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Exceptional Parental Longevity Associated with Reduced Risk of Alzheimer's Disease and Memory Decline

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Abstract

Objectives—To determine whether offspring of parents with exceptional longevity (OPEL) have a lower rate of dementia than offspring of parents with usual survival (OPUS).

Design—Community based prospective cohort study.

Setting—Bronx, New York

Participants—A volunteer sample of 424 non-demented, community residing older adults (age 75–85) recruited from Bronx County starting in 1980 and followed for up to 23 years.

Measurements—Epidemiologic, clinical and neuropsychological assessments were completed every 12 to 18 months. OPEL were defined as having at least one parent who reached the age of at least 85 years. OPUS were those for whom neither parent reached the age of 85 years. Dementia was diagnosed by case conference consensus based on DSM-III-R criteria without access to information on parental longevity. Alzheimer's disease was diagnosed using established criteria.

Results—Of 424 subjects, 149 (35%) were OPEL and 275 (65%) were OPUS. Mean age at entry for both groups was 79. In comparison with OPUS, the OPEL group had a reduced incidence of

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Alzheimer's disease (HR 0.57; 95% CI: 0.35 – 0.93). After adjusting for sex, education, race, hypertension, myocardial infarction, diabetes and stroke results were essentially unchanged. OPEL also had a significantly reduced rate of memory decline on the Selective Reminding Test (SRT) in comparison with the OPUS group ($p=0.034$).

Conclusion—OPEL develop dementia and Alzheimer's disease at a significantly lower rate than OPUS. This result is not explained by demographic or medical confounders. Factors associated with longevity may protect against dementia and Alzheimer's Disease.

Keywords

Memory decline; dementia; parental longevity; Alzheimer's disease

INTRODUCTION

Many elderly individuals age successfully, living in relatively good health, with little or no cognitive decline even in the tenth decade of life.¹ This profile of healthy aging runs in families: offspring of parents with exceptional longevity (OPEL) are more likely to be long-lived themselves and to have a reduced risk of death due to cancer and cardiovascular disease.² They also have favorable lipid profiles^{3,4} as well as a lower prevalence of hypertension, diabetes mellitus, heart attacks, and strokes.⁵ Family and twin studies have shown that genetics partially determine exceptional longevity.^{6–8} These results are also supported by basic science and animal studies.⁸

Studies examining the relationship of parental longevity to cognitive aging and dementia are rare and they generally use cross-sectional or retrospective designs. In addition, definitions of exceptional parental longevity have varied.⁷ Most prior studies have measured cognition using tests of mental status and self-reported memory complaints rather than detailed neuropsychological evaluations of specific cognitive domains.⁷ Longitudinal studies of OPEL and offspring of parents with usual survival (OPUS) using rigorous neuropsychological assessments are needed to clarify the influence of parental longevity on cognitive decline.

The Bronx Aging Study provides the opportunity to apply this approach. The study enrolled community residing subjects aged 75–85 from 1980 to 1983, and followed them for up to 23 years with annual clinical and neuropsychological assessments.⁹ The study included information on parental age at death, and extensive annual neuropsychological and neurological evaluations to determine memory decline and the incidence of dementia during follow-up. Herein, we use data from the Bronx Aging Study to test the hypothesis that parental longevity protects against memory decline and the onset of dementia.

METHODS

Study Population

The study design and recruitment methods for the Bronx Aging Study have been described previously.⁹ Briefly, English-speaking, community-residing volunteers between the ages of 75 and 85 years were enrolled. Exclusion criteria included previous diagnoses of dementia, idiopathic Parkinson's disease, liver disease, alcoholism, or known terminal illness, as well as visual or hearing impairment severe enough to interfere with completion of neuropsychological tests. The inception cohort had a median of eight years of education, was largely Caucasian (91 percent), and mostly female (64 percent). In order to rule out dementia, at baseline subjects were required to have a score of eight or less on the Blessed Information-Memory-Concentration (BIMC) test (range 0–32 with 0 indicating optimal

performance, 32 indicating worst performance).^{9–11} This test has high test-retest reliability (0.86) and its results correlate well with the pathological stages of Alzheimer's disease.^{9–11}

Subjects had follow-up visits every 12 to 18 months. Visits included medical histories, neurologic assessment and neuropsychological evaluations. Structured questionnaires were used to ascertain self-reported medical illnesses, medication use, and demographic data. Functional status was assessed with the subscale for activities of daily living from the Lawton Brody Scale.¹² Whenever possible, a close friend or family member was also interviewed by a study clinician in order to confirm the history and assess functional status. A total of 488 subjects were enrolled between 1980 and 1983. For the present analysis, we excluded 64 subjects: 17 who did not return after baseline and 47 for whom we could not ascertain information on the parental ages at death. The remaining 424 subjects (86.9 %) were included in the present study. Written informed consent was obtained at enrollment. The Albert Einstein College of Medicine Institutional Review Board approved the protocol.

Parental Longevity and Classification of Offspring

Study participants were asked whether each of their biological parents were still living. We ascertained the current age for each living parent, or the age at death for deceased parents. All of the subjects' fathers and all but two of their mothers had died by the time of enrollment. For the two living mothers at baseline, age at death was subsequently ascertained and used to define OPEL and OPUS status.

Subjects were divided into two groups based on parental longevity. OPEL had at least one parent who lived 85 years or longer. OPUS were persons who reported that neither parent lived beyond age 84 years. This cut-off age for "exceptional parental longevity" was selected based on the life expectancy around the time the parents were born. Given that the study cohort was born between 1896 and 1908, their parents were in general born prior to 1880. Parental survival to age 85 represents about a 40 year increase over the average life expectancy for a cohort born in 1900 (47.3 years)¹³, and is approximately the 75th percentile of the distribution of oldest parental age at death for the cohort (Mean 78.6, median 80, standard deviation 12.0, upper quartile was 86.5 years).

Although death was attributed to unnatural causes (e.g., accidents) in 25 parents, we treated age at death similarly for natural and unnatural causes. This has the potential effect of including some individuals who might be biologically OPEL in the OPUS group. We consider the implications of this potential misclassification on the interpretation of study results in the discussion.

Neuropsychological Evaluation

A neuropsychological battery was administered at each study visit.^{9,14} Tests included the Blessed Information Memory and Concentration Test (BIMC)¹⁰ and estimates of verbal (VIQ) and performance (PIQ) intelligence quotients according to the Wechsler Adult Intelligence Scale (WAIS), among others.^{9,15} The Selective Reminding Test (SRT)¹⁶ was added to the study in 1982, and was administered at annual visits thereafter. Selective Reminding is a verbal list-learning and free-recall procedure conducted over multiple trials, with selective presentation on each recall trial of only those items not recalled on the immediately preceding trial. Twelve unrelated words were presented at the initial trial, followed by five additional trials involving selective reminding. The sum of words successfully recalled over the course of all six trials (range 0–72) was used as the measure of memory performance. This measure was selected because it has been shown to be sensitive to early changes in memory and for the prediction of future dementia.^{17, 18}

Diagnosis of Dementia

At each follow-up visit, subjects with possible cognitive decline underwent a diagnostic work-up. Possible cognitive decline was defined on the basis of worsening scores on the BIMC¹⁰ (a decline of four points or more, or to a total of more than seven errors), a pattern of worsening scores on neuropsychological tests, or reports of cognitive decline from friends, relatives or study staff. When dementia was suspected, the workup included computed tomographic (CT) scanning and blood tests (complete blood count, routine chemical screen, liver and thyroid function tests, measurement of vitamin B₁₂ and folate levels, and serologic testing for syphilis).⁹ A diagnosis of dementia was assigned at consensus case conferences. In our initial case conferences the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (DSM-III) or, after 1986, the revised third edition (DSM-III-R) were followed.^{19–21} Because updated criteria for the diagnosis of dementia and particular types of dementia were introduced after the study began²⁰, the entire sample was re-conferenced in 2001 to ensure uniformity of diagnosis. Thereafter, the updated criteria were applied on an ongoing basis in case conferences. The re-conferencing procedure involved a neurologist and a neuropsychologist who had not participated in the original diagnostic conferences.²¹ Dementia was diagnosed according to the DSM-III-R criteria.²⁰ Disagreement between raters was resolved by a second neurologist, blinded to the original diagnosis. Dementia subtype was assigned according to the criteria for probable or possible Alzheimer's disease published by the National Institutes of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association²², the criteria for probable, possible, or mixed vascular dementia published by the Alzheimer's Disease Research Centers of California,²³ and dementia with Lewy bodies according to the 1999 revised consensus criteria for probable or possible disease.²⁴

Data Analysis

Baseline characteristics were compared using descriptive statistics, applying non-parametric tests as appropriate to contrast subjects based on parental longevity (OPEL vs. OPUS) and dementia status at follow-up. Separate Cox proportional hazards models were used to evaluate the association of parental longevity with risk of developing any dementia and specifically Alzheimer's disease. Unadjusted analyses as well as those adjusted for demographic variables (sex, ethnicity and education), medical comorbidities, smoking and lipid profiles are reported. In the Cox model, age was used as the time-scale. Therefore, the hazard function can be interpreted as the age-specific incidence function for dementia. Including age as a non-parametric term in this way provides a more flexible and effective control of age than the widely used alternative which treats age as a covariate and uses follow-up time as the time scale.²⁵ Proportional hazards assumptions of the models were examined analytically and graphically and were adequately met. To examine whether vascular risk index or dyslipidemia mediate the effect of OPEL on the risk of dementia, the coefficients of OPEL status in the Cox model with and without adjusting for the mediator were compared using the method of Lin et al. 1997.²⁶ The effect of parental longevity on memory decline on the SRT was examined using linear mixed effects model with random intercept and random slope, adjusting for gender, race/ethnicity and education. The 'linear age' term in the model was centered at age 85 and represents the average linear trend of decline in memory over time in the OPUS group. The interaction term between 'OPEL' and 'linear age' represents the difference in the linear rate of memory decline between OPEL and OPUS.

RESULTS

Demographic Characteristics

Among the 424 individuals in the analysis, 149 (35.1%) were OPEL and 275 (64.9%) were OPUS (Table 1). OPEL and OPUS subjects had similar mean ages at enrollment (about 79) and did not differ in distribution by gender, race or education. OPEL were less likely to have hypertension or diabetes. OPUS were more likely to have history of cardiac disease and had slightly higher triglycerides and LDL cholesterol levels although the differences were not statistically significant (Table 1). Baseline cognitive status was also similar in the two groups (Table 1).

Dementia and Alzheimer's Disease as Outcomes Measures

During 2680 person-years of follow-up (mean follow-up, 6 years; range: 1 – 23) dementia developed in 113 subjects (Alzheimer's disease in 80; vascular, mixed, or other dementia in 33). Subjects who developed dementia were slightly older at baseline (Table 2). Though cognitive performance was in the normal range at baseline for all subjects, those who later developed dementia had higher baseline BIMC scores (reflecting greater cognitive impairment) and reduced performance on a variety of baseline neuropsychological tests (Table 2).

The OPEL group had a reduced lifetime risk of any dementia as compared to the OPUS group and a significantly delayed onset of dementia (Figure 1). We modeled the onset of dementia and Alzheimer's disease separately using Cox proportional hazards models (Table 3). The hazard ratio (HR) for OPEL versus OPUS for any dementia was 0.64 (95% confidence interval (CI): 0.43 – 0.97), indicating that OPEL were 36% less likely than the OPUS group to develop dementia. Additional models adjusted for gender, education and race/ethnicity (Model 2), and for self-reported history of hypertension, myocardial infarction, diabetes and stroke (Model 3). In order to reduce the number of terms in the model, we also treated the comorbidities listed in model 3 as a vascular risk index, defined as the sum of the number of conditions present (Model 4). In each case, the magnitude of the risk reduction remained similar in the adjusted models though the upper bound of the 95% CI included one. Further adjustment for ever smoking and dyslipidemia (LDL cholesterol > 130, or HDL < 40 mg/dl) also did not change the parameter estimates, and the effects of the additional covariates were non-significant (Model 5).

OPEL had a reduced risk for Alzheimer's disease (Model 1, Table 3). The estimated hazard ratio remained essentially unchanged and significant after adjusting for gender, race and educational level (Model 2), or after additional adjustment for hypertension, myocardial infarction, diabetes and stroke (Model 3). The effect of OPEL remained significant and the parameter estimate increased minimally after adjustment for the vascular comorbidity index (Model 4), or the vascular index plus smoking and dyslipidemia (Model 5).

Effects on Memory

We examined performance on the Selective Reminding Test (SRT) in a mixed effects model which included gender, education, race and age as covariates, and OPUS versus OPEL status as the independent variable. These results, depicted graphically in Figure 2, demonstrate that among OPEL memory declined more slowly as a function of age than it did in the OPUS group. The rate of decline with age was reduced by 30% in the OPEL group ($p=0.034$).

DISCUSSION

This longitudinal study shows that exceptional parental longevity is associated with a reduced risk of dementia, particularly for Alzheimer's disease. We defined exceptional parental longevity as having at least one parent reach the age of 85. Using this definition, among OPEL, the rate of dementia was reduced by 30 percent, and the rate of Alzheimer's disease was reduced by more than 40 percent compared to the OPUS. We also found that exceptional parental longevity was associated with a significant reduction in the rate of memory decline with age. Thus, having exceptionally long-lived parents protects against dementia, Alzheimer's disease, and memory decline.

For Alzheimer's disease, the association remained significant after adjusting for demographic variables, and after adjustment for history of myocardial infarction, hypertension, diabetes and stroke (Models 3, 4). The association of OPEL with AD was no longer significant after additional adjustment for smoking and dyslipidemia although the magnitude of the hazard ratio was unchanged (p-value for testing the difference between the OPEL effects in models 4 and 5 is 0.889.²⁶ Similarly, the association of parental longevity with the risk of dementia lost statistical significance in adjusted models, though the magnitude of the hazard ratios remained similar. In the model which included adjustment for smoking and dyslipidemia, 49 subjects were lost, including 15 with incident dementia, due to missing data on these additional covariates. Thus, reduced power may explain the loss of significance.

OPEL have been reported to have reduced risk of cardiovascular disease, hypertension, diabetes mellitus, and dyslipidemia^{27–29}. These cardiovascular factors are also risk factors for dementia and Alzheimer's disease,³⁰ thus their reduced prevalence in OPEL could contribute to the reduced rate of Alzheimer's disease and of memory decline. This conceptual model suggests that cardiovascular disease or vascular risk factors mediate the relation of parental longevity to dementia. In the current study, OPUS had slightly less favorable lipid levels, and were more likely to report diabetes and hypertension. However, adjustment for these cardiovascular risk factors only slightly attenuated the magnitude of the protective effect of exceptional parental longevity (p-value for testing the difference is 0.455). We therefore conclude that differences in cardiovascular risk profiles are not likely to be the sole explanation for these findings.

Other factors associated with parental longevity and a reduced risk of dementia may tend to aggregate within families. We adjusted for education but do not have data on personality type, diet and other habits which might contribute to this association. Finally, it is possible that a survivorship bias may be muting the effects of these risk factors on the association. All members of the cohort had survived to age 79 at baseline. Thus, individuals most susceptible to the impact of vascular risk and those with the highest risk burden may have died at younger ages and been excluded from the cohort.

Because exceptional parental longevity is partially under genetic control, genetic factors could contribute to our findings. For example, carrying an apolipoprotein ε4 allele (ApoE ε4) is a well established risk factor for declining cognitive function, incident AD and clinical dementia.^{31, 32} Several studies have shown that the relative frequency of the ApoE ε4 allele is reduced in cohorts consisting of older individuals^{33, 34} and among the children of long-lived parents.³⁵ Thus, a reduced frequency of ApoE ε4 alleles could contribute to the protective effect of exceptional parental longevity. We were not able to examine this in this population, as DNA samples were not available for the majority of the cohort.

A polymorphism in the gene for Cholesteryl Ester Transfer Protein (CETP) has been associated with both longevity and a reduced risk of cognitive decline.^{36–41} Several loss of

function polymorphisms of this gene have been associated with high HDL levels and a large lipoprotein particle size distribution, which may contribute to its effects on both longevity and cognition, though results vary among studies.^{3, 36–41} In prior work in independent samples, we found that subjects with exceptional longevity and their offspring had larger HDL cholesterol particle sizes, which were associated with a lower prevalence of hypertension, cardiovascular disease, and the metabolic syndrome.^{3, 28} As noted above, we do not have banked specimens for this population and therefore cannot assess CETP genotype or lipoprotein particle size. In an independent sample, we found that carriers of the CETP405V variant had reduced risk of memory decline as well as incident AD and all-cause dementia.⁴²

In addition to the issues mentioned above, our study has several other limitations. Our subjects were community-residing volunteers from the Bronx, over the age of 75. Results need to be replicated and extended to systematically recruited representative samples. Although standard criteria and well-established procedures were used to make the diagnoses of dementia and Alzheimer's disease, some misclassification is inevitable. Additionally, attrition is a concern in any longitudinal study, though we had good follow-up over a long observational period, reducing the potential influence of selective attrition. The definition of exceptional parental longevity is based on reports from participants. However, others have reported that recall of parental age of death has been shown to be accurate, with 80% correctly reported within one year.⁴³ There were 25 subjects in the OPUS group whose parents died from unnatural causes, leading to potential misclassification. Analyses excluding these 25 individuals did not alter the magnitude of the HR for dementia and Alzheimer's disease. Finally, the definition of exceptional parental longevity is somewhat arbitrary. Thus, we performed sensitivity analyses using 90 as the definition for the OPEL group and the HR remained unchanged. Additional analyses using mixed models and various definitions of OPEL (e.g., at least one parent survived to age 80, 90, 95) consistently showed that OPEL have lower rates of memory decline.

In this sample, exceptional parental longevity was associated with a reduced risk of developing any dementia and Alzheimer's disease. The reduction in risk was seen both when we divided the cohort into two groups based upon a cutoff of parental age at death of 85, as well as when treated parental age at death as a continuous variable. Further research is warranted to replicate our results and to extend our understanding of the biological or genetic associations underlying decreased risk of dementia in offspring of parents with exceptional longevity.

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References

1. Perls T. Dementia-free centenarians. *Exp Gerontol*. 2004; 39:1587–1593. [PubMed: 15582273]
2. Terry DF, Wilcox M, McCormick MA, et al. Lower all-cause, cardiovascular, and cancer mortality in centenarians' offspring. *J Am Geriatr Soc*. 2004; 52:2074–2076. [PubMed: 15571545]
3. Atzmon G, Rincon M, Rabizadeh P, et al. Biological evidence for inheritance of exceptional longevity. *Mech Ageing Dev*. 2005; 126:341–345. [PubMed: 15621216]
4. Terry DF, Wilcox MA, McCormick MA, et al. Cardiovascular disease delay in centenarian offspring. *J Gerontol A Biol Sci Med Sci*. 2004; 59:385–389. [PubMed: 15071083]

5. Atzmon G, Schechter C, Greiner W, et al. Clinical phenotype of families with longevity. *J Am Geriatr Soc.* 2004; 52:274–277. [PubMed: 14728640]
6. Karasik D, Demissie S, Cupples LA, et al. Disentangling the genetic determinants of human aging: Biological age as an alternative to other survival measures. *J Gerontol A Biol Sci Med Sci.* 2005; 60:574–587. [PubMed: 15972604]
7. Payami H, Montee K, Kaye J. Evidence for familial factors that protect against dementia and outweigh the effect of increasing age. *Am J Hum Genet.* 1994; 54:650–657. [PubMed: 8128962]
8. Vijg J, Suh Y. Genetics of longevity and aging. *Annu Review Med.* 2005; 56:193–212.
9. Katzman R, Aronson M, Fuld P, et al. Development of dementing illnesses in an 80-year-old volunteer cohort. *Ann Neurol.* 1989; 25:317–324. [PubMed: 2712531]
10. Blessed G, Tomlinson E, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry.* 1968; 114:797–811. [PubMed: 5662937]
11. Grober E, Dickson D, Sliwinski MJ, et al. Memory and mental status correlates of modified Braak staging. *Neurobiol Aging.* 1999; 20:573–579. [PubMed: 10674422]
12. Lawton MP, Brody E. Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist.* 1969; 9:179–186. [PubMed: 5349366]
13. Arias, E. National Vital Statistics Reports (NVSS); United States Life Tables, 2002. Vol. 53. Centers for Disease Control and Prevention; 2004.
14. Hall CB, Ying J, Kuo L, et al. Estimation of bivariate measurements having different change points, with application to cognitive ageing. *Stat Med.* 2001; 20:3695–3714. [PubMed: 11782027]
15. Masur D, Sliwinski M, Lipton RB, et al. Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. *Neurology.* 1994; 44:1427–1431. [PubMed: 8058143]
16. Buschke H. Selective reminding for analysis of memory and learning. *J Verbal Learning and Verbal Behavior.* 1973; 12:543–550.
17. Masur DM, Fuld PA, Blau AD, et al. Distinguishing normal and demented elderly with the Selective Reminding Test. *J Clin Exp Neuropsychol.* 1989; 11:615–630. [PubMed: 2808653]
18. Masur DM, Fuld PA, Blau AD, et al. Predicting development of dementia in the elderly with the Selective Reminding Test. *J Clin Exp Neuropsychol.* 1990; 12:529–538. [PubMed: 2211975]
19. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington DC: American Psychiatric Association; 1980.
20. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3. Washington DC: American Psychiatric Association; 1987.
21. Verghese J, Lipton RB, Hall CB, et al. Abnormality of gait as a predictor of Non-Alzheimer's dementia. *New Engl J Med.* 2002; 347:1760–1767.
22. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* 1984; 34:939–944. [PubMed: 6610841]
23. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular disease proposed by the State of California Alzheimer's disease Diagnostic and Treatment Centers. *Neurology.* 1992; 42:473–480. [PubMed: 1549205]
24. McKeith IG, Perry EK, Perry RH. Report of the second Dementia with Lewy Body International Workshop: diagnosis and treatment. *Neurology.* 1999; 53:902–905. [PubMed: 10496243]
25. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med.* 2004; 23:3803–3820. [PubMed: 15580597]
26. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. *Statistics in Medicine.* 1997; 16:1515–1527. [PubMed: 9249922]
27. Perls TT, Wilmoth J, Levenson R, et al. Life-long sustained mortality advantage of siblings of centenarians. *Proc Natl Acad Sci USA.* 2002; 99:8442–8447. [PubMed: 12060785]
28. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA.* 2003; 290:2030–2040. [PubMed: 14559957]

29. Zureik M, Galan P, Bertrais S, et al. Parental longevity and 7-year changes in blood pressures in adult offspring. *Hypertension*. 2005; 46:287–294. [PubMed: 15983237]
30. Launer LJ. Demonstrating the case that AD is a vascular disease: Epidemiologic evidence. *Ageing Res Rev*. 2002; 1:61–77. [PubMed: 12039449]
31. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to β -amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer's disease. *Proc Natl Acad Sci USA*. 1993; 90:1977–1981. [PubMed: 8446617]
32. Feskens EJM, Havekes LM, Kalmijn S, et al. Apolipoprotein e4 allele and cognitive decline in elderly men. *BMJ*. 1994; 309:1202–1206. [PubMed: 7987151]
33. Tivlis RS, Strandberg TE, Juva K. Apolipoprotein E phenotypes, dementia and mortality in a prospective population sample. *J Am Geriatr Soc*. 1998; 46:712–715. [PubMed: 9625186]
34. Schachter F, Faure-Delanef L, Guenot F, et al. Genetic associations with human longevity at the APOE and ACE loci. *Nat Genet*. 1994; 6:29–32. [PubMed: 8136829]
35. Reed T, Carmelli D, Robinson TS, et al. More favorable midlife cardiovascular risk factor levels in male twins and mortality after 25 years of follow-up is related to longevity of their parents. *J Gerontol A Biol Sci Med Sci*. 2003; 58:367–371. [PubMed: 12663700]
36. Luoma PV. Gene activation, apolipoprotein a-I/high density lipoprotein, atherosclerosis prevention and longevity. *Pharmacol Toxicol*. 1997; 81:57–64. [PubMed: 9298501]
37. Burke GL, Arnold AM, Bild DE. Factors associate with healthy aging: the cardiovascular health study. *J Am Geriatr Soc*. 2001; 49:254–262. [PubMed: 11300235]
38. Merched A, Xia Y, Visvikis S, et al. Decreased high-density lipoprotein cholesterol and serum apolipoprotein A-I concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiol Aging*. 2000; 21:27–30. [PubMed: 10794845]
39. Atzmon G, Gabriely I, Greiner W, et al. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. *J Gerontol A Biol Sci Med Sci*. 2002; 57:712–715.
40. Barzilai N, Atzmon G, Derby CA, et al. A genotype of exceptional longevity is associated with preservation of cognitive function. *Neurology*. 2006; 67:2170–2175. [PubMed: 17190939]
41. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. *JAMA*. 2003; 290:2030–2040. [PubMed: 14559957]
42. Sanders AE, Wang C, Katz M, et al. Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia. *JAMA*. 2010; 303:150–158. [PubMed: 20068209]
43. Barraclough BM, Bunch J. Accuracy of dating parent deaths: Recollected dates compared with death certificate dates. *Brit J Psychiat*. 1973; 123:573–574.

Figure 1.
Survival plots for dementia by OPEL/OPUS
OPUS – Offspring of parents with usual survival
OPEL – Offspring of parents with exceptional longevity

Figure 2.

Expected values for the Selective Reminding Test (SRT) by OPEL/OPUS status

SRT – Selective Reminding Test (range 0–72, unimpaired > 26)

OPUS – Offspring of parents with usual survival

OPEL – Offspring of parents with exceptional longevity

Table 1

Baseline Demographic and Health Characteristics of Offspring of Parents with Usual Survival (OPUS) and Offspring of Parents with Exceptional Longevity (OPEL).

Variable	OPUS (N=275)	OPEL (N=149)	P-value *
Demographics			
Age, years (Mean $\pm$ SD)	79.0 $\pm$ 3.0	79.4 $\pm$ 3.2	0.21
Female, N (%)	184 (67%)	86 (59%)	0.06
Caucasian, N (%)	247 (90%)	139 (93%)	0.23
Education $\geq$ High School, N (%)	135 (48%)	79 (53%)	0.33
Co-Morbidities, N (%)			
Hypertension	154 (56%)	60 (40%)	0.002
Cardiac Disease	41 (15%)	16 (11%)	0.30
Stroke	19 (7%)	12 (8%)	0.58
Diabetes	36 (13%)	10 (7%)	0.04
Thyroid Disease	33 (12%)	19 (13%)	0.78
Ever Smoked	127 (46%)	79 (53%)	0.16
Lipid Profile, Mean $\pm$ SD			
Triglycerides (mmol/L)	1.62 $\pm$ 1.02	1.53 $\pm$ 0.78	0.86
HDL (mmol/L)	1.17 $\pm$ 0.34	1.17 $\pm$ 0.39	0.69
LDL (mmol/L)	3.91 $\pm$ 1.19	3.70 $\pm$ 0.96	0.09
Neuropsychological Tests, (Normal Range), Mean $\pm$ SD			
BIMC (0–4)	2.4 $\pm$ 2.1	2.4 $\pm$ 2.1	0.64
WAIS-PIQ (85–115)	103.1 $\pm$ 12.4	105.0 $\pm$ 13.1	0.16
WAIS-VIQ (85–115)	109.1 $\pm$ 15.6	110.8 $\pm$ 15.7	0.34

* For categorical variables, Chi Squared or Fischer's exact test were used. For others, the Wilcoxon rank-sum test was used.

BIMC – Blessed Information Memory Concentration Test

HDL – High Density Lipoprotein cholesterol

LDL – Low Density Lipoprotein cholesterol

OPUS – Offspring of Parents with Usual Survival

OPEL – Offspring of Parents with Exceptional Longevity

WAIS-PIQ – Wechsler Adult Intelligence Scale – Performance IQ

WAIS-VIQ – Wechsler Adult Intelligence Scale – Verbal IQ

Table 2

Baseline Neuropsychological Characteristics and Dementia Risk Factors by Dementia Status at Last Follow-up.

Variable	Dementia free (N = 311)	Dementia (N = 113)	P-value*
Demographics			
Age, years (Mean $\pm$ SD)	78.9 $\pm$ 3.1	79.7 $\pm$ 3.0	0.02
Female, N (%)	193 (62%)	76 (67%)	0.36
Caucasian, N (%)	286 (92%)	101 (89%)	0.45
Education $\geq$ High School, N(%)	165 (53%)	49 (43%)	0.10
Parental Dementia, N(%)	56 (18%)	19 (17%)	0.83
Neuropsychological Tests, (Normal Range), Mean $\pm$ SD			
BIMC (0–4)	2.1 $\pm$ 1.8	3.3 $\pm$ 2.4	<.0001
WAIS-PIQ (85–115)	105.7 $\pm$ 12.1	98.0 $\pm$ 12.6	<.0001
WAIS-VIQ (85–115)	111.6 $\pm$ 15.3	104.1 $\pm$ 15.2	<.0001
Zung Depression scale (0–49)	45.7 $\pm$ 10.1	48.2 $\pm$ 11.0	0.13

* For categorical variables, Chi Squared or Fischer's exact test were used. For others, the Wilcoxon rank-sum test was used.

BIMC – Blessed Information Memory Concentration Test

WAIS-PIQ – Wechsler Adult Intelligence Scale – Estimated Performance IQ

WAIS-VIQ – Wechsler Adult Intelligence Scale – Estimated Verbal IQ

Table 3

Estimated Hazard Ratios (95% Confidence Interval) from Cox Proportional Hazard Models Assessing Parental Longevity (OPEL vs OPUS) as a Predictor of Dementia.

Outcome	Model 1*	Model 2†	Model 3‡	Model 4§	Model 5
All dementia	0.64 (0.43–0.97)	0.68 (0.45–1.02)	0.70 (0.46–1.05)	0.69 (0.46–1.04)	0.70 (0.47–1.06)
Alzheimer’s Dementia	0.57 (0.35–0.93)	0.60 (0.37–0.99)	0.61 (0.37–0.99)	0.59 (0.36–0.97)	0.62 (0.36–1.07)

* Model 1: OPEL versus OPUS using age as the time scale.

† Model 2: Model 1 + (gender, education, race/ethnicity).

‡ Model 3: Model 2 + (hypertension, myocardial infarction, diabetes mellitus, stroke).

§ Model 4: Model 2 + vascular index (sum of conditions present: hypertension, myocardial infarction, diabetes mellitus, stroke).

Model 5: Model 2+ vascular index + ever smoking + dyslipidemia.