UC Irvine
UC Irvine Previously Published Works

Title
LATE and potential estrogen-related risk factors collected 30 years earlier: The 90+ Study

Permalink
https://escholarship.org/uc/item/75q5n3dt

Journal
Journal of Neuropathology & Experimental Neurology, 82(2)

ISSN
0022-3069

Authors
Paganini-Hill, Annlia
Montine, Thomas J
Bukhari, Syed A
et al.

Publication Date
2023-01-20

DOI
10.1093/jnen/nlac119

Copyright Information
This work is made available under the terms of a Creative Commons Attribution License, available at https://creativecommons.org/licenses/by/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Journal of Neuropathology & Experimental Neurology, 2023, **82**, 120–126
https://doi.org/10.1093/jnen/nlac119
Advance access publication 23 December 2022
Original Article

LATE and potential estrogen-related risk factors collected 30 years earlier: The 90+ Study

Annlia Paganini-Hill, PhD,[1]* Thomas J. Montine, MD, PhD,[2] Syed A. Bukhari, MS,[2] Maria M. Corrada, ScD,[1,3] Claudia H. Kawas, MD,[1,4] S. Ahmad Sajjadi, MD, PhD[1]

[1]Department of Neurology, University of California, Irvine, California, USA
[2]Department of Pathology, Stanford University, Palo Alto, California, USA
[3]Department of Epidemiology, University of California, Irvine, California, USA
[4]Department of Neurobiology and Behavior, University of California, Irvine, California, USA

*Send correspondence to: Annlia Paganini-Hill, Clinic for Ageing Research and Education, 24361 El Toro Road #150, Laguna Woods, CA 92637, USA; E-mail: apaganin@uci.edu

ABSTRACT

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) is a recently described neuropathological construct associated with dementia. This study aimed to investigate in an autopsy study, LATE-NC and its associations with potential estrogen-related risk factors collected about 30 years before death. Participants were part of The 90+ Study and had, as part of the Leisure World Cohort Study, provided information on menstrual and reproductive variables and details of use of estrogen replacement therapy (ERT). No menstrual and reproductive variable showed an association with LATE-NC. Use of ERT, especially long-term use (15+ years) and more recent use (within 1 year of completing the questionnaire), was associated with reduced risk. The odds were significantly lower for long-term (0.39, 95% confidence interval [CI]: 0.16–0.95) and recent use (0.39, 95% CI: 0.16–0.91) compared with no use. In conclusion, we found that women who reported long-term ERT in their 50s and 60s had a significantly reduced odds of harboring LATE-NC when they died in the 10th and 11th decades of their lives. Our study adds to the existing literature reporting seemingly protective effect of peri- and postmenopausal ERT against neurodegenerative dementia.

KEYWORDS: Estrogen replacement therapy, LATE, Menstrual history, Neuropathologic change, Reproductive history, Risk factors, TDP-43

INTRODUCTION

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently described neuropathological construct associated with dementia (1). Given that the oldest-old are at greatest risk of LATE and persons of advanced age constitute a growing demographic group, the number of persons with LATE is increasing (1, 2).

Although the neuropathological changes related to LATE (LATE-NC) have been observed in around 40% of aged brains in large autopsy cohorts (3), research is sparse and our understanding of LATE is limited (1). More research focused on LATE, including epidemiological studies, is needed. Identification of risk factors, protective influences, and other correlates may help prevent or predict LATE. Females are more likely to survive to advanced old age than males, which places them at increased lifetime risk for LATE (3). Therefore, this study aimed to investigate in an autopsy study of 90+ year-olds, LATE-NC and its associations with potential estrogen-related risk factors collected 30 years before death.

MATERIALS AND METHODS

Study population

Participants were part of The 90+ Study, a longitudinal study of aging and dementia among people aged 90 years and older (2, 4). These individuals were originally members of the Leisure World Cohort Study (LWCS), a population-based epidemiological health study established in the early 1980s of a California retirement community (Leisure World Laguna Hills) (5, 6). This cohort is composed of moderately affluent, highly educated, and health-conscious individuals; two-thirds are women. Persons alive and aged 90 years and older on January 1, 2003, on January 1, 2008, and on or after January 1, 2009 were invited to participate in The 90+ Study. Of the 2009 eligible cohort members, 1629 (81%) joined The 90+ Study but 303 died and were never seen, 216 were "telephone participants," and 151 "active by informants." Of the remaining 959, 308 consented to brain autopsy. Brain autopsy was available for 264, of whom 200 (76%) were female.

© The Author(s) 2022. Published by Oxford University Press on behalf of American Association of Neuropathologists, Inc.
All rights reserved. For permissions, please email: journals.permissions@oup.com

Brain autopsy and pathological classification

The brain specimens were procured by the University of California, Irvine Alzheimer's Disease Research Center neuropathology team and sent to the Department of Pathology at Stanford University who performed the brain autopsies blinded to clinical diagnosis. TAR DNA-binding protein 43 (TDP-43) was categorized based on anatomical location: none, limited to amygdala, involving hippocampus, or spread to cortex (1). We considered LATE-NC present if TDP-43 was found in any of the above anatomical locations.

Alzheimer disease (AD) neuropathological change (AD-NC) was defined using the National Institute on Aging-Alzheimer's Association criteria, which incorporates Thal Phase for Aβ plaques, Braak staging for neurofibrillary tangles, and Consortium to Establish a Registry for AD staging for neuritic plaques and categorized as none, low, intermediate, and high (7, 8).

Dementia determination

Clinical diagnosis of dementia was made applying Diagnostic and Statistical Manual of Mental Disorders 4th edition criteria (9) in a multidisciplinary consensus diagnostic conference done after a participant's death. All information on the participant except neuropathological findings was used in determination of dementia. In-person assessments performed every 6 months until death included a neurological examination, a neuropsychological test battery (10) including the Mini-Mental State Examination (MMSE) (11), videos of semistructured interviews about their daily life and questions to test their memory, and a brief examination of their gait. Information was also collected from informants, medical records, and death certificates.

Potential estrogen-related risk factors collected in 1980s

The Leisure World Cohort was established in the 1980s (1981–1985) when participants completed a postal health survey (5, 6, 12). The questionnaire included a section on menstrual and reproductive history and use of estrogen replacement therapy (ERT). This survey asked of the women: age at first menstrual period, ever pregnant, age at first child, number of children, age at last menstrual period, hysterectomy, age at hysterectomy, number of ovaries removed, age at first ovary removal, and age at second ovary removal. Questions about ERT (age started, current use, and age stopped) were asked separately for oral, injectable, and cream or suppository estrogens. For Premarin (the most commonly used oral estrogen), dose is distinguishable by pill color and questions asked for all doses taken and the dose taken for longest amount of time. Total number of years taken were asked separately for Premarin, other oral estrogens, injectable estrogens, and cream or suppository estrogens. The categories used for continuous variables, including estrogen use, were used in previous publications and are tertiles based on the distributions in the total LWCS (13).

Statistical analyses

Participant characteristics are reported as numbers and proportions for categorical variables and means and standard deviations for continuous variables. We compared LWCS variables in those with and without LATE-NC by neuropathological evaluation, in participants in The 90+ Study with and without neuropathological evaluation, in LWCS participants eligible to join The 90+ Study who did and did not join, and in those LWCS participants aged 90+ years who were eligible and not eligible to join The 90+ Study based on the recruitment timeframe of The 90+ Study. To compare the means of continuous variables between groups, we used the 2-sample t-test. To compare the proportions of categorical variables between groups, we used χ^2 test or Fisher exact test.

Odds ratios (ORs) of LATE-NC (yes vs no) for potential risk factors as measured by the LWCS were estimated using logistic regression analysis and adjusted for age at LWCS entry, age at death, and education (college graduate no/yes), and additionally for AD-NC pathology (none-low/intermediate-high). Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Table 1 shows the demographic and neurological characteristics of the 200 women included in the analyses. The average age at LWCS entry was 69 years (range: 53–87), the average age at death was 98 (range: 90–107), and the average number of years from entry to death was 29 (range: 18–40). Of the 68 women with LATE-NC, 8 were limited to the amygdala (stage I), 54 involved the hippocampus (stage II), and 6 had spread to the cortex (stage III). Because our unpublished data suggest all stages of LATE pathology are associated with dementia and due to the number of cases limited to the amygdala or with spread to the cortex were small, we compared LATE-NC present versus absent. Those with LATE-NC were on average 1.1 year older than those without and this difference was statistically significant. Overall, 60% of the participants died with dementia and the frequency was significantly higher in those with LATE-NC (73% vs 42%). As expected, those with LATE-NC had worse MMSE scores at the evaluation closest to death (14.1 vs 20.4). AD-NC was more frequent in those with LATE-NC than those without ($p = 0.01$); intermediate/severe AD was seen in 88% of those with LATE-NC versus 67% in those without. On the other hand, participants with LATE-NC were similar to those without in age at LWCS entry, interval from LWCS entry to death, postmortem interval, brain weight, education, and ApoE4 allele frequency (Table 1).

Although no menstrual and reproductive variable showed an association with LATE-NC (Table 2), use of ERT, especially long-term use (15+ years) and more recent use (within 1 year of completing the questionnaire), was associated with reduced risk. Table 3 shows the ORs and 95% confidence intervals (CIs) (both unadjusted and adjusted for age at LWCS entry, age at death, and education [college graduate no/yes]) of LATE-NC for use of ERT. The adjusted OR of LATE-NC for users of ERT compared with nonusers was not statistically significant (0.60, 95% CI: 0.31–1.16). However, the odds were significantly lower for long term (0.39, 95% CI: 0.16–0.95) and recent use (0.39, 95% CI: 0.16–0.91). On further analysis examining last use and duration combined,

Table 1. LATE-NC from brain autopsy of female 90+ year-old participants in the LWCS

	LATE-NC		
	No (n = 132)	Yes (n = 68)	p value for t-test
	Mean ± standard deviation (range)		
Age at entry in LWCS (years)	69.1 ± 4.9 (53–79)	69.3 ± 5.4 (54–87)	0.72
Age at death (years)	97.9 ± 3.5 (90–107)	99.0 ± 3.5 (92–106)	0.03
Interval LWCS entry to death (years)	28.8 ± 4.8 (19–40)	29.7 ± 4.4 (18–38)	0.22
Postmortem interval (hours) (n = 128, 68)*	9.2 ± 13.1 (1.0–85.7)	6.8 ± 7.6 (2.3–60.7)	0.11
Brain weight (n = 122, 67)*	1106 ± 113 (865–1412)	1076 ± 109 (880–1336)	0.08
MMSE at last examination (n = 126, 64)*	20.4 ± 9.0 (0–30)	14.1 ± 9.6 (0–29)	<0.0001
Interval from last MMSE to death (months) (n = 126, 64)*	6.9 ± 10.0 (0.2–82.9)	10.1 ± 14.7 (0.2–84.5)	0.12
	Number (%)		p value for χ^2
Education—college graduate	53 (40%)	32 (47%)	0.37
ApoE 4 allele (n = 127, 63)*	29 (23%)	11 (17%)	0.45
ApoE 2 allele (n = 127, 63)*	18 (14%)	8 (13%)	1.00
Postmortem case conference diagnosis (n = 131, 68)*			<0.0001
Normal	38 (29%)	6 (9%)	
CIND	38 (29%)	12 (18%)	
Dementia	55 (42%)	50 (73%)	
AD-NC			0.01
None	16 (12%)	2 (3%)	
Low	28 (21%)	6 (9%)	
Intermediate	47 (36%)	30 (44%)	
High	41 (31%)	30 (44%)	

* Numbers indicate the number of participants with available data for each column.

it appeared that within the same last use category, long-term duration (15+ years) users had lower odds of LATE-NC than short-term (≤14 years) users (Table 3). Similarly, within the same duration category, more recent (0–1 year ago) users had lower odds of LATE-NC than those who used ERT longer ago (Table 3). However, the only category with statistically significant lower odds than nonusers was long-term recent users (OR = 0.34 [0.12–0.97]). The strength or significance of associations did not change with further adjustment for AD-NC (none-low/intermediate-high).

Of the 8877 LWCS women, nearly half (49%, n = 4357) reached the age of 90 (Table 4). As recruitment into The 90+ Study did not start until 2003, 1573 were eligible for recruitment and 1272 (81%) joined the study. Use of ERT in women who reached age 90 (55%) was similar to that observed in all women (56%). Not unexpectedly, age at LWCS entry was younger and ERT use was greater in those eligible to join The 90+ Study in 2003 or later. However, those who joined were older (69.3 vs 66.6) than those not joining and their use of ERT was greater (67% vs 59%). No significant differences were observed for ERT between those with and without neuropathological evaluation.

DISCUSSION

In this study, we found that 90+ year-old female participants who had reported long-term use of ERT at the average age of 69 years (range: 53–87) had a reduced likelihood of LATE-NC at death of an average 3 decades later (18–40 years). The strengths of the study include collection of data on ERT use decades before death, possibly before development of neuropathologic change. Additionally, the LWCS is a population-based study which was formed by inviting all residents of the retirement community to participate and included 61%. Those attaining the age of 90+ in 2003 or later were invited to join The 90+ Study and 81% joined. A possible limitation is that our data on ERT use are self-reported using a postal survey. However, we have evidence to support their validity. We previously demonstrated good agreement of ERT self-reports with medical and pharmacy records in a sample of Leisure World residents (14). Although the medical chart provided only a limited history as it was initiated at the time of entry into the community, self-reported estrogen use had a 75% agreement, dose an 80% agreement, and duration an 89% agreement within 2 years between interview and medical chart. Additionally, in studies in this community of the relationships between ERT data and various disease outcomes (hip fracture and breast cancer), consistent risk ratios were obtained using self-report and medical record data (15, 16). Another limitation of the study is that our cohort is primarily white, moderately affluent, and highly educated. This may limit the generalization of our results to more diverse groups. As with all autopsy studies, factors influencing autopsy consent may introduce selection bias although we observed no differences in ERT use between those with and without autopsy. However, those who were eligible to join The 90+ Study but did not were younger and fewer used ERT than those who joined. Additionally, our sample is relatively small.

Few studies have investigated the potential association of LATE-NC with past medical histories and, to our knowledge, none has investigated the possible link between LATE-NC and estrogen-related factors. Besser et al. (17) investigated

Table 2. LATE-NC from brain autopsy of female 90+ year-old participants in the LWCS: potential menstrual and reproductive risk factors from 1980s questionnaire

	LATE-NC		
	No (n = 132)	Yes (n = 68)	p value for $\chi 2$
	Number (%)		
Age at menarche (mean ± SD)	13.1 ± 1.4	13.4 ± 1.4	0.33
≤12 years	44 (33%)	19 (28%)	
13 years	44 (33%)	19 (28%)	
14+ years	44 (33%)	30 (44%)	
Number of children (n = 132, 67)* (mean ± SD)	1.7 ± 1.3	1.8 ± 1.6	0.69
0	31 (23%)	16 (24%)	
1	18 (14%)	11 (16%)	
2	54 (41%)	22 (33%)	
3+	29 (22%)	18 (27%)	
Age at first child (n = 132, 66)*			0.94
≤20 years	6 (5%)	4 (6%)	
21–24 years	30 (23%)	15 (23%)	
25–29 years	37 (28%)	20 (30%)	
30+ years	28 (21%)	11 (17%)	
No child	31 (23%)	16 (24%)	
Menopause			0.82
Natural	82 (62%)	42 (62%)	
Surgical without bilateral oophorectomy	25 (19%)	10 (15%)	
Bilateral oophorectomy	17 (13%)	11 (16%)	
Surgical NOS	8 (6%)	5 (7%)	
Menopause			1.00
Natural	82 (62%)	42 (62%)	
Artificial	50 (38%)	26 (38%)	
Age last menstrual period (n = 131, 68)* (mean ± SD)	47.8 ± 6.4	48.3 ± 5.1	0.83
≤44 years	38 (29%)	17 (25%)	
45–54 years	76 (58%)	42 (62%)	
55+ years	17 (13%)	9 (13%)	
Weight at last menstrual period (n = 130, 67)* (mean ± SD)	129 ± 16	126 ± 16	0.59
≤120 pounds	42 (32%)	25 (37%)	
121–138 pounds	57 (44%)	30 (45%)	
139+ pounds	31 (24%)	12 (18%)	
Reproductive period (years) (n = 131, 68)* (mean ± SD)	35 ± 6.4	35 ± 5.0	0.69
<34	44 (34%)	26 (38%)	
34–37	43 (33%)	23 (34%)	
38+	44 (34%)	19 (28%)	

* Numbers indicate the number of participants with available data for each column.

potential risk factors and neuropathological characteristics associated with LATE-NC in 616 autopsied participants from the National Alzheimer's Coordinating Center (NACC) (>75 years at death, mean = 86 years, 49% female). Among 253 with LATE-NC (defined as TDP-43 inclusions in the limbic region [amygdala, hippocampus, or entorhinal/inferior temporal cortex]) and 363 without LATE-NC, congestive heart failure was the only medical history variable that was associated with reduced likelihood of LATE-NC. As in our study, ApoE genotype was not associated with LATE-NC. In The 90+ Study participants, we have found that histories of hypertension and osteoarthritis were associated with lower likelihood of LATE-NC (18).

Another line of evidence supporting a possible protective effect of estrogen against LATE-NC comes from studies on amyotrophic lateral sclerosis (ALS). TDP-43 is also the proteinopathy signature of ALS (19). Studies using ALS mouse models have shown that estrogen might protect neurons against TDP-43 pathology (20) and improve neuronal plasticity (21). Moreover, a study on TDP-25 cell lines demonstrated the effect of the selective estrogen receptor modulator raloxifene on enhancing the viability of 25-kDa C-terminal fragment of TDP-43 by enhancing autophagy and suppressing apoptosis (22). Similar effects were observed with 17 beta-estradiol (22).

Previous epidemiological studies investigating the association of AD and ERT further corroborate our findings. Although LATE-NC and AN-DC have differing neuropathological hallmarks, they may share upstream risk factors and disease mechanisms. Brains that harbor AD-NC tend to contain TDP-43 proteinopathy at rates higher than those lacking AD-NC (1, 3). Several case-control and prospective cohort studies have reported reduced risk of AD among users of ERT and meta-analyses suggest reduction of about one-third (23).

Table 3. LATE-NC from brain autopsy of female 90+ year-olds participants in the LWCS: ERT from 1980s questionnaire

	LATE-NC				
	No (n = 132) Number (%)	Yes (n = 68)	OR (95% CI)	Adjusted* OR (95% CI)	Adjusted† OR (95% CI)
ERT					
No	31 (23%)	23 (34%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Yes	101 (77%)	45 (66%)	0.60 (0.31–1.14)	0.60 (0.31–1.16)	0.54 (0.27–1.09)
Duration of ERT					
No estrogen	31 (23%)	23 (34%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤3 years	29 (22%)	12 (18%)	0.56 (0.23–1.32)	0.49 (0.20–1.19)	0.47 (0.19–1.18)
4–14 years	35 (27%)	23 (34%)	0.89 (0.42–1.88)	0.92 (0.43–1.99)	0.80 (0.35–1.80)
15+ years	37 (28%)	10 (15%)	0.36 (0.15–0.88)	0.39 (0.16–0.95)	0.35 (0.14–0.89)
Last use of ERT					
No estrogen	31 (23%)	23 (34%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
15+ years ago	20 (15%)	14 (21%)	0.94 (0.39–2.25)	0.89 (0.39–2.18)	0.94 (0.37–2.40)
2–14 years ago	38 (29%)	19 (28%)	0.67 (0.31–1.46)	0.66 (0.30–1.46)	0.55 (0.24–1.27)
0–1 year ago	43 (33%)	12 (18%)	0.38 (0.16–0.87)	0.39 (0.16–0.91)	0.33 (0.13–0.82)
Dose of Premarin ERT (n = 125, 56)‡					
None	31 (30%)	23 (41%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≤0.625 mg	34 (32%)	18 (32%)	0.71 (0.32–1.57)	0.72 (0.32–1.60)	0.58 (0.25–1.34)
≥1.25 mg	40 (38%)	15 (27%)	0.51 (0.23–1.13)	0.51 (0.23–1.14)	0.50 (0.21–1.16)
Type of ERT					
No estrogen	31 (23%)	23 (34%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Oral only	54 (41%)	33 (49%)	0.82 (0.41–1.65)	0.80 (0.40–1.62)	0.75 (0.36–1.58)
Oral + other	42 (32%)	10 (15%)	0.32 (0.13–0.77)	0.34 (0.14–0.82)	0.29 (0.12–0.74)
Injection or cream only	5 (4%)	2 (3%)	0.54 (0.10–3.03)	0.49 (0.08–2.89)	0.28 (0.04–1.72)
Last use/duration of ERT					
None	31 (23%)	23 (34%)	1.00 (reference)	1.00 (reference)	1.00 (reference)
15+ years ago, ≤14 years	20 (15%)	14 (21%)	0.94 (0.39–2.25)	0.88 (0.36–2.16)	0.93 (0.37–2.39)
15+ years ago, 15+ years	0	0			
2–14 years ago, ≤14 years	26 (20%)	15 (22%)	0.78 (0.34–1.79)	0.74 (0.31–1.75)	0.64 (0.26–1.58)
2–14 years ago, 15+ years	12 (9%)	4 (6%)	0.45 (0.13–1.57)	0.48 (0.13–1.72)	0.36 (0.10–1.36)
0–1 years ago, ≤14 years	18 (14%)	6 (9%)	0.45 (0.15–1.31)	0.46 (0.15–1.41)	0.34 (0.11–1.10)
0–1 years ago, 15+ years	25 (19%)	6 (9%)	0.32 (0.11–0.92)	0.34 (0.12–0.97)	0.33 (0.11–0.98)

* Adjusted for age at LWCS entry, age at death, and education (college graduate no/yes).
† Adjusted for age at LWCS entry, age at death, education (college graduate no/yes), and AD-NC (none-low/intermediate-high).
‡ Numbers indicate the number of participants with available data for each column.

Although the one clinical trial (Women's Health Initiative Memory Study [WHIMS]) of continuous combined estrogen plus progestogen hormone therapy initiated at age 65+ years provides moderate evidence of increased risk of dementia (AD was not specifically addressed) (24), the timing of ERT has been suggested as playing an important role (25). Because ERT is often started during the peri- or early postmenopause for treatment of vasomotor symptoms, estrogen use in observational studies generally occurred at a relatively young age. WHIMS findings might not generalize to women who initiated hormone therapy much closer to the time of menopause and/or used unopposed ERT. Three observational studies offer evidence for an early temporal window during which hormone therapy might reduce risk of AD or dementia (26–28). In the large Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) case-control study, reduction in AD risk was evident only among younger postmenopausal women (26). In the Kaiser Permanente study, self-reported use at midlife (mean age 49 years), coupled with no record of hormone therapy prescriptions in a pharmacy database during a 5-year period nearly 3 decades later, was associated with a significant reduction in risk of all-cause dementia while late life hormone prescriptions without midlife use were associated with significantly increased risk (27). In the Cache County cohort study of healthy postmenopausal women aged 65 years and older, self-reported initiation of hormone therapy within 5 years of menopause was linked to a significant reduction in incident AD, whereas later initiation did not alter risk (28). Another randomized trial (Multiple Outcomes of Raloxifene Evaluation [MORE]) in postmenopausal women with osteoporosis assessed similar endpoints, comparing raloxifene to placebo (29). Compared with those taking placebo, women receiving 120 mg/day of raloxifene for 3 years had a 33% lower risk of mild cognitive impairment and a somewhat lower risk of AD (relative risk = 0.52, 95% CI: 0.22–1.21).

In conclusion, we found that women who reported long-term ERT in their 50s and 60s had significantly reduced odds of harboring LATE-NC when they died in the 10th and 11th decades of their lives. Our study adds to the existing literature reporting seemingly protective effect of peri- and postmenopausal ERT against neurodegenerative dementia. Strengths of the study include follow-up of a population-based cohort from

Table 4. Baseline demographic and ERT from 1980s questionnaire as reported by LWCS women.

	LWCS all n = 8877	LWCS aged 90+ n = 4357	Not eligible 90+ Study n = 2784	Eligible 90+ Study n = 1573	Not joined 90+ Study n = 301	Joined 90+ Study n = 1272	No autopsy n = 1072	Autopsy n = 200
				Mean ± standard deviation				
Age at LWCS entry (years)				$p < 0.0001$				
	73.2 ± 7.4 (44–101)	75.1 ± 7.6 (50–101)	78.6 ± 6.1 (50–101)	68.8 ± 5.6 (52–87)	66.6 ± 6.3 (52–82)	69.3 ± 5.3 (53–87)	69.4 ± 5.3 (53–86)	69.1 ± 5.1 (53–87)
Age at death (years)			$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	
	90.0 ± 7.4 (59–110)	95.0 ± 7.6 (90–110)	94.0 ± 3.1 (90–110)	96.7 ± 5.6 (90–110)	95.8 ± 3.5 (90–107)	96.9 ± 3.6 (90–110)	96.6 ± 3.6 (90–110)	98.2 ± 3.6 (90–107)
				n (%)				
ERT			$p < 0.0001$		$p = 0.01$			
No	3863 (43%)	1943 (45%)	1403 (51%)	540 (34%)	123 (41%)	417 (33%)	363 (34%)	54 (27%)
Yes	4987 (56%)	2404 (55%)	1373 (49%)	1031 (66%)	178 (59%)	853 (67%)	707 (66%)	146 (73%)
Duration of ERT			$p < 0.0001$		$p = 0.03$			
No estrogen	3863 (44%)	1943 (45%)	1403 (51%)	540 (35%)	123 (41%)	417 (33%)	363 (34%)	54 (27%)
≤3 years	1505 (17%)	754 (18%)	463 (17%)	291 (19%)	58 (19%)	233 (18%)	192 (18%)	41 (20%)
4–14 years	1811 (21%)	827 (19%)	423 (16%)	404 (26%)	66 (22%)	338 (27%)	280 (26%)	58 (29%)
15+ years	1537 (18%)	768 (18%)	438 (16%)	330 (21%)	53 (18%)	277 (22%)	230 (22%)	47 (24%)
Last use of ERT			$p < 0.0001$		$p = 0.03$			
No estrogen	3863 (44%)	1943 (45%)	1403 (51%)	540 (35%)	123 (41%)	417 (33%)	363 (34%)	54 (27%)
15+ years ago	1553 (18%)	814 (19%)	597 (22%)	217 (14%)	31 (10%)	186 (15%)	152 (14%)	34 (17%)
2–14 years ago	1876 (21%)	889 (21%)	452 (17%)	437 (28%)	74 (25%)	363 (29%)	306 (29%)	57 (29%)
0–1 year ago	1444 (17%)	655 (15%)	283 (10%)	372 (24%)	72 (24%)	200 (24%)	245 (23%)	55 (27%)
Dose of Premarin ERT			$p < 0.0001$		$p = 0.07$			
None	3863 (55%)	1943 (57%)	1403 (65%)	540 (44%)	123 (49%)	417 (41%)	363 (42%)	54 (34%)
≤0.625 mg	1467 (21%)	723 (21%)	359 (17%)	354 (28%)	60 (24%)	294 (29%)	242 (28%)	52 (32%)
≥1.25 mg	1709 (24%)	770 (22%)	385 (18%)	385 (30%)	70 (28%)	315 (31%)	260 (30%)	55 (34%)
Type of ERT			$p < 0.0001$		$p = 0.06$			
No estrogen	3863 (44%)	1943 (45%)	1403 (51%)	540 (35%)	123 (41%)	417 (33%)	363 (34%)	54 (27%)
Oral only	3061 (35%)	1451 (34%)	821 (30 %)	630 (40%)	106 (35%)	524 (41%)	437 (41%)	87 (44%)
Oral +other	1365 (15%)	656 (15%)	348 (13%)	308 (20%)	55 (18%)	253 (20%)	201 (19%)	52 (26%)
Injection and/or cream only	529 (6%)	281 (6%)	194 (7%)	87 (6%)	15 (5%)	72 (6%)	65 (6%)	7 (3%)
Last use/duration of ERT			$p < 0.0001$					
None	3863 (44%)	1943 (45%)	1403 (51%)	540 (35%)	123 (41%)	417 (33%)	363 (34%)	54 (27%)
15+ years ago, ≤14 years	1450 (17%)	755 (18%)	547 (20%)	208 (13%)	30 (10%)	178 (14%)	144 (14%)	34 (17%)
15+ years ago, 15+ years	91 (1%)	53 (1%)	45 (2%)	8 (0.5%)	1 (0.3%)	7 (0.6%)	7 (0.6%)	0
2–14 years ago, ≤14 years	1254 (14%)	561 (13%)	243 (9%)	318 (20%)	50 (17%)	268 (21%)	227 (21%)	41 (21%)
2–14 years ago, 15+ years	616 (7%)	324 (8%)	206 (8%)	118 (8%)	24 (8%)	94 (7%)	78 (7%)	16 (8%)
0–1 years ago, ≤14 years	603 (7%)	261 (6%)	93 (3%)	168 (11%)	44 (15%)	124 (10%)	100 (9%)	24 (12%)
0–1 years ago, 15+ years	829 (10%)	390 (9%)	187 (7%)	203 (13%)	28 (9%)	175 (14%)	144 (14%)	31 (15%)

early old age when ERT was reported to brain autopsy at extreme old age, pathological confirmation as opposed to clinical diagnosis, and robust data collection methods. Further research is required to establish the mechanism through which ERT exerts its neuroprotective effects.

FUNDING

This work was supported by the National Institutes of Health [grants R01CA32197, R01AG21055, and UF1AG057707]; the Earl Carroll Trust Fund, University of Southern California, Los Angeles, CA [grant]; and Wyeth-Ayerst Laboratories, Philadelphia, PA [grant 93-022-MA].

ACKNOWLEDGMENTS

ApoE genotyping was done by the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD), which receives support under a cooperative agreement grant (U24AG021886) from the National Institute on Aging.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Nelson PT, Dickson DW, Trojanowski JQ, et al. Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. Brain 2019;142:1503–27
2. Corrada MM, Berlau DJ, Kawas CH. A population-based clinicopathological study in the oldest-old: The 90+ Study. Curr Alzheimer Res 2012;9:709–17
3. Nelson PT, Brayne C, Flanagan ME, et al. Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: Combined data from 13 community-based or population-based autopsy cohorts. Acta Neuropathol 2022;144:27–44
4. Paganini-Hill A, Kawas CH, Corrada MM. Lifestyle factors and dementia in the oldest-old: The 90+ Study. Alzheimer Dis Assoc Disord 2016;30:21–6
5. Paganini-Hill A, Ross RK, Henderson BE. Prevalence of chronic disease and health practices in a retirement community. J Chronic Dis 1986;39:699–707
6. Paganini-Hill A, Chao A, Ross RK, et al. Exercise and other factors in the prevention of hip fracture: The Leisure World study. Epidemiology 1991;2:16–25
7. Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement 2012;8:1–13
8. Montine TJ, Phelps CH, Beach TG, et al.; Alzheimer's Association. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach. Acta Neuropathol 2012;123:1–11
9. American Psychiatric Association. Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th edn. Washington, DC: American Psychiatric Association; 1994
10. Whittle C, Corrada MM, Dick M, et al. Neuropsychological data in nondemented oldest old: The 90+ Study. J Clin Exp Neuropsychol 2007;29:290–9
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98
12. Paganini-Hill A, Ross RK, Henderson BE. Endometrial cancer and patterns of use of oestrogen replacement therapy: A cohort study. Br J Cancer 1989;59:445–7
13. Paganini-Hill A, Corrada MM, Kawas CH. Prior endogenous and exogenous estrogen and incident dementia in the 10th decade of life: The 90+ Study. Climacteric 2020;23:311–5
14. Paganini-Hill A, Ross RK. Reliability of recall of drug usage and other health-related information. Am J Epidemiol 1982;116:114–22
15. Ross RK, Paganini-Hill A, Gerkins VR, et al. A case–control study of menopausal estrogen therapy and breast cancer. JAMA 1980;243:1635–9
16. Paganini-Hill A, Ross RK, Gerkins VR, et al. Menopausal estrogen therapy and hip fractures. Ann Intern Med 1981;95:28–31
17. Besser LM, Teylan MA, Nelson PT. Limbic predominant age-related TDP-43 encephalopathy (LATE): Clinical and neuropathological associations. J Neuropathol Exp Neurol 2020;79:305–13
18. Sajjadi SA, Bukhari S, Scambray K, et al. Impact and risk factors of limbic predominant age-related TDP-43 encephalopathy neuropathologic change in an oldest old cohort. Neurology 2022; (in press)
19. Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006;314:130–3
20. Huang SL, Wu LS, Lee M, et al. A robust TDP-43 knock-in mouse model of ALS. Acta Neuropathol Commun 2020;8:3
21. Handley EE, Reale LA, Chuckowree JA, et al. Estrogen enhances dendrite spine function and recovers deficits in neuroplasticity in the prpTDP-43(A315T) mouse model of amyotrophic lateral sclerosis. Mol Neurobiol 2022;59:2962–76
22. Zhou F, Dong H, Liu Y, et al. Raloxifene, a promising estrogen replacement, limits TDP-25 cell death by enhancing autophagy and suppressing apoptosis. Brain Res Bull 2018;140:281–90
23. Song YJ, Li SR, Li XW, et al. The effect of estrogen replacement therapy on Alzheimer's disease and Parkinson's disease in postmenopausal women: A meta-analysis. Front Neurosci 2020;14:157
24. Shumaker SA, Legault C, Kuller L, et al.; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291:2947–58
25. Henderson VW. Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after menopause. J Steroid Biochem Mol Biol 2014;142:99–106
26. Henderson VW, Benke KS, Green RC, et al.; MIRAGE Study Group. Postmenopausal hormone therapy and Alzheimer's disease risk: Interaction with age. J Neurol Neurosurg Psychiatry 2005;76:103–5
27. Whitmer RA, Quesenberry CP, Zhou J, et al. Timing of hormone therapy and dementia: The critical window theory revisited. Ann Neurol 2011;69:163–9
28. Shao H, Breitner JC, Whitmer RA, et al.; Cache County Investigators. Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. Neurology 2012;79:1846–52
29. Yaffe K, Krueger K, Cummings SR, et al. Effect of raloxifene on prevention of dementia and cognitive impairment in older women: The multiple outcomes of raloxifene evaluation (MORE) randomized trial. Am J Psychiatry 2005;162:683–90