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Preservation of cognitive and functional ability as markers of longevity

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Abstract

Longevity is a complex biological process for which the phenotypes have not been established. Preservation of cognitive and physical function may be important and preservation of these functions is, in part, inherited. We investigated the relation between rate of change in cognitive and functional abilities in probands and risk of death in their siblings. Probands were classified as showing no decline, slow, medium, or rapid rate of decline, based on the slope of change in cognitive and physical/functional factors over three or more assessments. Siblings of probands who did not decline on measures of memory, visuospatial/cognitive function or ADL skills were approximately half as likely to die as siblings of probands who had the most rapid decline. The reduction in risk of death in siblings of probands who did not decline in was primarily observed among siblings of probands who were older than 75 years, suggesting that genetic influences on life span may be greater at older ages. There was no association between probands' rate of change in language, IADL skills, upper or lower extremity mobility and risk of death in siblings. The results of the present study identify phenotypes associated with preserved cognitive and functional abilities which may serve as markers for longevity.

Keywords: Longevity; Heritability; Phenotype; Memory; Function

1. Introduction

The heritability of longevity has been estimated from investigations of human twins, isolated and founder populations [11]. Monozygotic twins are twice as likely to be concordant for total years of life as dizygotic twins [23]. Overall, heritability of life span is approximately 20–30% [23,33,40]. Genetic influences on life span appear to be greater at extreme old age. Siblings of centenarians were four times as likely to live beyond 85 years as were siblings of individuals who did not survive past 73 years [43], and first degree relatives of individuals who lived beyond 95 years were twice as likely to survive to the same age as were relatives of controls [22,28].

The biological mechanisms mediating longevity are still unknown. Findings from centenarian and twin studies suggest that preservation of cognitive and physical function is important. In the New England Centenarian study, individuals who lived to extreme old age were found to have been healthy and independent for most of their lives [24]. Offspring of centenarians have favorable lipid profiles and lower relative prevalence of heart disease, hypertension and diabetes [1,12]. Genetic influences on general and specific cognitive function are substantial in studies of human twins [13,14,37,38,42,44,56]. About half the variance in cognitive function can be accounted for by genetic differences [42]. McClearn et al. [37] studied the heritability of cognitive function in Swedish twins 80 years of age and older and showed that genetic influences on cognitive performance continue into old age. Apolipoprotein E (APOE) has been proposed as one candidate gene consistently associated with longevity and memory function [31,34,36,45,50]. Data

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concerning the heritability of physical and functional ability are more limited, but support the hypothesis that genetic influences contribute to individual differences in function and that preservation of physical and functional ability may be associated with longevity [8,10,16].

Genetic factors may influence both the level as well as the rate of change in cognitive and physical functions [41]. Whether or not the genes that influence cognitive and physical function at a given age are the same as those that influence the rate of change in these functions remains unknown. In this study, preservation of cognitive and functional abilities was investigated in relation to survival in family members. We also investigated the relation between survival in families and the rate of change in cognitive and functional abilities in younger and older probands and across three ethnic groups.

2. Methods

2.1. Subjects and setting

Data were included from individuals participating in a prospective study of aging and dementia in 2126 Medicare recipients, 65 years and older, residing in northern Manhattan. A stratified random sample of 50% of all persons older than 65 years was obtained from the Health Care Finance Administration (HCFA) [57]. All persons were sent a letter from HCFA explaining that they had been selected to participate in a study of aging by investigators at Columbia University. The participation rate was 73% and did not differ by ethnic group. Each person received the same medical, neurological, and neuropsychological evaluations at regular 18-month intervals. At the baseline examination, 327 participants (15%) were found to be demented, leaving 1799 participants for the prospective study of incident AD. The cohort has been followed since 1992, but the data included in this analysis were gathered by 2001. Over the study period, the annual mortality rate has been 8.1%, the overall refusal rate has been 10% and the annual incidence rate of Alzheimer's disease (AD) has been 3%, leaving 1051 probands after the first follow-up [36]. To address the study aims, there were 961 of the 1051 probands in the cohort (91.4%) who had at least three measures of memory, cognitive, language or physical and function scores from which rates of change could be computed. Family history data were available for 734 of these 961 probands (76.4%). We then excluded all probands who developed dementia after the first follow-up ($n = 61$), leaving 673 nondemented probands with 2533 siblings to be included in the analysis (Fig. 1). The mean number of siblings was 4.74 per proband (range 1–18).

Ethnic group was classified by participants' self-report into white, African-American, and Hispanic. Participants were asked if they considered themselves white, African-American or other, and then asked if they were

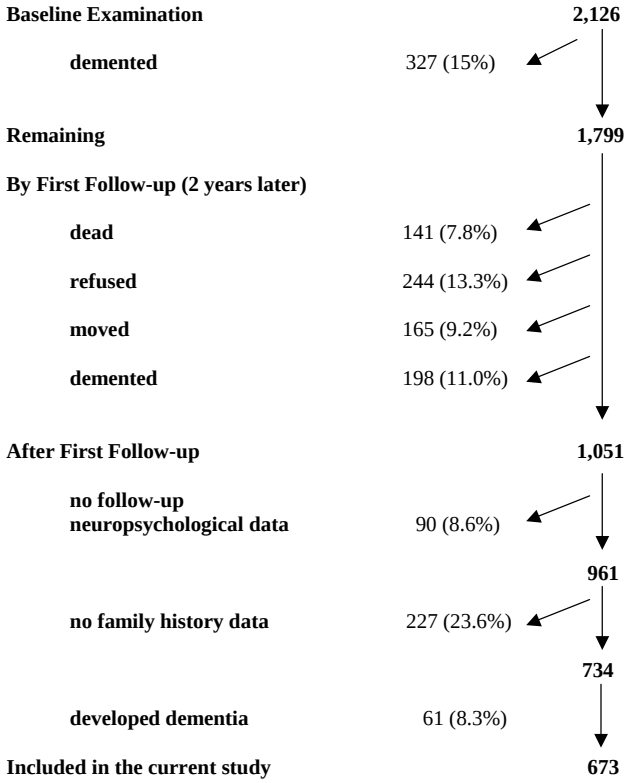

Fig. 1. Nondemented probands with family history.

Hispanic. If Hispanic, the country in which they were born was queried. Most of those classified as Hispanic were of Caribbean origin (84%), predominantly from the Dominican Republic, with the remainder from Mexico and Central America. Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of Columbia Presbyterian Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

2.2. Clinical evaluation

All participants (probands) received structured neurologic and functional assessments by physicians. Past medical history was recorded with specific attention to stroke, trauma, medications, recreational drug use and common age-related conditions such as heart disease, diabetes, thyroid disorders and cancer. All probands underwent a standardized neuropsychological battery [52] that included: orientation from the modified Mini-Mental State Examination [17]; language using the Boston Naming Test [25], the Controlled Word Association test [3], category naming, the Complex Ideational Material Subtest and the repetition of phrases from the Boston Diagnostic Aphasia Evaluation [21]; abstract reasoning from the WAIS-R Similarities subtest [59], and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale [35]; visuospatial ability using the Rosen Drawing Test [48] and the Benton Visual Retention

Test, and a matching version of the Benton Visual Retention Test [4]. Memory was evaluated using the multiple choice version of the Benton Visual Retention test [4] and the seven subtests of the Selective Reminding Test [7]. Information from the neurological, psychiatric and neuropsychological assessments were reviewed in a consensus conference comprised of neurologists, psychiatrists, and neuropsychologists. Based on this review all participants were assigned to one of three categories: dementia, cognitive impairment or normal cognitive function. For physical/functional domains, we used self-reported ability to perform basic and instrumental activities of daily living, assessed at the interview and at time of the medical and neurological examination by the physician. The field interview contained several functional assessment scales, including a modification of the Katz Index of Activities of Daily Living [26], Lawton Instrumental Activities of Daily Living [30], and CARE Activity Limitation, Mobility, and Self-Perceived Health scales [20]. The physician administered the Blessed Dementia Rating Scale [5] and the Schwab and England Rating Scale [53].

2.3. Family history

Family history information was ascertained using a structured telephone interview with nondemented probands and with an informant for demented probands. Informants were most often spouses, children, or siblings of patients or siblings of patients. For the analyses included here, only the information on relatives of nondemented probands was employed. The interview inquired about information on demographics for each first-degree relative (current age, age at death, sex, years of education) and about past and current medical history for each relative. We obtained vital status on relatives from probands and, where possible, cause of death was obtained from the closest relatives of the deceased.

2.4. Apolipoprotein E (APOE) genotyping

Blood was obtained from probands for APOE genotyping at the baseline visit. APOE genotyping was carried out as described in a previous study [57].

2.5. Classification of rate of change

A factor analysis was performed using data from the baseline assessment of the entire cohort with the 15 neuropsychological measures using a principal component analysis with varimax rotation and Kaiser normalization [29]. This analysis yielded three factors: (1) A memory factor, where the seven subtests of the Selective Reminding Test were the main contributors [7]. (2) A visuospatial/cognitive factor (cognitive factor), in which visuospatial and tests of reasoning were the main contributors. These included the Rosen Drawing Test [48], matching and recognition components of the Benton Visual Retention Test [4] and the Identities and Oddities of the Mattis Dementia Rating Scale [35]. (3) A language factor, where language measures were the main contributors; The Boston Naming Test [25], the Controlled Oral Word Association test [3] and the WAIS-R Similarities [59]. Component scores for each subject at each visit were calculated by adding the scores of the measures that contributed most to each factor. While use of a component score based on summing scores from a number of different tests can be difficult to interpret because of scaling differences between the tests, it provides a wider range of scores more suitable for analyzing decline. To obtain a stable estimate of slope, we restricted the analysis to probands with at least three cognitive assessments. We computed the slope of the memory, cognitive and language factor scores. Probands were classified as showing no decline if the slope of the factor scores were equal or greater than zero. Then for the remaining probands, we used tertiles of the slopes showing declines for each factor to classify the probands as showing slow, medium or rapid rate of decline. Classification of rate of change in physical/functional abilities employed a similar procedure to that used for cognitive factors. Functional scores were based on the ability to carry out basic activities of daily living (ADL) and instrumental activities of daily living (IADL). Physical factor measures included lower extremity mobility and upper extremity mobility. Probands were classified as showing no decline if the slopes of the functional or physical scores showed no change or improved and were classified as declining if the slopes showed decline. We also used a combined phenotype based on probands without decline in all three factors for memory, visuospatial and ADL skills to identify probands who had preserved cognitive function in several domains, suggesting exceptional aging characteristics. We hypothesized that siblings of these probands would have the most favorable survival experience.

2.6. Data analysis

All analyses were restricted to the siblings of the probands to avoid cohort effects related to secular trends in survival between parent and offspring generations. We investigated the associations between rate of change in cognitive and physical/functional ability in the probands and total years of survival in their siblings. We used X^2 tests, t tests and analysis of variance to compare the characteristics of probands with no decline or with slow, medium or rapid rates of decline in cognitive and physical/functional scores. We used logistic regression to estimate the association between rate of change in probands and the likelihood of death in their siblings. With multiple siblings per proband included in the analysis, the correlation in survival within families would be expected to be greater than that between families. This correlation does not affect the consistency of the estimate of relative risk by rate of change, but it can bias estimation of the standard errors of the coefficients. To limit this, we used generalized estimating equations (GEE) to conduct the logistic regression analyses [60]. GEE considers multiple measures per individual and the fact that the characteristics

of each individual over time are correlated. The repeated measures for each subject are treated as a cluster. In this analysis, siblings were treated as the repeated measure of the proband's family. We estimated the odds ratio (OR) of death in siblings associated with rate of cognitive or physical/functional change in the proband, adjusting for sibling age, sex, education and ethnicity. Age was classified as age at death for the deceased and age at the time of the last interview for surviving siblings. To account for a possible healthy survivor bias and to determine whether influences on life span were greater at older ages, we repeated the logistic regression in models stratified by proband age at entry into the study (≤75 years versus >75 years). Additional logistic regression models were also stratified by sibling sex, ethnic group and the proband's APOE genotype. APOE genotypes were available for 650 of the 673 probands included in the analysis. Analyses were conducted using SPSS v. 11 and SAS v. 8.

3. Results

3.1. Proband characteristics

Probands were more likely to show declines in memory than in the visuospatial/cognitive measures or in language factor scores (Table 1). Probands were also more likely to show declines in instrumental activities of daily living (IADL) and in lower extremity mobility than in upper extremity mobility or in basic activities of daily living (ADL)

Table 1
Proband demographic characteristics by cognitive factors

Proband characteristics	No decline	Slow decline	Medium decline	Rapid decline
Memory factor				
Sample size	169	163	165	167
Age at entry (mean ± S.D.)*	74.9 (5.2)	75.3 (6.0)	75.5 (5.0)	76.9 (5.8)
Sex (*n*, %)				
Female	121 (71.7)	119 (73.0)	114 (69.1)	117 (70.1)
Male	48 (28.4)	44 (27.0)	51 (30.9)	50 (29.9)
Ethnicity (*n*, %)				
White/Non-Hispanic	41 (24.3)	25 (15.3)	31 (18.8)	28 (16.8)
African-American	40 (23.7)	45 (27.6)	45 (27.3)	61 (36.5)
Hispanic	88 (52.0)	93 (57.1)	89 (53.9)	78 (46.7)
Education (mean ± S.D.)	8.9 (4.9)	8.5 (4.6)	8.4 (4.5)	8.9 (4.5)
One or more APOE e4 allele*	36 (22.0)	45 (28.1)	54 (34.6)	60 (37.3)
Cognitive factor				
Sample size	416	85	85	87
Age at entry (mean ± S.D.)*	75.1 (5.2)	76.0 (6.2)	76.7 (6.2)	77.2 (6.2)
Sex (*n*, %)				
Female	288 (69.2)	64 (75.3)	67 (78.8)	60 (69.0)
Male	128 (30.8)	21 (24.7)	18 (21.2)	27 (31.0)
Ethnicity (*n*, %)				
White/Non-Hispanic	87 (20.9)	15 (17.6)	17 (20.0)	12 (13.8)
African-American	113 (27.2)	24 (28.2)	28 (32.9)	27 (31.0)
Hispanic	216 (51.9)	46 (51.8)	40 (47.1)	48 (55.2)
Education (mean ± S.D.)	8.9 (4.6)	8.2 (4.7)	8.3 (4.2)	8.6 (4.8)
One or more APOE e4 allele*	106 (26.6)	32 (39.0)	26 (31.0)	34 (40.0)
Language factor				
Sample size	252	104	101	101
Age at entry (mean ± S.D.)*	74.7 (5.3)	74.8 (4.9)	75.5 (5.8)	77.3 (6.2)
Sex (*n*, %)				
Female	171 (67.9)	80 (76.9)	74 (73.3)	76 (75.2)
Male	81 (32.1)	24 (23.1)	27 (26.7)	25 (24.8)
Ethnicity (*n*, %)				
White/Non-Hispanic	54 (21.4)	21 (20.2)	20 (19.8)	10 (9.9)
African-American	64 (25.4)	29 (27.9)	29 (28.7)	37 (36.6)
Hispanic	134 (53.2)	54 (52.0)	52 (51.5)	54 (53.5)
Education (mean ± S.D.)*	8.6 (4.6)	9.0 (4.5)	8.9 (4.6)	7.4 (4.2)
One or more APOE e4 allele*	67 (27.3)	28 (28.6)	31 (32.0)	43 (43.9)

* $P < 0.05$.

Table 2
Proband demographic characteristics by physical/functional factors

Proband characteristics	No decline	Decline
Activities of daily living (ADL)		
Sample size	563	106
Age at entry (mean ± S.D.)*	75.2 (5.4)	77.9 (6.7)
Sex (*n*, %)*		
Female	385 (68.4)	91 (85.8)
Male	178 (31.6)	15 (14.2)
Ethnicity (*n*, %)		
White/Non-Hispanic	112 (20.0)	18 (17.1)
African-American	158 (28.3)	33 (31.4)
Hispanic	289 (51.7)	54 (51.4)
Education (mean ± S.D.)	8.7 (4.6)	8.8 (4.6)
One or more APOE e4 allele	168 (30.9)	74 (28.2)
IADL		
Sample size	397	274
Age at entry (mean ± S.D.)*	74.7 (5.0)	77.2 (6.3)
Sex (*n*, %)*		
Female	264 (66.5)	214 (78.1)
Male	133 (33.5)	60 (21.9)
Ethnicity (*n*, %)		
White/Non-Hispanic	84 (21.3)	47 (17.3)
African-American	119 (30.1)	73 (26.9)
Hispanic	193 (48.6)	151 (55.7)
Education (mean + S.D.)	9.0 (4.7)	8.2 (4.5)
One or more APOE e4 allele	119 (31.0)	78 (29.5)
Lower extremity mobility		
Sample size	345	321
Age at entry (mean ± S.D.)*	74.7 (5.0)	76.8 (6.1)
Sex (*n*, %)*		
Female	232 (67.2)	241 (75.1)
Male	113 (32.8)	80 (24.9)
Ethnicity (*n*, %)		
White/Non-Hispanic	66 (19.2)	64 (20.1)
African-American	103 (30.0)	88 (27.6)
Hispanic	174 (50.7)	167 (52.4)
Education (mean + S.D.)	9.0 (4.4)	8.4 (4.8)
One or more APOE e4 allele	105 (31.6)	91 (29.3)
Upper extremity mobility		
Sample size	426	243
Age at entry (mean ± S.D.)*	75.3 (5.4)	76.4 (6.0)
Sex (*n*, %)		
Female	292 (68.5)	184 (75.7)
Male	134 (31.5)	59 (24.3)
Ethnicity (*n*, %)		
White/Non-Hispanic	78 (18.5)	52 (21.5)
African-American	127 (30.1)	64 (26.4)
Hispanic	217 (51.4)	126 (52.1)
Education (mean ± S.D.)	8.7 (4.6)	8.7 (4.7)
One or more APOE e4 allele	123 (29.7)	74 (31.9)

* $P < 0.05$.

(Table 2). Probands with and without declines in memory, visuospatial/cognitive or language factor scores did not differ in the distribution of sex, education or ethnic group (Table 1), while probands showing the most rapid declines in these factors were older and more likely to have an APOE ε4 allele than probands who did not decline (Table 1). Probands showing declines in physical/functional factor scores were also older and more likely to be female than those who did not decline, but did not differ significantly from those who did not decline in the distribution of ethnic group or in the proportion with an APOE ε4 allele (Table 2). Table 3 shows the characteristics of the rates of decline for the cognitive factors.

3.2. Survival in siblings

Siblings of probands who did not decline on measures of memory, visuospatial/cognitive function or on ADL skills were approximately half as likely to die as siblings of probands who had the most rapid decline, (OR = 0.5, 95% CI: 0.4–0.8; OR = 0.6, 95% CI: 0.4–0.9; OR = 0.6, 95% CI: 0.4–0.8, respectively (Table 4). There was no association between proband rate of change in language, IADL skills, or lower or upper extremity mobility and survival in their siblings. Estimates of the likelihood of death in siblings were similar in univariate and multivariate models, suggesting that the association between proband rate of change and sibling survival was not confounded by differences between groups in the distribution of sibling age, sex, level of education or ethnicity (Table 4). We repeated these analyses, including the proband's age and the presence or absence of an APOE ε4 allele in the model as covariates, since both age and the frequency of the ε4 allele were higher in probands with the most rapid rates of decline than in probands without decline. There was little change in the likelihood estimates, suggesting that proband age and the presence ε4 allele did not act as confounders of the relation between rate of decline and likelihood of death in siblings (e.g., for decline in memory, the odds ratios were 0.51 and 0.57 for those without decline compared to those with rapid decline, before and after adding proband age and the presence of an ε4 allele to the model, respectively). When we used a combined phenotype based on probands without decline in all three factors for memory, visuospatial and ADL skills, there was a 86% reduction in risk of death among siblings of probands who did not decline compared with those showing rapid decline (OR = 0.14, 95% CI, 0.05–0.40).

In stratified analyses, the association between proband rate of change and sibling survival was not modified by sibling sex, or the presence of an APOE ε4 allele in the proband. We also compared sibling survival across ethnic groups. The pattern of survival in siblings by rate of change in probands' memory, language, ADL and IADL scores was similar across ethnic groups, but differed slightly for extremity factors. There was a 60% reduction in risk of death among siblings of white probands who did not decline in lower mobility extremity (OR = 0.4, 95% CI, 0.2–0.8) and a 40% reduction in risk of death among siblings of African-American probands who did not decline in upper extremity mobility (OR = 0.6, 95% CI, 0.4–0.9), but no association in other

Table 3
Characteristics of rate of cognitive decline in probands

Characteristics	No decline	Slow decline	Medium decline	Rapid decline
Memory factor				
Sample size	169	163	165	167
Mean	6.16	−2.5	−7.3	−15.9
Standard deviation	6.7	1.3	1.7	5.9
Range	37.1 to 0.01	−0.02 to −0.46	−4.7 to −10.4	−10.5 to −54.9
Cognitive factor				
Sample size	416	85	85	87
Mean	5.0	−0.6	−1.9	−5.9
Standard deviation	4.8	0.3	0.5	3.4
Range	25.5 to 0.0	−0.01 to −1.2	−1.21 to −2.7	−2.74 to −21.2
Language factor				
Sample size	252	104	101	101
Mean	0.25	−0.1	−0.3	−0.9
Standard deviation	0.3	0.01	0.01	0.5
Range	2.6 to 0.0	0.01 to −0.2	−0.21 to 0.4	−0.42 to −2.8

ethnic groups. Adjustment for the presence of a history of stroke, heart disease, diabetes, thyroid disorders and cancer in the siblings, or adjustment for these medical conditions and body mass index (BMI) in the probands, did not change the association between rate of change in memory, visuospatial/cognitive or ADL skills and sibling survival (OR = 0.5, 95% CI, 0.4–0.7 for memory, OR = 0.7, 95% CI, 0.5–0.9 for visuospatial/cognitive function, OR = 0.7, 95% CI, 0.5–0.9 for ADL skills after adjustment for a history of these medical conditions in siblings; OR = 0.5, 95% CI, 0.4–0.7 for

Table 4
Survival in siblings by rate of decline in probands

Proband characteristics	No. siblings (% deceased)	Univariate odds ratio (95% CI)	Multivariate odds ratio[a] (95% CI)
Memory factor			
Rapid decline	585 (48.0)	1.0 (reference)	1.0 (reference)
Medium decline	664 (40.8)	0.7 (0.6–1.0)	0.7 (0.5–1.0)
Slow decline	588 (41.3)	0.8 (0.6–1.1)	0.8 (0.5–1.2)
No decline	662 (32.8)	0.6 (0.4–0.8)*	0.5 (0.4–0.8)*
Cognitive factor			
Rapid decline	339 (51.0)	1.0 (reference)	1.0 (reference)
Medium decline	289 (46.4)	0.8 (0.6–1.2)	0.7 (0.4–1.2)
Slow decline	320 (37.8)	0.6 (0.4–0.9)*	0.6 (0.3–0.9)*
No decline	1585 (38.0)	0.6 (0.4–0.8)*	0.6 (0.4–0.9)*
Language factor			
Rapid decline	365 (44.7)	1.0 (reference)	1.0 (reference)
Medium decline	350 (41.4)	1.1 (0.8–1.6)	0.8 (0.5–1.4)
Slow decline	409 (36.7)	0.8 (0.5–1.1)	0.7 (0.5–1.1)
No decline	992 (40.2)	0.8 (0.6–1.1)	0.8 (0.5–1.2)
Activities of daily living (ADL)			
Decline	338 (49.7)	1.0 (reference)	1.0 (reference)
No decline	2177 (39.2)	0.6 (0.5–0.9)*	0.6 (0.4–0.8)*
Instrumental ADL			
Decline	980 (43.0)	1.0 (reference)	1.0 (reference)
No decline	1542 (39.0)	0.9 (0.7–1.1)	0.8 (0.6–1.0)
Lower extremity mobility			
Decline	1128 (42.0)	1.0 (reference)	1.0 (reference)
No decline	1384 (38.9)	0.9 (0.7–1.1)	0.9 (0.7–1.1)
Upper extremity mobility			
Decline	851 (43.9)	1.0 (reference)	1.0 (reference)
No decline	1664 (38.9)	0.8 (0.7–1.0)	0.8 (0.6–1.0)

[a] Multivariate logistic regression, adjusted for sibling age, sex, level of education and ethnicity.
* $P < 0.05$.

Table 5
Survival in siblings by rate of decline in probands and proband age at enrollment 29

	<75 years at enrollment		>75 years at enrollment	
	No. siblings (% deceased)	Odds ratio (95% CI)[a]	No. siblings (% deceased)	Odds ratio (95% CI)
Memory factor				
Rapid decline	277 (35.4)	1.0 (reference)	308 (59.4)	1.0 (reference)
Medium decline	382 (35.1)	0.8 (0.5–1.4)	282 (48.6)	0.7 (0.4–1.1)
Slow decline	284 (32.7)	0.9 (0.5–1.5)	304 (49.3)	0.6 (0.4–1.1)
No decline	354 (31.1)	0.6 (0.4–1.1)	308 (34.7)	0.4 (0.2–0.6)*
Cognitive factor				
Rapid decline	119 (31.9)	1.0 (reference)	220 (61.4)	1.0 (reference)
Medium decline	140 (36.4)	1.2 (0.6–2.4)	149 (55.7)	0.7 (0.3–1.3)
Slow decline	182 (36.3)	1.2 (0.6–2.5)	138 (39.9)	0.4 (0.2–0.7)*
No decline	862 (32.6)	1.1 (0.6–2.0)	723 (44.4)	0.5 (0.3–0.8)*
Language factor				
Rapid decline	178 (38.2)	1.0 (reference)	187 (50.8)	1.0 (reference)
Medium decline	169 (27.2)	0.6 (0.3–1.1)	181 (54.7)	1.0 (0.5–2.0)
Slow decline	218 (36.7)	0.9 (0.5–1.9)	191 (36.6)	0.5 (0.3–0.8)*
No decline	590 (36.3)	0.9 (0.6–1.6)	402 (46.0)	0.7 (0.4–1.3)
Activities of daily living (ADL)				
Decline	117 (29.1)	1.0 (reference)	221 (60.6)	1.0 (reference)
No decline	1179 (34.0)	1.2 (0.6–2.4)	998 (45.4)	0.5 (0.3–0.7)*
Instrumental ADL				
Decline	362 (31.5)	1.0 (reference)	618 (49.7)	1.0 (reference)
No decline	941 (34.2)	1.2 (0.8–1.7)	601 (46.6)	0.9 (0.6–1.2)
Lower extremity mobility				
Decline	487 (33.9)	1.0 (reference)	618 (49.7)	1.0 (reference)
No decline	807 (33.3)	1.0 (0.7–1.4)	601 (46.6)	0.9 (0.7–1.4)
Upper extremity mobility				
Decline	393 (37.7)	1.0 (reference)	458 (49.3)	1.0 (reference)
No decline	903 (31.8)	0.7 (0.5–1.1)	761 (47.4)	0.9 (0.6–1.3)

[a] Multivariate logistic regression, adjusted for sibling age, sex, level of education and ethnicity.
* $P < 0.05$.

memory; OR = 0.6, 95% CI, 0.4–0.8 for visuospatial/cognitive function; OR = 0.6, 95% CI, 0.5–0.8 for ADL skills after adjustment for the presence of a history of these medical conditions and BMI in probands).

We repeated the logistic regression analyses within strata defined by proband's age at enrollment (≤75 years or >75 years). The reduction in risk of death in siblings of probands who did not decline in memory, visuospatial/cognitive or ADL skills was strongest for siblings of probands who were older than 75 years at enrollment (Table 5). There was a 60% reduction in risk of death among siblings of probands who did not decline on measures of memory (OR = 0.4, 95% CI: 0.2–0.6) and a 50% reduction in risk of death among siblings of probands who did not decline in visuospatial/cognitive or ADL skills (OR = 0.5, 95% CI, 0.3–0.8 and OR = 0.5, 95% CI, 0.3–0.7, respectively) (Table 5). Among siblings of younger probands, there were no significant associations between sibling survival and the probands' rate of change in cognitive, language, ADL, IADL, lower extremity mobility or upper mobility factors (Table 5).

4. Discussion

Siblings of probands who did not decline on measures of memory or visuospatial/cognitive function or ADL skills were approximately half as likely to die as siblings of probands who had the most rapid rate of decline. The relation of rate of change to likelihood of death did not vary by sex or ethnicity, despite higher death rates among men and among African-Americans. The reduction in risk of death was greater for siblings of probands who were older than 75 years than for siblings of probands who were 75 years or younger. The relation of cognitive decline to likelihood of death in siblings was strongest and most consistent for the memory factor. Siblings of probands who did not decline on any cognitive factor had the most favorable survival experience, compared with those with the most rapid declines in the three cognitive factors. Overall, our findings suggest that preservation of cognitive and functional skills may be components of a phenotype associated with longevity.

Our findings are consistent with other studies suggesting the familial aggregation of survival. In Iceland, first degree

relatives of individuals living to the 95th percentile of surviving age were twice as likely to also survive to the 95th percentile as relatives of controls [22]. Life-span data on all relatives of a cohort of individuals in Utah born between 1870 and 1907 who lived to be at least 65 years of age were used to estimate the influence of family history on the relative risk of longevity. Siblings of probands who reached the 97th percentile of excess longevity (age 95 for men and age 97 for women) were 2.3 times as likely to reach the 97th percentile of longevity as siblings of probands who died at younger ages [28]. Our finding that the reduction in risk of death in siblings of probands who did not decline in memory, visuospatial/cognitive or ADL skills was strongest for siblings of probands who were older than 75 years at enrollment is consistent with the results of these studies and with findings from studies of centenarians that suggest that genetic influences on life span appear to be greater at extreme old age [43,44]. Our findings are noteworthy because the study participants were not selected for extreme longevity.

A recent study used a frailty model to estimate the relative importance of genetic and environmental factors on age at onset of dementia and death in Swedish Twins, describing variation in the onset of disease and mortality in one model [47]. Genetic effects were estimated to account for about one-third, and shared environmental effects for about one-half, of the variation in dementia hazards between individuals. In our study, the decreased risk of death in siblings associated with no decline or with a low rate of cognitive decline in probands is likely to be a composite of shared genetic and shared environmental effects. Our finding that siblings of probands with no decline or with low rates of cognitive decline are half as likely to die as siblings of probands with rapid rates of decline is consistent with the estimates of genetic and shared environmental effects for age at onset of dementia described above [47]. Further, the reduced risk of death may be associated with reduced risk of dementia.

The phenotypes associated with longevity are not fully established. Findings from elderly cohorts and from centenarian studies suggest that preservation of cognitive and physical function is important and that preservation of these functions is, in part, inherited [43]. In a retrospective study of New England centenarians, 100–109 years of age, 89% were still living independently at 93 years, 73% at 97 years and 35% at 102 years [24]. Survival to extreme old age in probands was associated with fewer age-related diseases or chronic disorders, and with favorable health profiles in their offspring [1,12,58]. In contrast, findings from the Italian Multicenter Study on Centenarians suggested that many centenarians reach old age despite limitations in cognitive and functional abilities [18]. In most studies, cognitive impairment has been shown to be strongly associated with mortality in both healthy and demented elderly. In population-based cohorts of the elderly, those with mild as well as severe cognitive impairment have been found to have an increased risk of death [2,6,19,27,51,54]. Adjustment for a variety of health conditions, lifestyle factors, and sociodemographic characteristics did not decrease the mortality risk associated with poor cognitive function [6,19,32,49,54]. In this study, adjustment for common age-related disease in probands or in siblings did not change the associations between proband rate of change and likelihood of survival in siblings. The influence of specific age-related disease genes on survival is likely to be small because any one disease cannot account for a high proportion of overall population mortality [9,11]. Overall, these studies suggest that preservation of cognitive function has an independent and important influence on survival and this is supported by our findings. The majority of studies used a global assessment of cognitive performance, such as the Mini-Mental State Examination (MMSE), as the measure of cognitive function, whereas only a few studies have used tests based on information processing or fluid intelligence, learning and memory. A number of studies of cognitive function and mortality have focused on age-related risk for dementia, rather than normal aging. Thus, determination of the cognitive phenotypes associated with healthy aging and longevity requires fuller investigation with neuropsychological tests specifically targeted to processes affected by normal aging.

Longevity is a complex biological process for which the phenotypes have not been established. It is likely to include many different components, and for each component, the influence of genetic and environmental factors are likely to differ. In this study, we found that preservation of memory, visuospatial/cognitive and ADL skills in the proband predicted survival in siblings. The heritability for memory and other cognitive functions estimated from twin studies is substantial [13,15,37,38,42,44,55]. Plomin et al. [44] found heritability for a general cognitive ability in twins to be 0.80, with heritability for verbal and speed of processing tests about 0.50, and for memory 0.40. Swan and colleagues found that the genetic component of verbal recall and recognition may be as high as 56% [56] and most studies have yielded estimated for various cognitive functions within these ranges [16,39,55]. Data on the heritability of rate of change in cognitive and functional abilities is limited and most studies have found lower estimates of heritability for rate of change phenotypes than the estimates from cross-sectional studies [16,46,55]. Differences in results may be related to differences in the study populations examined, analytic methods and the nature of the phenotypes employed.

Our study is limited by the nature of the clinical variables and scales we used which may have determined how well change in probands could be measured. The measurement of memory and other cognitive functions by psychometric testing is more precise and yields scores that are more truly quantitative and more likely to indicate subtle change over time than is the assessment of ADL, IADL or ratings of upper and lower extremity mobility. Our study is limited also because we did not have data on cognitive function or cognitive decline in siblings. Thus, we were not able to determine whether the improved survival in siblings was related to their preservation of cognitive function. Family-based stud-

ies, with longitudinal assessment of cognitive function in all family members, will be required to support our hypothesis that cognitive function, especially preservation of memory, in old age represents one of several key traits that contribute to the overall phenotype of longevity. Further refinement of these and additional phenotypes, and characterization of the patterns of familial aggregation and transmission of healthy survival will be required to establish candidate phenotypes for genetic analysis.

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