Postmenopausal Estrogen Replacement Therapy and the Risk of Alzheimer Disease

Sudha Seshadri, MD; Gwen L. Zornberg, MD, ScD; Laura E. Derby, DSc; Marian W. Myers, MPH; Hershel Jick, MD; David A. Drachman, MD

Background: Previous studies have examined the relation between postmenopausal estrogen replacement therapy (ERT) and the risk of Alzheimer disease (AD). The findings have been inconsistent, since some studies have been interpreted as showing a protective effect while others have reported no effect.

Objective: To determine whether exposure to ERT is associated with a reduced risk of AD.

Design: Population-based nested case-control study.

Setting: The United Kingdom–based General Practice Research Database.

Patients: The base cohort consisted of women who were recipients of ERT (n=112481) and a similar cohort of women who did not use estrogens (n=108925). The 2 cohorts were restricted to women born on or before January 1, 1950. From the 2 cohorts, we identified and verified 59 newly diagnosed cases of AD and 221 matched control subjects.

Main Outcome Measures: Prior and current use of ERT in cases compared with controls.

Results: Among the 59 newly diagnosed cases of AD, 15 (25%) were current estrogen users, while among the controls, 53 (24%) were current users. The adjusted odds ratio comparing all current estrogen recipients with nonrecipients was 1.18 (95% confidence interval, 0.59-2.37). In estrogen users who took the drug for 5 years or longer compared with nonusers, the odds ratio was 1.05 (95% confidence interval, 0.32-3.44). Odds ratios were similar for estrogen recipients who received estrogens alone and recipients who received combined estrogen-progestin treatment.

Conclusion: The use of ERT in women after the onset of menopause was not associated with a reduced risk of developing AD.

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An estimated 15% of older women will develop Alzheimer disease (AD) during their lifetimes, and treatments that might reduce this risk are of great interest. A sharp decline in estrogen levels characterizes aging and menopause; the risks of developing osteoporosis and coronary artery disease—2 other conditions that affect women in their postmenopausal years—appear to be decreased by postmenopausal estrogen replacement therapy (ERT). Many basic neural mechanisms suggest that estrogen could beneficially affect the brain areas and processes involved in AD. Estrogen can enhance neuronal survival, inhibit apoptosis, and promote synaptogenesis and synaptic plasticity alone and synergistically with nerve growth factor. It increases levels of acetylcholine in the basal forebrain and hippocampus, serves as an antioxidant protecting neurons from the toxic effects of β-amyloid and glutamate, enhances repair of neuronal injury via apolipoprotein E–dependent mechanisms, and improves cerebral blood flow. However, biological plausibility alone does not establish a beneficial effect.

Some recent studies7-14 have suggested that ERT may be associated with a reduced risk or delayed age at onset of AD, while several other studies have found no apparent protective or palliative effect on the course of the illness. Many studies had significant methodologic drawbacks, including the unreliability and incompleteness of the ERT exposure history and the use of prevalent cases.7,11-13,15,16

The final results of 2 ongoing randomized trials21,22 of ERT for preventing dementia are unlikely to be available for a decade. In the interim, evaluation of the
PATIENTS AND METHODS

Information from the General Practice Research Database (GPRD) was used in the study. Since 1987, more than 3 million residents of the United Kingdom have been enrolled by selected general practitioners who use office computers and have agreed to provide data made anonymous for research purposes to the GPRD. Recorded information includes patient characteristics, diagnoses, drugs dispensed, referrals to consultants, and hospitalizations. Prescriptions are written directly on the computer, and the details are automatically transcribed into the patients‘ computer records. Information on referrals and hospitalizations in the general practitioners‘ manual medical files has been shown to be recorded in the computerized database more than 90% of the time.23,24 A modification of the Oxford Medical Information System is used to classify medical diagnoses, and a coded dictionary based on the Prescription Pricing Authority’s dictionary is used for prescriptions.

The GPRD provides full contemporaneous longitudinal information on patients who attended some 300 general practices for as long as 11 years and allows retrospective evaluation of drug effects. More than 70 studies using the GPRD have been published in peer-reviewed journals.

STUDY POPULATION

We identified all women in the population born on or before January 1, 1930, who had received at least 1 prescription for a systemic (oral or transdermal) estrogen preparation between January 1, 1990, and October 31, 1998. For comparison with the ERT-exposed cohort, a cohort of women also born on or before January 1, 1950, who had not received estrogens at any recorded time, was matched to the ERT users based on age within 3 years, physician’s practice, and date of registration. The 2 cohorts represent the base population from which the nested case-control evaluation was conducted. Estrogen replacement therapy—exposed and ERT-unexposed women diagnosed as having alcoholism, other drug addiction, psychotic disorders, Parkinson disease, stroke, motor neuron disease, deep vein thrombosis, pulmonary emboli, or cancer (except nonmelanoma skin cancers) recorded in the database before a diagnosis of AD were excluded from the study population.

In the base population, 83% of the women were aged 59 years or younger, 14% were between the ages of 60 and 69 years, and only 3% were older than 70 years. Among the women who used ERT in the underlying cohorts, only 0.4% were aged 80 years or older. Among all ERT users in the base population, 1 to 2 prescriptions were recorded for 20%, 3 to 10 for 37.5%, and 11 or more for 42.5%. Each prescription typically covered a period of 3 months.

NESTED CASE-CONTROL ANALYSIS

Identification and Validation of AD Cases

We identified all women who had a first-time computer diagnosis of AD, senile dementia, or presenile dementia between January 1, 1992, and October 31, 1998, from the base cohorts of ERT users and nonusers, without knowledge of their use of ERT. For each woman identified as a case, the general practitioner was sent a request for depersonalized copies of all referral letters, diagnostic tests, and clinical notes concerning the diagnosis of dementia. To determine the final case status, the computerized and clinical records of potential patients with AD were reviewed by 2 neurologists specializing in AD (S.S. and D.A.D.) without knowledge of the subject’s ERT exposure. Subjects were considered to have developed incident AD if (1) they had no prior evidence of dementia based on information in the clinical records and (2) there was evidence of the development of dementia and a first-time diagnosis of AD after the date of study initiation.

The diagnosis of AD was based on National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD.25 Subjects were included in the ERT-exposed cohort only if they used no other hormone preparations. With nonusers, yielding a relative risk estimate adjusted for BMI and smoking of 1.25 (95% CI, 0.59–2.37) after adjusting for BMI and smoking (Table 3). When past ERT recipients were combined with current users, the risk of developing AD did not change substantially, resulting in a relative risk estimate of 1.19 (95% CI, 0.62–2.27) comparing any use with no use. Similarly, the risk of developing new-onset AD among current users of estrogen combined with progestin, or without progestin, did not differ materially compared with nonusers (Table 4).

Further stratification of women who used ERT by duration of use produced no substantial differences in effect (Table 3). Compared with nonusers, ERT use for less than 3 years or for 3 to 4 years resulted in adjusted relative risk estimates (ORs) of 1.68 and 0.89, respectively (Table 3). Comparing ERT users for 5 or more years with nonusers yielded a relative risk estimate adjusted for BMI and smoking of 1.05. Adjustment of the regression model for additional variables, such as hypercho-
required to have evidence of dementia (defined as impairment of memory with deficits in at least 2 other domains of cognitive function) by history and clinical examination, and documented progression for at least 6 months. The likely cause of established dementia was based on historical information and clinical examination data (including neuropsychological testing) and on the results of laboratory investigations (hematological and biochemical variables, serum vitamin B12, and thyroid hormone levels, neuroimaging [computed tomography, magnetic resonance imaging, single photon emission computed tomography, and, when available, cerebrospinal fluid and electroencephalographic recordings]). The presumptive diagnosis of the 2 reviewing neurologists (S.S. and D.A.D.) was compared with the diagnosis made by the consulting specialist (neurologist, psychiatrist, or consultant geriatrician). Only when the reviewing and treating physicians concurred on a diagnosis of AD was the subject included as a case.

From the computer records, we initially identified 128 women with a new diagnosis of dementia or possible AD for review of medical records. Based on this review, we classified 62 women as meeting NINCDS-ADRDA criteria for probable (n=49) or possible (n=13) AD. Sixty-six potential cases of dementia, AD, or both were excluded (Table 1) after review of the case histories. Of those with a GPRD diagnosis of AD, for whom adequate data were available, 84% (43/51) were considered to have probable or possible AD, using NINCDS-ADRDA criteria. To simplify the interpretation of the findings, we restricted the primary analysis to current ERT users. (Three exposed cases whose last prescription for estrogen was >1 year before the date of diagnosis were defined as past users.) There remained 59 cases of AD that we included in the primary analysis. These subjects had been in a GPRD practice for the entire study period (or until death) and had medical information for at least 2 years before diagnosis. The date of diagnosis in each case was used as the index date from which the initiation of current ERT use was determined for matched control subjects.

Control Selection
For each of the 62 cases, we randomly selected up to 4 women as controls from the 2 base cohorts, matched to the cases on age within 5 years, physician’s practice, index date, and date of first prescription in the database. The same exclusion criteria that were applied to the cases were applied to the controls.

Exposure to Estrogens
Women who had received estrogen for at least 1 year and had their last prescription within 1 year before the index date of the diagnosis of AD and the same date in controls were classified as current users. Women who used estrogen were characterized according to the presence or absence of combined treatment with progesteron and oral or transdermal formulations.

The duration of treatment with ERT was determined from the prescriptions recorded in the computer files of the GPRD. We made an a priori decision to define a biologically meaningful ERT exposure as use for at least a year. Consequently, of the 15 cases and 53 controls who had “ever” received ERT, 2 cases (13%) and 6 controls (11%) were categorized as nonusers based on minimal use. Of these minimal users, 88% (7/8) had been prescribed only a single prescription for 3 months or less. We categorized the ERT users further by duration of use.

Data Analysis
We conducted a matched analysis using conditional logistic regression to calculate the relative risk estimates (odds ratios [ORs]) and 95% confidence intervals (CIs) of developing AD, adjusting for smoking and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters). The analyses were performed with the SAS statistical software package, version 6.12 (SAS Institute Inc, Cary, NC).

In this cohort-based study with an average follow-up of more than 5 years, we found no material evidence that current ERT use in postmenopausal women reduced the risk of developing AD. The risk estimate comparing all current ERT users with nonusers was 1.18 (95% CI, 0.59–2.37). For ERT users who received the drug for 5 years or more compared with nonusers, it was 1.05 (95% CI, 0.32–3.44). Odds ratio estimates were similar in women who used unopposed estrogens and for those who also used progestins.

The study design used is highly unusual and can only be applied to a data resource with comprehensive and well-documented information on drugs prescribed and clinical diagnoses over a long period. It allowed us to identify all women who were prescribed systemic estrogen preparations and a comparable cohort of women who were not, and to identify those women in both cohorts who developed a clinical diagnosis of dementia. Extensive paper clinical records were available, which allowed for an appraisal of the validity of the diagnosis and the time of first diagnosis. Such a design is highly efficient because it provides long-term follow-up information on a large group of all ERT users and a comparable sample of nonusers. While the design yields fewer cases of the illness of interest (in this case, AD) than a study based on the total population of menopausal women, it nevertheless provides sufficient valid information to provide a reasonably precise comparison of risks among women in the 2 cohorts. Furthermore, an efficient case-
control analysis can be performed that allows for more precise control of relevant risk factors.\textsuperscript{27}

We examined the incidence of newly diagnosed AD among unselected community-based individuals who were not noted to be cognitively impaired on clinical assessment for at least 2 years while under general practice physician care. The study of incident cases limits the number of cases of AD compared with studies of patients with prevalent AD,\textsuperscript{7,8,11-13,15,16} as does the relatively young age of the base population. However, requiring that all subjects not have dementia for at least a year reduced the possibility of important misclassification of exposure. Furthermore, since estrogen could act differentially on vascular dementia and AD, we included only those incident cases of AD that met stringent, standardized criteria for the diagnosis.

Previously published observational studies of ERT and the risk of AD used highly relevant major differences in study design. For example, in the case-control study of Brenner et al,\textsuperscript{17} newly diagnosed cases (n=107) of AD (average age, 77 years) were identified from an Alzheimer’s Disease Registry based on an extensive evaluation of physical and laboratory tests for this diagnosis. Exposure to estrogens was derived from fully documented complete and accurate pharmacy files.\textsuperscript{17} This study yielded relative risk estimates carefully controlled for age, comparing ERT users with nonusers, of 1.1 (95% CI, 0.6-2.18), a result that was virtually identical to the estimate found in our study.

By contrast, Tang et al\textsuperscript{9} reported a follow-up study of 1124 elderly women (mean age, 74.2 years) in whom the diagnosis of AD was based on a series of standardized tests for AD. The history of exposure to estrogen at

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 59)</th>
<th>Controls (n = 221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>66.7</td>
<td>65.2</td>
</tr>
<tr>
<td>ERT exposure, mean, y</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3 (5.1)</td>
<td>7 (3.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (23.7)</td>
<td>47 (21.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (1.7)</td>
<td>6 (2.7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>6 (10.2)</td>
<td>20 (9.0)</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td>&lt;23</td>
<td>13 (22.0)</td>
</tr>
<tr>
<td>23-26.9</td>
<td>18 (30.5)</td>
<td>64 (29.0)</td>
</tr>
<tr>
<td>≥27</td>
<td>5 (8.5)</td>
<td>55 (24.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (39.0)</td>
<td>64 (29.0)</td>
</tr>
<tr>
<td>Cigarette smoking status</td>
<td>Nonsmoker</td>
<td>35 (59.3)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10 (17.0)</td>
<td>32 (14.5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>3 (5.1)</td>
<td>29 (13.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>11 (18.6)</td>
<td>29 (13.1)</td>
</tr>
</tbody>
</table>

*Data are given as the number (percentage) of subjects unless otherwise indicated. ERT indicates estrogen replacement therapy; BMI, body mass index.

Table 1. Reasons for Exclusion of Potential Cases of Incident Alzheimer Disease

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular dementias</td>
<td>12</td>
</tr>
<tr>
<td>Non-Alzheimer disease degenerative dementia</td>
<td>7</td>
</tr>
<tr>
<td>Metabolic conditions (hypothyroidism, metastatic carcinoma, chronic obstructive airway disease, etc)</td>
<td>8</td>
</tr>
<tr>
<td>Other neurological conditions (subdural hematoma, head injury, etc)</td>
<td>5</td>
</tr>
<tr>
<td>Depressive disorder with pseudodementia</td>
<td>7</td>
</tr>
<tr>
<td>Uncertain cause (patient refused testing)</td>
<td>2</td>
</tr>
<tr>
<td>Inadequate documentation of dementia</td>
<td>21</td>
</tr>
<tr>
<td>No documentation of dementia progression</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of Subjects Included in the Primary Nested Case-Control Analysis According to Case Status*

*Adjusted for body mass index and cigarette smoking. ERT indicates estrogen replacement therapy.†Data are given as the number (percentage) of subjects.‡Referent.§Use for 1 year or longer.
any time was obtained by patient interview only at the start of follow-up. Fourteen percent of the women gave a history of any estrogen use at the start of follow-up, but only 2% were current users at the start of follow-up. No further information was obtained on ERT use after the initial interview. Women who reported ever use of ERT for less than 1 year (average, 4 months) were reported to have a substantially reduced risk of AD (OR, 0.47). The finding of a reduced risk in women who had ever used ERT for less than 1 year (in whom an effect on AD seems unlikely) suggests that substantial misclassification of ERT use may have been present. The lack of an accurate, well-documented, continuous history of drug use is an important limitation of the study by Tang et al.

To our knowledge, only 1 prior published observational study used previously recorded computerized prescription information; the remainder required patient or surrogate interviews or record abstraction to obtain a history of drug use. Some studies evaluated prevalent cases of AD, where information on drug exposure and onset of disease is likely to be of limited validity. Design problems are likely to explain, at least in part, the conflicting results.

We considered the possibility that our negative results were due to selection bias, whereby subjects with early memory loss were prescribed ERT as a prophylactic measure against the development of AD, but this is unlikely because the suggestion that ERT might protect against AD was not well-known at the time that most of the information on ERT use was recorded. In addition, there was no effect when women who used ERT for 5 or more years were compared with nonusers.

Correspondingly, the data from 3 recent randomized placebo-controlled trials of ERT treatment in women diagnosed as having AD at enrollment indicated that short-term (≤1 year) ERT use does not alter the progression of the established illness, or materially improve the symptoms of AD. In our analyses, we focused deliberately on reduction of risk (delaying the onset or preventing AD), and found no substantial effect.

This report is not a direct study of the association between BMI and AD, but subjects in the highest BMI category showed an independent, lower risk for AD. Modest amounts of confounding by BMI were present, since the frequency of estrogen use was highest in the largest BMI group, and women in that category were less likely to be diagnosed as having AD. Previous research on women with AD also showed that cases tended to be thinner than comparison subjects.

The findings from this study need to be interpreted with care for the following reasons. First, the number of recorded past ERT users was small, and our primary analysis was restricted to current estrogen users. However, the analysis of combined past and current ERT use on the risk of AD did not differ materially from current use alone. It remains possible that extensive distant past use, or use at a critical perimenopausal period, may be more effective in lowering the risk for AD. This seems unlikely since we found no effect in subjects who were long-term users. In this study, we chose not to include historically derived data on past estrogen use (before establishment of the computerized database in 1987), since introducing retrospective undocumented estimates of ERT use would have diminished the quality of our information on ERT exposure.

Second, we did not examine other risk factors for AD, such as level of education, APOE genotype, or familial risk. To reduce the degree of confounding by educational level, we matched cases to controls within the same physician’s practice, the local practice serving as a surrogate for educational and socioeconomic levels.

Third, our study is limited in size because of restriction of the study population to incident rather than prevalent cases and, most important, because of the relative youth and health of ERT users in our population. It is possible that genetic influences are more likely to determine the development of AD at this age, whereas environmental exposures such as estrogen replacement may be more relevant at older ages. Because of secular trends in estrogen use in the United Kingdom, women aged 80 years and older—the women at highest risk for AD—rarely used estrogens, reducing the quantity of information on a possible ERT effect in the most elderly age groups. In a population in which only a small percentage have been exposed to ERT, the matched cohort design, as previously noted, maximized efficiency by enabling us to detect all incident cases of AD occurring among ERT users and a comparable group of nonusers. Despite this, the proportion of included women who were exposed to ERT in this study is larger than in several recent studies that have found a protective effect.

The possibility exists that chance, residual confounding, or unknown biases may explain the null findings of this observational study. By careful matching of all newly diagnosed cases of AD to controls, and using prospectively collected data on exposure and outcome, we attempted to minimize this possibility.

In summary, our findings indicate that ERT use in postmenopausal women is not associated with a substantially reduced risk of AD, and highlight the need for restraint in advocating postmenopausal ERT for this purpose.

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