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Hormone replacement therapy and reduced cognitive decline in older women

The Cache County Study

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Article abstract—*Objective:* To examine the association between postmenopausal hormone replacement therapy (HRT) and the trajectory of global cognitive change with age. *Methods:* The Modified Mini-Mental State Examination (MMSE) was administered to a population sample of 2,073 nondemented, community-dwelling female residents of Cache County, UT, aged 65 and older. Current and past HRT and other medications at a baseline interview and at follow-up 3 years later were assessed. Between interviews, a telephone Women's Health Questionnaire was administered to assess initial exposure, duration, and recency of HRT. Generalized estimating equation marginal models were used to evaluate the cross-sectional and longitudinal relations of HRT and modified MMSE score. Also assessed were effects with multivitamins and calcium supplements as exposures likely to reflect a "healthy lifestyle" among HRT users. Model covariates included the presence of *APOE* ϵ4 alleles, age, education, concurrent depression, several chronic diseases, and self-perceived general health. *Results:* Age, lower education, depression, and *APOE* ϵ4 were all associated with lower baseline modified MMSE scores. With these covariates in the model, lifetime HRT use was associated with better baseline modified MMSE scores and a slower rate of decline. Stratification by *APOE* genotype did not alter these effects. Apparent benefits with HRT were attenuated but remained significant after elimination of scores from participants with incident dementia. A significant interaction between age and HRT indicated the strongest effects in women aged 85 and older. Measures of age at initial use of HRT, duration, and recency of exposure did not improve the models. No effects were seen with the "healthy lifestyle" control exposures. *Conclusions:* In a population cohort of older women, lifetime HRT exposure was associated with improved global cognition and attenuated decline over a 3-year interval. Improvements were greatest in the oldest old.

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Recent epidemiologic studies have suggested that postmenopausal hormone replacement therapy (HRT) may yield cognitive benefits by delaying or preventing the onset of AD.[1-3] Data from heterogeneous populations of healthy aging women also suggested that HRT use was associated with better baseline cognitive function and attenuation in verbal memory[4] and global cognitive declines.[5,6] One prior report[6] suggested that HRT benefits were specific to those without a *APOE* ϵ4 allele, the polymorphic genetic locus for apolipoprotein E. In addition, other cohort and matched case-control studies of healthy postmenopausal women have failed to observe memory and other cognitive benefits with HRT.[7-9]

See the Appendix on page 2215 for a list of the Cache County Study Group members.

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The inconsistency of these findings may reflect methodological difficulties including failure to control on unmeasured or unsuspected sources of confounding beyond age, educational attainment, and genotype at *APOE*. For example, HRT users may have different health habits than nonusers.[10,11] This and other unsuspected confounders are best controlled in randomized trials. Trials have recently tested HRT in established AD and reported null findings.[12-14] Failure to treat established disease does not imply failure to prevent disease onset, however, and two ambitious randomized primary prevention trials of HRT are underway in nondemented women. Unfortunately, the results of those trials will not be available for several years.

Short of randomization, one may achieve some control of unmeasured confounding by conducting comparisons of HRT users versus nonusers in populations that are relatively homogeneous in lifestyle and health habits. We therefore conducted an observational study in a total population sample of older (age 65+) residents of a single county that is characterized by relative homogeneity in environmental influences, health-seeking behaviors, access to health care, and overall lifestyle. Previous reports from this population[15] have suggested that its nondemented women who were past or present HRT users had better cross-sectional scores on the Modified Mini-Mental State Examination (MMSE)[16] after adjustment for several sociodemographic and health variables. Because longitudinal investigations offer better inference about temporal relationships, we also studied this cohort to determine whether HRT was associated with the maintenance of global cognitive function over time. Results indicated that lifetime exposure to HRT in older women was associated with better maintenance of modified MMSE score.

Methods. *Participants.* Study participants were female residents of Cache County, UT, a geographically isolated, close-knit population, 90% of whom are members of the Church of Jesus Christ of Latter-Day Saints (LDS).[15,17] LDS doctrine prohibits alcohol and tobacco use, and the local lifestyle is associated with exceptional longevity[18,19] and low rates of chronic diseases that can affect cognition.[20-22] Persons aged 65 and older on January 1, 1995, were eligible for the study, which began field work in 1995. Over 99% of the study population and all of its female participants were Caucasian. Detailed information on eligibility and recruitment has been previously reported.[17,23]

Among eligible women, 2,928 (90%) completed a baseline interview in 1995–96 (Wave I). The interview included a slightly abridged version of the 100-point modified MMSE and a simplified version of the depression section of the Diagnostic Interview Schedule.[24] We obtained demographic information, occupational history, psychiatric history, medical history, and a detailed history of medication use. We also recorded a detailed medicine chest inventory of all prescribed and over-the-counter medications in current use and obtained buccal material for *APOE* genotyping.[25,26] Using a multistage screening and assessment protocol,[17] we then identified 226 women with prevalent dementia.

In 1998–99, as part of a study of incident dementia,[23] we attempted to collect 3-year follow-up interview data (Wave II) from women whose baseline evaluation had indicated they had no dementia. The Wave II interview asked questions about interval medication history and again included a comprehensive medicine chest inventory. We then used a similar multistage assessment procedure to identify individuals with recent onset of dementia.[23] Near the midpoint of the 3-year interval between the Wave I and Wave II screening efforts, we were able to administer a detailed telephone Women's Health Questionnaire (WHQ). Specifically, we asked women, "Have you ever taken estrogen replacement therapy and, if so, for how long?" This questionnaire requested detailed information about past and present use of HRT, including information about age at first use, duration, and recency of use. One item on the Wave I screening and WHQ interview overlapped, enabling determination that reliability of report was high (Cohen's $\kappa = 0.78$ using full sample), while instances of disagreement were modest.

For our analyses, we excluded all of those with prevalent dementias (n = 226), stroke up to Wave II (n = 201), and anyone who did provide WHQ data (n = 366). We thus had 2,073 women available for analysis at Wave I. Of these, 273 women died before Wave II or otherwise did not complete the Wave II modified MMSE, leaving 1,800 women with complete data available for longitudinal analyses. We conducted these analyses in two ways. One approach included all data regardless of participants' results at later-stage Wave II dementia evaluations. The other discarded follow-up data from the 123 women who received a Wave II diagnosis of incident dementia. The latter approach was intended to test specifically whether HRT is associated with preservation of cognition within the range of "normal" age-related cognitive function and separate from any influence on the onset of dementia per se.

A comparison of the participant sample with the 273 subjects not studied because of intercurrent death, stroke, or nonresponse revealed several differences. The nonrespondent group was older and had less formal education, lower baseline modified MMSE scores, poorer perceived health, and more frequent reports of depression, diabetes, or myocardial infarction than did women who completed all phases of study (in bivariate χ^2 tests, all $p < 0.005$). Furthermore, proportionately fewer nonparticipants reported ever taking HRT than did participants ($p = 0.001$). A comparison across age groups of mortality rates and other reasons for loss to follow-up between Waves I and II revealed an expected increase in mortality with increasing age, from 2.4% in the 65- to 75-year age group to 11.2% in the oldest age group. Attrition due to stroke was somewhat more common in the 75- to 85- year olds than in the other two groups but did not appear to interact with HRT use. Rates of dementia were highest in the oldest age stratum only among nonusers. Among past and current users, rates of dementia were nearly equivalent across the two older age strata. These latter findings will be examined in more detail in a separate report on AD incidence. Finally, data missing for other unspecified reasons were most common

in the two younger age strata and did not appear to interact with HRT use.

Statistical analyses. In addition to traditional bivariate χ^2 and *t*-test group comparisons with two-tailed $\alpha = 0.05$, we constructed a series of multiple regression models. These regression analyses used generalized estimating equation (GEE) marginal modeling.[27] This technique affords several advantages.[28] In the present context, it accounted for correlations in repeated measurements on an individual and obviated the need to transform skewed modified MMSE scores to approximate normality. It also allowed us to model exposure using all data available at baseline (n = 2,073) as well as at follow-up (n = 1,800) and to capture time-dependent covariates (e.g., depression) that could influence cognitive change. Finally, this marginal modeling approach allowed us to examine simultaneously and independently the cross-sectional and longitudinal associations between HRT and modified MMSE scores.

In the following GEE equation,

$$3MS_{ij} = \beta_0 + \beta_1 \text{time}_{ij} + \beta_2 \text{HRT}_{il} + \beta_3(\text{time}_{ij}\text{-X-HRT}_{il}) + \ldots + \epsilon_{ij}$$

the subscript *i* refers to individual subjects and the subscript *j* to time of assessment. A primary GEE model (Model I) included only main effect terms for HRT use and study time and an interaction effect of those variables. The term β_0 is the model intercept, which represents the mean modified MMSE score for non-HRT users at baseline or time 0; β_1 estimates the mean modified MMSE change over the study time interval for HRT nonusers (reference group); and β_2 estimates cross-sectional differences in mean modified MMSE score across levels of the exposure (HRT user status) at baseline. Significant *p* values for β_2 indicate a difference in cross-sectional modified MMSE score between the two exposure classes. The β_3 coefficient estimates the longitudinal effect of the interaction term between exposure and time and thus estimates the difference in rate of change (decline) on the modified MMSE across the levels of exposure. Significant *p* values for β_3 indicate different rates of change in modified MMSE score as a function of HRT use, after adjustment for the cross-sectional effect of HRT. The final ϵ_{ij} is a residual error term. An adjusted GEE Model II expanded on Model I by adding both time-invariant and time-dependent covariates (e.g., education and current depression, respectively) but no further interaction terms. Model covariates included age, education, presence of one or more *APOE* ϵ4 alleles and current major depression, along with self-perceived general health and a reported history of diabetes, hypertension, and myocardial infarction. The last four health factors were modeled as time-dependent variables to adjust for changes in health status during the 3-year follow-up interval. Given mixed evidence regarding potential interactions between the *APOE* genotype and effects of HRT use,[4,6] we also stratified according to the presence or absence of this allele and conducted GEE analyses using a three-way interaction term: *APOE* ϵ4 status × HRT × time.

Because inspection of the data suggested an interaction between age and effect of HRT, we also constructed a more complex Model III that built on Model II by including the terms β_4 ($\text{age}_{ij} \times \text{HRT}_{i1}$), β_5 ($\text{age}_{i1} \times \text{time}_{ij}$), and the three-way interaction term β_6 ($\text{age}_{i1} \times \text{HRT}_{i1} \times \text{time}_{ij}$). The latter evaluated whether HRT use was associated with a better preservation of modified MMSE score over time as the age of subjects increased. Finally, to graphically depict the results of the three-way interaction term in Model III, we reconstructed Model II in subgroups stratified by three decades of age, 65 to 74, 75 to 84, and 85+ years. The resulting residualized mean modified MMSE scores for each subgroup were then graphically depicted.

We also used WHQ data to categorize HRT use into dichotomous (ever versus never) and trichotomous (current versus past versus never) categories. We assessed duration of HRT use by summing across all periods of reported use and then divided users into three groups (<3 years, 3 to 10 years, >10 years) for comparisons with a reference group of nonusers. Recency of HRT use was trichotomized into "current users" who had continued HRT through the follow-up interval, "recent users" who had stopped HRT within 10 years of their Wave II interview, and "former users" who had stopped HRT earlier. Separately, we identified "early users" who reported HRT use within the first 8 years following menopause and compared them with late users (>8 years after menopause) and nonusers.

Analyses of multivitamin and calcium supplement use as "healthy lifestyle" controls. A positive effect of HRT in these analyses might simply represent confounding by a "healthy lifestyle" effect in which HRT is a surrogate indicator for the tendency of some women to take specific steps to preserve their health and longevity. In a post hoc effort to investigate such possible confounding, we therefore conducted separate GEE analyses that substituted multivitamin or calcium supplement use (from the medicine chest review of current medicines at Waves I and II) for HRT as potential predictors of cognitive trajectory. We reasoned that positive results with HRT, but not with either of the two control exposures, would suggest a "real" HRT effect unrelated to more general health-related behaviors. In other analyses, we added both the calcium and the multivitamin use variables in models with HRT to see whether inclusion of these two "healthy lifestyle" covariates would modify an observed HRT association with cognitive trajectory (results not shown).

Results. *Sample characteristics.* A majority of the sample, 58%, reported some use of postmenopausal HRT. Mean duration of HRT use among prior users was 6 years and among current users 17 years. Fifty-two percent of users were currently taking HRT at baseline. The most common form of HRT, taken by 77% of current users, was an oral unopposed estrogen preparation (Premarin; Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA). Table 1 presents the characteristics of the participant sample categorized as nonusers, past users, and current HRT users. Past and current HRT users were younger and had more formal education, higher baseline modified MMSE scores, and lower prevalence of diabetes mellitus and myocardial infarction than nonusers (all $p < 0.05$.) Past users differed from current and nonusers in that they included a smaller proportion with one or more *APOE* ϵ4 alleles, they reported fewer health problems in the preceding 3 months, and they had lower prevalence of major current depression and hypertension. By comparison, current users reported more health problems than past and nonusers within the last 3 months, a counterintuitive finding generally consis-

tent with that previously reported in this population.[15] Age-stratified comparisons of HRT use revealed that the majority of women between 65 and 75 (49%) and between 75 and 85 (65%) were exposed to HRT, whereas only 23% of those in the 85+ age group were past or current users. This trend away from estrogen exposure in the oldest age group was expected given that the purported benefits of HRT have emerged relatively recently and that older adults may be more resistant than younger adults to adopting new therapies.

GEE models including all data. Results of GEE Models I and II comparing lifetime HRT users versus nonusers are presented in table 2. Similar models examining HRT use as a trichotomous variable (past, present, or current use) were no more predictive of modified MMSE outcomes than were models using dichotomous categories ($p > 0.10$). Thus, we describe only the latter here. The unadjusted Model I shows a significant cross-sectional association with HRT use such that users' scores averaged about 2.9 points higher. This finding is similar to that reported from previous cross-sectional analyses of the Cache County cohort.[15] The time term in the current analysis suggests that the reference group of nonusers showed about a −1.4-point change (decline) in modified MMSE score over the study interval. The time × HRT term further suggests that lifetime HRT use modified this change by +1.5 points so that users showed no decline (−1.4 + 1.5 = +0.1).

Model II (table 2) is an adjusted GEE analysis that incorporates a number of covariates shown in preliminary bivariate tests to have significant effects on cross-sectional modified MMSE performance (a number of other chronic diseases showed no such effect). These cross-sectional associations are confirmed in the model, which shows that lower modified MMSE scores at baseline were associated independently with age, with the presence of one or more *APOE* ϵ4 alleles with fewer years of education and with current major depression. However, participants' ratings of perceived general health were not significantly associated with baseline modified MMSE score. In this adjusted model, HRT use was associated with an attenuated but significant 1-point increase in baseline modified MMSE score. The longitudinal effect of lifetime HRT use on change in modified MMSE score was essentially the same as in the unadjusted model (−1.4 + 1.5 = +0.1). We further determined that there was no apparent difference in the association of HRT and cognitive trajectory among users of opposed (e.g., PremPro; Wyeth-Ayerst) versus unopposed (e.g., Premarin) estrogen therapies ($p > 0.10$). Finally, separate GEE models that stratified on presence of *APOE* ϵ4 revealed no significant effect of *APOE* genotype on the association of HRT and cognitive trajectory ($p > 0.10$). Similarly, a GEE term for the interaction of *APOE* ϵ4 × HRT × time was not significant ($p > 0.10$).

To evaluate an apparent nonhomogeneity of effects with HRT use at different ages, we constructed a more elaborate Model III that included age interaction terms (table 2). All three such terms were significant ($p < 0.005$), indicating that age modified the association of lifetime HRT use and change in modified MMSE score. For example, Model III suggests that near the population mean age of 76, HRT nonusers experienced an additional interval change of −0.33 modified MMSE point with each added year of age. By contrast, the comparable age-related alteration of interval change among HRT users was −0.12 modified MMSE point, an improvement of 0.21 point. The interaction term age × HRT × time predicted a greater HRT effect at age 85 (−4.15 modified MMSE points over the 3-year interval versus −1.33 points, a difference of 2.82 points) but a lesser effect at age 70 (+0.75 point over the 3-year interval versus +0.47 point, a difference of −0.28 point). To depict the significant three-way interaction in this model, we reconstructed Model II using separate age strata at baseline of 65 to 74, 75 to 84, and 85+. The figure suggests that the apparent inverse association of HRT and modified MMSE decline is negligible in the youngest subgroup, moderate in 75 to 84 year olds, and strongest in the oldest subgroup.

GEE results after exclusion of scores reflecting incident dementia. To test whether the observed HRT effects represented a modification of "normal" age-related cognitive decline, as opposed to prevention of incident dementia, we next excluded Wave II modified MMSE scores of the 123 women who had developed incident dementia during the study interval. Excluding these 123 scores from the analyses, we observed patterns of association that were similar to the preceding results but were somewhat mitigated (table 2). The magnitude of the HRT "benefit" on modified MMSE decline was halved from about +1.5 to about +0.74 point. Age-stratified mean change data (not presented) and results of the GEE Model III including the three-way (age × HRT × time) interaction term essentially replicated findings in the full sample. The reduced model suggested that an annual change among nonusers of −0.18 modified MMSE point at age 76 was modified by +0.11 point to −0.07 point.

Table 1 *Baseline characteristics (SD) of participants (n = 2073) according to current or prior use of HRT after menopause*

Characteristics	Never users	Past users	Current users
n*	839	390	763
Age, y	77.03 (7.20)†	74.57 (5.79)	72.32 (5.59)
Education, y	12.65 (2.32)†	12.95 (2.30)	13.12 (2.12)
Modified MMSE score (of 100)	90.06 (7.12)†	92.81 (5.00)	93.38 (4.67)
Presence of ≥1 *APOE* e4 allele, %	262 (31.2)†	101 (25.9)	228 (29.9)‡
Health problem(s) in past 3 months, %	211 (25.1)‡	136 (34.9)	251 (32.9)†
Major current depression, %	30 (3.6)‡	20 (5.1)	36 (4.7)†
Diabetes, %	102 (12.2)†	33 (8.5)	61 (8.0)‡
Myocardial infarction, %	72 (8.6)†	30 (7.7)	49 (6.4)
Hypertension, %	406 (48.4)†	189 (48.5)	366 (48.0)†

* Eighty-one individuals who reported lifetime use of HRT did not provide adequate data to establish if they are currently still on HRT.
† $p < 0.001$.
‡ $p < 0.01$.

HRT = hormone replacement therapy; MMSE = Mini-Mental State Examination.

Table 2 *GEE marginal models regressing baseline and follow-up modified MMSE scores onto lifetime use of HRT in all older women who were nondemented at baseline and a restricted sample that excluded all cases of incident dementia at follow-up*

	All nondemented at baseline			Excluding incident dementia		
Variables	Model I β	Model II β	Model III β	Model I β	Model II β	Model III β
Time	−1.393*	−1.381*	−1.211*	−0.373	−0.363	−0.350
HRT use	2.900*	1.031*	1.539*	2.590*	1.049*	1.403*
Time × HRT	1.479*	1.464*	0.958†	0.759†	0.748†	0.517‡
Baseline age		−0.469*	−0.452*		−0.400*	−0.413*
APOE e4 allele		−0.891†	−0.872†		−0.562‡	−0.535‡
Education		0.718*	0.704*		0.724*	0.712*
Depression		−1.489†	−1.417†		−0.913‡	−0.897‡
General health		−0.391	−0.392		−0.660†	−0.645†
Age × HRT			0.163*			0.138*
Age × time			−0.327*			−0.187*
Age × HRT × time			0.207*			0.111†
Reference score	90.109	90.447	90.436	90.577	90.684	90.681

Reference group represents nonusers with a median baseline age of 76 years and mean education of 12 years.

* $p < 0.0005$.
† $p < 0.005$.
‡ $p < 0.05$.

GEE = generalized estimating equation; HRT = hormone replacement therapy.

Early exposure to HRT and duration and recency effects. These analyses excluded scores from women with incident dementia, as described above, because such detailed self-reported information was presumed to be less reliable. There were no substantial associations between the HRT exposure categories (longer versus shorter duration, more versus less recent, or early versus later exposure) and observed improvement in modified MMSE scores.

"Healthy lifestyle" control exposures. We observed no substantial effects in GEE marginal models that investigated association of multivitamin use with modified MMSE scores in cross-section or decline over time (all $p > 0.10$). A similar analysis with calcium supplements revealed a cross-sectional association, such that users' baseline modified MMSE scores were 1.07 points higher on average than those of nonusers ($p < 0.001$). However, an observed longitudinal effect of +0.15 point was barely notable ($p > 0.500$). Inclusion of multivitamin and calcium use as covariates in HRT Model II did not substantially alter the relation of HRT and cognition.

Discussion. This study substantially extends earlier cross-sectional findings in the Cache County cohort,[15] showing an apparent longitudinal benefit of lifetime HRT use on global cognitive function as measured by the modified MMSE. Other studies had suggested improved maintenance of memory in healthy older HRT users.[4,29-32] The present findings suggest that HRT use is associated with better maintenance of abilities on a more global measure of cognitive function, the modified MMSE, after age 75. The size of this apparent effect (e.g., a decrease of 1.50 points in the annual rate of modified MMSE decline at the mean age of 76) suggests that the effects apparent with HRT use are clinically as well as statistically significant. Although such an effect may seem modest on a 100-point scale, the distribution of modified MMSE scores in Cache County women was strongly skewed toward a 100-point ceiling and was relatively restricted, with a SD of 6.6 points.

Because we excluded women with prevalent dementia from these analyses, our results do not speak to the possible utility of HRT for the treatment of dementia symptoms. They are, however, consistent with the notion that HRT might help prevent the onset of dementia in women with mild or prodromal cognitive difficulty. We will report more detailed analyses on the latter question elsewhere. Here we note that the apparent effects with HRT were retained in restricted analyses that eliminated follow-up scores of women with incident dementia.[4] This finding suggests that, apart from any possible preventive effect on dementia onset, HRT may mitigate "normal" age-related cognitive decline (granting the possibility that such decline may itself be a prodrome of AD).

Relative to other epidemiologic samples,[2,33] the size of the Cache County cohort of long-lived women and its relatively high proportion of HRT users provided us an unusual opportunity to examine whether there was variation with age in the inverse association of HRT and cognitive decline. Our results suggest that the apparent effects of HRT are greatest among the oldest old. In other words, those who

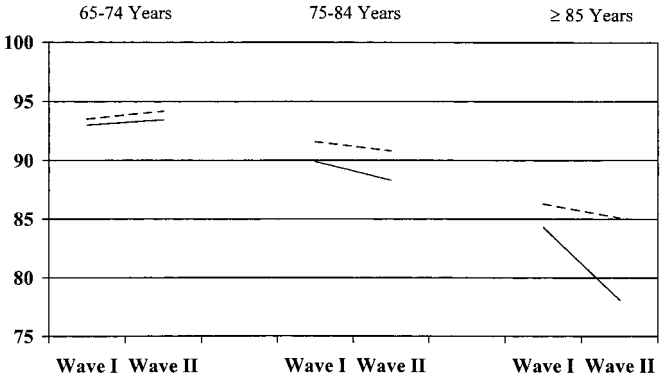

Figure. The Model II adjusted effect of hormone replacement therapy on Modified Mini-Mental State Examination scores in "ever users" (dashed lines) vs "never users" (solid lines) over a 3-year interval, stratified by age groups with baseline ages of 65 to 74, 75 to 84, and 85+ years.

stand to lose the most cognitively appear to gain the most from HRT exposure. The increasing association of HRT and cognitive trajectory in later years, particularly after age 85, may reflect latent benefits that become apparent as cognitive reserve is progressively depleted with age or as individuals reach an age where they are increasingly likely to have prodromal AD. A similar association with age was seen in cross-sectional results from the Rancho Bernardo study.[5] Our observation of no meaningful association of HRT with cognitive trajectory before age 75 may indicate a true absence of effect before this age; alternatively, such effects might become apparent with the use of more sensitive or domain-specific cognitive test measures. Further study will be needed to judge which interpretation is correct.

Notwithstanding our efforts to control for confounding influences, the present observational results cannot be regarded as conclusive. Definitive conclusions about the effects of HRT on cognition in aging can result only from randomized trials of HRT for prevention of AD and mitigation of age-related cognitive decline. There are at least two such trials currently in progress.[13,14] If they observe rates of cognitive decline and effects with HRT similar to those reported here, then reasonably sized samples should demonstrate cognitive benefits of HRT within a few years of follow-up. Consistent with this optimistic perspective is the observation that the average duration of HRT use among our participants was only about 6 years, in keeping with new reports on the extension of brain reserve and neuronal plasticity into later age.[34-36] Other current findings with implications for future trials work include our failure (and that of others) to find substantial association between duration or recency of HRT use and degree of apparent cognitive benefit.

We emphasize that our results in healthy women do not contradict recent findings that HRT fails to mitigate or reverse progression of cognitive impairment in AD.[2,12,14,37] Others have suggested that by the time AD symptoms appear, vulnerable neurons with estrogen receptors have degenerated to a point beyond recovery under trophic influences.[14] A variety of neurobiological mechanisms have been proposed to explain the protective effects of HRT on cognition.[38,39] These include maintenance of neural circuitry, enhancement of cerebral blood flow, promotion of cholinergic and serotonergic activity, and protection against neuronal apoptosis.

Limitations. Despite its advantages, the Cache County cohort poses some limitations on interpretation of our results. Its relative homogeneity and good health characteristics limit generalizability to other populations. Its health-conscious culture may account for its unusually high rate of lifetime HRT use. With its many aims, the Cache County Study was not focused on broad-range characterization of cognitive abilities over time. We were therefore able to study only global cognitive function using the modified MMSE. A more comprehensive cognitive assessment would presumably have improved sensitivity to HRT-related benefits, if any, over an interval of only 3 years.[28]

Our methods are susceptible to recall bias, although such bias would intuitively seem less likely for HRT than for other pharmacologic exposures. Also, as is true in all observational studies, we cannot exclude other uncontrolled or unsuspected sources of confounding. We did, however, control for depression, perceived health at baseline, and prevalent and incident diseases known to affect cognition. We also used several methods to address the potential for a "healthy user" bias, including parallel analyses of multivitamin and calcium supplement use. The apparent benefits were observed only with HRT use. Overall, our results suggest that HRT use is associated with reduced cognitive decline, particularly in the oldest age groups. Definitive demonstration of HRT effects will require randomized trials among healthy older women.

Appendix

Other Cache County Study investigators who contributed to this project: James C. Anthony, PhD; James Burke, MD; Chris Corcoran, PhD; Robert Green, MD; Michael Helms, MS; Carole Leslie, MS; Constantine Lyketsos, MD; Richard Miech, PhD; Ronald Munger, PhD; Maria C. Norton, PhD; Ingmar Skoog, MD, PhD; Martin Steinberg, MD; Nancy West, MS; and Bonita Wyse, PhD.

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