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Parental longevity is associated with cognition and brain ageing in middle-aged offspring

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Abstract

Background: offspring of long-lived individuals have lower risk for dementia. We examined the relation between parental longevity and cognition and subclinical markers of brain ageing in community-dwelling adult offspring.
Methods: offspring participants with both parents in the Framingham Heart Study, aged ≥55 years and dementia-free underwent baseline and repeat neuropsychological (NP) testing and brain magnetic resonance imaging (MRI). Parental longevity was defined as having at least one parent survive to age ≥85 years. To test the association between parental longevity and measures of cognition and brain volumes, we used multivariable linear and logistic regression adjusting for age, sex, education and time to NP testing or brain MRI.
Results: of 728 offspring (mean age 66 years, 54% women), 407 (56%) had ≥1 parent achieve longevity. In cross-sectional analysis, parental longevity was associated with better scores on attention (beta 0.21 ± 0.08, $P = 0.006$) and a lower odds of extensive white matter hyperintensity on brain MRI (odds ratio 0.59, 95% CI: 0.38, 0.92, $P = 0.019$). The association with white matter hyperintensity was no longer significant in models adjusted for cardiovascular risk factors and disease. In longitudinal analysis (6.7 ± 1.7 years later), offspring with parental longevity had slower decline in attention (0.18 ± 0.08, $P = 0.038$), executive function (beta 0.19 ± 0.09, $P = 0.031$) and visual memory (beta −0.18 ± 0.08, $P = 0.023$), and less increase in temporal horn volume (beta −0.25 ± 0.09, $P = 0.005$). The associations persisted in fully adjusted models.
Conclusion: parental longevity is associated with better brain ageing in middle-aged offspring.

Keywords: *brain ageing, brain imaging, cognition, longevity, neuropsychological testing, older people, parental longevity*

Introduction

Offspring of long-lived individuals are less likely to develop age-related diseases and have better preservation of physical function in contrast to comparison groups [1–3]. The Bronx Aging Study reported that offspring of long-lived parents have a lower risk for dementia and Alzheimer's disease (AD) and a slower rate of memory decline compared with offspring of parents with usual survival [4]. In that study parental longevity was self-reported, raising concern about misclassification of parental longevity status. Furthermore, the study did not adjust for several important potential confounders including parental dementia and genotypes known to be associated with both longevity and cognition such as *APOE ε4* [5–7].

The aim of this study was to examine the relation between parental longevity and measures of cognition and markers of brain ageing in middle-aged community-dwelling adult offspring both cross-sectionally and longitudinally using the Framingham Heart Study (FHS) cohorts. We hypothesised that adult children of long-lived parents would have better cognitive performance assessed with neuropsychological (NP) testing and preserved volumetric brain measures on brain magnetic resonance imaging (MRI) than adult children of parents with usual survival.

Methods

Study sample

The FHS was started in 1948 to study determinants of cardiovascular disease. The original cohort comprised 5,209 participants. The offspring of the original cohort (and spouses of the offspring) were enrolled into the Offspring cohort in 1971–75 and have been examined every 4–8 years [8]. Surviving Offspring participants who attended the seventh research examination (1998–2001, $n = 3,539$) were invited to participate in NP testing and brain MRI from 1999 to 2005; 71% ($n = 2,523$) underwent NP testing and 2,214 had a brain MRI. Participants were excluded from this study if they did not have both parents in the original cohort ($n = 1555$), if they had known dementia, stroke or other neurological conditions ($n = 39$), or were aged <55 years at the time of NP assessment ($n = 201$). The final study sample included 728 Offspring participants who underwent NP testing of whom 639 Offspring participants also had a brain MRI. All participants were invited to undergo a second NP testing and brain MRI. For the longitudinal analysis, 562 of 728 (77%) participants underwent repeat NP testing and 450 of 639 (70%) participants underwent a second brain MRI between 2005 and 2009. The Boston University Medical Center Institutional Review Board approved the study protocols and all participants provided informed consent.

Parental longevity

Parental longevity was defined as having at least one parent who survived to age 85 years or older [4]. This age cut-point was chosen to be consistent with the prior report [4]. Usual parental survival was defined as having both parents die prior to age 85 years. All deaths were adjudicated by a panel of three FHS senior investigators. Parental age at death was validated with medical records and death certificate data.

NP testing assessment

All participants were administered a comprehensive NP test battery by trained examiners [9]. Tests were representative of multiple cognitive domains and included: (i) the Wechsler Memory Scale (WMS) Logical Memory test (LM-d) provides a measure of delayed recall or long-term verbal memory; (ii) the WMS Visual Reproductions test (VR-d) provides a measure of delayed visual memory recall; (iii) the WMS Paired Associates Learning test (PAS-d) measures verbal learning; (iv) the Halstad-Reitan (H-R) Trails A tests simple attention; (v) H-R Trails B-Trails A is a measure of executive function that has been adjusted for attention and motoric effects (Trails B-A); (vi) the Wechsler Adult Intelligence Similarities Test (SIM) is a measure of abstract reasoning skills; (vii) the Boston Naming Test (BNT) total score without cues is a measure of language, and (viii) the Hooper Visual Organisation Test (HVOT) is a measure of visuoperceptual skills. The Trails A, Trails B-A, BNT and HVOT scores were log-transformed for analysis to normalise their distributions.

Brain MRI imaging

Brain MRI imaging was obtained on all participants using a 1 or 1.5- Tesla Siemens Magnetom with T2-weighted double spin-echo coronal sequences acquired according to previously established protocols [10]. All images were read centrally blinded to parental longevity status using QUANTA 6.2, a custom-designed analysis software package, used on the Ultra 5 workstation (Sun Microsystems, Santa Clara, CA, USA). The protocols for quantifying total and regional brain volumes along with inter-rater reliabilities have been reported [11, 12]. Briefly, total cerebral brain volume (TCBV) is computed as the ratio of the total brain parenchymal volume to total cranial volume to account for head size differences. Hippocampal brain volume (HPV), frontal lobar brain volume (FBV), temporal brain volume (TBV), temporal horn volume (THV) and white matter hyperintensity volume (WMHV) were computed as ratios to total cranial volume. THV is often recognised as a surrogate measure of HPV and was included because longitudinal measures of HPV were not available. WMHV and THV were log-transformed to normalise their distribution. As previously reported, using WMHV, 5-year age-group-specific z scores were created and participants with z scores >1 were defined as having large-WMHV [13]. Finally, the presence of silent cerebral infarcts (SCIs) was recorded.

Covariates

Educational attainment was self-reported. Risk factors were directly measured at Offspring examination 7 (1998–2001) and included hypertension defined as systolic blood pressure ≥140 mmHg/≥90 mmHg or use of anti-hypertensive medication; diabetes defined as fasting blood glucose >125 mmol/dl or use of glucose-lowering medication and current cigarette smoking defined as smoking at least one cigarette per day in the year preceding the examination. In addition, prevalent atrial fibrillation and prevalent cardiovascular disease were identified and validated using medical records and previously established criteria [14].

Statistical analysis

Continuous outcomes were transformed for analysis to standard deviation units. For cross-sectional analyses, positive NP values indicate better cognitive performance and higher measures on brain MRI indicate better brain structure with the exception of Trails A and Trails B-A (which are completion times), WMH and THV, where greater values indicate poorer brain ageing. The annual change in NP test measures and brain MRI volumes was calculated as the difference between the last and first measurement divided by the time interval between the two measurements. For analysis of annualised change, negative values on NP tests indicate a decline in cognitive performance and for brain MRI negative values indicate a decline, again with the exception of Trails A, Trails B-A, WMH and THV where positive values indicate a worsening in brain structure.

To examine the association between parental longevity and measures of cognition and brain volumes (cross-sectionally and longitudinally), we used multivariable linear or logistic regression models adjusting for age, sex and time to NP assessment or brain MRI. For NP test measures, we additionally adjusted for education. In fully adjusted models, we additionally adjusted for hypertension, diabetes, current smoking, prevalent cardiovascular disease and prevalent atrial fibrillation. For the longitudinal analyses, we additionally adjusted for baseline measurement of the NP test or brain MRI volume. Betas (adjusted differences in means) and standard errors or odds ratios and 95% confidence intervals are presented to report the magnitude of effect of parental longevity on cognitive test performance and brain MRI volumes in adult offspring. We conducted investigations of age, sex and *APOE ε4* interactions and conducted stratified analyses where interactions were present ($P < 0.05$). In secondary analyses, we additionally adjusted for parental dementia in the subsample with this information available. There were too few incident dementia events in offspring ($n = 37$) to examine the association with parental longevity. All analyses were performed using the Statistical Analyses System software version 9.2 (SAS Institute, Cary, NC, USA).

Results

Of 728 Offspring participants, 407 (56%) had at least one parent who achieved longevity: 243 offspring had a long-lived mother, 76 had a long-lived father and 88 had both a long-lived mother and a long-lived father. The Offspring sample had a mean age of 66 ± 6 years, was 54% women and 23% were carriers of the *ApoE ε4* genotype (Table 1).

Table 1. Characteristics of the study sample by parental longevity status

Mean (SD) or (%)	Parental longevity[a] ($n = 407$)	Parental usual survival[a] ($n = 321$)	*P*-value
Age, years	66 (6)	65 (6)	<0.001
Women (%)	54	55	0.72
Education, <high school (%)	2	3	0.004
Education, high school degree (%)	55	66	
Education, college (%)	43	31	
Hypertension (%)	48	52	0.28
Diabetes (%)	12	18	0.015
Current smoking (%)	6	14	<0.001
Cardiovascular disease (%)	10	15	0.036
Atrial fibrillation (%)	3	3	0.71
ApoE ε4 genotype carriers (%)	23	23	0.91
MMSE score (%)	29.0 (1.2)	28.8 (1.6)	0.007
Parental dementia (%)	28	21	b

MMSE, Mini-Mental State Examination.

[a]Parental longevity = at least one parent alive at age ≥85 years; parental usual survival = both parents deceased at age <85 years.

[b]Information available on parental dementia by age 85 years on $n = 324$.

Offspring with at least one long-lived parent have less age-related disease compared with Offspring of parents with usual survival.

Association of parental longevity with cognitive performance

Baseline cognitive performance

Mean values for each of the NP tests are provided in Supplementary data available in *Age and Ageing* online, Table S1. Parental longevity was associated with significantly better scores on Trails A (beta −0.21 ± 0.08, $P = 0.006$); the association persisted in the fully adjusted model (Supplementary data are available in *Age and Ageing* online, Table S2**,** beta −0.18 ± 0.08, $P = 0.019$). Parental longevity was not associated with other domains of cognition (Table 2). We did detect a significant interaction of parental longevity with offspring age for the association with the LM-d test ($P = 0.036$). However, in age stratified analyses (age <65 years versus age 65 and older), no significant associations were detected. There were no other significant interactions detected.

Change in cognitive performance

For the 557 participants with repeated measurement of NP testing, the mean time between the baseline and follow-up testing was 6.7 ± 1.7 years, range 1–11 years. Parental longevity was associated with slower decline in attention (Trails A, beta −0.18 ± 0.08, $P = 0.038$) executive function (Trails B-A, beta −0.19 ± 0.09, $P = 0.031$) and visual memory (VR-d, beta −0.18 ± 0.08, $P = 0.023$) (Table 2). The associations persisted in the fully adjusted model (Supplementary data are available in *Age and Ageing* online Table 2). No other tests of cognition were associated with parental longevity. We did not observe any significant interactions.

Association of parental longevity with brain MRI measures

Baseline brain MRI

Mean values for brain MRI volumes are shown in Supplementary data available in *Age and Ageing* online, Table 1. Parental longevity was associated with significantly lower odds of large-WMHV (Table 3, odds ratio 0.59, 95% confidence interval 0.38, 0.92, $P = 0.019$). The association was attenuated in the fully adjusted model (Supplementary data are available in *Age and Ageing* online, Table 2**,** odds ratio 0.67, 95% confidence interval 0.42, 1.07). There was no association between parental longevity and the other MRI measures. We did observe interactions between parental longevity and *ApoE ε4* in their associations with HPV ($P = 0.016$) and temporal lobe brain volume ($P = 0.007$). Among *ApoE ε4* carriers only ($n = 146$), parental longevity was associated with significantly lower hippocampal volume (beta −0.36 ± 0.16, $P = 0.030$) and temporal lobe volume (beta −0.35 ± 0.16, $P = 0.027$).

Table 2. Association of parental longevity and cross-sectional and longitudinal measures of cognition in adult offspring

	Cross-sectional ($n = 728$)		Longitudinal, annualised change[b] ($n = 557$)	
Test	Beta estimate ± SE	*P*-value	Beta estimate ± SE	*P*-value
Logical memory delayed	0.01 ± 0.07	Ns	−0.03 ± 0.08	Ns
Visual reproduction delayed	0.07 ± 0.07	Ns	**0.18 ± 0.08**	**0.023**
Paired associates delayed	0.09 ± 0.07	Ns	−0.12 ± 0.08	Ns
Trail Making Test A[a]	**−0.21 ± 0.08**	**0.006**	**−0.18 ± 0.08**	**0.038**
Trail Making: Test B-Test A[a]	0.05 ± 0.07	Ns	**−0.19 ± 0.09**	**0.031**
Similarities Test	0.11 ± 0.07	Ns	−0.03 ± 0.08	Ns
HVOT [a]	0.14 ± 0.07	Ns	0.05 ± 0.09	Ns
BNT[a]	0.06 ± 0.07	Ns	0.08 ± 0.09	Ns

The bold values are statistically significant.

Model: adjusted for age, sex, education, time to NP assessment; longitudinal change analysis additionally adjusted for baseline value of the test. Beta estimates (adjusted differences in means) and standard errors are presented to report the magnitude of effect of parental longevity on cognitive test performance in adult offspring.

ns, not significant ($P > 0.05$).

[a]Natural log-transformed.

[b]Mean follow-up time 6.7 ± 1.7 years, range 1–11 years; annualised change in NP test measures was calculated as the difference between the last and first measurement divided by the time interval between the two measurements.

Table 3. Association of parental longevity and cross-sectional and longitudinal brain MRI measures in adult offspring

	Cross-sectional ($n = 639$)		Longitudinal: annualised change[b] ($n = 450$)	
	Beta estimate ± SE or odds ratio (95% CI)	*P*-value	Beta estimate ± SE	*P*-value
TCBV	0.02 ± 0.07	ns	0.13 ± 0.11	ns
Hippocampal volume	−0.03 ± 0.08	ns	N/A	ns
Frontal lobe volume	−0.05 ± 0.07	ns	0.01 ± 0.09	ns
Temporal lobe volume	−0.01 ± 0.08	ns	−0.05 ± 0.09	ns
Temporal horn volume[a]	−0.05 ± 0.07	ns	**−0.25 ± 0.09**	**0.005**
WMHV[†]	−0.11 ± 0.07	ns	−0.09 ± 0.08	ns
Large-WMHV	**0.59 (0.38, 0.92)**	**0.019**	N/A	
SCI	0.87 (0.55, 1.38)	ns	N/A	

The bold values are statistically significant.

Model: adjusted for age, sex, time to brain MRI; longitudinal analysis additionally adjusted for baseline value. Beta estimates (adjusted differences in means) and standard errors or odds ratios and 95% confidence intervals are presented to report the magnitude of effect of parental longevity on brain MRI volumes in adult offspring.

N/A, not available; ns, not significant ($P > 0.05$).

[a]Natural log-transformed.

[b]Mean follow-up time 6.7 ± 1.7 years; annualised change in brain MRI volumes was calculated as the difference between the last and first measurement divided by the time interval between the two measurements.

Change in brain MRI measures

Parental longevity was significantly associated with smaller annualised increase in THV (beta −0.25 ± 0.09, $P = 0.005$), and the effect was not changed in the fully adjusted model. No other associations between parental longevity and change in brain volumes were observed. Significant interactions between parental longevity and offspring age (age <65 years versus age 65 years and older) for TCBV ($P = 0.035$) and TBV ($P = 0.018$) were detected. Stratified analyses revealed a significant association in offspring age <65 years ($n = 233$): parental longevity was associated with improved annualised change in TCBV (beta 0.35 ± 0.16 $P = 0.033$). In offspring age 65 years and older ($n = 270$), no significant association between parental longevity and annualised change in TCBV was observed.

Secondary analyses

In secondary analyses, we further adjusted for parental dementia and parental stroke and did not observe any substantive change in the associations.

Discussion

In our community-based sample, adults in early old age with long-lived parents had better preserved performance on tests of attention, executive function and visual memory when compared with adults with parents with a typical lifespan. Older adults with long-lived parents also had less structural changes associated with vascular brain ageing as evidenced by lower odds of large-WMHV on MRI at baseline and less decline in temporal horn volume, an indication that the hippocampus also was relatively preserved. ApoE4 positivity however attenuated the protective effect of parental longevity in baseline measures of the hippocampus and temporal lobe. Further age was a mediator for total brain volume where those <65 years of age with long-lived parents had bigger brains, an effect not seen for those 65 and older. Our group and others have previously shown that measures of WMHV are associated with cognition even among healthy individuals including the domains of attention and executive function [15–17]. Our results are consistent with a recent report from

the Long Life Family Study that demonstrated that adult offspring of pro-bands recruited for exceptional survival performed better on multiple tasks including tasks requiring attention compared with spouse controls without a family history of longevity [18]. Early markers of cognition and volumetric changes in the brain identified with MRI in asymptomatic offspring might serve as important endophenotypes in the search for genes influencing longevity and provide insights into the biological mechanisms of brain ageing and ageing in general.

Preservation of cognition is an important marker of longevity [19]. Cognitive function measured both in old age [20, 21] and in mid-life [20] is related to life expectancy. In the Dutch Longitudinal Study Among the Elderly, the rate of decline in cognition among older adults had an adverse impact on survival [22]. In a large longitudinal cohort study of older adults, those that maintained cognitive function had a lower risk for death and functional decline [21]. Interestingly, longevity genes identified from animal models were found to influence human cognition in older adults in the Lothian 1936 Birth Cohort Study [23]. Offspring of long-lived parents in our sample had better attention and preserved executive function even when accounting for cardiovascular risk factors and diseases consistent with the finding in the Bronx Aging Study that Offspring of parents with exceptional longevity develop dementia and AD at lower rates [4]. Factors contributing to longevity thus may also have a beneficial effect on cognitive function into old age.

Offspring of long-lived individuals have more favourable cardiovascular risk profiles and less cardiovascular disease [24, 25] than Offspring of parents with a shorter lifespan. Cardiovascular diseases and risk factors make up the Framingham Stroke Risk Profile that is associated with poorer cognitive performance in multiple domains including attention in large population-based samples of individuals free of stroke and dementia [26, 27]. Moreover, mid-life cardiovascular risk factors are associated with decline in executive function a decade later [28]. Vascular risk factor scores may also be a valuable tool in predicting late-onset AD [29]. Therefore, perhaps it is not surprising that in our sample Offspring of long-lived parents performed better on some cognitive tests in particular in the domains of attention and executive function.

Offspring of long-lived parents have lower odds of large-WMHV that was attenuated in the fully adjusted models suggesting that the association was mediated by cardiovascular disease and its risk factors. The concomitant finding of deficits in attention which have been linked to WMH is consistent with prior work demonstrating that mid-life cardiovascular risk factors accelerate vascular brain ageing [28].

Our study has strengths and limitations that merit comment. The study is community based with vital status on the parents of the adult offspring. The Offspring have direct measurement of risk factors and validation of cardiovascular diseases along with the careful assessment of NP testing and brain MRI. Participants underwent *ApoE ε4* genotyping. However, our sample is primarily white and therefore findings cannot be generalised to other race/ethnic groups. The relationship between longitudinal annualised change in temporal horn volume and parental longevity was in the unexpected direction. Practice effects on neuropsychological testing may have underestimated potential changes in the longitudinal analysis. There were too few cases of incident dementia to examine the association between parental longevity and Offspring dementia. Many of the Offspring were in mid-adulthood at the time of NP assessment, an age too young to be at risk for dementia and thus were excluded from the sample. This criterion limited our sample size. However, with longer follow-up of the Offspring cohort we will be able to conduct this investigation. Finally, we did not correct for multiple testing; however, the overall pattern of our results suggests they are real rather than chance observations. Nonetheless our results should be considered exploratory until confirmed in other community-based studies.

Conclusion

In conclusion, in our community-based sample, Offspring of long-lived parents performed better on tests of attention and had preserved executive function compared with Offspring of parents of usual survival. Further, Offspring of long-lived parents had less vascular brain ageing likely mediated through lower levels of cardiovascular risk factors.

Key points

- Parental longevity was associated with better brain ageing in middle-aged Offspring.
- Offspring with long-lived parents had slower decline in attention, executive function and visual memory.
- Parental longevity was also associated with less structural changes on brain MRI:
  - lower odds of large-WMHV at baseline;
  - less decline in temporal horn volume.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in *Age and Ageing* online.

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