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A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease:

The Baltimore Longitudinal Study of Aging

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Article abstract—Previous reports have suggested that estrogen replacement therapy (ERT) in women may exert a protective effect on their risk of developing Alzheimer's disease (AD). We investigated this relationship in the Baltimore Longitudinal Study of Aging (BLSA), a prospective multidisciplinary study of normal aging conducted by the National Institute on Aging. The sample consisted of 472 post- or perimenopausal women followed for up to 16 years in the BLSA. We documented ERT prospectively at each BLSA visit, and we categorized women who had used oral or transdermal estrogens at anytime as ERT users. We used Cox proportional hazards models with time-dependent covariates to estimate the relative risk of developing AD after ERT as compared with women who had not used estrogen replacement. Approximately 45% of the women in the cohort had used ERT, and we diagnosed 34 incident cases of AD (NINCDS/ADRDA criteria) during follow-up, including nine estrogen users. After adjusting for education, the relative risk for AD in ERT users as compared with nonusers was 0.46 (95% CI, 0.209–0.997), indicating a reduced risk of AD for women who had reported the use of estrogen. Our data did not show an effect for duration of ERT usage. Our finding offers additional support for a protective influence of estrogen in AD. Randomized clinical trials are necessary to confirm this association, which could have significant public health impact.

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Alzheimer's disease (AD) is one of the most frequent obstacles to healthy aging in the United States.[1] The disorder afflicts twice as many women,[2,3] in part because of the shorter life expectancy for men. Thus, the identification of factors that could influence the clinical expression of dementia in women would have a substantial impact on the societal burden of AD.

Several studies have implicated estrogen in the

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maintenance of brain structure and function, particularly in areas known to degenerate in AD.[4,5] If the decline in estrogen levels experienced by women during menopause contributes to the development of age-associated cognitive loss or AD, estrogen replacement therapy (ERT) could provide a potential strategy for improving cognitive health in women and delaying the onset of AD.

Previous studies of the possible effects of ERT on the development of AD have been inconclusive. Although some investigators have found no association between estrogen use and AD,[6-8] three studies have suggested that women who use ERT are less likely to develop AD. In two case-control investigations,[9,10] AD patients enrolled in longitudinal protocols were less likely to be using estrogen replacement on initial evaluation than nondemented control subjects. Clinic-based studies, however, may reflect different prescribing practices for women with AD rather than a protective effect of ERT. Moreover, medical record information on ERT usage was substantiated differently for patients (surrogate informants) and control subjects (self-report). However, two population-based studies have also indicated that estrogen may reduce the risk of AD. One study [11] showed a reduced risk of AD over 1 to 5 years of follow-up in subjects who had reported using ERT (RR .40, CI 0.22 to 0.85). Moreover, age at onset of AD was significantly lower in women who had taken estrogen than in those who did not. A second investigation,[12,13] designed as a case-control study nested within a population-based study, found that the risk of AD and related dementias was less in estrogen users than in nonusers (odds ratio, 0.65; 95% CI, 0.49 to 1.03). This result was enhanced by the AD risk decreasing significantly with increasing estrogen dose and with increasing duration of estrogen use. A limitation of this study was case ascertainment from death certificates, a method that may underestimate AD by up to 70%.[14]

The Baltimore Longitudinal Study of Aging[15] (BLSA) has been collecting ERT data since enrollment of women began in 1978, allowing us to investigate use of ERT and risk of developing AD in this prospective study of normal aging conducted by the National Institute on Aging (NIA).

Methods. *Subjects.* Five hundred fourteen post- or perimenopausal women who had been followed for up to 16 years in the BLSA/NIA were eligible for the study. The mean age at enrollment was 61.5 years (range 28 to 94). The women in this sample had a high level of education, with 63% of the group having college or graduate degrees, 24% having some college, and 14% percent having high school education or less. Mean (± SD) ages of menopause were 46.4 ± 6.5 and menarche were 12.7 ± 1.5. The women were predominately white (92%), and 29% had undergone hysterectomy.

Every 2 years, subjects returned to the Gerontology Research Center (GRC/NIA) for 2.5 days of multidisciplinary evaluations that included medical history, medication usage (including estrogens), physical and neurologic examinations, neuropsychological and functional assessments, and numerous other physiologic and psychological procedures. Subjects who became inactive (no visits to the GRC in 3 years) were generally examined in their place of residence.

Women who had ever used oral or transdermal estrogens were considered ERT users. Women who had used only estrogen creams were included in the nonuser group because this form of therapy generally does not significantly increase circulating levels of estrogens. Premenopausal use of oral contraceptives was also not included in the user group because this therapy is considered replacement dosing for the endogenous production of ovarian estrogens. Use of ERT was documented every 2 years.

Information on past and present duration of ERT use was reported by subjects via categorical assignment (i.e., <6 months, 7 months to 1 year, etc.) rather than total months of ERT use. Because duration data were collected as categories, subjects were assigned the midpoint of the interval as the duration of ERT exposure. For example, women who reported using ERT for 1 to 5 years were assigned 3 years of use. Past use and present use were added to obtain the total duration of ERT exposure.

Dementia was diagnosed by neurologic examination and appropriate laboratory and imaging studies. All AD subjects met DSM-III-R[16] criteria for dementia and NINCDS-ADRDA[17] criteria for definite (n = 1), probable (n = 18), or possible AD (n = 15).

Analysis. The objective of the statistical analysis was to estimate the relative risk (RR) of developing AD associated with ERT. A Cox proportional hazards regression analysis[18] was chosen as the method of analysis. Chronologic age was used as the time scale, thus enabling the analysis to control for age. The model compares each case of AD with all subjects in the study who are alive and free of AD at the age when the AD case was diagnosed. For example, a subject diagnosed at age 75 would be compared with respect to ERT and other covariates to all noncases who are also 75 years old. The set of all people who are compared with each AD case is called a risk set. Individuals are eligible to enter risk sets at ages after their age of entry into the BLSA.[19] A time-dependent binary covariate was defined as 0 before ERT use and one after ERT use. Education was also included in the model as a binary variable (greater or equal to 16 years versus less than 16 years of education).

Other variables examined individually included age at menopause, age at menarche, years of natural cyclic estrogen exposure, duration of menopause, and surgical menopause. The risk of AD was also examined in relation to duration of ERT use where total duration was defined as a categorical variable: no use, >0 to 5 years, 5 to 10 years, and >10 years of ERT use. Finally, an additional analysis was performed that included a time-dependent binary covariate for use of nonsteroidal anti-inflammatory drugs (NSAIDs), which have been reported to have a protective effect in AD.[20-23] The RRs for the Cox model were estimated using SAS PROC PHREG version 6.10.

Results. Of the 514 women eligible for the study, 230 (45%) reported use of ERT and 8% were missing data on ERT use. Only 5% of the ERT users had used estrogen patches; the remainder had used one of the oral formulations. ERT users and nonusers did not differ in education, menopause duration, or ages of enrollment, menarche, and

Table *Estimated RR and 95% CI of AD associated with duration of use of ERT: results from a Cox regression model*

Variable	β-coefficient	RR	95% CI	*p*
0 yr	—	1.000	—	—
>0–5 yr	−0.814	0.443	0.130–1.507	0.19
>5–10 yr	−1.084	0.338	0.045–2.517	0.29
>10 yr	−0.693	0.500	0.500–0.170	0.21
Education*	0.258	1.294	0.627–2.671	0.49

* Education was defined as a dichotomous covariate (<16 yr vs. ≥16 yr) in all models.

AD = Alzheimer's disease.

menopause. There was also no difference in education or AD rate in women with missing ERT data and those who had ERT information. During the follow-up period, 34 incident cases of AD were diagnosed of 472 women with ERT data. Among these cases, there were nine women who reported use of ERT.

The RR for the development of AD was 0.457 (95% CI, 0.209 to 0.997) when ERT users were compared with nonusers in the BLSA. Education was not a significant factor in the model, perhaps because of the relatively narrow education range in this cohort (RR, 0.24; 95% CI, 0.620 to 2.609). Other variables that were examined did not affect the results of this study, including age at menopause, age at menarche, years of natural cyclic estrogen exposure, menopause duration, and surgical menopause. An analysis excluding women who reported surgical menopause did not significantly affect the RR of AD in ERT users. The RRs for all duration of use categories, after adjusting for education, were less than one but were not statistically significant. We were unable to detect any increase in protective effect with increasing duration of ERT usage as shown in the table.

The RR for ERT use in the model that included NSAID use as a time-dependent covariate was 0.49 (95% CI, 0.23 to 1.07). The RR for NSAID use and AD was 0.45 (95% CI, 0.21 to 0.98). Because the same results occurred when ERT and NSAID use were examined separately, it appears that the effects are independent of each other. Because of the small number of women taking both medications, the interaction between these two variables could not be examined.

Discussion. The results of this study in the BLSA support previous observations of a protective influence of estrogen replacement in the development of AD.[9-11] The strengths of prospective investigation (longitudinal data collection obtained directly from the subject before definition of case status) significantly minimize many of the biases inherent in most case-control investigations. But the study is observational, and the effect was not related to duration of therapy as might be predicted. Moreover, the BLSA is not representative of the general population in terms of education, socioeconomic status, and estrogen usage. Also, we cannot evaluate the effect of individual estrogen components, dosages, or routes of delivery because subjects used a variety of oral formulations and few subjects used estrogen patches.

Extending the epidemiologic observations, however, are several other lines of evidence relating estrogen replacement to improved brain structure and function in women with AD, in nondemented women, and in animal models. In studies of women with AD, estrogen replacement can produce cognitive and affective improvement[24-27] and may potentiate the effect of tacrine in the treatment of AD.[25] A randomized clinical trial of estrogen replacement in women with AD is currently in progress (Alzheimer's Disease Cooperative Study Unit funded by NIA).

In nondemented women, studies have shown beneficial effects of estrogen on cognition and memory in some[29-32] but not all[33,34] investigations. In a series of studies, Sherwin and colleagues reported that estrogen treatment, compared with placebo, was associated with superior verbal memory performance after surgical menopause[35,36] and that women receiving ERT had better performance on a paragraph recall task compared with untreated women.[34] Additional support for a role of estrogen in modulating cognitive performance comes from studies of menstrual cycle variation in premenopausal women that demonstrate systematic cognitive and memory fluctuations during high and low estrogen phases of the cycle.[35-38]

Possible biologic mechanisms for a protective influence of estrogen on cognitive function are suggested by investigations demonstrating direct effects of estrogen on neurotransmitter activity and neuronal development. Estrogen has also been shown to exhibit antioxidant activity,[42] inhibit apolipoprotein E levels in plasma,[25] and influence other processes that may be relevant to AD.[43] Estrogen-sensitive neurons are present in both men and women, particularly in the limbic system, cerebral cortex, and basal forebrain.[5] These neurons degenerate in AD, causing a loss of cholinergic innervation.[44,45] The effects of estrogen, however, may be different in women and men. Estradiol, the most prevalent ovarian estrogen in humans, increases the activity of choline acetyltransferase in the basal forebrain of ovariectomized rats, whereas male rats do not show a response.[46] Other studies in animals have suggested that estrogen enhances the growth of cholinergic neurons,[47] is necessary for maintenance of dendritic spine density in CA1 hippocampal pyramidal cells,[4] and regulates NMDA receptors in the hippocampus.[48] Acute estrogen administration increases cere-

bral glucose use in ovariectomized rats.[49] In addition, estrogen receptors co-localize with low-affinity nerve growth factor receptors in cholinergic neurons,[5] implying possible synergistic effects that may contribute to neuronal survival. Recent observations of decreased hippocampal volumes and memory deficits in women with Turner's syndrome who do not produce normal levels of estrogens and other gonadal hormones suggest that estrogen affects human brain morphology.[50]

Overall, considerable evidence suggests a direct effect of estrogen on brain structure and function, particularly for women. The potential benefits of ERT in relation to AD and cognitive loss require further study, ideally in the setting of a randomized prevention trial. Hormonal manipulations may provide a potential strategy for delaying or ameliorating the morbidity of AD in a large segment of the aging population.

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EEG spectral abnormalities and psychosis as predictors of cognitive and functional decline in probable Alzheimer's disease

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Article abstract—We examined whether either psychotic features (e.g., delusions and hallucinations) or EEG abnormalities are associated with more rapid progression of Alzheimer's disease (AD). AD patients with psychosis have exhibited more EEG abnormalities than those without psychosis, and both abnormal EEG and psychosis have been noted to be predictors of functional and cognitive decline in AD. Ninety-five probable AD patients participating in a longitudinal study of dementia had an EEG and a semistructured psychiatric interview at baseline. Using EEG spectral analysis, we classified records as normal/abnormal based on the parasagittal mean frequency. Patients with abnormal EEGs were more functionally (e.g., Blessed Rating Scale for activities of daily living) and cognitively (e.g., Mini-Mental State) impaired than patients with normal EEG. AD patients with psychosis were only more functionally impaired than patients without psychosis. A two-factor analysis showed no interaction between abnormal EEG and psychosis. In addition, using a Cox proportional hazard model adjusted for age and education, the presence of an abnormal EEG or psychotic symptom at study entry was associated with higher risk of reaching severe cognitive and functional impairment during follow-up. Neither abnormal EEG nor the presence of psychosis predicted death. These results indicate that both abnormal EEG and psychosis are independent predictors of disease progression but not of physical survival.

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The EEG of Alzheimer's disease (AD) patients may show a variety of abnormalities, including slowing of the occipital dominant rhythm, increase in delta and theta activity, and reduction of beta activity.[1-11] Patients in early stages of the disease can have normal EEGs, but prominent EEG abnormalities occur with increasing frequency as the severity of the dementia increases.[2,6,7] In addition, longitudinal studies have shown that AD patients with EEG abnormalities early in their course deteriorate more rapidly than patients without such abnormalities, have a greater frequency of institutionalization,[5,11] and are more likely to be dead at 1-year follow-up.[9]

Psychotic symptoms (e.g., delusions, hallucina-

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