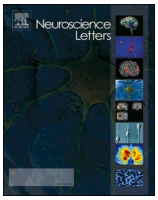
Neuroscience Letters 784 (2022) 136737

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Association between late maternal age and age-related endophenotypes in the Long Life Family Study

Sandra Barral [a,b,c,*], Stacy L. Andersen [d], Thomas T. Perls [e], Harold Bae [f], Paola Sebastiani [g], Kaare Christensen [h], Bharat Thyagarajan [i], Joseph Lee [a,b,c], Nicole Schupf [a,b,c,j]

[a] The Taub Institute for Research in Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, New York, NY, USA
[b] G.H. Sergievsky Center, Columbia University Medical Center, New York, NY, USA
[c] The Department of Neurology, Columbia University Medical Center, New York, NY, USA
[d] Boston University School of Medicine, Department of Medicine, Boston, MA, USA
[e] Department of Medicine, Boston University School of Medicine, Boston, MA, USA
[f] School of Biological and Population Health Sciences, College of Public Health and Human Sciences, Oregon State University Corvallis, OR, USA
[g] Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA
[h] University of Southern Denmark, Odense, Denmark, Department of Epidemiology, Biostatistics and Biodemography, Odense, Denmark
[i] Department of Laboratory Medicine and Pathology, University of Minnesota Medical School, Minneapolis, MN, USA
[j] The Department of Epidemiology, Joseph P. Mailman School of Public Health, Columbia University Medical Center, New York, NY, USA

ARTICLE INFO

Keywords:
Long-lived families
Late maternal age
Age-related endophenotypes

ABSTRACT

Extended maternal age has been suggested as marker of delayed age-associated disabilities. We use the Long Life Family Study (LLFS) offspring generation to investigate the association between extended maternal age at last childbirth and healthy-aging endophenotypes. We hypothesize that women with extended maternal age at last childbirth will exhibit healthier endophenotype profiles compared to younger mothers. The association between maternal age and age-related endophenotypes previously derived in LLFS was assessed using Generalized Estimating Equations to adjust for relatedness. The quartiles of the maternal age at last childbirth were modeled as the independent variables. Univariate analyses tested the association between maternal age at last childbirth and age at clinical assessment, education, field center, Apolipoprotein E (*APOE*) genotype, depression, stress, smoking and successful pregnancies. Only the variables significantly associated in the univariate analyses were considered in secondary multivariate analyses. Univariate analyses showed that compared to older mothers (age at last birth $\geq$35), mothers 30 years old or younger at last childbirth are less educated (12 $\pm$ 3 years versus 13 $\pm$ 3 years) and have a higher frequency of smoking (9% versus 3% for maternal age $\geq$35). Results showed that older mothers (age at last birth $\geq$31–34 or $\geq$ 35) demonstrated significantly better cognitive profiles ($p = 0.017$ and $p = 0.021$ respectively) compared with mothers with last childbirth age $\leq$30. Later maternal age among women from long-life families is associated with a better cognitive profile, supporting the hypothesis that later age at childbirth may be a marker for healthy aging.

1. Introduction

Much of the research on late maternal age has reported on the associated negative risks, i.e., older maternal age has been associated with increased probability of disorders such as Down syndrome, autism, or cancer [6,10,24] in their offspring as well as increased mortality risk for the mother. On the other hand, recent literature documents important benefits and advantages among children who are born to older parents. Studies in Swedish and British populations [7] adjusting for the secular trend of the time period have shown that children born to older mothers have higher cognitive abilities, and lower mortality.

There is also a growing body of research on how childbearing at older ages affects the health and wellbeing of the mother. Advanced maternal age is also associated with a higher risk of pregnancy-specific complications, such as preeclampsia, intrauterine growth restriction, preterm birth, and stillbirth [5,23].The population-level improvements over the 20th century (increased life expectancy, and cognitive abilities among other factors) might counterbalance the risks associated with

* Corresponding author at: G. H. Sergievsky Center & Taub Institute, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA.
E-mail address: smb2174@cumc.columbia.edu (S. Barral).

https://doi.org/10.1016/j.neulet.2022.136737
Received 6 May 2022; Received in revised form 2 June 2022; Accepted 10 June 2022
Available online 13 June 2022

advanced maternal age. Older maternal age can also be associated with socioeconomic resources that may help to alleviate the stress that comes with caring for a child [11].

Studies on the associations between women's reproductive history and health outcomes such as disability, chronic diseases, and mental health [20] have shown that women entering motherhood at a young age exhibited poorer health outcomes and earlier mortality [5]. There are also social and behavioral factors implicated, i.e., younger mothers may live in poorer housing, have lower educational attainment and be more likely to engage in detrimental habits. In contrast, consistent findings from several research groups [1,8,13,16,21] have reported on the positive association between late maternal age and longevity, suggesting that extended maternal age at last childbirth may be a marker for healthy aging.

In the present study, we use a Long Life Family Study sample to investigate whether women with extended maternal age at last childbirth have healthier profiles than women who gave birth to their last child at younger ages using previously reported LLFS healthy-aging endophenotypes [19].

2. Material and methods

2.1. Study population

LLFS is a longitudinal, family-based study (551 families consisting of two generations of 4,559 family members) to determine the genetic and phenotypic traits that increase the probability of survival to extreme ages and to determine the sub-phenotypes of exceptional survival. Details about study design can be found elsewhere [14,22]. In order to minimize the effect of secular trends across generations in childbearing, the analysis sample was restricted to the offspring generation.

2.2. LLFS age-related endophenotypes

We used the age-related biomarker constructs previously described in the LLFS cohort [19]. Briefly, results from factor analysis conducted in LLFS' participant's phenotypic data for 28 traits revealed five different age-related endophenotypes (LLFS factors, LFs): LF1 was dominated by physical activity and pulmonary function measures, LF2 loaded with metabolic measures, LF3 consisted of cognitive traits, LF4 reflected blood pressure related traits, and LF5 largely comprised of cardiovascular traits.

2.3. Statistical analysis

Differences in the degrees of association between maternal age and the age-related endophenotypes we assessed using General Linear Models in Generalized Estimating Equations (GEE) to adjust for differences in family size and relatedness among LLFS participants. The five age-related endophenotypes (LF1: cognition, LF2: physical_pulmonary, LF3: metabolic_cardiovascular, LF4: blood pressure and LF5: cardiovascular) were modeled separately as the dependent variable. We classified maternal age at last childbirth into 4 quartiles: Quartile 1 (Q1: $\leq$27 years old), Quartile 2 (Q2: 28–30 years old), Quartile 3 (Q3: 31 to 34 years old) and Quartile 4 (Q4: $\geq$35 years old). We excluded one person whose age at last birth was <20. Based on the limited sample size, we expect that the association effects will be modest and will be more evident when using quartiles of maternal age. To examine whether mothers who had their last birth at older age had healthier aging profiles in the five aging domains, quartiles of maternal age were categorized using a dosage model: quartiles 1 and 2 were considered as the reference group (coded as 0); quartiles 3 and 4 were coded as 1 and 2 respectively. Years of education was categorized into less than high school (<12 years) or high school completion or higher ($\geq$12 years). As an indicator of socio-economic status, we used the question: "During most of your life, how hard was it for you and your family to pay for the very basics (food, clothing and housing)". The five possible categories (hard, very hard, fine, easy and very easy) were dichotomized into low (hard, and very hard) and medium/high socioeconomic status (fine, easy, and very easy).

Univariate analyses were adjusted for age at clinical assessment, education, field center, the presence/absence of the Apolipoprotein E (*APOE*) e4 allele due to its reported association with poorer cognition [15], depression, smoking, stress (all self-reported diagnosis and coded as dichotomous variables), and number of successful pregnancies. Only the variables significantly associated in the univariate analyses (age, education, field center, smoke and number of pregnancies) were considered in secondary multivariate analyses. The same multivariate models were additionally performed in an analysis stratified by education categories.

The characteristics of the LLFS sample stratified by quartiles of the maternal age at last child are provided in Table 1.

We did not find any significant differences in the frequencies of *APOE*_E4 allele, depression and stress when comparing mothers in the first two quartiles of the age at last childbirth distribution with mothers in the third and fourth quartiles. We found a significantly higher frequency of smoking among mothers who were young at last childbirth ($\leq$30 years old) when compared with those having children at later ages, 9% versus 3% ($p < 0.001$). Variables found to be significantly associated with quartiles of maternal age in the univariate analyses were used as covariates in generalized estimated equations analyses (age, education, field center, smoking and number of successful pregnancies).

Results from generalized estimated equations analysis (Table 2) showed that compared with younger women (age at childbirth $\leq$30 years), women 31 or 35 years of age at last childbirth showed significantly better cognitive function ($p = 0.017$ and $p = 0.021$, respectively). Younger mothers at childbirth exhibited average cognitive scores 2.5 times lower than women aged 35 or older at childbirth (0.23 ± 0.11 versus 0.58 ± 0.14). None of the other age-related endophenotypes appeared associated with maternal age. Results stratifying by education also demonstrated a significant association between childbirth at older ages (31 or 35 years) and better cognitive performance (Exp(B) = 1.65, 95% Confidence Interval = 1.05–2.60, $p = 0.031$ and Exp(B) = 1.44, 95% C.I. = 1.00–2.06, $p = 0.046$, respectively) within the completion of highschool or higher strata ($n = 793$). Results within the less educated group also showed the same direction of association although did not reach significance; possibly due to limited sample size ($n = 389$).

3. Discussion

Our results suggest that extended maternal age among women from long-life families is associated with better cognitive health at older ages. Several studies [9,17,18] investigating the association between timing of birth with cognitive function have also reported that older age at last

Table 1
Characteristics of the LLFS study sample (N = 1,185) stratified by quartiles of age at last child.

variables	q1 ± q2	q3	q4	p
N	613	322	250	
maternal age (min–max, avg ± SD)	20–30, 27 ± 3	31–34, 32 ± 1	35–47, 36 ± 2	<0.001
current age (avg ± SD)	62 ± 8	60 ± 3	59 ± 9	<0.001
high school education (%)	60	70	80	<0.001
low socioeconomic status (%)	9	7	9	0.351
*APOE*_e4 (%)	21	21	21	0.962
depression (%)	18	23	24	0.106
smoking (%)	9	6	3	0.002
stress (%)	24	21	27	0.757
number of pregnancies (avg ± SD)	2 ± 1	2 ± 1	3 ± 1	<0.001

q1, q2, q3 and q4 represent the quartiles of the maternal age at last child.

Table 2
Generalized estimated equations secondary analysis results of maternal age's quartiles and age-related endophenotypes.

domain	Parameter	B	SE	Exp(B)	p	q1 ± q2	q3	q4
Cognition	q3	0.48	0.20	1.61	**0.017**	0.23 ± 0.11	0.58 ± 0.14	0.70 ± 0.17
	q4	0.36	0.15	1.43	**0.021**			
	age	−0.09	0.01	0.92	0.000			
	education	1.13	0.18	3.10	0.000			
	site	0.25	0.09	1.28	0.004			
	smoke	0.00	0.31	1.00	1.000			
	no. pregnancy	−0.12	0.07	0.89	0.092			
Physical_Pulmonary	q3	0.23	0.15	1.26	0.120	−2.74 ± 0.08	−2.53 ± 0.11	−2.52 ± 0.12
	q4	0.22	0.13	1.24	0.093			
	age	−0.17	0.01	0.85	0.000			
	education	0.46	0.14	1.59	0.001			
	site	−0.46	0.06	0.63	0.000			
	smoke	−0.38	0.26	0.68	0.145			
	no. pregnancy	0.01	0.06	1.01	0.834			
Metabolic_Cardiovascular	q3	−0.14	0.23	0.87	0.535	−0.89 ± 0.13	−0.99 ± 0.15	−1.03 ± 0.20
	q4	−0.10	0.19	0.90	0.585			
	age	0.06	0.01	1.06	0.000			
	education	−0.91	0.19	0.40	0.000			
	site	0.28	0.09	1.32	0.001			
	smoke	0.18	0.33	1.19	0.591			
	no. pregnancy	0.24	0.09	1.27	0.007			
Blood Pressure	q3	−0.28	0.19	0.75	0.134	0.42 ± 0.10	0.29 ± 0.12	0.14 ± 0.15
	q4	−0.14	0.16	0.87	0.393			
	age	0.10	0.01	1.10	0.000			
	education	−0.56	0.15	0.57	0.000			
	site	−0.41	0.07	0.66	0.000			
	smoke	0.34	0.29	1.40	0.246			
	no. pregnancy	−0.01	0.07	0.99	0.861			
Cardiovascular	q3	−0.16	0.17	0.86	0.344	0.33 ± 0.09	0.24 ± 0.10	0.17 ± 0.14
	q4	−0.09	0.14	0.91	0.507			
	age	0.02	0.01	1.02	0.028			
	education	−0.15	0.13	0.86	0.251			
	site	−0.56	0.06	0.57	0.000			
	smoke	0.12	0.29	1.13	0.664			
	no. pregnancy	−0.04	0.06	0.96	0.528			

Quartiles of maternal age were categorized using a dosage model: quartiles 1 and 2 were considered as the reference group (coded as 0); quartiles 3 and 4 were coded as 1 and 2 respectively. The last three columns represent the average and standard deviation values of the corresponding age-related endophenotype for each of the maternal age quartiles (q1 ± q2, q3 and q4).

birth was associated with better cognitive functioning in mothers.

We have previously reported on the role of cognitive performance as an indicator of healthy aging, i.e., showing that offspring of probands from the Long Life Family Study (LLFS) showed better cognitive performance on multiple cognitive tasks compared with individuals without a family history of longevity [4]. Additionally, we demonstrated that exceptional episodic memory performance strongly aggregates in the LLFS families [3] and that this might be genetically modulated [2].

Previous studies of associations between older maternal age and longer survival suggest that slower aging of the reproductive system and a delay in or escape from aging related diseases that adversely impact upon fertility translates into overall slower aging and compression of aging related disability and diseases (including Alzheimer's disease) towards the end of extreme old age [16]. Others have hypothesized that longer estrogen exposure is beneficial for cognitive function. Human and animal studies have shown that estrogen has a significant role in overall brain health and cognitive function, suggesting its role in promoting memory and learning [12]. The associations remained significant even after adjusting for a number of factors (health, activities, social contacts, socio-economic factors, etc.).

The study has some limitations. First, the limited sample size of the study may account for the lack of association between maternal age and the other age-related endophenotypes considered (physical and pulmonary, metabolic blood pressure and cardiovascular traits). Second, because the measures of cognitive performance are crossectional, we cannot exclude the possibility that older women at childbirth have a better cognitive profile at first visit compared to younger mothers. Third, our analyses were restricted to the LLFS offspring generation, while the age-related endophenotypes were originally derived considering both LLFS generations, which might have influenced the results. Fourth, accuracy of the effect of depression and stress variables used as covariates in the analyses might be affected due to their self-reported diagnosis. Follow-up studies in larger and ethnically diverse populations should be undertaken to replicate our results.

These findings are also consistent with the hypothesis that women who successfully have children at older age have protective genetic variants that slow aging and may contribute to their later maternal age.

4. Ethics approval and consent to participate

Recruitment, informed consent and study procedures were approved by the Institutional Review Boards of all participating sites.

CRediT authorship contribution statement

S. Barral, J. Lee and Schupf: Study conceptualization, data curation and formal analysis, and writing of the manuscript. S.L. Andersen, T. T. Perls, P. Sebastiani, H. Bae, K. Christensen, B. Thyagarajan: Methodology, writing and editing of the manuscript.

Funding

The present work has been supported through National Institute of Aging grant U19 AG063893.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] H. Bae, K.L. Lunetta, J.M. Murabito, S.L. Andersen, N. Schupf, T. Perls, P. Sebastiani, S. Long Life Family, Genetic associations with age of menopause in familial longevity, Menopause 26 (2019) 1204–1212.

[2] S. Barral, S. Cosentino, K. Christensen, A.B. Newman, T.T. Perls, M.A. Province, R. Mayeux, Long Life Family, Common genetic variants on 6q24 associated with exceptional episodic memory performance in the elderly, JAMANeurol 71 (2014) 1514–1519.

[3] S. Barral, S. Cosentino, R. Costa, S.L. Andersen, K. Christensen, J.H. Eckfeldt, A. B. Newman, T.T. Perls, M.A. Province, E.C. Hadley, W.K. Rossi, R. Mayeux, S. Long Life Family, Exceptional memory performance in the Long Life Family Study, Neurobiol Aging 34 (2013) 2445–2448.

[4] S. Barral, S. Cosentino, R. Costa, A. Matteini, K. Christensen, S.L. Andersen, N. W. Glynn, A.B. Newman, R. Mayeux, Cognitive function in families with exceptional survival, Neurobiol Aging 33 (619) (2012) e611–e617.

[5] C.-L. Cooke, S.T. Davidge, Advanced maternal age and the impact on maternal and offspring cardiovascular health, Am. J. Physiol. Heart Circ. Physiol. 317 (2) (2019) H387–H394.

[6] M.S. Durkin, M.J. Maenner, C.J. Newschaffer, L.C. Lee, C.M. Cunniff, J.L. Daniels, R.S. Kirby, L. Leavitt, L. Miller, W. Zahorodny, L.A. Schieve, Advanced parental age and the risk of autism spectrum disorder, Am. J. Epidemiol. 168 (2008) 1268–1276.

[7] A. Goisis, D.C. Schneider, M. Myrskyla, The reversing association between advanced maternal age and child cognitive ability: evidence from three UK birth cohorts, Int. J. Epidemiol. 46 (2017) 850–859.

[8] E. Grundy, O. Kravdal, Reproductive history and mortality in late middle age among Norwegian men and women, Am. J. Epidemiol. 167 (2008) 271–279.

[9] M. Heys, C.Q. Jiang, K.K. Cheng, W.S. Zhang, S.L.A. Yeung, T.H. Lam, G.M. Leung, C.M. Schooling, Life long endogenous estrogen exposure and later adulthood cognitive function in a population of naturally postmenopausal women from Southern China: the Guangzhou Biobank Cohort Study, Psychoneuroendocrino 36 (2011) 864–873.

[10] K.J. Johnson, S.E. Carozza, E.J. Chow, E.E. Fox, S. Horel, C.C. McLaughlin, B. A. Mueller, S.E. Puumala, P. Reynolds, J. Von Behren, L.G. Spector, Parental age and risk of childhood cancer a pooled analysis, Epidemiology 20 (2009) 475–483.

[11] R. Margolis, M. Myrskyla, A global perspective on happiness and fertility, Popul. Dev. Rev. 37 (2011) 29–56.

[12] J.M. Matyi, G.B. Rattinger, S. Schwartz, M. Buhusi, J.T. Tschanz, Lifetime estrogen exposure and cognition in late life: the Cache County Study, Menopause- J. North Am. Menopause Soc. 26 (2019) 1366–1374.

[13] H.-G. Muller, J.-M. Chiou, J.R. Carey, J.-L. Wang, Fertility and life span: late children enhance female longevity, J. Gerontol. A Biol. Sci. Med. Sci. 57 (5) (2002) B202–B206.

[14] A.B. Newman, N.W. Glynn, C.A. Taylor, P. Sebastiani, T.T. Perls, R. Mayeux, K. Christensen, J.M. Zmuda, S. Barral, J.H. Lee, E.M. Simonsick, J.D. Walston, A. I. Yashin, E. Hadley, Health and function of participants in the Long Life Family Study: a comparison with other cohorts, Aging (Albany NY) 3 (2011) 63–76.

[15] M.C. O'Donoghue, S.E. Murphy, G. Zamboni, A.C. Nobre, C.E. Mackay, APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review, Cortex 104 (2018) 103–123.

[16] T.T. Perls, L. Alpert, R.C. Fretts, Middle-aged mothers live longer, Nature 389 (1997) 133.

[17] S.L. Read, E.M.D. Grundy, Fertility history and cognition in later life, J. Gerontol. B-Psychol. 72 (2017) 1021–1031.

[18] J. Ryan, I. Carrière, J. Scali, K. Ritchie, M.-L. Ancelin, Life-time estrogen exposure and cognitive functioning in later life, Psychoneuroendocrino 34 (2) (2009) 287–298.

[19] J. Singh, N. Schupf, R. Boudreau, A.M. Matteini, T. Prasad, A.B. Newman, Y. Liu, K. Christensen, C.M. Kammerer, Association of aging-related endophenotypes with mortality in 2 cohort studies: the long life family study and the health, aging and body composition study, Am. J. Epidemiol. 182 (2015) 926–935.

[20] M. Sironi, G.B. Ploubidis, E.M. Grundy, Fertility History and Biomarkers Using Prospective Data: Evidence From the 1958 National Child Development Study, Demography 57 (2020) 529–558.

[21] F. Sun, P. Sebastiani, N. Schupf, H. Bae, S.L. Andersen, A. McIntosh, H. Abel, I. T. Elo, T.T. Perls, Extended maternal age at birth of last child and women's longevity in the Long Life Family Study, Menopause 22 (2015) 26–31.

[22] M.K. Wojczynski, S.J. Lin, P. Sebastiani, T.T. Perls, J. Lee, A. Kulminski, A. Newman, J.M. Zmuda, K. Christensen, M.A. Province, NIA long life family study: objectives, design, and heritability of cross sectional and longitudinal phenotypes, J. Gerontol. A Biol. Sci. Med. Sci. (2021).

[23] C. Wolfson, A. Gemmill, D.M. Strobino, Advanced maternal age and its association with cardiovascular disease in later life, Womens Health Issues 32 (3) (2022) 219–225.

[24] P.W. Yoon, S.B. Freeman, S.L. Sherman, L.F. Taft, Y. Gu, D. Pettay, W.D. Flanders, M.J. Khoury, T.J. Hassold, Advanced maternal age and the risk of Down syndrome characterized by the meiotic stage of chromosomal error: a population-based study, Am. J. Hum. Genet. 58 (1996) 628–633.