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Mary Ann Liebert
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Maternal Longevity is Associated With Reduced Risk but an Earlier Onset of Alzheimer's Disease in Offspring

Miguel Tábuas-Pereira, MD[1,2,3], Francisco Mano, MD[4], Catarina Bernardes, MD[1,2,3], João Durães, MD[1,2,3], Marisa Lima, PhD[2], Kaitlyn DenHaan, BSc[5], Kimberly Paquette, BSc[5], Célia Kun-Rodrigues, BSc[5], Susana Carmona, PhD[5], Teresa Tábuas, MSc[6], Pedro Faustino, MD[1,2,3], Mariana Ruth Coelho, MD[2], Anuschka Silva-Spínola, PhD[3,7], Diana Duro, PhD[2], Maria Rosário Almeida, PhD[1,3], João Malva, PhD[1,3,8,9], Inês Baldeiras, PhD[1,3], José Brás, PhD[5,*], Rita Guerreiro, PhD[5,*], and Isabel Santana, PhD[1,2,3,**]**

Abstract

Introduction: While human longevity has increased significantly over the last 2 centuries, the time spent in good physical and cognitive health has not risen proportionately. The incidence of Alzheimer's disease (AD) increases with age, but parental longevity is often associated with better offspring health and lower AD risk. This study aimed to investigate the relationship between parental longevity and AD. **Methods:** We included patients with AD and cognitively healthy subjects (over 75 years), collecting family history data, namely maternal and paternal age at death. We performed a logistic regression to evaluate the association of parental longevity and AD risk and linear regression models for the association with age of onset and CSF biomarkers, adjusting for confounders. **Results:** We analyzed 3069 participants from a Portuguese cohort, including 893 AD patients and 2176 cognitively healthy controls. Maternal longevity was inversely associated with AD risk (OR: 0.989, 95%CI = [0.982, 0.997], $P = 0.005$). In AD patients, higher maternal age of death was associated with an earlier disease onset ($\beta = -0.081$, 95%CI = [−0.148, −0.013], $P = 0.019$). No associations were found between parental longevity and CSF biomarkers. **Discussion:** Maternal longevity appears protective against AD risk but is linked to an earlier onset in patients. This may indicate that protective factors for AD could become detrimental once AD is triggered. These findings highlight the complex interplay of genetic, environmental, and potentially epigenetic influences on AD.

[1]Clinical Academic Center of Coimbra (CACC), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[2]Neurology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[3]Centre for Innovative Biomedicine and Biotechnology (CIBB), Universidade de Coimbra, Coimbra, Portugal
[4]Dermatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[5]Department of Neurodegenerative Science, Van Andel Institute, Grand Rapids, MI, USA
[6]Instituto Politécnico de Bragança, Bragança, Portugal
[7]Centre for Informatics and Systems, Department of Informatics Engineering, University of Coimbra, Coimbra, Portugal
[8]Faculty of Medicine, Institute of Pharmacology and Experimental Therapeutics, University of Coimbra, Coimbra, Portugal
[9]Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (iCBR), University of Coimbra, Coimbra, Portugal

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**Equally contributing senior authors. *Current affiliation: Regeneron, Regeneron Genetics Center, Westchester, New York, USA.

Corresponding Author:
Miguel Tábuas-Pereira, MD, Neurology Department, Centro Hospitalar e Universitário de Coimbra, praceta Prof. Mota Pinto, Coimbra 3004-561, Portugal.
Email: miguelatcp@gmail.com

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Background

Over the last two hundred years, human longevity has been substantially increased, largely attributed to improvements in sanitation and the treatment of infectious diseases.[1] However, the time spent with good physical and cognitive health did not rise proportionately, as aging is associated with the accumulation of chronic comorbidities.[2] In fact, at older ages, the incidence of Alzheimer's disease (AD) increases,[3] suggesting that longer lifespans are associated with a higher risk of AD.

Conversely, parental longevity is associated with a better general health and survival of offspring, with both genetic and shared environmental factors contributing to that association.[4,5,6,7] In addition, offspring of long-lived parents have been shown to have better cognitive functioning[7,8,9,10] and a reduced risk of AD.[11] Recent studies have shown that parental longevity is associated with greater brain volume of the offspring, especially in the hippocampus, parahippocampal gyrus, middle temporal lobe, and primary sensorimotor cortex.[12]

AD is a highly heritable condition, with an estimated heritability of up to 80%.[13] It can therefore be hypothesized that if positive family history is a risk factor for AD, as it is the case for most complex diseases, great longevity in one's parents may act as a protective factor in descendants. In fact, it has been documented that centenarians may have a reduced incidence of AD,[14,15] suggesting that there are some underlying resilience factors, many of those being probably genetic.

Several genes have been associated with both longevity and AD.[16,17] The gene with the largest impact on both traits is *APOE*. In fact, *APOE* ε4 allele, the most important genetic risk factor for AD is also associated with decreased longevity.[18,19] Other longevity associated genes, such as *KLOTHO*[20,21] and SIRT1[22] have also been extensively linked to AD pathophysiology.

In this study, we aim to investigate the relationship between parental (paternal and maternal) ages of death and the risk of Alzheimer's disease.

Methods

Participants' Selection and Characterization

Cases. We included patients from a cohort of AD patients followed at the Dementia Clinic, Neurology Department of University Hospital of Coimbra, Portugal, regardless of the age of onset. This center serves the central region of Portugal, comprising around 2.2 million people. All patients underwent a thorough diagnostic investigation including standard clinical evaluation, neuropsychological assessment, laboratory analysis, and imaging studies. Per routine, ALL patients under 75 years of old at the first evaluation are proposed to CSF collection or amyloid-PET. AD diagnosis was established by the most recent criteria.[23,24]

Controls. Controls were collected in communities, nursing homes and in the hospital (patients for other non-neurological conditions and relatives that came with patients to the clinic). All had a collateral history of normal cognitive status and functioning, and a normal score in the MMSE. To decrease the odds of future dementia, *only cognitively unimpaired subjects with more than 75 years* of age at the time of the collection were included. Subjects with a diagnosis (or suspicion of) of Parkinson's disease, Amyotrophic Lateral Sclerosis or other form of neurodegenerative disorder were excluded.

Family history was collected with subjects and relatives, through a systematic questionnaire.[25] The questionnaire asked for place of birth of the father and the mother, age of death, cause of death (if known), history of dementia, and age of onset of the dementia, number of siblings, number of sisters and brothers, age of death (if deceased), cause of death, history of dementia in any of the siblings, age of onset of the dementia.

Considering the increase in life expectancy and the restructuring of the education system in the last century,[2] year of birth was included as a covariate in most analysis. With time, the level of compulsory education increased, with increased levels of education being compulsory with time. In general, younger patients are part of a group in which compulsory education is significantly higher.

APOE and CSF Analysis

For *APOE* genotyping, DNA was isolated from whole EDTA-blood using a commercial kit (Roche Diagnostics GmbH, Manheim, Germany) and *APOE* genotype was determined by polymerase chain reaction-restriction fragment length polymorphisms assay.[26] CSF was obtained by lumbar puncture and biomarkers (Aβ42, t-tau and p-tau) measurements were performed as previously reported by Baldeiras et al.[27] Pre-analytical and analytical procedures were done in accordance with the Alzheimer's Association guidelines for CSF biomarkers determination.[28] External quality control of the assays was performed under the scope of the Alzheimer's association quality control program for CSF biomarkers.[28] CSF

biomarkers were classified as normal/abnormal according to previously reported laboratory reference values.[29]

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics (version 26). Data normality was assessed using the Kolmogorov–Smirnov test. Categorical variables are presented as frequencies and were compared using chi-square tests. Ordinal or discrete variables are reported as means for ease of interpretation, but statistical analyses were performed using median values, and group comparisons were conducted using Mann–Whitney U tests.

Parental Longevity and Odds of Developing AD. The full sample was used to examine the association between paternal and maternal longevity and the odds of developing AD. Logistic regression models were employed to assess the relationship between paternal and maternal age at death and AD status. Because all controls were older than 75 years - introducing a potential bias toward longer survival - analyses were repeated in age-matched subgroups (75-80 and 80-85 years).

Endophenotypes and Parental Longevity. To evaluate the impact of parental longevity on AD endophenotypes, separate linear regression models were fitted to examine associations between parental age at death and AD-related biomarkers. These analyses were restricted to a subset of participants for whom cerebrospinal fluid (CSF) biomarker data were available (regardless of age of onset).

All model assumptions were verified. Statistical significance was set at $\alpha = 0.05$.

Ethics

The present research complied with the ethical guidelines for human experimentation stated in the Declaration of Helsinki and was approved by the Ethics Board of Coimbra University Hospital. An informed consent was obtained from all the participants or their legal next of kin after the aims and procedures of investigation were fully explained by a member of the study group.

Results

We have included 3069 subjects, 893 (62.4% female) with AD, 2176 (64.6% female) cognitively healthy controls (age at collection over 75). 312 of the AD patients had data on CSF AD biomarkers.

Demographic variables, *APOE* genotypes and biomarker levels distribution are described on Table 1. Considering the increase in life expectancy and the restructuring of the education system in the last century,[2] some results were adjusted for year of birth (marked with *), as younger patients are part of a group in which compulsory education is significantly higher. AD patients have a lower age at collection, a higher level of education and their parents had a lower age of death.

Correlation between variables of interest in AD patients are depicted in supplemental table 1. Maternal age of death was correlated with age of onset only. Paternal age of onset did not correlate with any of the relevant variables.

To better understand the relationship between paternal and maternal ages of death and the risk of developing AD, we performed a logistic regression with diagnosis as the outcome, adjusted for possible confounders (Table 2). Maternal age of onset, positive family history, the number of APOE ϵ4 alleles, education and the year of birth were significantly associated with the risk of developing AD. Considering that the 2 groups are different in terms of age at data collection, we calculated the same regression model on different age groups (75-80, 80-85 and over 85), in order to homogenize compared groups in terms of age of onset and year of birth. Characterization of the different group stages may be found in supplemental table 2.

To study the association of paternal and maternal ages of death and other relevant variables (age of onset, CSF Aβ42, CSF Tau and CSF p-tau), we performed 4 linear regression models, adjusted for possible confounders, only in the patients' subset, which are depicted in Table 3. The characterization of this subset may be found in supplemental table 3. Maternal age of death was associated with the age of onset, but not with the other endophenotypes. We found no associations with the paternal age of death and the studied outcomes.

Discussion

In a large Portuguese cohort of patients and controls, we demonstrate an association between maternal longevity and a reduced risk of developing AD. However, among patients who develop AD, greater maternal longevity is associated with an earlier age at disease onset.

Parental longevity has been previously linked to a reduced risk of developing AD.[14] That association was reported in a relatively small study including 113 individuals who developed dementia and restricted to participants older than 75 years. In contrast, our study extends these findings in a large, well-characterized cohort that includes both early- and late-onset AD cases, thereby strengthening the robustness and generalizability of the observed association.

A recent large study in cognitively unimpaired older adults reported an association between maternal history of dementia and increased amyloid deposition on PET imaging.[30] This finding is consistent with our results, supporting a role for maternal factors in modulating AD risk in offspring. In our study, however, neither paternal nor

Table 1. Sample Characterization, Showing the Distribution of Relevant Variables and How They Compare Between AD Patients and Controls.

	Controls	AD patients	Total	*P*
Age at collection (years)	85.3 ± 5.7	77.7 ± 8.4	83.1 ± 7.4	**<0.001**
Age of AD onset (years)	-	71.7±9.1	-	-
Female sex (n, %)	1405 (64.6)	557 (62.4)	1962 (63.9)	0.624
Education (years)	3.9 ± 3.4[a]	5.4 ± 4.1[a]	4.3 ± 3.7[a]	**<0.001**
≥APOE ϵ4 allele (n, %)	266 (16.0)	392 (47.9)	658 (26.5)	**<0.001**
Paternal age of death (years)	73.1 ± 18.0[a]	72.0 ± 30.15[a]	72.8 ± 14.7	**0.001**
Maternal age of death (years)	77.9 ± 17.7[a]	76.3 ± 29.7[a]	77.5 ± 14.3	**0.002**
CSF Aβ42 (pg/mL)	-	521.7 ± 201.7	-	-
CSF Aβ42/Aβ40 ratio (pg/mL)	-	0.050 ± 0.02	-	-
CSF Tau (pg/mL)	-	649.6 ± 365.8	-	-
CSF phosphorylated-tau (pg/mL)	-	107.9 ± 64.0	-	-

AD, Alzheimer's Disease; *APOE*, (Apolipoprotein E); CSF, Cerebrospinal Fluid. Bold are for results significant wiht alpha <0.05.
[a]adjusted for year of birth.

maternal age at death was associated with any AD CSF biomarkers, suggesting that the variation in AD risk related to parental longevity is more likely mediated by other resilience mechanisms rather than by direct effects on the canonical AD pathological cascade. Several mechanisms may contribute to this relationship. Parental longevity has been associated with better overall health, reduced cardiovascular risk[31] and lower cortical atrophy, particularly in brain regions highly relevant to AD, such as the hippocampus, parahippocampal gyrus, and medial temporal lobe.[12] Neuroinflammation modulation may also be a key factor. In fact, there is an overlap between genetic risk factors of AD and ageing, with an enrichment in networks expressed by microglia responding to ageing and oligodendrocyte function, highlighting their importance in the resilience of the brain against both ageing and AD.[32] In general, individuals with a family history of long-lived parents may inherit a more resilient brain, independent of AD mechanisms, therefore explaining the absence of relationship with AD mechanisms surrogates.

Table 2. Results of the Logistic Regression for the Odds of Having Alzheimer's Disease, Including Only Subjects (Patients and Controls) Between 75 and 80, Subjects Between 80 and 85, Subjects Over 85 and the Whole Sample.

	OR, 95%CI, *P*			
	[75–80]	[80–85]	>85	Whole sample
n	**693**	**919**	**926**	**3069**
Year of birth	**0.440, [0.376, 0.515], *P* < 0.001**	**0.501, [0.437, 0.575], *P* < 0.001**	0.999, [0.903, 1.107], *P* = 0.991	**1.171, [1.151, 1.192], <0.001**
Sex	1.058, [0.648, 1.728], *P* = 0.821	1.448, [0.895, 2.344], *P* = 0.132	0.802, [0.396, 1.624], *P* = 0.540	0.947, [0.771, 1.162], 0.600
Education	1.025, [0.957, 1.097], *P* = 0.482	0.993, [0.927, 1.064], *P* = 0.836	1.040, [0.949, 1.138], *P* = 0.401	**1.022, [0.994, 1.050], 0.124**
Number of *APOE* ϵ4 alleles	**3.804, [2.353, 6.149], *P* < 0.001**	**4.298, [2.675, 6.903], *P* < 0.001**	**3.220, [1.490, 6.956], *P* = 0.003**	**3.652, [2.960, 4.507], <0.001**
Positive family history	**2.683, [1.614, 4.459], *P* < 0.001**	**2.348, [1.417, 3.890], *P* = 0.001**	1.472, [0.570, 3.803], *P* = 0.425	**2.525, [1.975, 3.227], <0.001**
Paternal age of death	0.987, [0.971, 1.004], *P* = 0.137	1.003, [0.988, 1.018], *P* = 0.715	0.996, [0.975, 1.019], *P* = 0.753	0.994, [0.987, 1.000], 0.060
Maternal age of death	**0.982, [0.965, 0.998], *P* = 0.029**	**0.982, [0.968, 0.996], *P* = 0.013**	0.990, [0.968, 1.011], *P* = 0.348	**0.988, [0.981, 0.995], 0.001**

OR, Odds Ratio, CI, Confidence Interval; *APOE*, Apolipoprotein E. Bold are for results significant wiht alpha <0.05.
75–80: Nagelkerke R^2 = 0.549, −2 log likelihood = 446.381, $\chi^2(686,7)$ = 308.069, $P < 0.001$.
80–85: Nagelkerke R^2 = 0.378, −2 log likelihood = 528.249, $\chi^2(912,7)$ = 213.527, $P < 0.001$.
>85: Nagelkerke R^2 = 0.040, −2 log likelihood = 291.258, $\chi^2(919,7)$ = 10.303, $P < 0.001$.
Whole sample: Nagelkerke R^2 = 0.399, −2 log likelihood = 2495.354, $\chi^2(3062,7)$ = 941.472, $P < 0.001$.

Table 3. Results of the Linear Regression Models for Different Studied Endophenotypes (β, [95% Confidence Interval], *P*).

	Age of onset	CSF Aβ42	CSF Tau	CSF phosphorylated-tau
Maternal age of death	**−0.081, [−0.148, −0.013], *P* = 0.019**	0.491, [−1.214, 2. 197], *P* = 0.571	−0.531, [−1.964, 0.901], *P* = 0.466	0.134, [−0.126, 0.394], *P* = 0.311
Paternal age of death	0.013, [−0.047, 0.072], *P* = 0.671	−1.032, [−2.494, 0.431], *P* = 0.166	0.104, [−1.129, 1.337], *P* = 0.868	−0.085, [−0.309, 0.138], *P* = 0.453
Age of onset	-	**15.513, [9.987, 21.039], *P* < 0.001**	**−9.647, [−14.409, −4.855], *P* < 0.001**	**1.909, [1.049, 2.769], *P* < 0.001**
Year of birth	-	**13.566, [7.824, 19.307], *P* < 0.001**	**−7.497, [−12.431, −2.563], *P* = 0.003**	**1.738, [0.851, 2.624], *P* < 0.001**
Sex	0.477, [−1.285, 2.240], *P* = 0.594	−5.632, [−48.781, 37.518], *P* = 0.797	22.597, [−13.559, 58.753], *P* = 0.220	−0.654, [−7.238, 5.929], *P* = 0.845
Education	**−0.311, [−0.479, 0.143], *P* < 0.001**	0.836, [−3.358, 5.031], *P* = 0.695	−1.229, [−4.751, 2.293], *P* = 0.493	0.011, [−0.630, 0.651], *P* = 0.974
APOE ϵ4 allele	0.820, [−0.354, 1.994], *P* = 0.170	−16.848, [−45.586, 11.890], *P* = 0.249	2.115, [−22.089, 26.320], *P* = 0.864	−0.148, [−4.543, 4.248], *P* = 0.947
CSF Aβ42	**0.007, [0.002, 0.012], *P* = 0.003**	-	0.089, [−0.012, 0.190], *P* = 0.084	−0.004, [−0.023, 0.014], *P* = 0.661
CSF Tau	**−0.009, [−0.014, -0.003], *P* = 0.004**	0.126, [−0.017 0.269], *P* = 0.084	-	**0.164, [0.155, 0.174], *P* < 0.001**
CSF phosphorylated-tau	**0.034, [0.002, 0.066], *P* = 0.039**	−0.176, [−0.967, 0.615], *P* = 0.661	**4.998, [4.707, 5.270], *P* < 0.001**	-

CSF, Cerebrospinal Fluid; Aβ42, Amyloid-Beta$_{42}$. Bold are for results significant wiht alpha <0.05.
Age of onset: R^2 = 0.089, F(293, 8) = 4.579, P < 0.001; CSF Aβ42: R^2 = 0.126, F(275, 9) = 5.415, P < 0.001; CSF Tau: R^2 = 0.833, F(275, 9) = 152.922, P < 0.001; CSF Ptau: R^2 = 0.834, F(275, 9) = 154.623, P < 0.001.

A recent study reported an association between paternal history of dementia and increased vulnerability to amyloid-β–related tau spread.[33] While our findings point predominantly toward maternal effects, we cannot exclude a contribution of paternal longevity, as trends toward an association were observed in specific age strata (Table 2, age group 75-80). Moreover, a previous study in this same cohort showed that paternal history of dementia was associated with increased CSF phosphorylated tau levels.[25] Differences in lifespan and educational attainment between men and women may partly explain why maternal associations are more readily detectable, as women generally live longer and historically have had lower educational levels, potentially increasing the likelihood of manifest cognitive impairment. On the other side, factors such as modulation of the intrauterine environment[34,35] and mitochondrial inheritance[36] may play a role in risk modulation. Nonetheless, well-established sex-specific differences in AD risk suggest that investigating protective and risk factors modulated by sex may yield important insights into disease mechanisms.

Despite the overall protective association of maternal longevity with AD risk, we observed an inverse relationship between maternal age at death and age at AD onset among patients. This finding cannot be readily explained by a generalized brain resilience model. One possible explanation is sample-related bias: controls were required to be older than 75 years, which enriches the control group for longer-lived individuals and, consequently, for longer-lived parents. To address this concern, we repeated the logistic regression analyses for different age groups, and the association remained significant and directionally consistent (Table 2). Although linear regression analyses were limited by the small number of older patients with available CSF biomarkers, correlation analyses also supported associations in the same direction. Other factors, such as maternal age at childbirth - which has been associated with both increased longevity and increased AD risk[37,38]) - or environmental exposures do not adequately explain this paradoxical relationship. Similarly, epigenetic mechanisms alone are unlikely to fully account for these findings.

One possible interpretation is that genetic and shared environmental factors associated with increased parental longevity may confer protection against AD onset in offspring. However, having parents who live longer may also impose additional caregiving, emotional, and socioeconomic burdens on some individuals, potentially leading to earlier symptom manifestation or accelerated disease progression in those already predisposed to AD. Reduced social engagement, increased stress, sleep disruption, and financial strain may indirectly contribute to this effect.

Alternatively, certain genetic or environmental factors that are generally protective may become detrimental once AD pathology is triggered. These factors may involve immune, inflammatory, metabolic, synaptic, or other biological pathways. Supporting this hypothesis, several genes have been shown to exert opposing effects on longevity and AD risk,[17] including *CLU, PTK2B, ABCA7, CHRNE, SORL1, IL34, ADAM10,* and *CASS4*. A recent study identified enrichment of longevity- and AD-associated genes in networks related to microglial aging responses and oligodendrocyte function.[32] Taken together, our findings suggest that increased maternal longevity may reflect a protective homeostatic state that, once AD pathology emerges, becomes maladaptive—potentially through immune or metabolic mechanisms.

Our study has some limitations. The main one is that the longevity has changed a lot in the last century, and probably at different rates across different Portuguese regions, making it difficult to account for that on our analysis. Diagnosis was not determined pathologically, but was made by experienced neurologists in a tertiary hospital, and a good amount of patients had CSF biomarkers and/of amyloid PET imaging. This was also done only in one center, limiting generalizability for other populations. We did not include analysis of other comorbidities, such as brain vascular burden, that may interfere with the age of onset.

In conclusion, our study supports the notion that parental - particularly maternal - longevity confers protection against the development of AD, likely through global brain resilience mechanisms rather than specific amyloid or tau pathways. Paradoxically, among individuals who do develop AD, greater maternal longevity is associated with an earlier age at disease onset.

Author Contributions

conception and design of the study: MTP, FM, JB, RG, IS. acquisition and analysis of data: MTP, FM, CB, JD, ML, KD, KP, CKR, SC, TT, PF, MRC, ASS, DD, MRA, JM, IB. drafting the manuscript or figures: MTP, FM, KD, KP, JB, RG, IS

Declaration of Conflicting Interests

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ORCID iDs

Miguel Tábuas-Pereira https://orcid.org/0000-0002-3988-614X
João Durães https://orcid.org/0000-0001-9671-593X
Marisa Lima https://orcid.org/0000-0003-4200-9284
Pedro Faustino https://orcid.org/0000-0002-5399-5414

Data Availability Statement

Data is available by contacting the corresponding author (Miguel Tábuas-Pereira).

Supplemental Material

Supplemental material for this article is available online.

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