sample (only 10% of the sample had died), death was analyzed as a categorical variable. The higher heritability compared with the present study of Danish twins was expected because the trait under study was "liability to death" and not "age at death". Although non-shared environmental factors might be thought to play a major role regarding accidental deaths, exclusion

Table 4 Heritability of longevity for the birth cohorts 1870–1900

Model	Sex	Genetic variance	Environmental variance	Total variance	Heritability[a]
DE submodel	Males	1.14	3.27	4.41	0.26
	Females	1.14	3.92	5.06	0.23
AE submodel	Males	0.99	3.41	4.40	0.23
	Females	0.99	4.07	5.06	0.20

[a] Heritability equals genetic variance/total variance

of deaths caused by trauma gave no significant change in heritability. Unfortunately, we could not further explore this question in the present study, as information on the cause of death is not yet available for the Danish twin population. Jarvik et al. (1960) followed a sample of 853 twin pairs for 12 years including only pairs with at least one of the twins surviving to the age of 60. However, at the end of the follow-up period, both twins had died in only 35% of the twin pairs. Mean intra-pair difference in lifespan was found to be higher in DZ (6 years) than in MZ twins (3 years) suggesting genetic influences on lifespan. Wyshak (1978) followed 972 twin pairs born 1870–1980 until death but was unable to establish zygosity diagnosis and could therefore not provide heritability estimates.

In an adoption study by Sørensen et al. (1988), genetic influences on premature death in adult adoptees were explored. A total of 960 adoptees were followed until the age of 58. The death of a biological parent before the age of 50 resulted in a relative risk of death in the adoptees of 1.71 for all causes, whereas the death of the adoptive parent resulted in a relative risk in the adoptees close to unity. The relationship was weaker if the adoptive or biological parent died before the age of 70 rather than 50. The study suggests the presence of genetic influences on premature death, whereas family environment was unimportant; this is consistent with the results in the present study.

Regarding the type of genetic influence, there is good reason to expect non-additive genetic influences on traits such as human longevity (Fisher 1930; Lykken 1982; Lykken et al. 1993). Fisher's fundamental theorem of natural selection states that if characters related to fitness, such as fertility and longevity, have undergone strong selection, additive genetic variance will be exhausted and only non-additive genetic variance will remain. Selection has no effect on non-additive genetic variance, because genetic effects resulting from interaction within or between loci are not transmitted from generation to generation. Non-additivity is a mechanism by which genetic variation for a fitness-related character can be maintained.

Longevity might be determined not only by direct genetic transmission but also by indirect effects arising from the transmission of genes that determine frailty or susceptibility to illness or death (Vaupel 1988). Studies based on The Danish Twin Register by Yashin and Iachine (1995) indicate a heritability of frailty of 0.5, which, together with the results of the present study, suggests that genes probably affect longevity by altering the risk of death at different ages rather than by directly determining age at death. In this context, the interaction between genes and environment becomes important. Robust people may die young and frail people in old age, depending on the individual's exposure to environmental stress. Hence, it might be fruitful for future research to focus on the search for frailty genes (Gerdes U, Olsen H, Andersen-Ranberg K, Vaupel J, Jeune B (in preparation)) and gene-environment interaction to explain human longevity.

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