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Genetic and Environmental Influences on Functional Abilities in Danish Twins Aged 75 Years and Older

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Background. Functional abilities vary widely among elderly persons. The determinants of this variation are probably multiple and include normal aging processes as well as disease expression. This study estimates the relative importance of genetic and environmental factors to variation in functional abilities in elderly persons.

Methods. We conducted a survey among all Danish twins aged 75 years and older who were identified in the population-based Danish Twin Registry. Interviews were conducted with 77% (7% by proxy responders) of the 3099 individuals in the study population. Functional abilities were assessed by validated Danish survey instruments and were scored on three scales. Heritability (proportion of the population variance attributable to genetic variation) was estimated using structural equation analyses.

Results. Structural equation analyses revealed a substantial heritability (34%–47%) for the three functional ability scores among the women aged 80 years and older compared with a more modest heritability (15%–34%) among the women aged 75–79 years. The remaining variation could be attributed to individuals' nonfamilial environments. Comparisons of the functional abilities of twins with living versus deceased co-twins also suggested a difference in the genetic influence for the two age groups. Although heritability estimates were uniformly low in the male participant sample, the size of the sample was not sufficiently large to allow for precise estimates of heritability.

Conclusion. For women we found that the effect of genetic factors on functional abilities increases with age and accounts for one third to one half of the variation among individuals aged 80 years and older. An understanding of the genetic mechanisms underlying functional abilities in the oldest individuals may enhance the possibilities for improving health in the elderly population by modifying environmental factors.

FUNCTIONAL abilities are central to the health and quality of life of elderly persons. Although functional abilities are influenced by numerous biological, physiological, and cognitive processes as well as by diseases (1,2), even minor limitations in functional abilities (both self-reported and objectively measured) predict the later incidence of severe disabilities and mortality (3,4), despite the fact that there is no doubt that functional abilities decline for different reasons in different people.

A prevailing assumption in gerontology is that the accumulation of unique environmental exposures during a long life is the key determinant of health at older ages (5). Alternatively, evolutionary biologists have argued that there is less selective pressure against deleterious genetic mutations first expressed late in life than against mutations expressed early in life. This hypothesis predicts an increase in genetic variance among the oldest individuals (6).

Little information is available on the relative influence of genes and environment on health in elderly persons (5). Twin studies of cardiovascular diseases suggest that at younger ages, death from coronary heart disease is strongly influenced by genetic factors, although this genetic effect decreases at older ages (7). Furthermore, the effect of genetic factors on the serum levels of some but not all lipids appears to decrease with age (8,9). Studies on cognitive functioning and dementia among twins suggest a strong genetic influence on these phenotypes at older ages (10,11). However, these studies were all based on twin pairs in which both twins were alive at old ages, making the results vulnerable to selection bias.

The present study estimated the relative contribution of genetic and environmental factors to the variation in functional abilities among elderly persons. The study was based on an interview survey among Danish twins aged 75 and older. In this age group, most twins have a deceased co-twin. Because studying pairs in which both twins are alive might introduce an oversampling of healthy twin individuals, we included all twins who were 75 years and older, regardless of whether the co-twin was alive.

METHODS

Study Population

The Danish Twin Registry includes twin pairs born in Denmark between 1870 and 1910 and same-sex pairs born

between 1911 and 1930 (12). Our study comprised all registered Danish twins who were 75 years or older on January 1, 1995, regardless of whether the co-twin was alive, for a total of 3099 individuals. Face-to-face interviews were completed during a 3-month period (February–April 1995) by 100 interviewers, and a total of 2401 interviews were conducted, corresponding to a participation rate of 77% (7% completed by proxy). Both twins participated in a total of 480 pairs. The response rate was significantly higher for men (81%) than for women (74%; $p < .01$). The responders and nonresponders were similar in terms of age distribution and monozygotic-dizygotic ratio. The mean age for responders and nonresponders of both sexes was within 0.6 year of 81 years. The previous 18 years of hospital admission patterns were nearly identical for female responders and nonresponders, although the male nonresponders tended to have slightly fewer hospitalizations than did the responders (for more details, see [13]). Figure 1 gives descriptive characteristics of the sample.

Assessment of Functional Abilities

The assessment of functional abilities was based on self-report, which has generally been found to be reliable and valid (14,15). An instrument that focuses on mobility and upper- and lower-limb functioning was used. This instrument has previously been validated in Denmark, and it has been shown to discriminate levels of functional abilities among community-dwelling elderly persons through the use of questions about tiredness and need for personal assistance with regard to functional abilities (4,16). The instrument was extended to include assessment of need for equipment or aids in relation to functional abilities, based on results showing that equipment and aids can improve functional abilities in elderly persons (17). All the items from the Katz Index of Activities of Daily Living were included (18), as well as questions about the ability to see and hear, and about more demanding activities such as running. The functional abilities section comprised 26 questions, which are summarized in Table 1. All the items referred to what the participant was able to do on the day of the interview.

To identify meaningful quantitative subscales, we factor analyzed the 26 items in the total twin sample. All items were rated on a 1 to 4 scale: 4 = can do without fatigue; 3 = can do with fatigue or minor difficulties; 2 = can do with aid or major difficulties; 1 = cannot do. In the factor analyses, three factors had an eigenvalue of more than 1, but few of the items loaded on the third factor. Therefore, a two-factor solution was adopted (Table 1). The first factor loaded highest on items dealing with ability to walk, run, climb stairs, and carry weights and was interpreted to reflect a dimension of strength. The second factor loaded highest on items dealing with ability to dress and wash oneself and get in and out of bed, and was interpreted to reflect a dimension of agility. Scores for the two dimensions were calculated by taking the average response of items loading highest on the factor or having judged to be relevant for that dimension. The internal consistency reliability estimate for the Strength scale was .93 in both the male and female participant samples for both the in-person and the proxy interviews. The re-

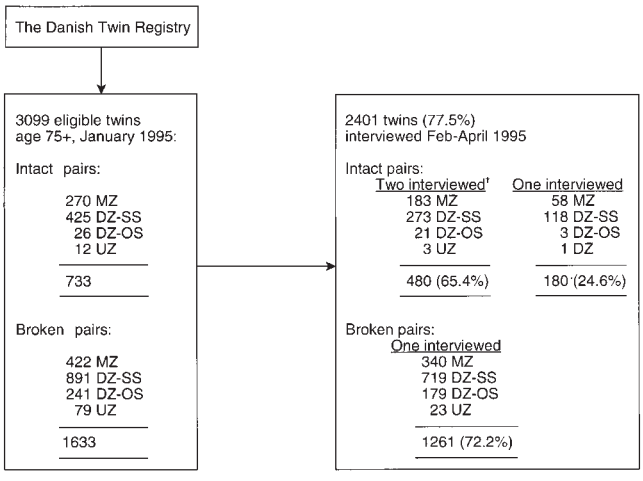

Figure 1. Response pattern in the 1995 wave of the Longitudinal Study of Aging Danish Twins. Intact refers to twin pairs in which both twins were alive and were identified in the Danish Twin Registry. Broken refers to twin pairs in which only one twin was alive and identified in the registry. MZ = monozygotic; DZ-SS = dizygotic same-sex; DZ-OS = dizygotic opposite-sex; UZ = unknown zygosity. Functional ability scores were obtained for both co-twins (listed under "Two interviewed") in 182 MZ and 269 DZ-SS pairs (Table 3).

Table 1. Functional Abilities and Factor Pattern Matrix

	Loading	
Functional Ability	Factor 1	Factor 2
Get up from a chair and a bed	.45	*.68*
Walk around in the house	*.57*	.63
Able to go to the toilet	.46	*.61*
Walk up and down stairs one floor	*.72*	.45
Walk up stairs to the second floor	*.76*	.36
Able to get outdoors	*.73*	.42
Able to walk 400 meters without resting	*.75*	.41
Do light exercise	*.67*	.23
Do hard exercise	*.50*	−.01
Walk in nice weather for 1/2 to 1 hour	*.82*	.29
Walk in bad weather for 1/2 to 1 hour	*.80*	.18
Run 100 meters	*.61*	−.00
Carry 5 kilos	*.70*	.26
Wash upper part of body	.43	*.62*
Wash lower part of body	.46	*.68*
Wash hair	.50	*.52*
Dress upper part of body	.19	*.84*
Dress lower part of body	.22	*.84*
Take socks and shoes on and off	.35	*.75*
Comb hair	.06	*.72*
Cut toenails	.49	*.23*
Cut fingernails	.21	*.59*
Chew hard food	.26	.20
Eat without help	−.01	.67
Read ordinary newspaper text	.12	.27
Hear conversation between three or more persons	.21	.06

Notes: Loadings are based on the two-factor solution in the total sample of interviewed twins (n = 2401, of whom 2384 [99%] completed the functional ability section). Two scales were formed: a Strength scale and an Agility scale based on the nature of the functional abilities and the factor loadings. The 11 abilities italicized in the factor 1 loadings form the Strength scale, and the 11 abilities italicized in the factor 2 loadings form the Agility scale.

liability estimates for the Agility scale were also the same for men and women and equaled .91 for the in-person interview and .93 for the proxy interview. These values indicate very reliable scales. The correlation was .77 between the Strength and Agility scales. Finally, a total score was computed by summing the items on the Strength and Agility subscales. Age-sex effects can bias analyses of twin resemblance (19). Therefore, scores were adjusted for the effects of age and sex by subtracting an age-sex-specific mean (Table 2). Because of the small number of dizygotic opposite-sex pairs, all twin resemblance analyses were restricted to same-sex twins.

Analyses of Twin Similarity

In humans, two types of twinning occur: monozygotic twins share all their genetic material, and dizygotic twins, like ordinary siblings, share, on average, 50% of their genes. In the classic twin study, monozygotic and dizygotic intraclass correlations for a trait are compared. A significantly higher correlation in monozygotic twins indicates that genetic factors play an etiological role. To estimate the heritability of the functional ability scales (i.e., the proportion of the population variance attributable to genetic variation), we analyzed the twin data by using standard biometric models (20). It was assumed that the total variance (V) in a scale could be decomposed as $V = A + D + C + E$, where A refers to the variance contribution of additive genetic effects, D refers to the variance contribution of genetic effects due to dominance (intralocus interaction), C refers to the variance contribution of shared environmental effects (i.e., environmental factors that are shared by reared-together twins and are thus a source of their similarity), and E refers to the variance contribution of nonshared environmental effects (i.e., environmental factors that are not shared by reared-together twins and are thus a source of their dissimilarity). Assuming that shared environmental effects contribute equally to the resemblance of monozygotic (MZ) and dizygotic (DZ) twins, the expected twin covariances are given by

$$\mathrm{cov(MZ)} = A + D + C$$

$$\mathrm{cov(DZ)} = (1/2)A + (1/4)D + C\,.$$

Variance components were estimated from the observed twin variances and covariances by the method of maximum likelihood using the Mx software (21). The observed twin variances and covariances were stratified on sex and age groups. To correct for unequal variances between twin 1 and twin 2 in some of the smaller subgroups, we double-entered the data and adjusted the degrees of freedom accordingly.

Results

Functional ability scores decreased with age; this result was most pronounced on the Strength scale (Table 2). Figure 2 shows the unadjusted mean scores for female twin pairs and illustrates the higher variability in functional abilities in the group aged 80 years and older. Among the 75- to 79-year-old participants, variability occurs less as the result of a "ceiling" effect. To assess how much of the variability in the functional ability scores that could be attributed to interviewer effect, we completed a one-way analysis of variance (ANOVA), with interviewer as independent variable. We found that only a negligible proportion of the variation could be attributed to interviewer effect, although the interviewer effect also included potential regional differences because each interviewer covered only one or two counties.

For female participants, all the monozygotic intraclass correlations were statistically significantly larger than 0 and consistently exceeded the corresponding dizygotic correlations for all three scales in both age groups (Table 3). The female twin correlations were higher compared with the male twin correlations, and the correlations among the female twin pairs aged 80 years and older exceeded those of the 75- to 79-year-old twin pairs. When the analyses were restricted to the 126 monozygotic twin pairs in which the two twins had not lived together for more than 50 years and who currently were in contact only monthly or more rarely, no decrease in monozygotic correlation was observed for either men or women.

Biometrical analyses revealed that for all three scales (Agility, Strength and Total scales), a model including additive genetic factors and nonshared environment was the best fitting model (lowest Akaike Information Criteria) (22) when parameter estimates were allowed to vary by sex and

Table 2. Functional Ability Scores Among All Twins Participating in the Longitudinal Study of Aging Danish Twins

Functional Ability Score	75–79 Years		80–84 Years		85–89 Years		90+ Years	
	Males (n = 357)	Females (n = 614)	Males (n = 290)	Females (n = 489)	Males (n = 168)	Females (n = 322)	Males (n = 38)	Females (n = 106)
Strength								
Mean	3.2	3.1	2.9	2.6	2.5	2.2	2.1	2.0
SD	0.82	0.80	0.96	0.90	0.92	0.88	0.90	0.87
Agility								
Mean	3.7	3.7	3.4	3.4	3.2	3.1	2.8	2.6
SD	0.69	0.60	0.87	0.83	0.84	0.93	1.0	1.1
Total								
Mean	3.5	3.4	3.2	3.1	2.9	2.7	2.5	2.4
SD	0.67	0.60	0.81	0.75	0.77	0.81	0.85	0.87

Notes: The study participants included twins with unknown zygosity and twins from opposite-sex pairs. The scores are the mean of the items comprising that scale. Maximum score = 4.0, corresponding to being able to do all activities in the scale without any limitations; minimum score = 1.0, corresponding to not being able to perform any of the activities in the scale.

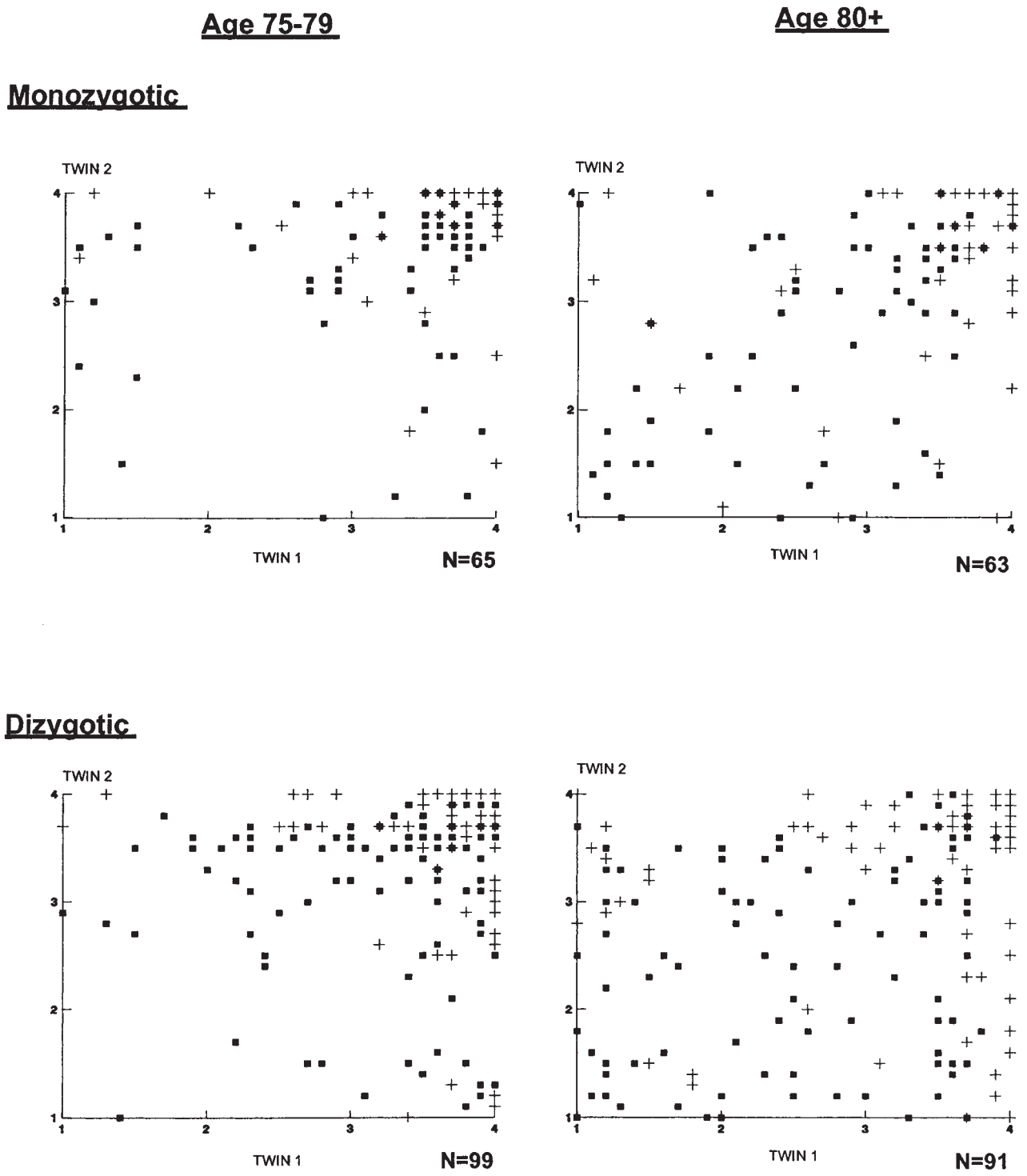

Figure 2. Physical ability scores among elderly Danish female twin pairs. The black boxes indicate strength, and the pluses indicate agility. Maximum score = 4.0, corresponding to being able to perform all activities on the scale without any limitations; minimum score = 1.0, corresponding to being unable to perform any of the activities on the scale.

age group (Table 4). Thus, both the dominance (D) and the shared environment (C) factors were not needed to account for the observed data. Hierarchical models were analyzed to test whether the relative magnitude of genetic and environmental influences differs across age. The fit of the full model estimating separate parameters in the two age groups was compared with the fit of a constrained model specifying equality of the genetic and environmental parameters across age groups. Similar analyses were made for sex differences. For the Total scale, both the age and the sex differences

Table 3. Twin Intraclass Correlations for Age- and Sex-Adjusted Functional Ability Scores (Intact Same-Sex Pairs)

	Males			Females			Total		
	MZ	DZ	*p*	MZ	DZ	*p*	MZ	DZ	*p*
Ages 75–79									
Scale	(n = 27)	(n = 48)		(n = 65)	(n = 99)		(n = 92)	(n = 147)	
Strength	.09	−.11	.21	.27*	.02	.06	.22*	.02	.06
Agility	.17	−.01	.23	.20*	.04	.16	.19*	−.03	.05
Total	.13	−.01	.28	.26*	.04	.08	.22*	.02	.06
Ages 80+									
Scale	(n = 27)	(n = 31)		(n = 63)	(n = 91)		(n = 90)	(n = 122)	
Strength	−.07	−.03	.56	.50*	.18*	.01	.34*	.11	.04
Agility	.07	.06	.49	.43*	.19*	.05	.35*	.16*	.07
Total	−.06	−.01	.57	.49*	.19*	.02	.35*	.14	.05
All									
Scale	(n = 54)	(n = 79)		(n = 128)	(n = 190)		(n = 182)	(n = 269)	
Strength	.01	−.07	.33	.39*	.10*	<.01	.28*	.04	.01
Agility	.13	.05	.33	.35*	.13*	.02	.29*	.11*	.03
Total	.04	.00	.41	.40*	.13*	.01	.30*	.08	.01

Notes: MZ = monozygotic, DZ = dizygotic (same-sex), n = number of pairs. p gives the one-tailed p-value for testing the difference in the MZ and DZ twin correlations. The scores were log-transformed to reduce the skewness in the distribution.

*Correlation significantly different from 0 at $p < .05$, one-tailed.

were significantly different. For the Strength scale, no significant differences over age were observed, while for the Agility scale, the sex differences were nonsignificant (Table 5).

As seen in Table 2, there are age differences in the phenotypic variances (and also small sex differences). Therefore, models that fixed the genetic but not the environmental variance over sex and/or age groups were analyzed, but these models did not improve the fit. Neither did models with fixed environmental variance and varying genetic variance over sex and/or age groups.

The analyses revealed a substantial heritability (34%–47%) for the three functional ability scores among the women aged 80+ compared with a more modest heritability (15%–34%) among the 75- to 79-year-old women. The heritability estimates were uniformly low in the small male sample.

Because functional ability level is associated with mortality and because we found that the heritability for functional abilities increases with age, we would expect the poorest functioning for twins who lost their co-twin at older ages, but not necessarily at younger ages. Therefore, we compared the functional abilities of twins with living versus deceased co-twins (Table 6). Co-twin status (coded as either living, deceased prior to age 80, or deceased at age 80 or older) was significantly associated with both the Strength (F = 3.1, df = 2, p = .04) and Agility (F = 4.4, df = 2, p = .01) scores. This analysis revealed that the overall significant effect was in both cases due to the relatively poor functioning of twins whose co-twins died at or after age 80, because no significant difference in functioning was observed for those twins whose co-twins had died prior to the age of 80. Moreover, the same pattern of results emerged when the analysis was restricted to those who were 80 years and older, so that these results are not an artifact of the manner by which the data were adjusted for age.

Discussion

The estimate that one third to one half of the variation in functional abilities in women aged 80 years and older is caused by genetic factors could be an underestimation for several reasons. First, the interview focuses on functional abilities on the day of the interview and not "usual" abilities, because usual abilities are difficult to define in elderly persons who are experiencing a decline in function. This means that temporary deviations caused by current or recent acute diseases or accidents, for example, will introduce additional variability that will tend to decrease twin similarity.

Table 4. Biometrical Models for Functional Ability Scores Allowing for Sex and Age Differences

	Model Fit Index									
	χ^2				*p*			AIC		
Model	Strength	Agility	Total	*df*	Strength	Agility	Total	Strength	Agility	Total
AE	**4.0**	**8.4**	**5.2**	**8**	.86	.40	.73	**−12.0**	**−7.6**	**−10.8**
ACE	4.0	8.3	5.2	4	.41	.08	.27	−4.0	0.3	−2.8
ADE	2.9	7.8	4.4	4	.58	.10	.35	−5.1	−0.2	−3.6
CE	10.2	12.7	10.9	8	.25	.12	.21	−5.8	−3.3	−5.1
E	28.3	28.3	30.4	12	.01	.01	.00	4.3	4.3	6.4

Notes: The best-fitting model according to AIC (Akaike's Information Criterion = $\chi^2 - 2*$df) is given in boldface. A = additive genetic effects; D = genetic effects due to dominance; C = shared environment; and E = nonshared environment.

Table 5. Heritability for Functional Ability Scores Under an AE Model Allowing for Sex and Age Differences

	Heritability (95% CI)			
	Males		Females	
	75–79 Years	80+ Years	75–79 Years	80+ Years
Strength	.00 (.00–.31)	.00 (.00–.31)	.21 (.01–.40)	.47 (.28–.62)
Best submodel† (fixed over age)	.00 (.00–.21)	.00 (.00–.21)	.34 (.20–.47)	.34 (.20–.47)
Agility	.11 (.00–.41)	.12 (.00–.51)	.17 (.00–.37)	.44 (.23–.63)
Best submodel† (fixed over age)	.15 (.00–.32)	.37 (.18–.53)	.15 (.00–.32)	.37 (.18–.53)
Total	.08 (.00–.40)	.00 (.00–.34)	.21 (.01–.41)	.47 (.28–.62)
Best submodel† (no constraints)	.08 (.00–.40)	.00 (.00–.34)	.21 (.01–.41)	.47 (.28–.62)

Notes: CI = confidence interval. The first line in each scale represents a model that allows for sex and age differences.
†Best fitting submodel. The following submodels were considered with parameter estimates: fixed over age; fixed over sex; and fixed over sex and age.

Second, any measurement error or interviewer effect will also lead to decreased twin similarity (although the analyses did not suggest that these had any major impact). Finally, some health information was obtained by interview in about half of the 23% of the overall sample who did not want to participate, and information on the number of hospitalizations in the previous 18 years was available for all nonresponders (13). As in other studies of nonresponding twin pairs, there seems to be an excess of dizygotic pairs in which the members of the pair were especially discordant in their health profile. Apparently, very dissimilar twins (who most often are dizygotic) have less interest in participating in twin studies, perhaps to avoid comparisons (23). This selection bias tends to increase dizygotic correlations and hence to provide conservative heritability estimates.

The survey did not include objectively measured functional abilities, but self-reported degrees of disability have generally been found to be reliable and valid (14,15). We used an extension of a validated Danish instrument for assessing functional abilities among elderly persons. We have also analyzed the data without the extension and obtained similar results using an approach based on newly developed liability models for discrete traits (disabled/nondisabled) with age-dependent thresholds (24).

Twin studies are based on the assumption that the degree of intrapair environmental similarity is equal in monozygotic and dizygotic pairs. If, in fact, the environmental similarity is greater among monozygotic twins, an overestimation of the genetic influence occurs. However, it seems unlikely that shared environment should be of importance for these twins, the greater part of whom separated more than a half century ago. This conclusion was supported by the finding that the monozygotic correlations did not decrease when the analyses were restricted to twin pairs who had separated more than 50 years ago and who had limited recent contact.

The less pronounced genetic effects found among the 75- to 79-year-old women could reflect true age differences in heritability, although from an evolutionary point of view, there should be no reason to expect large differences between the two age groups because they are both well beyond reproductive age. A cohort effect cannot be ruled out, although it seems unlikely that such large changes occurred over one or two decades. Another possible explanation, which is illustrated in Figure 2, is that only among the oldest-old individuals does the variability in functional abilities become sufficient to detect significant genetic effects. At younger ages, when most elderly persons have good physi-

Table 6. Functional Ability Scores Stratified for Co-Twin's Status

	Both Twins in a Pair Participated				Participating Twins with Co-Twin who Died Before Age 80				Participating Twins with Co-Twin Who Died at Age 80 or Older†			
	Males		Females		Males		Females		Males		Females	
	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ	MZ	DZ
No. of individuals	110	158	256	388	121	239	136	336	23	37	47	66
Mean age (*SD*)	79.9 (4.2)	79.2 (3.9)	80.1 (4.0)	80.0 (3.9)	81.0 (4.1)	80.5 (4.2)	81.2 (4.9)	81.6 (4.9)	85.6 (3.3)	86.0 (3.8)	88.2 (3.8)	86.7 (3.5)
Functional ability scores‡												
Strength												
Mean	.15	−.06	.16	.02	−.08	.07	−.03	−.04	−.17	.11	−.21	−.25
SD	(.82)	(.92)	(.86)	(.85)	(.93)	(.89)	(80)	(.87)	(.93)	(.87)	(.84)	(.83)
SE	(.08)	(.07)	(.05)	(.04)	(.09)	(.06)	(.07)	(.05)	(.19)	(.14)	(.13)	(.10)
Agility												
Mean	.14	−.06	.12	.02	−.05	.06	.01	.01	−.22	.03	−.29	−.23
SD	(.63)	(.82)	(.68)	(.74)	(.87)	(.77)	(.75)	(.77)	(.97)	(.91)	(1.0)	(1.0)
SE	(.06)	(.07)	(.04)	(.04)	(.08)	(.05)	(.06)	(.04)	(.20)	(.15)	(.15)	(.13)

Notes: MZ = monozygotic; DZ = dizygotic (same-sex).
†Fifty-four twins who had co-twins with nonconfirmed status were excluded.
‡See Table 1 for score definitions. The scores are age- and sex-adjusted (see Table 2).

cal functioning, ceiling effects and measurement errors might overshadow some of the correlation. In our study, the male participant sample was small because of the poorer survival rate of men relative to women and not to differences in participation rates. Although heritability estimates were uniformly low in the male participant sample, the size of the sample was not sufficiently large to allow for precise estimates of heritability as reflected in the relatively large confidence intervals.

That functional abilities to a substantial degree were influenced by genetic factors among the oldest female participants does not exclude the potential for environmental intervention or modification. The other half of the variation in functional abilities was determined by environmental factors. Furthermore, the heritability estimate is population specific, and these elderly Danish citizens have probably experienced more homogeneous social conditions than those that exist in many other countries. In other cohorts with more diverse risk profiles, the influence of genetic factors may be less. Finally, in several examples, the function of genes depends on an interaction with environmental factors (25). If such environmental factors are very common, most of the variability in the trait arises from variation in the genes. However, once the interaction pattern is understood, environmental intervention may be designed, phenylketonuria being the classic example.

The data suggest that among the oldest-old women, who are the fastest growing and most disabled group in the industrialized world, genetic factors play an important role in determining functional abilities. This suggests that identification of the genetic factors that influence functional abilities at older ages might be feasible. To help identify such genes, one of the first tasks is to delineate the conditions or diseases through which the genetic factors affect functional abilities among the elderly. If identified, such genes could provide a basis for understanding basic aging processes and the health of the elderly population, and possibly open up avenues for preventing disabilities through environmental interventions.

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Data are available for other researchers. Please see www.pubpol.duke.edu/centers/ppa/index.html for details.

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