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## Sex differential effect of parental longevity on the risk of dementia.

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the effect of music therapy on individual neuropsychiatric symptoms.

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## SEX DIFFERENTIAL EFFECT OF PARENTAL LONGEVITY ON THE RISK OF DEMENTIA

*To the Editor:* Parental longevity (PL) has been previously associated with cardiovascular outcomes, diabetes mellitus, and cancer.<sup>1,2</sup> The relationship between PL and cognitive decline or dementia has been poorly studied, despite some evidence that individuals with exceptional PL develop dementia and Alzheimer's disease (AD) at a significantly lower rate.<sup>3,4</sup> Also, the observation that individuals with AD are more likely to have mothers with dementia suggests maternal transmission of AD,<sup>5</sup> which the observation of greater brain atrophy in offspring of mothers with AD and lower hippocampal volume in individuals with AD with a maternal history of dementia corroborates.<sup>6,7</sup> Whether there is a difference based on sex of the effect of parental longevity on offspring cognition has not been explored. The main objective of the current study was to determine the risk of overall cause of dementia associated with maternal and paternal longevity in a cohort of healthy elderly participants in southern Brazil.

For this report, data were used from a cohort study (Porto Alegre Longitudinal Aging) originally designed to evaluate healthy aging and dementia in community-dwelling individuals living in a southern Brazilian city. A complete description of the methods was published elsewhere.<sup>8</sup> Briefly, at baseline, 345 healthy individuals aged 60 and older without cognitive impairment were evaluated. The assessment consisted of questionnaires gathering demographic, social, and medical data and validated instruments to assess depression and psychiatric symptoms. Cognitive status was evaluated using the Brazilian version of the Mini-Mental State Examination<sup>9</sup> and the Clinical Dementia Rating Scale (CDR).<sup>10</sup> Dementia was defined as a CDR of 1 or greater. Health status was defined as an indicator variable. Individuals categorized as healthy did not have any chronic medical condition diagnosed by a physician (heart, lung, diabetes mellitus, cancer, or other chronic conditions). Socioeconomic status was estimated according to current total family income in minimum wages (a value defined by the Brazilian government—1 minimum wage = US\$353) divided by the number of persons dependent on it. A multivariate Cox proportional hazards model was used to assess the effect of age of

**Table 1. Cox Proportional Hazards Models for Mother and Father Age of Death**

Factor	Hazard Ratio (95% Confidence Interval)	P-Value
<b>Mother's age at death</b>		
Age of mother at death < 60	6.18 (1.46–26.16)	.01
Sex	0.43 (0.09–2.20)	.31
Education	0.89 (0.73–1.10)	.24
Health status	1.84 (0.36–9.55)	.47
Per capita income	0.99 (0.94–1.03)	.64
<b>Father's age at death</b>		
Age of father at death < 60	1.76 (0.44–7.10)	.43
Sex	0.49 (0.11–2.16)	.34
Education	0.89 (0.74–1.10)	.18
Health status	0.75 (0.19–2.97)	.68
Per capita income	0.97 (0.92–1.03)	.30

parent death, controlling for previously defined potential confounders (sex, education, health status, and per capita income). The age of parent death was entered in the model as a categorical variable (cut point of 60). Statistical significance was defined as  $P < .05$  with two-tailed tests. The local research and ethics review panel granted permission to perform the study (Table 1).

One hundred four subjects had all data required for the present analysis after 10 years of follow-up. During this period, 12 (11.5%) subjects developed dementia ( $CDR \geq 1$ ). Those with dementia were significantly older than those without dementia. Mother's age of death was greater in the group without dementia. The groups with and without dementia were similar in sex distribution, education, health status, per capita income, and age of father's death. Multivariate analysis, controlling for confounders, showed a greater risk of dementia in the group with mother's age of death of younger than 60 (hazard ratio = 6.18, 95% confidence interval = 1.46–26.16,  $P = .01$ ). The model for father's age of death did not show a significant effect.

The association between parental longevity and cognitive status was assessed once, as part of a longitudinal aging study.<sup>4</sup> In that study, having at least one parent with exceptional longevity ( $\geq 85$ ) was associated with less risk of AD, regardless of the sex of the progenitor. The use of exceptional longevity distinguishes that study from the current one, which could explain the different results. Limitations should be considered when interpreting the present findings (high dropout rate, residual confounding effect from other not directly assessed covariables—hypertension, smoking, dyslipidemias, alcoholism, physical activity). Further replication in other cohorts is necessary to confirm this effect, although possible mechanisms underlying it can be hypothesized. First, mothers who live longer could be more involved in their own and their offspring's health care, and this could influence their offspring's health status and cognition in adulthood in a more efficacious way than that of the fathers. Second, the transmission of mitochondrial deoxyribonucleic acid is exclusively by maternal lineage, and the findings reported herein could represent

this effect. Considering this genetic point of view, mitochondria have a well-known effect on aging and especially on neurodegenerative disorders, namely AD. The exact mechanism underlying the results remains unsolved, and more studies are needed to establish the real contribution of nature (genetics) and nurture (environment).

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## NUCLEOSOMES IN INDIVIDUALS WITH HIP FRACTURE WITH AND WITHOUT DELIRIUM

*To the Editor:* Delirium, an acute neuropsychiatric syndrome, is a common complication, particularly in individuals with hip fracture. Delirium is independently associated with impaired physical and cognitive recovery after the delirium symptoms have resolved, institutionalization, greater hospital costs, and greater mortality.<sup>1</sup>

High levels of cytokines in delirium were demonstrated in serum in medical patients, individuals with hip fracture, in the cerebrospinal fluid in individuals with hip fracture, and in post mortem brain tissue, suggesting an inflammatory pathogenesis.<sup>2–5</sup> Proinflammatory mechanisms may lead to cerebral cell damage, and cognitive dysfunction after delirium might be associated with this loss of cerebral neuronal cells.

It has been reported that dead cells or immune cells (e.g., neutrophils) release circulating cell-free deoxyribonucleic acid (DNA) in the form of nucleosomes and DNA-binding proteins such as histones upon activation.<sup>6,7</sup> Circulating DNA and DNA-binding proteins have been shown to be highly cytotoxic and to stimulate or perpetuate inflammatory responses,<sup>8,9</sup> so nucleosomes are a good measure of the proinflammatory response and cell death. No data are available on nucleosome levels in individuals with delirium.

## METHODS

This substudy was performed as part of a larger study investigating the pathophysiology of delirium. Study procedures have been described in detail elsewhere.<sup>4</sup>

A maximum of four blood samples was collected in every participant during their hospital stay under similar conditions at 11:00 a.m. on weekdays. For this substudy, samples were selected that were withdrawn the day before or after surgery to take into account the effect of surgery, with a maximum of one sample per participant.

Blood was kept on ice after withdrawal. Ethylenediaminetetraacetic acid plasma was obtained by centrifugation for 15 minutes at 1,780 g at 4°C, and aliquots were stored at 80°C. Nucleosome concentrations (U/mL) were measured using an enzyme-linked immunosorbent assay.<sup>10</sup>

Normal values in healthy subjects have previously been established as less than 5 U/mL.

## RESULTS

For this substudy, a random convenience sample consisting of 14 samples taken the day before surgery and 66 samples taken the day after was used; 16 of these were excluded because of undetectable nucleosome levels. Twenty-seven samples were available from individuals without delirium, and of the 37 individuals with delirium (58% of the total sample), 10 samples were taken before delirium, 23 during delirium, and four after delirium. Two samples had levels greater than 1,000 U/mL and were defined as outliers and excluded from further analyses. Individuals with delirium were older (85 vs 81,  $P = .04$ ) and were more likely to have preexisting cognitive impairment (68% vs 15%,  $P < .001$ ) and to be functionally impaired (65% vs 7%,  $P < .001$ ).

The median level of nucleosomes of the whole group was 68 U/mL before surgery and 64 U/mL after ( $P = .61$ ). The level of nucleosomes did not differ between participants with and without delirium (median 77 vs 60 U/mL,  $P = .34$ ) or between the groups before, during, and after and with no delirium ( $P = .50$ ). There was a significant difference between the three groups in median level of nucleosomes before ( $n = 10$ ; 74 U/mL, interquartile range (IQR) 31–151 U/mL), during ( $n = 23$ ; 77 U/mL, IQR 45–130 U/mL), and after ( $n = 4$ ; 110 U/mL, IQR 28–222 U/mL) delirium ( $P = .02$ ). Analysis using the Mann–Whitney test did not identify the groups responsible for this statistically significant difference.

## DISCUSSION

The current study showed for the first time high nucleosome levels in elderly adults with hip fracture with and without delirium. The results suggest cell death in all individuals as a result of an inflammatory response, most probably induced by the hip fracture and surgery because nucleosome levels were high in both groups.

To the knowledge of the authors, no other studies have investigated the association between nucleosomes and the course of delirium. The presence of cell-free DNA in the form of nucleosomes reflects cell death, most probably because of an inflammatory response,<sup>6,9</sup> although the origin of the nucleosomes detected in this study could not be established. Therefore, it is unclear from which dead cells nucleosomes were released in the present study. It is likely that hip fracture or surgical intervention was responsible for the nucleosomes released into the circulation. Because nucleosomes and DNA-binding proteins can induce an inflammatory response, released nucleosomes might perpetuate inflammation induced by hip fracture, which might render individuals susceptible to the development of delirium. Another possibility is that dead neuronal cells release nucleosomes, although it is unknown whether nucleosomes can pass through the blood–brain barrier or whether they can modulate permeability of the blood–brain barrier, because they are unspecific for the site of damage. Because of the small sample size, it was not possible to perform multivariate analyses to adjust for surgery, age, and