Postmenopausal Hormone Therapy and Its Association With Cognitive Impairment

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Background: Cognitive impairment is a common and potentially debilitating medical problem in older women. Postmenopausal hormone therapy (HT) has been associated with better cognitive function, but the literature is conflicting. Results of recent trials suggest that HT is inappropriate for prevention of heart disease, and we sought to determine the role of HT in the risk of cognitive impairment.

Methods: We measured HT use and cognitive function in a population-based cohort of 1462 postmenopausal women participating in the 5-year follow-up examination for the Epidemiology of Hearing Loss Study in 1998-2000. The cohort was defined in 1987-1988 by residency in Beaver Dam, Wis, and an age of 43 to 84 years. Women had also participated in the Beaver Dam Eye Study baseline examination in 1988-1990. Use of HT was assessed at the Beaver Dam Eye Study baseline (1988-1990), 5-year follow-up (1993-1995), and 10-year follow-up (1998-2000) visits. Cognitive impairment was defined as a low Mini-Mental State Examination score or a reported diagnosis of Alzheimer disease.

Results: Six percent of participants (n=94) were impaired; these women were significantly older and less educated than those who were unimpaired. In age- and education-adjusted analysis, current HT use was not significantly associated with cognitive impairment (odds ratio, 0.6; 95% confidence interval, 0.2-1.3). Similarly, cognitive impairment was not associated with past HT use or duration of HT use.

Conclusion: In this large population-based study, postmenopausal hormone therapy was not significantly associated with better cognitive function.

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low-up examinations for the EHLS were timed to coincide with the 5-year (1993-1995) and 10-year (1998-2000) follow-up examinations for the BDES. In fact, the visits were an average of 1 day apart. Cognition and physical and mental health status were measured at the EHLS 1998-2000 visit using the Mini-Mental State Examination (MMSE)\(^1\) and the 36-item Medical Outcomes Study Short Form Health Survey.\(^{12,13}\) respectively.

Baseline EHLS participants 75 years and older were invited to be reexamined for a substudy in 1995-1997, where trained interviewers administered the full MMSE.\(^1\) Using those data, we determined that people scoring well on the first 5 questions (including the aspects of orientation, attention, recall, and calculation for a total of 21 points) were unlikely to be scored as cognitively impaired on the full MMSE (which also includes questions on language, attention, and spatial skills for an additional 9 points). We therefore modified the protocol for the EHLS 5-year follow-up because of the relatively young age of the total cohort and time constraints. People who scored 15 or better on the first 5 questions did not complete the full MMSE. Participants who scored less than 80% were considered impaired (ie, a score of <17 on the abbreviated 21-point examination or <24 on the full 30-point MMSE). In the substudy of women 75 years and older, the sensitivity and specificity for this combined method were 96% and 93%, respectively, using the full MMSE as the gold standard. Of the 617 participants, 93.3% were accurately classified, and, therefore, misclassification was minimal.

As part of the BDES, at each of the baseline, 5-year, and 10-year visits, trained interviewers administered detailed questionnaires of reproductive history, current and past HT use, and past medical history, including a diagnosis of Alzheimer disease. Hormone replacement therapy use was confirmed by a physical inventory of the prescription bottles or products the participant brought to the visit. For this study, current HT use was defined as use at the 1998-2000 visit.

Postmenopausal status was defined as a history of surgical menopause (bilateral oophorectomy), natural menopause (≥ 1 ovary, an intact uterus, and cessation of menses for ≥ 6 months), or hysterectomy if they were older than 50 years. This cutoff age was chosen because 90% of women experienced natural menopause by this age. Of the 1520 postmenopausal women, 3.8% (n = 58) did not answer the question on current HT use or did not complete the MMSE. These 58 women did not significantly differ from the rest of the cohort in age, education, HT use, income, reproductive surgery, alcohol use, smoking status, body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), or mental health component score (data not shown).

Past HT use was defined as any past use, exclusive of current use. Information on past and current HT use at the baseline BDES examination and current use at the 1993-1995 and 1998-2000 follow-up examinations was used to compute the duration of HT use.

Serum estrone concentration was measured in 253 women at the BDES baseline visit in 1988-1990. These women were randomly selected from the subset of women who, at the baseline BDES visit, were without menses, were not currently using HT, and were without a personal history of cancer. Among these women, 77% (n = 196) were postmenopausal at the time of the 1998-2000 EHLS examination and had completed the MMSE. Serum samples were frozen for an average of 3.6 years at ~70°C until thawed and assayed. Commercial double-antibody radioimmunoassay kits (Pantex, Santa Monica, Calif) were used. The coefficients of intra-assay and interassay variability were 10% and 14%, respectively.

The institutional review board at the University of Wisconsin–Madison approved this project, and all of the participants gave written informed consent before participating.

**ANALYSIS**

Statistical software was used for all analyses (SAS; SAS Institute Inc, Cary, NC). To test differences in participant characteristics, a 2-tailed, unpaired t test was used for continuous variables and the \(\chi^2\) test for association was used with contingency tables for dichotomous variables. Multiple logistic regression was used to obtain odds ratios (ORs) for the presence of cognitive impairment in current HT users compared with noncurrent users. Covariates were added to the univariate regression model in a stepwise manner and were retained in the model if they satisfied at least 1 of 2 criteria: (1) their addition resulted in an appreciable change in the OR point estimate or (2) the covariate \(\chi^2\) values were less than .05 and were statistically significant based on the log likelihood test \((P < .05)\). Interactions were also tested between HT use and age, education, and measures of mental health.

This strategy was repeated for the past use and duration of use analyses. The effect of past use was tested by using indicator variables for current and past use, with never used as the reference. The effect of the duration of HT use was tested in 2 ways. The number of years of HT use was first used as a continuous variable (including never users) and second as a categorical variable (no use, <5 years of use, and ≥5 years of use).

Analyses testing the effect of age at menopause excluded women with hysterectomy but intact ovaries (for whom physiologic menopausal age is unknown). Age at menopause was divided into 3 categories: younger than 45 years, 45 to 54 years, and 55 years and older.

For the estrone analyses, the procedure outlined herein was repeated. Because the distribution was skewed, estrone levels were categorized. Categories were chosen by physiologic cutoff points: less than 5.5 ng/dL (204 pmol/L) (postmenopausal norm), 5.5 to 25.0 ng/dL (204-925 pmol/L) (premenopausal range), and greater than 25.0 ng/dL (925 pmol/L) (higher than premenopausal norms).

In addition, analyses were repeated using current HT use as determined by the 5-year follow-up examination, an average of 5.2 years before cognitive impairment ascertainment. Again, the procedure outlined herein was repeated, but the covariate data were from the 5-year follow-up visit (1993-1995).

Model covariates were chosen based on known differences between HT users and nonusers.\(^{14-16}\) Age, BMI, and the mental health component score from the Short Form Health Survey were coded as continuous variables. For descriptive purposes, normal weight was defined as a BMI of 18.5 to 24.0, overweight was defined as a BMI greater than 24.0, and obesity was defined as a BMI greater than 30.0, based on World Health Organization criteria.\(^{11}\) Categorical variables included education (completed high school vs did not complete high school), exercise (regular exercise to work up a sweat at least once a week vs no regular exercise), marital status (currently married vs not currently married), employment status (working part- or full-time vs not working), income (total household personal income for the past year of <$10000, $10000-49999, $50000-99999, $100000-199999, $200000-299999, $300000-449999, $450000-599999, or ≥$600000), and self-reported health status (excellent, good, fair, or poor). Covariates coded as indicator variables included smoking (past and current, with never as the referent) and alcohol use (0-14, 15-74, and ≥75 g of alcohol per week, with nondrinker as the referent). Fifteen grams of alcohol was considered 1 drink.

Analyses were rerun excluding certain participant subgroups. In general, participants with advanced dementia have less reliable questionnaire data, and their disease may discourage use of HT or may lead to discontinuing use. Thus, repeated
analyses excluded participants with a history of Alzheimer disease, participants with interviewer-assessed organic mental syndrome, and those with reproductive questionnaires completed mainly by surrogates. In addition, surgical menopause may have a different impact on the relationship between HT use and impaired cognition. Thus, a repeated analysis excluded participants with a history of bilateral oophorectomy. Finally, in older women, depression may present as cognitive impairment. In the primary analysis, we included the mental health component score as a potential covariate. A repeated analysis instead excluded participants with a low mental health component score (<30 points) and those using antidepressant medications (amitriptyline hydrochloride, paroxetine, fluoxetine, or sertraline hydrochloride).

## RESULTS

A total of 1462 postmenopausal women were included in the primary analysis; 25% (n = 369) were current HT users, and an additional 21% (n = 301) were past HT users. The participant characteristics are given in Table 1. The average participant age was 70 years (range, 53-97 years). Most women (81%) completed high school. Current HT users differed from noncurrent users in several respects: they were younger, more educated, and more often married, working, exercising, maintaining a normal weight, and with a history of reproductive surgery. Among current HT users, 54% were taking oral estrogen alone, 37% were taking oral estrogen-progestin, 8% were taking nonoral preparations, and less than 1% were taking oral progestin alone.

Six percent of the cohort (n = 94) was cognitively impaired. Of the impaired women, 19 (20%) had a diagnosis of Alzheimer disease. In univariate analysis, current HT users were 80% less likely to be cognitively impaired (OR, 0.2; 95% confidence interval [CI], 0.1-0.5). Adjusting for age, current HT users were less likely to be cognitively impaired, but the effect was to a smaller degree and the estimate was no longer statistically significant (OR, 0.5; 95% CI, 0.2-1.1). The covariates in the adjusted model were age and educational attainment; the other covariates or interaction terms did not add to the model. The OR for the association between current HT use and impaired cognition was 0.6 (95% CI, 0.2-1.3) (Figure and Table 2). The average Short Form Health Survey mental health component score did not differ in current HT users vs never users (55.3 vs 55.0).

In the past-use analysis, age and education again proved to be important covariates. Past HT use was not associated with cognitive impairment in the adjusted model (OR, 1.0; 95% CI, 0.6-1.8) (Figure and Table 2).

In the duration-of-use analysis, the mean duration of HT use was 3.4 years (range, 0-57 years). Current users had an average (SD) of 6.7 (9.4) years of use, and noncurrent users had an average (SD) of 1.2 (4.1) years of use. The duration of HT use was not associated with cognitive impairment in either the continuous or the categorical age-adjusted model. In the continuous model, after age and education adjustment, 5 years of use resulted in an OR of 0.9 (95% CI, 0.8-1.1) (Figure and Table 2).

Of women without hysterectomies, a total of 1172 reported their age at menopause and were included in the menopausal age analysis. Most women (67%) underwent menopause between ages 45 and 54 years, 20%...
underwent menopause before age 45 years, and 13% underwent menopause at 55 years or older. After adjustment for age and education, menopausal age was not associated with cognitive impairment (OR, 0.7; 95% CI, 0.3-1.8 for menopausal age ≥55 years vs <45 years).

A total of 196 women had estrone measurements. In this subset, the average estrone level was 8.3 ng/dL (307 pmol/L). Most of these women (63%) had estrone levels lower than 5.5 ng/dL (204 pmol/L), but 7% had levels greater than 25.0 ng/dL (925 pmol/L). Estrone levels increased with BMI, but this relationship was not statistically significant (P = .75). In the age-adjusted model, risk of cognitive impairment decreased with higher estrone levels, but the result was not statistically significant (OR, 0.20; 95% CI, 0.04-1.10 for >25.0 ng/dL [925 pmol/L] vs ≤5.5 ng/dL [204 pmol/L]) (Figure). The point estimate and the level of significance did not appreciably change when adjusting for any other covariates.

In an alternative analysis, where previous HT use was defined as use at the 5-year follow-up, approximately 5 years before the ascertainment of cognitive impairment, 1303 women were postmenopausal and had complete data. Previous HT use was not associated with cognitive impairment after adjustment for age and education (OR, 0.7; 95% CI, 0.3-1.8).

In the primary and secondary analyses, age was an influential factor in the relationship between HT use and impaired cognition. Yet, the interaction between use and age was not significant (P = .35). The covariates were reviewed by age and cognitive impairment stratification. These stratified analyses were limited by the fact that in the group younger than 65 years, only 7 women were cognitively impaired. Age- and education-adjusted analyses for those 65 years and older did not differ appreciably from analyses in the overall cohort. In addition, subset analyses excluding women with more severe cognitive impairment, women with surgical menopause, and those with depression did not differ appreciably from the primary analysis. Finally, although estrogen-only users were slightly older and slightly less educated than estrogen-progestin users, there was no difference in the prevalence of cognitive impairment between the groups. (Small numbers of current estrogen-progestin users precluded full statistical analyses.)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Referent Group</th>
<th>Participants, No.</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current HT use</td>
<td>Past use or never used</td>
<td>1460</td>
<td>0.6 (0.2-1.3)</td>
</tr>
<tr>
<td>Past HT use only</td>
<td>Never used</td>
<td>1420</td>
<td>1.0 (0.6-1.8)</td>
</tr>
<tr>
<td>Previous HT use†</td>
<td>No previous use</td>
<td>1303</td>
<td>0.7 (0.3-1.8)</td>
</tr>
<tr>
<td>Duration of HT use</td>
<td>Continuous model‡</td>
<td>1402</td>
<td>0.9 (0.8-1.1)</td>
</tr>
<tr>
<td>HT use of ≥5 y</td>
<td>Never used</td>
<td>1402</td>
<td>0.7 (0.4-1.4)</td>
</tr>
<tr>
<td>Age at menopause ≥55 y</td>
<td>&lt;45 y</td>
<td>1172</td>
<td>0.7 (0.3-1.8)</td>
</tr>
<tr>
<td>Estrone level ≥25.0 ng/dL (925 pmol/L)</td>
<td>&lt;5.5 ng/dL (204 pmol/L)</td>
<td>196</td>
<td>0.2 (0.1-1.1)</td>
</tr>
<tr>
<td>Age ≥65 y and current HT use</td>
<td>Past use or never used</td>
<td>934</td>
<td>0.6 (0.2-1.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HT, hormone therapy.
*Adjusted for age and education.
†Previous use is defined as current HT use 5 years before cognitive measurement.
‡The odds ratio and 95% CIs were calculated for 5 years of use.

In this large population-based cohort, there was no significant association between postmenopausal HT use and impaired cognition after adjustment for age and education, the strongest predictors of cognitive impairment. The absence of significant association was true in analyses of current HT use, past HT use, and duration of HT use.

Other investigators also did not demonstrate an association between HT use and general cognitive status. In the large Rancho-Bernardo cohort, current HT use was not associated with performance on the MMSE. The HT users scored only 0.2 points (total, 30 points) better than never users in an adjusted analysis. They also found no association by duration of use or dose of estrogen. In the even larger Nurses’ Health Study cohort, current HT use was not associated with performance on a telephone questionnaire of general cognition. They also found no consistent association by previous HT use (current use approximately 5 years before cognitive testing) or duration of use. Previous HT users scored 0.1 point (total, 41 points) worse than never users in an adjusted analysis. Other studies examining the effect of the duration of HT use and past HT use found no association. Finally, a benefit of HT was not demonstrated in longitudinal studies or in most trials of asymptomatic women.

A few large observational studies reached a different conclusion. However, in the Study of Osteoporotic Fractures cohort, current and past HT use was associated with better modified MMSE scores. However, the difference in scores was minimal, their analyses included log transformations, the modifications of the MMSE were not described, and the duration-of-use models were not significant. In addition, in their longitudinal analysis, no association was found. Second, in a cross-sectional study, current and past HT use was associated with better modified MMSE scores. However, the difference in scores was minimal, their analysis included a trichotomous variable of never-past-current use, and duration-of-use models were not significant. Third, in a cohort of Japanese Americans, current HT use was associated with better Cognitive Abilities Screening Instrument scores. However, the difference in scores was minimal, the analyses of current...
were likely to be underpowered. In their longitudinal analysis, unopposed estrogen use had only a modest benefit, and combination estrogen-progestin use showed a detriment. Finally, in an older cohort with infrequent current HT use, an HT benefit was found only in tests of memory and not in tests of abstraction and language.20

Some investigators have found that the HT preparation differentially affects cognition,20,27 but others have not.6,28 Other investigators20 have suggested that use of estradiol may be superior to conjugated estrogen use. In our study, the prevalence of cognitive impairment was similar between users of unopposed estrogen and users of estrogen-progestin. We did not collect information on the specific estrogen formulation used.

Clinical trials30 have found that women who already have Alzheimer disease do not benefit from HT, whereas observational studies have found that healthy women may reduce their risk of Alzheimer disease with HT,31,32 particularly if HT is used for 10 years or more.33 Our study outcome was cognitive impairment, including but not limited to Alzheimer disease, and, thus, it should not be directly compared with investigations of Alzheimer disease. However, our results do not support the hypothesis that early (perimenopausal) or long duration of HT use limits future Alzheimer disease,34 since we found that current use conferred more reduced risk of cognitive impairment than past, previous (3 years previous), and longer-term use. In addition, we did not find a difference in effect between women older and younger than 65 years, and we did not find an association when excluding the more severely impaired participants. On the other hand, as our cohort is relatively young, we may need to follow the cohort longer to determine any effect of HT on Alzheimer disease diagnosis.

There are several limitations to this study. First, HT adherence was not assessed. If impaired women who were prescribed HT were less likely than unimpaired women to consistently take the medication, an association would be missed. Alternatively, if women with memory problems were more likely to be prescribed HT (after the onset of memory problems), an association may not be found even if one exists. However, women with cognitive impairment may instead be less likely to be prescribed HT, if the prescribing physician wanted to avoid the additional adverse effects and risks of HT in a vulnerable population. Second, the effects of participation bias must be considered. If more impaired women who did not use HT dropped out of the study than impaired women who used HT, an association may be missed. In this study, women with incomplete information were less often HT users, although the number of women with incomplete information was small (n=58).

In the adjusted current use analyses, the OR point estimate suggested a 40% decrease in the prevalence of cognitive impairment, although this estimate was not statistically significant. Power calculations show that given the number of women in this study and a 2-tailed α of .05, this study had 80% power to detect a 50% reduction in cognitive impairment. On the other hand, the subset of estrone analyses had less than 200 participants and were likely to be underpowered.

Several groups of women have been shown to differentially benefit from HT. First, young women with menopausal symptoms are likely to have improved cognition and mood when taking HT.35 However, we did not find that younger women had a differential benefit of HT on cognition, although very few young women were impaired and menopausal symptoms were not assessed. In addition, excluding women with probable depression did not alter the results. Second, a study6 found that less-educated women had less cognitive decline during HT. However, we found no interaction between HT use and education. Third, apolipoprotein E ε4-negative women may differentially benefit from HT.21 The effects of apolipoprotein E were not examined in this study.

As the EHLS/BDES cohort is predominantly white, the findings may not be generalizable to nonwhites. However, a differential effect of HT by race has not been well established. A multiethnic study20 found a positive effect of HT but did not report an HT use × race interaction. In addition, the current cohort had a high prevalence of overweight and obesity, and BMI was positively correlated to endogenous estrogen levels. If endogenous estrogen levels were already greater than a theoretical threshold, this cohort may not have benefited from additional exogenous estrogen (ie, HT). However, BMI did not prove to be an important confounder, and although the prevalence of obesity in the Nurses’ Health Study cohort was less than half of the prevalence of obesity in this cohort, that study6 did not find an association between HT use and general cognitive status.

Finally, a general measure, the MMSE, was used to assess cognitive status in the present study. This instrument may not be sensitive to abnormal performance on only 1 or 2 aspects of cognition. For example, some researchers39 have suggested that HT preferentially affects verbal memory. However, careful systematic reviews40,41 have not found HT to consistently benefit verbal memory or any other single aspect of cognition.

It is useful to place the results of this study in the context of several large randomized controlled trials of HT. The Women’s Health Initiative Memory Study (WHIMS)37 is ancillary to the Women’s Health Initiative, which was primarily designed to assess the effect of HT on heart disease, breast cancer, and osteoporosis. The estrogen-progestin component of this trial was stopped early because of an unexpected increase in cardiovascular risk, and their results prompted the early termination of the WISDOM (Women’s International Study of Long Duration Oestrogen After Menopause) trial38 and its ancillary study of cognition as well as a partial cessation of recruitment in the PREPARE (Prevent Postmenopausal Alzheimer’s With Replacement Estrogens) trial,39 which was specifically designed to assess whether HT prevents dementia in a group at high risk for Alzheimer disease.

In the estrogen-progestin component, the WHIMS investigators37 found a nonsignificant 37% increase in the combined end points of probable dementia or mild cognitive impairment with approximately 4 years of estrogen-progestin. Although we also found a nonsignificant association, our point estimate did not suggest HT increased the risk of cognitive impairment. Our HT group was administered mostly unopposed estrogen. The
results of the WHIMS unopposed estrogen component are not expected for some time.

The adverse effects and contraindications to HT require relatively restrictive entry criteria for clinical trials, which may result in healthier homogeneous study populations that are not generalizable to most older women. For example, in WHIMS, 94% were high school graduates, whereas in our geographic cohort, 81% were high school graduates. Because of the health of the trial participants and the early stoppage, the number of impaired women was relatively small (3.3% had probable dementia or mild cognitive impairment, whereas in our cohort, 6.4% were impaired), and so their analysis by subsets and by specific dementia etiologies were limited. Thus, observational studies are still important for this question. In addition, observational cohorts permit study of HT initiated perimenopausally and continued for long periods. Some authors propose HT benefits cognition only when used in this manner, but our findings do not support this hypothesis.

In summary, we studied nearly 1500 women in a cohort based on a population rather than on recruited volunteers. Recall bias due to self-report of HT use was minimized by performing a physical inventory of current medications. Age and educational attainment were found to be important covariates and were included in regression models. Other measures of the “healthy HT user” were included in the analysis strategy. A single, valid end point of impaired cognition was used. The results consistently demonstrated no significant benefit of HT. Therefore, given the known harms of HT, this study does not support the use of HT for the sole purpose of preventing cognitive impairment.

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