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.
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 5.2 years before cognitive impairment ascertainment. 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. 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 <$1000, $1000-4999, $5000-9999, $10000-19999, $20000-29999, $30000-49999, $45000-59999, or ≥$60000), 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) 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 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. 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. 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 <$1000, $1000-4999, $5000-9999, $10000-19999, $20000-29999, $30000-49999, $45000-59999, or ≥$60000), 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 subsets. 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% under- 
went 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 less 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 statisti- 
cally significant (P = .75). In the age-adjusted model, 
risk of cognitive impairment decreased with higher 
estrone serum 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 signific-
ance did not appreciably change when adjusting for 
other covariates.

In an alternative analysis, where previous HT use 
was defined as use at the 5-year follow-up, approxi-
ately 5 years before the ascertainment of cognitive im-
pairment, 1303 women were postmenopausal and had 
complete data. Previous HT use was not associated with 
cognitive impairment after adjustment for age and edu-
cation (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 cogni-
tively 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 pri-
mary analysis. Finally, although estrogen-only users were 
slightly older and slightly less educated than estrogen-
progestin users, there was no difference in the preva-
ience of cognitive impairment between the groups. (Small 
numbers of current estrogen-progestin users precluded 
full statistical analyses.)

In this large population-based cohort, there was no sig-
ificant 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 analy-
ses of current HT use, past HT use, and duration of HT 
use.

Other investigators also did not demonstrate an as-
sociation 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 associ-
ation 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 asso-
ciation by previous HT use (current use approximately 5 
years before cognitive testing) or duration of use. Previ-
ous HT users scored 0.1 point (total, 41 points) worse than 
never users in an adjusted analysis. Other studies exam-
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ous HT users scored 0.1 point (total, 41 points) worse than 
never users in an adjusted analysis. Other studies exam-
ing 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 transfor-
mations, the modifications of the MMSE were not de-
scribed, and the duration-of-use models were not signifi-
cant. 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 modi-

Table 2. Association of HT With Cognitive Impairment

<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 (0.5-1.6)</td>
</tr>
<tr>
<td>HT use of &gt;5 y</td>
<td>Never used</td>
<td>1402</td>
<td>0.7 (0.4-1.4)</td>
</tr>
<tr>
<td>Age at menopause &gt;55 y</td>
<td>&lt;45 y</td>
<td>1172</td>
<td>0.7 (0.3-1.8)</td>
</tr>
<tr>
<td>Estrone level &gt;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. 
‡Continuous model: Previous HT use, 0; Past use only, 1; Current HT use, 2; Past use or never used, 3.

<https://www.archinternmed.com/163/10/2488>
use were unadjusted, and the past-use analysis was not significant. 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,35,36 particularly if HT is used for 10 years or more.31 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.37 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 study4 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, the study26 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 researchers36 have suggested that HT preferentially affects verbal memory. However, careful systematic reviews24,25 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 entrance 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 probably 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 authors34-35 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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