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Longevity Is Moderately Heritable in a Sample of Danish Twins Born 1870–1880

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The heritability of human longevity was investigated in a sample of 218 pairs of monozygotic (MZ) and 382 pairs of like-sex dizygotic (DZ) Danish twin pairs born 1870–1880. Twin similarity for age at death was significant for MZ twins but nonsignificant for DZ twins. The heritability (h^2) of life span estimated from the best-fitting biometrical model was statistically significant but moderate in magnitude ($h^2 = .333 \pm .058$). Heritability of longevity did not vary by gender, and the pattern of twin resemblance was more consistent with nonadditive as compared to additive genetic effects. In addition, evidence for a genetic association between premature and senescent deaths was observed. Although environmental factors accounted for a majority of the variance in life span, the relevant environmental factors appeared to be those that create differences rather than similarities among reared-together relatives. Findings are discussed in terms of their relevance for understanding the inheritance and evolution of human life span.

GERONTOLOGISTS have long speculated about the existence of genetic influences on individual differences in human longevity (e.g., Pearl, 1931). Genealogical studies have consistently established a significant but modest familial component to human life span (Cohen, 1964). Pearl's (1931) classic study of five large New England families provides an illustrative example. In this study, the father-son and father-daughter correlations for age at death were .061 ± .010 (n = 4,407) and .047 ± .011 (n = 3,689), respectively. That is, contrary to popular myth and the apparent practices of many life insurance companies, parental age at death appeared to have minimal, albeit nonzero, prognostic significance for offspring longevity.

Because familial resemblance may be the result of a shared environment as well as shared genes, observation only of a significant familial correlation in longevity provides equivocal evidence for the existence of genetic influences. Human geneticists have traditionally used twin and adoption studies to resolve the joint influence of genetic and environmental factors on familial resemblance, and both types of studies have been applied to the study of human longevity. In a sample of twin pairs with at least one member surviving past the age of 60 years, Jarvik et al. (1960) reported that the average intrapair difference in life span was significantly larger in 88 like-sex dizygotic (DZ) twin pairs than in 75 monozygotic (MZ) twin pairs. In a large sample of male, Caucasian, U.S. Armed Services veteran twins, Hrubec and Neel (1981) reported concordance for early death (prior to age 60 years) to be significantly greater among MZ as compared to DZ twins. In a Danish adoption study, Sorenson et al. (1988) reported that premature death (prior to age 50 years) of an adoptee was related to premature death of their biological but not adoptive relatives. Thus, both twin and adoption studies implicate genetic influences on individual differences in human longevity. Nonetheless, length of life was censored for a majority of the twins and adoptees in these studies, so that only a partial assessment of the importance of genetic influences on human life span could be provided.

As suggested by Hrubec and Neel (1981), the ideal design for a study of the genetics of longevity would involve following a large, genetically informative cohort from birth to death. The adoption and twin studies reviewed above, as well as other family studies of human longevity, have approached but not achieved this ideal. Moreover, although Wyshak (1978) did follow a large sample of like- (n = 680) and unlike-sex (n = 292) Mormon twins born between 1830 and 1850 to death, her inability to determine the zygosity of the like-sex twin pairs precluded unequivocal inferences about the existence of genetic influences. In the present study, we report similarity in age at death in a large sample of MZ (n = 218 pairs) and like-sex DZ (n = 382 pairs) Danish twins born between 1870 and 1880 and followed to death through the Danish registry system. These twin data have been analyzed previously using survival analysis methods (Hougaard et al., 1992; Vaupel et al., 1992). The focus of the present study is the use of traditional biometrical methods to estimate the heritability of human longevity.

Although low parent-offspring correlation may be thought to imply low heritability, the parent-offspring correlation provides only an indirect estimate of the magnitude of genetic effects. Geneticists use the heritability coefficient to index the total contribution of genetic factors to trait variability, and distinguish between narrow and broad sense heritability (Falconer, 1981). *Narrow sense heritability* gives the proportion of trait variance that is associated with additive genetic effects only (i.e., genetic effects that contribute to parent-offspring resemblance). *Broad sense heritability* gives the proportion of trait variance that is associated with all genetic effects, including nonadditive genetic effects which do not contribute to parent-offspring resemblance (i.e., genetic effects due to intralocus, dominance, and interlocus, epistasis, interactions). In the absence of shared environmental effects, the expected parent-offspring corre-

lation equals one-half the narrow sense heritability. Consequently, a parent-offspring correlation of .05 (as suggested by the Pearl study) is, if there are no familial environmental effects, consistent with a modest but nonetheless greater narrow sense heritability of 10%. More significantly, if there are substantial nonadditive genetic effects, the broad sense heritability can be large even when there is little or no parent-offspring resemblance.

Because it is difficult to establish the existence of nonadditive genetic effects in nonexperimental organisms, human geneticists have typically assumed complete additivity (Morton et al., 1983). Nonetheless, it is now apparent that there are substantial nonadditive genetic influences on many human characteristics (Lykken, 1982; Li, 1987; Lykken et al., 1993), and there is good reason to expect nonadditive genetic influences on human longevity. Selection (artificial or natural) is one mechanism whereby nonadditive genetic effects can gain salience relative to additive genetic effects. The effect of persistent and consistent application of selective forces is to exhaust additive, but not nonadditive, genetic variance (indeed, the rationale underlying the distinction between narrow and broad sense heritability is that the former, but not the latter, predicts response to selection). Survival, at least through one's reproductive years, is clearly related to reproductive fitness. Although one can only speculate as to whether present causes of mortality bear strong resemblance to the determinants of mortality during the Pleistocene (i.e., the environment of our evolutionary adaptation), a predominance of nonadditive over additive genetic effects would seem a reasonable hypothesis for human longevity. A second aim of the present study, then, is to determine whether twin resemblance for age at death is more consistent with nonadditive rather than additive genetic effects.

In summary, we present a study of a relatively large cohort of MZ and like-sex DZ twins followed from birth to death. This genetically informative sample allowed us to estimate the strength of genetic influences on individual differences in human longevity, and determine whether genetic influences were more likely to be due to nonadditive rather than additive gene effects.

METHOD

Sample. — The sample consists of like-sex twin members of the Danish Twin Register born between 1870 and 1880. The Danish Twin Register was established in 1954 and contains information on all twins born in Denmark between 1870 and 1910 and all like-sex twins born between 1911 and 1930 (Hauge, 1981). The computerized portion of the registry includes all pairs where both members were alive and living in Denmark at age 15 years. Although the register does contain some information on early twin deaths, because these early deaths were not consistently recorded and because pair zygosity was difficult to classify when one or both members died at an early age, we consider here only those twin pairs where both members survived to age 15.

Twin zygosity was determined by self-report questionnaire, a method which has been shown repeatedly to predict zygosity determined from serological markers with greater than 95% accuracy (Lykken, 1978; Hauge, 1981). The last follow-up of the twins to establish death status was completed in 1990. At that time, no twin born in the years 1870–1880 was known to be alive and living in Denmark. Nonetheless, age at death was unknown for the 1.4% of the twin sample who emigrated or were otherwise lost to follow-up. The sample used in the present study includes only those pairs where age at death was known for both members of the pair, that is, the small number of observations censored due to emigration were deleted prior to analysis.

Table 1 provides a descriptive breakdown of the sample. In total there were 218 MZ (117 female and 101 male) and 382 like-sex DZ (209 female and 173 male) twin pairs where both members survived to age 15 years and had a recorded age at death. Although one would normally expect approximately equal numbers of MZ and like-sex DZ twins in a representative sample of Caucasian twins (Bulmer, 1970), the excess number of like-sex DZ twins in the present sample owes to a relatively high infant mortality rate among MZ twins. A twin birth during the latter part of the 19th century was especially high-risk, as only 35% of Danish like-sex twin pairs born between 1870 and 1880 survived intact to age 15 years. Given that MZ twins are known to be more susceptible to pre- and

Table 1. Characteristics of the Sample of Danish Twins Born 1870–1880

	Female		Male		Total	
	MZ	DZ	MZ	DZ	MZ	DZ
No. of twin pairs	117	209	101	173	218	382
Age at death in years						
Mean	73.3	70.9	71.9	70.3	72.6	70.7
SD	16.6	17.8	15.9	16.8	16.3	17.3
Range	17.9–100.2	15.9–102.0	15.6–96.4	17.1–101.6	15.6–100.2	15.9–102.0
Age at death in percentile						
Mean	0.524	0.488	0.526	0.498	0.525	0.493
SD	0.284	0.288	0.282	0.285	0.283	0.287
Range	.026–.997	.029–.999	.033–.998	.039–.999	.026–.998	.029–.999

Note. In a two-way analysis of variance (zygosity and sex as the independent variables) of the Age at Death in Years data, the Zygosity effect was marginally significant ($F(1,1196) = 3.79, p = .052$) while the Sex ($F(1,1196) = 0.83, p = .36$) and Zygosity by Sex interaction ($F(1,1196) = 0.16, p = .69$) effects were not.

perinatal injury than are DZ twins (Bulmer, 1970), infant mortality rate was likely higher among MZ as compared to DZ twins. The effect of zygosity and sex on life span was investigated using a two-factor analysis of variance (ANOVA). Consistent with a higher rate of early mortality in MZ as compared with DZ twins, there is a slight, and marginally statistically significant, difference in mean age at death favoring MZ as compared to DZ twins $F(1,1196) = 3.79$; $p = .052$). Somewhat unexpected, however, is the absence of a significant sex effect ($F(1,1196) = 0.83$; $p = .362$). The relative underrepresentation of males as compared to female twins in the sample (274 vs 326 pairs), suggests that males were especially likely to suffer early mortality (i.e., death prior to 15 years of age), so that lack of a sex difference may, as was the case for zygosity, reflect long-term consequences of early-life selection for vitality. The Zygosity by Sex interaction effect from the ANOVA was nonsignificant ($F(1,1196) = 0.16$; $p = .688$).

Measures. — Age at death in the Danish Twin Register is recorded to the nearest day and was obtained from either the Danish Central Person Register, the Danish Central Registry of Deaths, or various regional public registries in Denmark. Comparison of age at death recorded in the Twin Register with age at death recorded in the Danish Cancer Registry (a registry of nearly all Danes who suffered a malignant neoplasm since 1942) in a sample of 718 jointly registered twins showed 99% agreement (Holm, 1983). Because the distribution of life spans was markedly negatively skewed (standardized skewness coefficient $= -1.06$; $p < .01$), analyses were completed both when age at death was measured in years and when it was measured as a percentile. Percentiles were computed separately in the male and female samples. As cause of death is available within the Danish registry system only for deaths that occurred after 1943, it is not considered as a covariate here.

Statistical methods. — The aims of the statistical analyses were (a) to assess twin resemblance for age at death, and (b) to determine the extent to which genetic and environmental factors contributed to the between-individual variability in life span. Twin similarity for age at death was measured using the intraclass correlation and mean absolute pair difference in age at death. Twin intraclass correlations were derived from a one-way ANOVA (with twin pair as the independent variable) using the formula, r = (MSB–MSW)/(MSB + MSW), where MSB and MSW are, respectively, the between- and within-pairs mean squares. Statistical comparisons of twin correlations were made using the Fisher z-transformation method, which yields a chi-square test statistic (Donner and Rosner, 1980).

Biometrical analysis of the twin data was based on the standard assumption that a quantitative phenotype, P (here age at death), can be expressed as linear additive function of unobserved genetic and environmental components (Eaves et al., 1989). That is, P = G + E, where G refers to genetic factors, and E refers to environmental effects. In the standard biometrical model, both G and E can be further decomposed as

$$P = (A + D + I) + (E_S + E_N),$$

where A refers to additive genetic effects, D refers to genetic effects due to dominance (i.e., intralocus interactions), I refers to genetic effects due to epistasis (i.e., interlocus interactions), E_S refers to shared environmental factors (i.e., those environmental factors that are shared by both members of a twin pair and thus contribute to their similarity), and E_N refers to nonshared environmental factors (i.e., those environmental factors that are not shared by the members of a twin pair and thus contribute to their dissimilarity). Assuming further that the genetic and environmental components are uncorrelated, the phenotypic variance, V_P, can be similarly decomposed as

$$V_P = V_A + V_D + V_I + V_S + V_N,$$

where V_A, V_D, V_I, V_S, and V_N are the variances associated with, respectively, additive genetic, dominance, epistatic, shared environmental, and nonshared environmental factors. Dividing both sides of the equation by the phenotypic variance norms the variance to 1.0 and thus represents the individual components as proportions of the total variance, or

$$1.0 = a^2 + d^2 + i^2 + s^2 + n^2,$$

where $a^2 = V_A/V_P$ or the proportion of variance associated with additive genetic effects, $d^2 = V_D/V_P$ or the proportion of variance associated with dominance genetic effects, $i^2 = V_I/V_P$ or the proportion of variance associated with epistatic genetic effects, $s^2 = V_S/V_P$, or the proportion of variance associated with shared environmental effects, and $n^2 = V_N/V_P$ or the proportion of variance associated with nonshared environmental factors. The broad-sense heritability coefficient, h^2, gives the proportion of phenotypic variance associated with all genetic effects or $h^2 = a^2 + d^2 + i^2$.

The correlation between any two relatives can be derived as a function of the variance components given above. In particular, the correlation between two MZ twins, r_{MZ}, is given by

$$r_{MZ} = a^2 + d^2 + i^2 + s^2$$

while the corresponding DZ correlation is given by,

$$r_{DZ} = 1/2a^2 + 1/4d^2 + ci^2 + s^2$$

where c is some unknown positive constant less than or equal to .25, which depends upon the number of interacting loci contributing to the epistatic effect.

A study of MZ and DZ twins alone would generate three observables, r_{MZ}, r_{DZ}, and the constraint that the five normed components sum to 1.0. The full model contains, however, six unknown parameters, the five variance components, and c. Consequently, additional constraints are needed. The standard approach to twin data is to assume that all genetic effects are additive, in which case $d^2 = i^2 = 0$ and c is irrelevant, so that the model reduces to three observables in three unknowns (a^2, s^2, and n^2; a model designated here as A-E). Alternatively, one could assume that all genetic effects are due to dominance, in which case $a^2 = i^2 = 0$, c is irrelevant, and the model again reduces to three observables in three unknowns (d^2, s^2, and n^2; a model designated here as D-E). One can also fit a pure environmental model to the twin data by constraining $a^2 = d^2 = i^2 = 0$, in which case there are three observables in two unknowns (s^2, and n^2; a

model designated here as E). Finally, a general nonadditive model can be fit to the twin data by noting that the MZ correlation can be expressed as $r_{MZ} = h^2 + s^2$ while the DZ correlation can be given by $r_{DZ} = kh^2 + s^2$, where h^2 equals the broad heritability and k equals a weighted average of 1/2, 1/4, and c (the weights depending upon the magnitude of the three genetic components of variance) and so has a theoretical range from 0.0 (complete nonadditivity) to 0.5 (complete additivity) (Tellegen et al., 1988). This general nonadditive model can be fit to the data under the assumption that there are no shared environmental effects (i.e., $s^2 = 0$), in which case the three unknown parameters, h^2, n^2, and k, can be estimated from the three observable statistics. This latter model is designated here as the H-E model.

For a given biometrical model, the unknown parameters can be estimated and hypotheses tested using the maximum likelihood method assuming multivariate normality (Martin et al., 1978). In the present application, parameters were estimated using LISREL VI (Jöreskog and Sörbom, 1986) following specifications given by Heath et al. (1989) to accommodate twin data structures. Four models were fit to the twin data: the A-E, D-E, E, and H-E models. The models were fit separately to the male and female data (the General case) as well as to the combined sample under the constraint that the male and female parameter estimates were equal (the No Sex Differences case). As the four models are not nested, selection of the best-fitting model was determined by minimizing the Akaike Information Criterion (AIC = chi-square goodness-of-fit statistic minus twice the degrees of freedom; Akaike, 1987).

RESULTS

Twin similarity. — Table 2 summarizes indices of twin similarity. In both the male and female samples, as well as overall, the MZ twin correlation exceeded the DZ twin correlation, although the difference in correlations did not quite attain the .05 level of significance in the male sample when age at death was measured in years. The consistent observation of greater MZ than DZ twin correlation implicates genetic influences on individual differences in length of life. Moreover, the MZ twin correlation consistently exceeded twice the DZ twin correlation, a pattern which suggests that genetic influences are nonadditive rather than additive (Plomin et al., 1990). In no case was the DZ correlation significantly greater than zero; this observation is consistent with earlier research indicating modest correlations in life span among first-degree relatives and suggests that there is little effect of common rearing (i.e., the shared environment) on human life span. As expected, correlations were larger when age at death was measured as a percentile rather than when it was measured in years.

Analysis of the absolute pair difference in age at death further confirms that MZ twins tend to be more similar in age at death than DZ twins (Figure 1). In the combined male and female sample, two members of an MZ twin pair died an average of 14.1 years (± *SE* of 1.0) apart, a value that was significantly smaller than the DZ mean of 18.5 years (± 0.8;

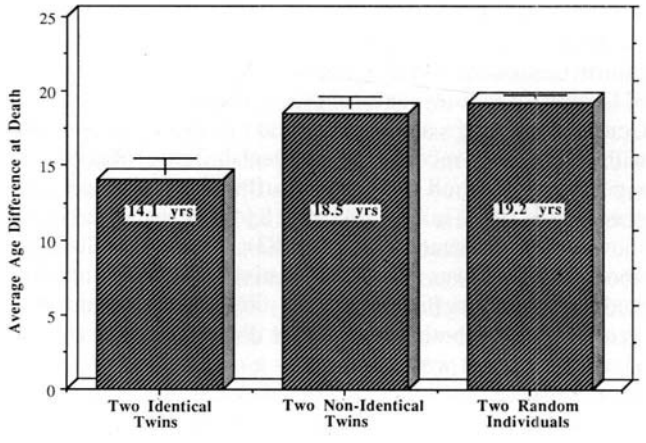

Figure 1. Average absolute difference in age at death (in years) between two members of a monozygotic (MZ) twin pair, two members of a dizygotic (DZ) twin pair, and two randomly selected same-sex individuals. Bars indicate one standard error of the mean. The average for MZ twins is significantly smaller than the average for DZ twins ($p < .001$), but the DZ average is not significantly different from the average based upon randomly constituted pairs ($p > .05$).

Table 2. MZ and DZ Twin Resemblance for Age at Death as Measured by the Twin Intraclass Correlation (*R*) and Mean Absolute Difference (Diff)

	Female			Male			Total		
	MZ	DZ	MZ/DZ *p*	MZ	DZ	MZ/DZ *p*	MZ	DZ	MZ/DZ *p*
No. of twin pairs	117	209		101	173		218	382	
Age at death in years									
Twin *R*	.228	−.013	.04	.235	.022	.08	.231	.001	<.01
Age Diff Mean	14.6	19.4	<.01	13.5	17.4	<.01	14.1	18.5	<.01
Age Diff *SD*	14.6	16.3		14.4	15.8		14.5	16.1	
Age at death in percentile									
Twin *R*	.310	.079	.04	.356	.081	.02	.329	.078	<.01
Age Diff Mean	.259	.317	<.01	.244	.312	<.01	.252	.315	<.01
Age Diff *SD*	.211	.230		.209	.227		.210	.229	

Note. MZ/DZ *p* entries give results of testing the significance of MZ/DZ differences. For correlations, differences were tested using a chi-square statistic; for means, differences were tested using a *t*-statistic. All *p*-values are two-tailed.

$t = 4.73, p < .001$). Moreover, the average pair difference in age at death for MZ, but not DZ, twins was significantly smaller than the average difference in age at death between two unrelated like-sex individuals randomly selected from the sample (19.2 ± 0.2 years), suggesting that while there is significant MZ twin similarity, the two members of a DZ twin pair resemble one another minimally if at all in age at death. The greater MZ than DZ twin similarity for age at death was not due to the existence of a relatively large number of MZ twins who were extraordinarily concordant for age at death, as both members of a twin pair died within one year of one another in only 5.0% of the MZ and 5.5% of the DZ pairs, a nonsignificant difference. It is also worth noting that the average twin differences in age at death reported here are substantially larger than those reported earlier by Jarvik et al. (1960): MZ average of 6.8 years and DZ average of 8.4 years. The relatively small average differences reported by Jarvik et al. can, however, be attributed to their having restricted their sample to twin pairs where both members had survived to at least age 60 years. As the present sample includes all twin pairs where both members survived into adulthood (i.e., age 15 years), the values reported here likely provide a more accurate measure of twin similarity at age of death than those reported by Jarvik et al.

Biometrical analyses. — Table 3 summarizes the results of the biometrical analysis of the twin data. For both the A-E and D-E models, the shared environmental component (i.e., s^2) was invariably estimated at its boundary value of zero; this outcome occurs whenever the MZ correlation is moderately large and the DZ correlation is near zero, as is the case here (Plomin et al., 1990). Consequently, results for these two models are reported for the case when s^2 was fixed at zero. The only model that failed to fit the observed twin data was the General E model ($\chi^2 = 9.64$ on 4 degrees of freedom; $p = .047$ when life span is measured as a percentile, and $\chi^2 = 9.22$ on 4 degrees of freedom; $p = .056$ when life span is measured in years). Consistent with the observed twin correlations, model fitting results indicate that genetic factors are needed to account for observed twin similarity in age at death.

In none of the models that included a genetic parameter did the chi-square goodness-of-fit test statistic attain statistical significance, indicating that all of these models satisfied conventional statistical criteria for goodness-of-fit. For both age at death in years and as a percentile, the best-fitting biometrical model by the AIC was the D-E model with no sex differences in parameter estimates. For this model, the estimated heritability was .220 ± .073 when age at death was measured in years, and .333 ± .058 when it was measured as a percentile. In both cases, the estimate of heritability suggests a moderate but statistically significant influence of genetic factors on length of life. Nonetheless, environmental factors accounted for a majority of the variance in life span (the estimated proportion being given by the complement of the heritability coefficient). The relevant environmental factors appeared, however, to be those that contribute to differences (i.e., nonshared influences) rather than similarities (i.e., shared influences) among reared-together members of a twin pair.

Genetic influences on early vs late deaths. — In order to determine whether genetic influences on length of life were stronger or weaker for early as compared to late deaths, we

Table 3. Results of Fitting Biometrical Models to the Twin Data

Model		Model Fit Index			Heritability Estimate	
		χ^2	df	p	Females	Males
Age at death in years						
A-E	General	6.13	4	.19	.132 ± .087	.172 ± .091
	No sex differences	8.09	6	.23	.148 ± .063	.148 ± .063
D-E	General	3.48	4	.48	.209 ± .102	.233 ± .102
	No sex differences[a]	5.33	6	.50	.220 ± .073	.220 ± .073
H-E	General	7.36	2	.12	.253 ± .100	.254 ± .104
	No sex differences	8.33	5	.21	.254 ± .072	.254 ± .072
E	General	9.22	4	.06	0.0	0.0
	No sex differences	11.16	6	.08	0.0	0.0
Age at death in percentile						
A-E	General	2.44	4	.66	.266 ± .077	.303 ± .083
	No sex differences	2.65	6	.85	.283 ± .056	.283 ± .056
D-E	General	0.09	4	.99	.315 ± .080	.356 ± .083
	No sex differences[a]	0.34	6	.99	.333 ± .058	.333 ± .058
H-E	General	0.08	2	.96	.315 ± .083	.358 ± .085
	No sex differences	0.33	5	.99	.334 ± .060	.334 ± .060
E	General	9.64	4	<.05	0.0	0.0
	No sex differences	9.76	6	.14	0.0	0.0

Note. Heritability estimate gives the proportion of variance associated with all genetic effects under that model. The proportion of variance associated with environmental factors is given by the complement of the heritability and thus has the same standard error as the heritability estimate. Models fitted were: A-E = Additive Genetic plus Nonshared Environment Model; D-E = Dominance plus Nonshared Environment Model; H-E = Nonadditive Genetic plus Nonshared Environment Model; and E = Shared plus Nonshared Environment Model. Models were fit both when estimates were allowed to vary by sex (the General case) and when parameter estimates were constrained to be equal in the two sexes (the No Sex Differences case).

[a] Best-fitting model by Akaike's Information Criterion (AIC).

determined co-twin life expectancy (estimated using the mean age at death in years) as a function of twin age at death in years. The results of this analysis are summarized in Figures 2A (for MZ twins) and 2B (for DZ twins). For MZs, twin death prior to age 40 years was not associated with a significant reduction in co-twin life span. However, MZ twin death after age 40 years is seen to have a strong and approximately linear effect on MZ co-twin life span. In contrast, DZ twin age at death appeared to have no demonstrable effect on co-twin longevity.

Figure 2A suggests that while extremely early MZ deaths (i.e., < age 40 years) may have limited prognostic significance for co-twin longevity, MZ death in middle age (i.e., age 40–60 years) portends a significant reduction in co-twin life span. The prognostic significance of an MZ twin death in middle age may be due to one of two factors: (1) an increased likelihood of co-twin death in middle age without further reduction in life span if co-twin survives middle age, or (2) a general reduction in co-twin life span regardless of whether that co-twin survives middle age. In order to explore this issue, MZ twins who died prior to age 60 years were classified as "premature" deaths, and those dying past the age of 60 years were classified as "nonpremature" deaths. Co-twin longevity was then explored as a function of premature versus nonpremature twin death. Two findings, summarized in Table 4, emerge from this analysis. First, as compared to the co-twins of nonprematurely dying MZ twins, the co-twins of prematurely dying MZ twins were also more likely to die prematurely. Secondly, even when the co-twins of prematurely dying MZ twins survived past age 60, 70, or even 80 years, they experienced significant reductions in their life spans relative to the co-twins of nonprematurely dying MZ twins. For example, the life expectancy of an 80-year-old MZ twin was shorter if his or her co-twin did not survive age 50 years than it would have been had the co-twin survived age 60. This intriguing observation suggests that rather than being etiologically independent, premature and senescent deaths may share a common genetic linkage.

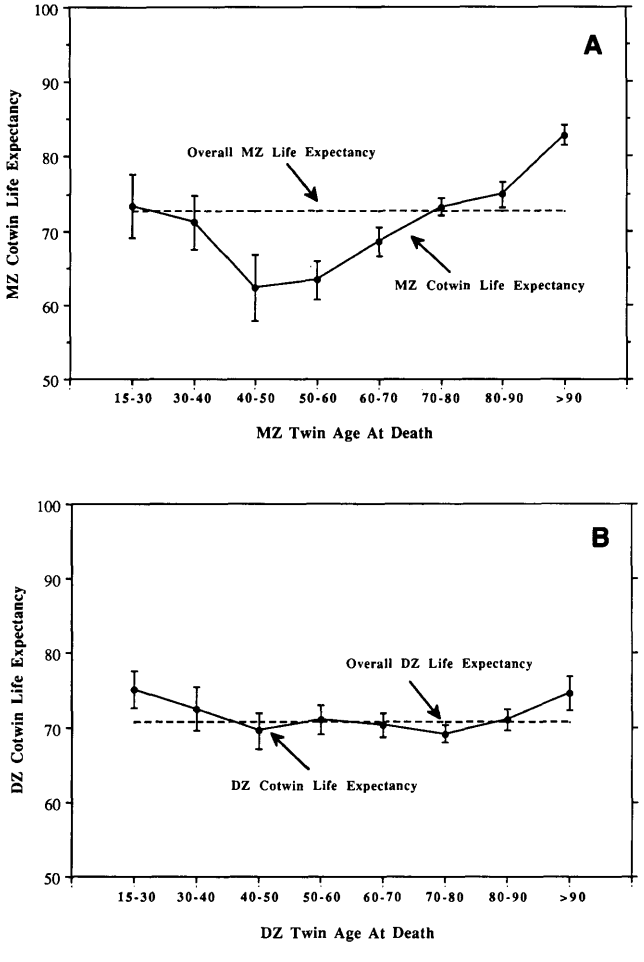

Figure 2. Average co-twin age at death as a function of MZ (2A) or DZ (2B) twin age at death. Solid line gives the mean age at death of all co-twins paired to twins dying in the relevant age interval. Error bars demarcate one standard error on either side of the mean. Dotted lines give the mean age at death of all twins of that zygosity.

DISCUSSION

The major empirical findings from this investigation are as follows: First, while MZ twins were consistently and significantly more similar in age at death than DZ twins, DZ twins were not significantly more similar in age at death than two

Table 4. Co-twin Longevity as a Function of Premature Death (Age Less than 60 Years) of an MZ Twin

	Status of MZ Twin		
	Premature Death (<60 years)	Nonpremature Death (>60 years)	*p*-value
Longevity of all co-twins			
N	77	359	
%	100.0	100.0	
Age at death (yrs)			
Mean	66.1	74.0	<.001
SD	16.1	16.0	
Longevity of co-twins surviving to age 60			
N	55	304	
%	71.4	84.7	<.01
Age at Death (yrs)			
Mean	74.3	79.5	<.001
SD	8.6	8.8	
Longevity of co-twins surviving to age 70			
N	35	261	
%	45.5	72.7	<.001
Age at death (yrs)			
Mean	79.6	81.8	<.05
SD	5.6	7.1	
Longevity of co-twins surviving to age 80			
N	18	142	
%	23.3	39.6	<.01
Age at death (yrs)			
Mean	84.2	87.2	<.01
SD	4.7	2.8	

Note. *p*-values give results of statistical comparison of the co-twins of prematurely versus nonprematurely dying MZ twins. For % surviving, comparison was made using a chi-square test statistic; for mean age at death, comparison was made using a *t*-statistic. In both cases, reported *p*-values are one-tailed.

randomly selected like-sex individuals. Biometrical analyses of the twin correlations indicated a moderate but statistically significant heritability for life span that did not vary across sex. Second, the pattern of twin similarity is more consistent with nonadditive rather than additive genetic effects. Third, environmental factors, which accounted for a majority of the variance in life span, were predominantly of the nonshared variety. And fourth, premature and senescent deaths appeared to be etiologically linked.

Heritability of life span. — The present results are consistent with earlier twin and adoption studies in indicating heritable differences in life span. Hrubec and Neel (1981) estimated the heritability of liability of death between the ages of 20 to 60 years to be approximately 50% in a sample of male Caucasian U.S. military veterans. Although the heritability estimates reported here (ranging between approximately 20% and 35%) are somewhat smaller than the estimate reported by Hrubec and Neel, it should be emphasized that the estimates reported here are *direct* estimates of the heritability of life span while the Hrubec and Neel estimate is an *indirect* estimate of the heritability of liability associated with dying within a given age range (i.e., between 20 and 60 years). That is, the Hrubec and Neel estimate does not apply to the full life span. In a study of Danish adoptees and their biological and adoptive parents, Sorensen et al. (1988) concluded that genetic factors exerted a strong influence on premature death between the ages of 16 and 58 years, especially when death was due to infection or vascular disease. Our results do not indicate, however, that early deaths are more genetically influenced than later deaths. Indeed, in our sample, early death (prior to age 40 years) appeared to be entirely environmentally mediated (Figures 2A and 2B).

Nonadditive vs additive genetic effects. — As in previous studies of first-degree relatives, we found a modest correlation in life span among DZ twins. One factor contributing to the relatively low DZ twin correlation is the strength of nonshared environmental influences; another factor appears to be the relative importance of nonadditive as compared to additive genetic effects. Nonadditive genetic effects are the result of interactions among gene effects at a single locus (i.e., dominance) or at multiple loci (i.e., epistasis). Because first-degree relatives are not likely to share all the genes contributing to an interacting system, nonadditive genetic effects are more likely to produce differences than similarities among first-degree relatives. Because MZ twins share all their genes identical by descent, however, nonadditive genetic effects do contribute to MZ twin similarity and are indicated when the MZ twin correlation is large relative to the DZ twin correlation. In the present study, MZ twin correlations for age at death were statistically significant and consistently exceeded twice the corresponding DZ values, a correlational pattern consistent with nonadditivity. Biometrical analysis of the twin data provided further support for the nonadditive hypothesis.

The finding of significant nonadditive genetic effects on human longevity is not entirely unexpected. Animal studies have demonstrated the importance of nonadditive genetic effects on life span (e.g., Luckinbill et al., 1988; Curtsinger et al., 1992), and nonadditivity is one mechanism by which genetic influences on a fitness-related character can be maintained. Although one might question the fitness relevance of survival into one's 60s, 70s, or 80s, we found evidence for an association between early and late deaths suggesting that longevity beyond one's reproductive years might be related to reproductive fitness.

The nature of environmental influence. — Although we found evidence for genetic influences, environmental factors clearly accounted for a majority of variance in age at death. Geneticists distinguish between two types of environmental influence: shared environmental influences that are attributable to common rearing effects (e.g., socioeconomic status of the rearing home, early life nutrition, etc.), and nonshared environmental influences that include all environmental factors that are not shared by reared-together individuals (i.e., accidents, adult nutrition, etc.). Our findings suggest that while nonshared environmental factors are significant, shared environmental factors have a trivial, if any, effect on length of life. This result is consistent with the finding reported by Sorenson et al. (1988) that early death of a biological but not adoptive relative predicted an individual's risk of premature death (i.e., early death of a relative predicted a reduced life span if that individual was genetically, but not necessarily environmentally, related).

Given no direct assessment of the environment or knowledge of cause of death in the twin sample, we can only speculate on the nature of the nonshared environmental influence on life span. Clearly, accidental death is one factor that would contribute to nonshared environmental influences. But nonshared environmental influences cannot be attributed entirely to "non-natural" causes of death. For example, for cancer, the MZ twin concordance is low and nonsignificantly different from the DZ twin concordance (Holm, 1983). A goal of future inquiries should be to identify the specific environmental and biological factors that mediate the inheritance of longevity.

The association between early and late deaths. — In the present study, two observations provide evidence supporting an association between early and late deaths. The first, and indirect, bit of evidence is the observation that MZ twins had a longer mean life span than DZ twins. As compared to DZ twins, MZ twins are more likely to suffer pre- and perinatal injury and are thus more likely to die in infancy. The relatively low number of MZ twins in this registry-based study is a consequence of differential infant mortality (Bulmer, 1970). Longer MZ than DZ mean life span may reflect early selection against the most frail MZ twins who would then not survive to be included in the present study (cf., Vaupel, 1988). The second, and more direct, bit of evidence is the observation that "premature" death (i.e., less than 60 years) of an MZ twin predicted reduced co-twin life span even in those cases where the co-twin's death was senescent (i.e., past the age of 80 years). Apparently, the genetic influence that underlies frailty in middle age is related, if not identical, to the genetic influence that underlies frailty late in life. Such an observation, if replicable,

would certainly call into question a sharp distinction between premature and senescent deaths.

Limitations. — There are several limitations to the present study that deserve mention. First, the validity of the twin study method depends upon the assumption that greater MZ than DZ phenotypic similarity is due to their greater genetic, and not environmental, similarity. The validity of this assumption needs to be assessed using alternative methodologies including the adoption method. We note, however, that the present results are entirely consistent with previous adoption studies of mortality. Second, the sample is relatively homogeneous with respect to biological and cultural background (i.e., they are all Caucasian Danes). Without additional information, it is impossible to judge the effect of this homogeneity on heritability estimation (i.e., one could envision scenarios whereby homogeneity increased, decreased, or had no effect on heritability), nor is it possible to evaluate the generalizability of the present results to other ethnic populations. There is a clear need for study of ethnic and cultural differences in the familial and genetic determinants of mortality. Finally, the sample studied was born more than a century ago, and medical practices as well as life expectancy have undergone significant changes over the past 100 years. Although it is impossible to determine whether these changes will affect the heritability of life span for those born, say, in the past 30 years, we note that others have reported the absence of secular trends in familial longevity correlations (Mayer, 1991).

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