Reduced Prevalence of Cognitive Impairment in Families With Exceptional Longevity

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IMPORTANCE Family studies of centenarians and long-lived persons have found substantial familial aggregation of survival to extreme ages; however, the extent to which such familial longevity is characterized by cognitively intact survival is not established.

OBJECTIVE To determine whether families with exceptional longevity are protected against cognitive impairment consistent with Alzheimer disease.

DESIGN Cross-sectional analysis.

SETTING Multisite study in New York, Massachusetts, Pennsylvania, and Denmark.

PARTICIPANTS A total of 1870 individuals (1510 family members and 360 spouse controls) recruited through the Long Life Family Study.

MAIN OUTCOME AND MEASURE Prevalence of cognitive impairment based on a diagnostic algorithm validated using the National Alzheimer’s Coordinating Center data set.

RESULTS The cognitive algorithm classified 546 individuals (38.5%) as having cognitive impairment consistent with Alzheimer disease. Long Life Family Study probands had a slightly but not statistically significant reduced risk of cognitive impairment compared with spouse controls (121 of 232 for probands vs 45 of 103 for spouse controls; odds ratio = 0.7; 95% CI, 0.4-1.4), whereas Long Life Family Study sons and daughters had a clearly reduced risk of cognitive impairment (11 of 213 for sons and daughters vs 28 of 216 for spouse controls; odds ratio = 0.4; 95% CI, 0.2-0.9). Restriction to nieces and nephews in the offspring generation attenuated this effect (37 of 328 for nieces and nephews vs 28 of 216 for spouse controls; odds ratio = 0.8; 95% CI, 0.4-1.4).

CONCLUSIONS AND RELEVANCE Rates of cognitive impairment characteristic of Alzheimer disease were relatively high. In the proband generation, rates were comparable across family members and spouse controls, whereas sons and daughters of probands had significantly lower rates than spouse controls. Results suggest a delayed onset of cognitive impairment in families with exceptional longevity, but assessment of age-specific incidence rates is required to confirm this hypothesis.
Exceptional longevity can be defined in a number of ways, including survival to a specific extreme age, disability-free survival (active life expectancy), disease-free survival (health expectancy), or cognitively intact survival. Family studies of centenarians and long-lived persons have found substantial familial aggregation of survival to extreme ages; however, the extent to which such familial longevity is characterized by cognitively intact survival is not established. Examination of the cognitive phenotype of familial longevity is particularly relevant as dementia prevalence rates in the oldest-old population are as high as, if not higher than, rates in lower age brackets. For example, in individuals aged 95 years and older, rates range from 40% to 74%; among centenarians, the upper end of the range extends to 100%.\(^7\)\(^-\)\(^10\)

The Long Life Family Study (LLFS) is a family-based cohort study examining the genetic and nongenetic factors associated with exceptional familial longevity. Characteristics of offspring have been of particular interest, as the study of offspring of long-lived family members may be more informative than the study of probands where compression of morbidity may produce less variation and make it more difficult to detect factors associated with exceptional longevity.\(^7\)\(^-\)\(^18\) Offspring in the LLFS families have been shown to have lower rates of diabetes mellitus, pulmonary disease, and peripheral arterial disease\(^19\) and higher cognitive scores\(^20\) than age-matched individuals. Our study examined the extent to which 2 generations of individuals in the LLFS cohort were protected against cognitive impairment characteristic of Alzheimer disease (AD).

Methods

LLFS cohort

The LLFS includes families selected for exceptional survival phenotypes in the United States (Boston, Massachusetts; New York, New York; and Pittsburgh, Pennsylvania) and Denmark. Probands were selected to be exceptionally long lived with at least 1 additional living sibling in the proband generation and at least 1 offspring of the proband or sibling willing to participate. Family eligibility and ascertainment have been previously described.\(^10\)\(^-\)\(^21\) Briefly, in the United States, potentially eligible individuals and their families were identified through 2 main sources: (1) mailings of study information to individuals aged 79 years and older who were enrolled in the Medicare program and resided in zip code areas located within a 3-hour driving distance from the 3 field centers (later restricted to ages ≥89 years based on the initial yield of families), and (2) individuals who contacted the field centers in response to media events, including television appearances, newspaper stories, and advertisements. All potential participants were interviewed over the telephone to assess eligibility and willingness to participate in the LLFS. Family eligibility was assessed using the following criteria: (1) at least 2 living siblings including the proband, (2) at least 1 living offspring of 1 of the 2 living siblings, and (3) demonstration of exceptional familial survival as measured by the Family Longevity Selection Score, a summary measure based on the survival experience of the proband and his or her siblings relative to what would be expected based on birth cohort-specific life tables and the availability of living subjects for study.\(^21\) Among eligible families, those with exceptionally old living siblings were given highest priority. Individuals judged to have moderate to severe dementia during the recruitment process were excluded from the study. Additionally, we also recruited and enrolled the spouses of all participants in both generations when available. Spouses of probands were recruited provided that they were the biological parent of the proband’s offspring, and spouses of probands’ siblings were recruited provided that they were the biological parent of the sibling’s offspring. Spouse controls provide a similarly aged comparison group not selected for family history of longevity and are used to adjust for common characteristics of family members such as diet, exercise, common environmental exposures, and common cultural practices, which are likely to be correlated. However, family history of longevity was not collected for spouse controls, and some spouse controls may have come from long-lived families.

In Denmark, identification of potentially eligible probands and their families proceeded as follows. First, individuals who would be aged 90 years and older during the study recruitment period were identified in the Danish National Register of Persons, which contains current information on names, including past names such as maiden names for women, addresses, place of birth, marriages, and vital status.\(^22\) Second, using information on the place of birth and names, parish registers available in regional archives were searched to locate the parents of the elderly individuals to identify siblings. Based on this information, potentially eligible families were identified and contact was made with potential probands to further assess the family’s eligibility for and willingness to participate in the LLFS, using criteria parallel to those used in the United States.

Dementia was ascertained via evaluation of the individual’s ability to describe the purpose of the study to the examiner and provide informed consent. It is therefore likely that only individuals with moderate to severe dementia were systematically excluded from this study.

Participants

Participants were selected for the current analyses in the following manner (Table 1). Of 4953 individuals from 539 families enrolled in the LLFS, 4938 were evaluated cognitively. The sample was then restricted to the 2694 individuals aged 65 years and older. Among LLFS participants aged 65 years and older, complete cognitive testing required for application of
the National Alzheimer's Coordinating Center (NACC)-based cognitive algorithm was available for 2053 participants and judged to be fully valid in 1896 of these participants (eg, free from deficits related to sensorimotor problems or environmental factors such as distractions during the test sessions). Of these, analyses were limited to the 1870 white individuals in the LLFS cohort given the small number (1.4%) of other ethnicities. The final sample included 1510 family members and 360 spouse controls. Using partners of long-lived subjects and their offspring as comparison groups avoids potential confounders because it is likely that they have a similar distribution of birth cohort, socioeconomic, and geographical backgrounds.

Table 2 and Table 3 show the characteristics of the family member and spouse control groups in the proband and offspring generations.

### Cognitive Assessment

Cognitive performance in all individuals was assessed with 8 of the 10 tests in the NACC Uniform Dataset. Specifically, participants were administered the Mini-Mental State Examination, a brief version of the logical memory subtest of the Wechsler Memory Scale–Revised23 consisting of only 1 paragraph to be recalled at immediate and delayed intervals, the Digit Span forward and backward tests, the animal fluency test, the vegetable fluency test, and the digit symbol subtest of the Wechsler Adult Intelligence Scale–Revised.

### Algorithm for Cognitive Impairment

Data from the NACC were used to create a diagnostic algorithm that would identify cognitive impairment consistent with AD in LLFS participants. A description of the algorithm development is available in the eAppendix in the Supplement.

### Statistical Analysis

We used generalized estimating equations to examine risk for cognitive impairment in families vs spouse controls, adjusting for age, education, study site, and family membership. Generalized estimating equations take into account the fact that characteristics of individuals within a family are likely correlated. Family membership for each participant is treated as a cluster. Sex was not included as a covariate in the model as the final cognitive algorithm was sex adjusted. Individuals within the same family were accepted for entry into the analysis, and family was treated as a cluster. In addition to examining the probands, we also examined siblings in this generation while excluding probands because probands, but not their siblings, were selected for longevity. Additionally, the offspring generation was examined within strata based on their relationship to the proband, first comparing sons and daughters vs spouse controls and then nieces and nephews vs spouse controls, to examine how effects of familial longevity were related to degree of kinship with the proband. Finally, not all families had spouse controls available. Therefore, we selected the subset of families with a spouse control and conducted conditional logistic regression for the likelihood of cog-

<table>
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<th>Characteristic</th>
<th>Value</th>
<th>Age, y</th>
<th></th>
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<tr>
<td></td>
<td>Controls (n = 138)</td>
<td>Proband Only (n = 348)</td>
<td>Proband Siblings (n = 603)</td>
<td>Controls (n = 222)</td>
<td>Sons and Daughters (n = 218)</td>
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<td>Age, mean (SD), y</td>
<td>83.84 (5.96)</td>
<td>93.58 (3.62)</td>
<td>87.78 (5.87)</td>
<td>70.51 (4.47)</td>
<td>69.61 (3.90)</td>
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<td>Education, mean (SD), y</td>
<td>10.40 (3.46)</td>
<td>10.48 (3.92)</td>
<td>10.01 (3.63)</td>
<td>11.33 (3.73)</td>
<td>12.35 (3.14)</td>
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<td>Female, No. (%)</td>
<td>108 (78.3)</td>
<td>144 (41.4)</td>
<td>328 (54.4)</td>
<td>77 (34.7)</td>
<td>143 (65.6)</td>
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<tr>
<td>Score, mean (SD)</td>
<td>27.29 (2.44)</td>
<td>26.05 (3.13)</td>
<td>25.66 (3.11)</td>
<td>28.48 (1.95)</td>
<td>28.89 (1.30)</td>
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<td>Immediate memory</td>
<td>8.06 (4.22)</td>
<td>9.54 (4.34)</td>
<td>8.50 (4.41)</td>
<td>11.92 (4.32)</td>
<td>13.02 (4.00)</td>
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<tr>
<td>Delayed memory</td>
<td>5.74 (4.15)</td>
<td>7.50 (4.43)</td>
<td>6.36 (4.55)</td>
<td>10.30 (4.80)</td>
<td>11.48 (4.23)</td>
</tr>
</tbody>
</table>

* Group differences were examined across probands vs controls and across sons and daughters vs controls.

* *P* < .001.
Cognitive Impairment in Families With Longevity

Results

Descriptive Statistics
The final sample of LLFS participants included 1870 of the 2694 individuals (69.4%) aged 65 years and older in the study. There was an approximately equal distribution of participants included from all 4 study sites, with each site contributing 21% to 27% of the final sample. The largest source of participant exclusion was the availability of complete cognitive testing, followed by the validity of the testing. Participants may have had incomplete or invalid testing due to a number of reasons including fatigue, refusal to continue, or inability to perform certain tests owing to physical disabilities. Given that such circumstances may be more likely to arise when evaluating an individual with cognitive impairment, current estimates regarding the prevalence of cognitive impairment and dementia may be an underestimate of the true rates in this sample.

Individuals in the proband generation with invalid testing were older than those with valid testing ($F_{1,1311} = 50.30; P < .001$) but had similar levels of education and a comparable proportion of men and women. There were no demographic differences as a function of test validity in the offspring generation.

Of the 1510 family members, 951 (63.0%) were from the proband generation and 559 (37.0%) were from the offspring generation. In contrast, in the spouse control group, 138 (38.3%) were from the proband generation and 222 (61.7%) were from the offspring generation. The final sample of 1510 LLFS family members represented 533 families. Age distributions are displayed in Table 2.

Demographic variables and cognitive scores were compared across spouse controls and family members, within the proband and offspring generations separately (Table 3). Probands were older than spouse controls, achieved lower scores on 6 of 8 cognitive tests in unadjusted analyses, and were less frequently female than members of the spouse control group (41.4% vs 78.3%, respectively). It should also be noted that probands were older than their siblings in a sex-adjusted analysis ($F_{1,914} = 146.366; P < .001$). First-degree relatives in the offspring generation were more frequently female than members of the spouse control group (65.6% vs 34.7%, respectively) and outperformed controls on 7 of 8 cognitive tests in unadjusted analyses.

Diagnostic Algorithm
The optimal algorithm for distinguishing between individuals clinically diagnosed as having probable AD and healthy controls in the NACC database included sex and performance on delayed logical memory, orientation to time and place, animal fluency, and digit symbol tests. See the eTable and eAppendix in the Supplement for a description of the algorithm development and validation. Neither age nor education, though significant predictors of case status, improved the area under the curve. The algorithm for determining an individual’s odds ratio (OR) [ie, log $P/(1 – P)$] was the following: $21.912 – (sex × .725) – (delayed memory × .541) − (orientation × 1.415) − (animal fluency × .146) – (digit symbol × .077). Sex was coded as male = 0 and female = 1. An individual’s score based on this algorithm was then entered into the following formula to determine the probability of that person being a case: $1/[1 + exp (−algorithm score)]$. Individuals with scores greater than or equal to 0.428660, the value that yielded the optimal balance between sensitivity (0.962) and specificity (0.982), were labeled as cases. The cognitive algorithm classified 546 individuals (38.5%) as having cognitive impairment consistent with AD.

Frequency of Cognitive Impairment in Families vs Controls
Age-, education-, and study site–adjusted generalized estimating equation models predicting cognitive impairment (based on the algorithm) as a function of family status (relative vs spouse control) were conducted separately in the proband and offspring generations. In the proband generation, the age distributions of relatives vs spouse controls did not overlap at the oldest ages (>95 years), where there were only a few spouse controls. To provide a comparison between comparatively aged elders, we restricted the analysis of the proband generation to individuals between ages 80 and 95 years. Thus, relatives and spouse controls were stratified by 2 age groups: 80 to 95 years (proband generation) and 65 to 79 years (offspring generation). In the proband generation, compared with similarly aged spouse controls, LLFS probands had a slightly but not statistically significantly reduced risk of cognitive impair-
ment (OR = 0.7; 95% CI, 0.4-1.4) (Table 4). Examination of the probands’ siblings eliminated this trend (OR = 1.1; 95% CI, 0.7-1.7). In contrast, LLFS sons and daughters had a clearly reduced risk of cognitive impairment compared with similarly aged spouse controls (OR = 0.4; 95% CI, 0.2-0.9), but risk in nieces and nephews in the offspring generation did not differ from that in spouse controls (OR = 0.8; 95% CI, 0.4-1.4).

Not all families had spouse controls available. We restricted the analysis to families with spouse controls and used conditional logistic regression (conditioning on family membership), and we found comparable results. The likelihood of cognitive impairment for sons and daughters compared with spouse controls was 0.3 (95% CI, 0.1-0.7), while the likelihood of cognitive impairment for probands compared with spouse controls was 0.8 (95% CI, 0.4-1.8). As in the initial analysis, the likelihood of dementia for nieces and nephews or siblings of the probands did not differ from their spouse control groups (Table 5).

We estimated dementia-free survival by 5-year age groups in LLFS family members vs controls using data from both the offspring and proband generations. As shown in the Figure, a higher proportion of LLFS family members than controls were dementia free until age 90 years. After age 95 years, however, LLFS probands had a high prevalence of dementia.

Discussion

The familial aggregation of specific exceptional longevity has not been well established. In particular, it is not known to what extent long-lived families are free of dementia or cognitive impairment characteristic of AD. Approximately 5.4 million Americans are estimated to have AD, with 5.2 million of these older than 65 years. An estimated 13% of people aged 65 years or older have AD, with prevalence rates that increase steadily in older age groups.24

Preservation of cognitive function may be important in longevity, and preservation is at least in part inherited. Elderly individuals with cognitive impairment have an increased risk of death even after adjustment for a variety of health conditions, lifestyle factors, and sociodemographic characteristics.25-34 In studies of twins and families, genetic influences on cognitive function are found to be substantial and to continue into old age.35-41 Population-based twin studies in Denmark and Sweden of late-life physical and cognitive functioning demonstrate that genetic factors account for approximately 20% to 30% of variability in life span,42-43 and genetic factors may become increasingly important at the oldest ages.44 Several genotypes have been associated with higher levels of global cognition in oldest-old persons. The cholesteryl ester transfer protein gene (CETP) codon 405 isoleucine to valine variant (CETP VV) has been found to protect against age-related cognitive decline and to lower risk for dementia,45,46 although a recent study did not support this finding47 and another suggested that the effects of the gene may be modified by APOE e4 carrier status.48

Offspring of parents with exceptional longevity have been shown to have a lower rate of incident dementia and slower rates of memory decline than offspring of parents with typical survival rates.49 These results are consistent with previously published findings from the current study demonstrating that scores on select cognitive tests were higher on average in the LLFS offspring generation than in spouse controls.50 Several lines of evidence thus suggest that being part of a long-lived family offers some protection against cognitive decline, but the extent to which individuals remain relatively protected against dementia throughout life is unclear.

Table 5. Conditional Likelihood of Cognitive Impairment in Long-Lived Individuals and Their Relatives vs Spouse Controls, Adjusted for Age, Education, and Study Site

<table>
<thead>
<tr>
<th>Group</th>
<th>At Risk, No.</th>
<th>Affected, No. (%)</th>
<th>Age of Cases, Mean (SD)</th>
<th>AOR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 65-79 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sons and daughters</td>
<td>109</td>
<td>6 (5.5)</td>
<td>69.6 (3.6)</td>
<td>0.3 (0.1-0.7)</td>
</tr>
<tr>
<td>Nieces and nephews in offspring generation</td>
<td>224</td>
<td>30 (13.4)</td>
<td>71.4 (4.6)</td>
<td>1.5 (0.8-2.9)</td>
</tr>
<tr>
<td>Spouse controls</td>
<td>216</td>
<td>28 (13.0)</td>
<td>71.7 (4.5)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Aged 80-95 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proband</td>
<td>94</td>
<td>49 (52.2)</td>
<td>91.9 (2.4)</td>
<td>0.8 (0.4-1.8)</td>
</tr>
<tr>
<td>Siblings in proband generation</td>
<td>249</td>
<td>120 (48.2)</td>
<td>89.2 (4.2)</td>
<td>1.1 (0.7-1.8)</td>
</tr>
<tr>
<td>Spouse controls</td>
<td>103</td>
<td>45 (43.7)</td>
<td>86.9 (3.8)</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

Abbreviation: AOR, adjusted odds ratio.
* Adjusted for age, education, and study site.
This study investigated the extent to which individuals selected from long-lived families were protected against cognitive impairment characteristic of AD. The presence of cognitive impairment was classified by applying cognitively driven research criteria, validated against data from the NACC. We hypothesized that being a member of a long-lived family would confer greater protection against cognitive impairment than being a spouse control.

Table 4 displays the proportion of individuals who met criteria for cognitive impairment consistent with AD within each generation and as a function of their relationship to the proband. Criteria were met by 52.2% of probands vs 43.7% of their spouse controls, whereas they were met by 5.5% of sons and daughters vs 13.0% of their spouse controls. Based on our cognitive algorithm, only sons and daughters of probands had significantly lower rates of cognitive impairment than similarly aged spouse controls. The beneficial effect of membership in a long-lived family was attenuated (and no longer significant) in second-degree relatives (nieces and nephews). Moreover, family members and spouse controls in the proband generation demonstrated comparable overall rates of cognitive impairment. One of every 2 members of the proband generation in exceptionally long-lived families met our criteria for cognitive impairment.

The high prevalence of cognitive impairment found in the proband generation falls within the upper range of dementia estimates for similarly aged individuals who were not selected for familial longevity and is comparable to the rates of dementia seen in the East Boston study, which estimated the prevalence of AD among 3623 elders in a white, urban, working-class community.50 It should again be emphasized that the current study did not include assessment of cognitively mediated daily functioning (eg, instrumental activities of daily living such as balancing a checkbook) and therefore does not speak directly to rates of dementia in the LLFS sample. Nevertheless, the cognitive algorithm demonstrated 96% sensitivity and 98% specificity with regard to clinical diagnoses of AD in the NACC sample, increasing our confidence that characterizing LLFS subjects along these lines approximates clinical dementia diagnoses. Moreover, most of those who were labeled as cases by the cognitive algorithm in the NACC and had autopsy data demonstrated AD pathology or another pathological diagnosis (87.3%; eAppendix in the Supplement). Conversely, most of those who were not labeled as cases by the algorithm demonstrated normal to low levels of pathology on autopsy (75.8%). The sensitivity and specificity of the algorithm varied depending on how conservatively the pathological gold standard was defined and demonstrated an optimal trade-off of sensitivity and specificity when discriminating between any pathological diagnosis vs normal or low levels of AD pathology insufficient for a diagnosis.

Numerous studies in the past 2 decades have produced variable dementia rates for individuals older than 85, 90, and 95 years and among centenarians.38 Yaffe et al39 recently reported the prevalence of dementia in 1299 women aged 85 years and older to be 17.8%, whereas other reports in this age group have been as high as 50%.30,37 Yaffe and colleagues suggest that the relatively low figure may reflect their consideration of mild cognitive impairment (23%) as separate from dementia, whereas other studies may collapse these groups. When limited to individuals aged 90 years and older, dementia rates have been reported to be 45% in women and 28% in men.53 Once individuals are aged 95 years and older, rates range from as low as 40% to as high as 74%.7,55 Heeren et al44 reported that 23% of all individuals older than 85 years met criteria for dementia, as compared with 32% of those aged 90 to 94 years and 41% of those aged 95 years and older. Certainly, participant selection and the nature of the diagnosis are highly influential on prevalence rates and are likely to account for the large discrepancies within various age groups.

In contrast to the findings within the proband generation, cognitive impairment was less frequent in sons and daughters of long-lived family members (5.5%) than in their age-matched spouse controls (13.0%), although the protective effect of familial longevity did not extend to second-degree relatives in the offspring generation including nieces and nephews (11.3%). This difference between first- and second-degree offspring may in part reflect the fact that probands were older than their siblings, thus their children have a greater chance of receiving longevity genes than children of the probands’ younger siblings who may or may not reach extreme old age. The age difference between probands and their siblings reflects the fact that probands could be sampled only if they had at least 1 living sibling, and this increases the chance that younger siblings would be sampled rather than older siblings.

Overall, our results appear to be consistent with a delayed onset of disease in long-lived families, such that individuals who are part of exceptionally long-lived families are protected earlier but not later in life (Figure).59 This hypothesis needs to be tested in cohort studies that can examine incident dementia.

Limitations of this study included a lack of data on cognitively mediated daily functioning to determine the integrity of everyday independence and activities of daily living and thus the true prevalence of dementia in our sample. However, the algorithm used to identify cognitive impairment characteristic of AD demonstrated very high levels of sensitivity and specificity in distinguishing between individuals with probable AD and healthy controls who underwent clinical and functional assessments through the NACC. Moreover, the algorithm demonstrated high sensitivity and specificity against pathological diagnoses of dementia. Second, our study had limited availability of age-matched spouse controls in the proband generation. Although the age distributions of family members and controls were largely overlapping, 50% of family members were older than 91 years, whereas 75% of controls were younger than 85 years. This limited our ability to make comprehensive comparisons at each age range across the 2 groups. Third, our study was limited by lack of follow-up to assess dementia incidence. Fourth, the spouse control groups do not necessarily exclude individuals from long-lived families because family history was not obtained and Family Longevity Selection Scores were not calculated for spouse controls. The presence of a long-life genotype in spouse controls would tend...
to lead to an underestimate of the difference between family members and controls and would tend to attenuate the relative risk. Therefore, our analyses may underestimate the reduction in dementia risk among sons and daughters of long-lived probands. A final issue is that only individuals with valid cognitive testing were included in the analyses. These individuals were younger than those with invalid testing in the proband generation and were therefore less likely to have cognitive deficits, leading to a possible underestimate of dementia in this sample in general.

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