Hormone Replacement Therapy and Incidence of Alzheimer Disease in Older Women

The Cache County Study

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Context Previous studies have shown a sex-specific increased risk of Alzheimer disease (AD) in women older than 80 years. Basic neuroscience findings suggest that hormone replacement therapy (HRT) could reduce a woman's risk of AD. Epidemiologic findings on AD and HRT are mixed.

Objective To examine the relationship between use of HRT and risk of AD among elderly women.

Design, Setting, and Participants Prospective study of incident dementia among 1357 men (mean age, 73.2 years) and 1889 women (mean age, 74.5 years) residing in a single county in Utah. Participants were first assessed in 1995-1997, with follow-up conducted in 1998-2000. History of women's current and former use of HRT, as well as of calcium and multivitamin supplements, was ascertained at the initial contact.

Main Outcome Measure Diagnosis of incident AD.

Results Thirty-five men (2.6%) and 88 women (4.7%) developed AD between the initial interview and time of the follow-up (3 years). Incidence among women increased after age 80 years and exceeded the risk among men of similar age (adjusted hazard ratio [HR], 2.11; 95% confidence interval [CI], 1.22-3.86). Women who used HRT had a reduced risk of AD (26 cases among 1066 women) compared with non-HRT users (58 cases among 800 women) (adjusted HR, 0.59; 95% CI, 0.36-0.96). Risk varied with duration of HRT use, so that a woman's sex-specific increase in risk disappeared entirely with more than 10 years of treatment (7 cases among 427 women). Adjusted HRs were 0.41 (95% CI, 0.17-0.86) for HRT users compared with nonusers and 0.77 (95% CI, 0.31-1.67) compared with men. No similar effect was seen with calcium or multivitamin use. Almost all of the HRT-related reduction in incidence reflected former use of HRT (9 cases among 490 women; adjusted HR, 0.33 [95% CI, 0.15-0.65]). There was no effect with current HRT use (17 cases among 576 women; adjusted HR, 1.08 [95% CI, 0.59-1.91]) unless duration of treatment exceeded 10 years (6 cases among 344 women; adjusted HR, 0.55 [95% CI, 0.21-1.23]).

Conclusions Prior HRT use is associated with reduced risk of AD, but there is no apparent benefit with current HRT use unless such use has exceeded 10 years.

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COMPARED WITH MEN, WOMEN appear to be at increased risk of Alzheimer disease (AD) after ages 80 to 85 years.[1-3] Postmenopausal depletion of endogenous estrogens may contribute to this risk. Estrogens may exert several neuroprotective effects on the aging brain, including inhibition of β-amyloid formation, stimulation of cholinergic activity, reduction of oxidative stress-related cell damage, and protection against vascular risks.[4]

Several studies have examined whether hormone replacement therapy (HRT) is associated with reduced risk of AD in older women. Early case-control study results of this association were mixed.[5-13] One such study reported no relation of AD and HRT ascertained from pharmacy records within a 10-year period of observation.[14] Another study using prescription records showed an inverse relation of AD with lifetime HRT use.[15] Two prospective studies[16,17] suggested a benefit of lifetime HRT use, but the most recent study,[18] conducted using the UK General Practice Research Database, showed no relation of AD to HRT prescriptions within a 10-year period of ob-

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servation. Thus, the relationship of HRT and AD remains uncertain.

In the large Cache County cohort,[3] we analyzed prospective data on the association of HRT and AD in elderly women. We examined whether a reduction in risk with HRT, if any, varied with the number of ε4 alleles at *APOE,* the polymorphic genetic locus for apolipoprotein E. Finally, we assessed whether apparent benefits with HRT varied in relation to duration and recency of exposure.

METHODS

Study Population

The Cache County Study is a longitudinal investigation of the prevalence and incidence of AD and other dementias in relation to genetic and environmental risk factors. Details of the study protocol have been published previously.[3,19] Briefly, between 1995-1997 we used a multistage screening and assessment protocol (wave I) to diagnose cases of dementia among 5677 elderly residents of Cache County, Utah. More than 97% of the 5092 initial participants (90% of those aged ≥65 years, including 2928 women) provided buccal DNA for genotyping at *APOE*. Three years later, between 1998-2000, we used similar procedures to diagnose new cases of dementia (wave II) among the surviving at-risk population of 4119 (2401 women).[3] Essentials of the screening procedures and study protocol are shown in FIGURE 1.

Participants were screened with the Modified Mini-Mental State examination (3MS)[20] or, for those unable to participate, an informant questionnarie[21] followed by the Dementia Questionnaire (DQ)[22] administered to collateral informants (spouses, companions, or others knowledgeable about the respondents). Participants with screening results suggesting a cognitive disturbance then underwent a clinical assessment. Collateral informants provided a medical history, a dementia symptom checklist, and a chronological history of cognitive symptoms; specially trained nurses conducted a structured neurological examination; and psychometric technicians administered a 1-hour battery of neuropsychological tests. A geriatric psychiatrist and neuropsychologist then reviewed the results and assigned working diagnoses of dementia (*Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* criteria) or other cognitive syndromes; 83.9% of these subjects still living were then examined by a board-certified geriatric psychiatrist, and among these, 65.9% underwent routine laboratory diagnostic testing for differential diagnosis. All this information was then considered by a panel of experts, who identified dementia and assigned diagnoses of AD[23] and other disorders using standard criteria.

Among all study participants, we identified 152 individuals (98 women, 54 men) with incident dementia. To these we added 33 individuals (25 women, 8 men) who had an onset of dementia detected in the later stages of wave I (before the start of wave II), yielding a total of 185 incident cases (123 women, 62 men). The estimated sensitivity of the screening protocol for detection of incident dementia was 89% (K. Hayden et al, unpublished data, 2002). Of the women with incident dementia, 88 had diagnoses of definite, probable, or possible AD.[23] A second diagnosis of another dementing illness was entered for 12 of these AD cases. Of the 62 men with incident dementia, 35 had an AD diagnosis, 8 of these with another dementing illness. A comparison with neuropathological findings in 54 individuals suggested that the accuracy of our AD diagnoses is similar to typical rates reported from university AD clinics (eg, positive predictive value, 90%; B. Plassman et al, unpublished data, 2002). Another 1801 women completed the wave II study procedures sufficiently to assess their cognitive status and were found to be free of dementia. Of these, 298 underwent all stages of evaluation, including clinical assessment; the other 1503 showed no evidence of dementia on screening measures and were not further evaluated. Unaffected men numbered 1322, of whom 249 completed a clinical assessment.

Exposure Assessment

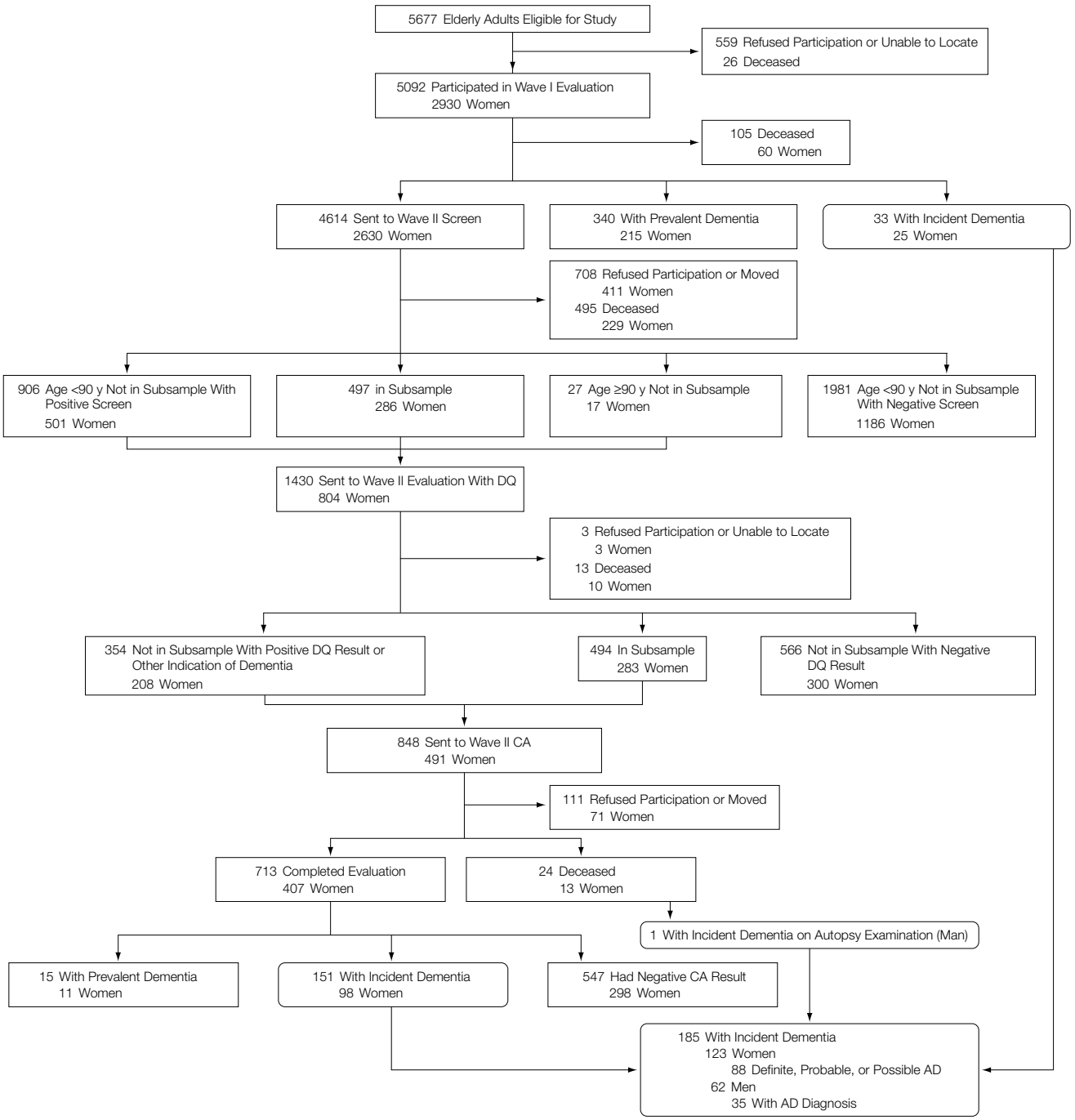
The initial wave I interview provided 2 sources of information on HRT. Women were asked if they had ever taken HRT and, if so, for how long. They were also asked about use over the prior 2 weeks of any medicines, including HRT. Interviewers then viewed these current medications and recorded the name, dose, and usage indication for each. Although 18 women developed incident AD within 30 months of their wave I interviews, none appeared to have substantial cognitive impairment when interviewed, and all therefore provided their own exposure information.

We first classified HRT according to report of lifetime use, categorizing participants as "exposed" if they endorsed ever having taken HRT or if HRT was among their current medicines. Complete data for HRT exposure were available from 1866 (98.8%) of the 1889 women. Omitting 10 HRT users (1%) who did not report their duration of use, we classified exposures into duration strata of less than 3 years, 3 to 10 years, and more than 10 years. Finally, we classified exposed women as current vs former users, the latter being individuals who endorsed HRT exposure at some point but did not have HRT among their current medicines. Among the current HRT users, 72% were taking an unopposed oral estrogen preparation.

Statistical Analysis

We compared characteristics of HRT users and nonusers using χ^2 tests for categorical variables and 2-sample *t* tests for continuous measures. We then used discrete-time survival analysis[24] to compare risks of incident AD among HRT users and reference groups of nonusers and of men. We considered each year under observation as a discrete time interval. Participants entered the analytic pool at the age of their wave I interview and were then considered year by year until they either developed AD or underwent wave II screening. Hazard ratios (HRs) were estimated by odds ratios in logistic models that accommodated multiple covariates.

Figure 1. Screening Procedures and Protocol for Detection and Evaluation of Dementia and Alzheimer Disease in the Cache County Study



An at-risk population of 4614 was identified for screening at wave II. These included a high-risk subsample of 497 participants identified previously (wave I)[19] who were asked to complete all phases of the protocol regardless of their screening results. Based on results of screening with the Modified Mini-Mental State examination (3MS)[20] or, for those unable to participate, the Informant Questionnaire for Cognitive Disorders in the Elderly (IQCODE)[21] and the Dementia Questionnaire (DQ)[22] administered to collateral informants of selected participants, we sought a clinical assessment (CA) of 848 individuals. Among 713 completed CAs, we identified 151 individuals with incident dementia and 15 whose (prevalent) dementia had gone undetected in wave I. One individual died before we could complete the examination, but a brain autopsy confirmed the presence of Alzheimer disease (AD). Thirty-three individuals with milder cognitive syndromes developed incident dementia during the later stages of wave I. The 185 individuals with incident dementia included 123 with AD (88 women). A comparison group of 3123 unaffected participants (1801 women) included the following: 1981 participants (1186 women) who were not in the subsample but screened negative on the 3MS/IQCODE; 566 participants (300 women) who were not in the subsample but screened negative on the DQ; 547 participants (298 women) who underwent CA and were found to be free of dementia; and 29 participants (17 women) in the subsample who refused to participate, died, or moved away prior to the CA but showed no evidence of cognitive disturbance in their screening results.

Table 1. Demographic Characteristics by Hormone Replacement Therapy (HRT) Use of the Men and Women Completing Waves I and II of the Cache County Study (n = 3246)

	Men	Women With No HRT Use	Women With Any HRT Use	Women Missing HRT Use Data
No.	1357	800	1066	23
Age, mean (SD), y	73.2 (6.1)*	76.2 (7.0)	73.1 (5.8)†	79.1 (8.7)
Years of education, mean (SD)	14.1 (3.4)*	12.7 (2.3)	13.1 (2.2)†	12.5 (3.5)
APOE ϵ4 alleles, No. (%)				
0	930 (68.5)	549 (68.6)	735 (68.9)	13 (56.5)
1	378 (27.9)	224 (28.0)	305 (28.6)	7 (30.4)
2	40 (2.9)	17 (2.1)	23 (2.2)	0 (0)
Missing	9 (0.7)	10 (1.3)	3 (0.3)	3 (13.0)
Alzheimer disease, No. (%)				
Yes	35 (2.6)*	58 (7.3)	26 (2.4)†	4 (17.4)
No	1322 (97.4)*	742 (92.8)	1040 (97.6)†	19 (82.6)

*Difference compared with all women significant at $P<.01$.
†Difference compared with HRT nonusers significant at $P<.01$.

We fit a series of models that were built on a "base model" for AD incidence that had previously yielded a good fit to the data for both men and women.[3] That model included terms for age, age-squared, and years of education, as well as dummy-coded terms for the presence of 1 or 2 *APOE* ϵ4 alleles, and interactions between age and the *APOE* ϵ4 terms. It also included terms for sex and its statistical interaction with age, but the current analyses that considered only women omitted those terms. We fit the discrete-time logistic models using SAS version 8 software (SAS Institute Inc, Cary, NC) and report parameter estimates with 95% profile likelihood confidence intervals (CIs).

RESULTS

TABLE 1 presents the characteristics of the current analytic sample of men and women, the latter categorized by HRT use. Missing data on HRT use were relatively rare; women who did not provide this information tended to be older and slightly less educated than women who did. There were 411 living women who did not participate in the initial assessment of wave II; they were less likely to report HRT use ($P<.001$) and had lower 3MS scores ($P<.001$) at baseline than participating women. Among the remainder, 1066 women (56.4%) reported use of HRT at any time, with a mean exposure duration of 11.6 years. These users were significantly younger and more educated than nonusers.

Between the initial interview and the follow-up procedures (3 years), 35 men (2.6%) and 88 women (4.7%) developed AD. Univariate analyses suggested that AD was significantly more common for women than for men ($\chi^2_1=9.37$, $P=.002$), but less common among women with a history of HRT compared with nonusers ($\chi^2_1=24.62$, $P<.001$). Similarly, unadjusted estimates of the hazard for AD (TABLE 2, models 1 and 2) were significantly higher for women than for men, but were lower among women who reported HRT use than a reference group of nonusers.

We next constructed a series of multiple discrete-time logistic models that included the covariates of the base model[3] (FIGURE 2A and the remainder of Tables 2 and 3). Figure 2A shows AD incidence modeled for men and women with 13 years of education (the sample median) and no ϵ4 alleles at *APOE* (the most numerous group). The hazard for men and for women appears roughly equal until age 80 years, but the base model's significant sex-by-age interaction term[3] implies a substantial added risk for women after this age. This risk is indicated by an adjusted HR of 2.11 (95% CI, 1.22-3.86) among women vs men older than 80 years.

We next estimated the modification in women's risk with HRT after controlling for the covariate terms of the base model (Table 2, model 3). Comparing this adjusted estimate with the unadjusted figure (model 2) showed only a slight shift of the HR toward the null. The adjusted estimate did not change appreciably (results not shown) when we added terms separately for comorbid conditions including diabetes mellitus, cardiovascular disease, and depression, as well as for the use of nonsteroidal anti-inflammatory drugs (NSAIDs).[25] To investigate whether the apparent reduction in AD risk among HRT users might simply reflect their tendency toward a healthy lifestyle, we also added terms post hoc for use of multivitamins and of calcium supplements (both obtained at the initial wave I interview) as plausible indicators of such a tendency. Model 4 shows that neither of these terms was significantly associated with risk of AD. Their inclusion as covariates also yielded no appreciable change in the point estimate of the relative hazard among HRT users. To examine whether the HRT effect varied with age or with number of *APOE* ϵ4 alleles, we added terms to model 3 for interactions between HRT and these covariates. Lack of an apparent interaction between HRT and age (model 5) suggested that the effect with HRT did not vary over the life span. The interactions between HRT and presence of 1 or 2 *APOE* ϵ4 alleles also failed to reach statistical significance (model 6), although there was some suggestion that risk reduction with HRT may be greater in women with 2 ϵ4 alleles ($P=.19$).

TABLE 3 shows variation in the apparent HRT effect with duration and recency of exposure. We first examined risk estimates among the 3 categories of usage duration (model 7). Longer duration was associated with greater reduction in risk of AD. Figure 2B shows this graphically, depicting the age-specific hazards modeled for women with no *APOE* ϵ4 alleles and 13 years of education; Figure 2B also shows the risk for men with these same characteristics. The increased hazard of AD among women vs men in late old age is again apparent. The added risk for women appears greatest for those with no reported use of HRT.

This sex-specific risk was attenuated, however, with increasing years of HRT exposure. The estimated hazard for women who had used HRT for more than 10 years was similar to that for men (vs men, adjusted HR, 0.77; 95% CI, 0.31-1.67).

Model 8 shows risk estimates for women with HRT use after separation of current and former users. Compared with nonusers, only former users showed significantly reduced risk. Partitioning as before into 3 categories of usage duration (model 9), we observed an incremental reduction in apparent risk for former users with longer history of use. Former users with more than 10 years of exposure had an estimated 5-fold lower risk of AD. Among current users, however, there was no suggestion of reduced risk with 10 or fewer years of exposure, and only a modest reduction thereafter among 344 women.

COMMENT

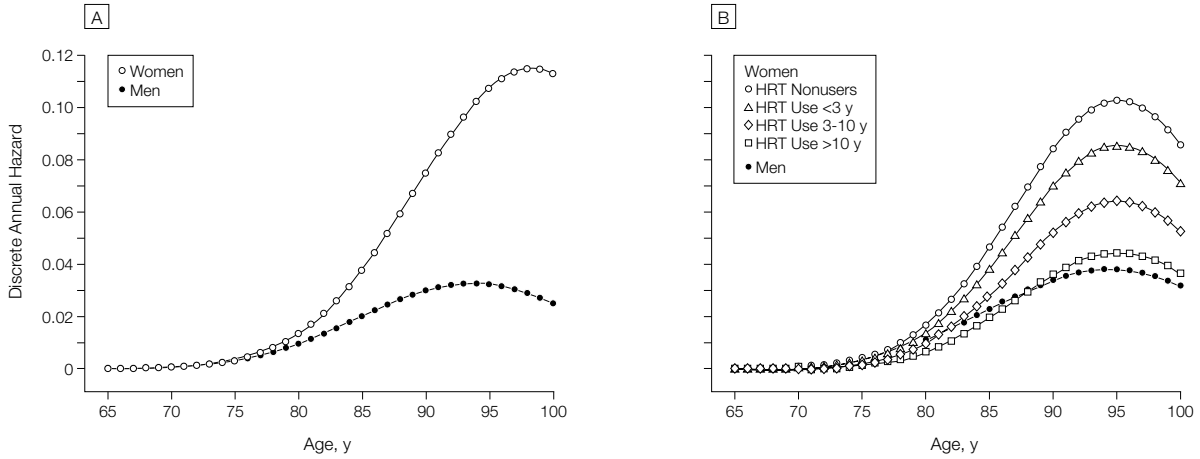
These findings extend those of 2 previous prospective studies[16,17] and provide new evidence to suggest a protective effect of HRT. As in the previous studies, the adjusted risk of incident AD among lifetime HRT users was reduced to little more than half that among nonusers. This effect appeared to be stronger among women with 2 ϵ4 alleles at *APOE,* but given the small numbers available, the interpretation of this finding is uncertain. One previous prospective study examined the effects with HRT across *APOE* genotypes, suggesting a slightly greater apparent effect with HRT in women who had 1 ϵ4 allele.[16] Only half the sample in that study had been genotyped at *APOE*, however, and none of the 9 women with 2 ϵ4 alleles in that study had ever used HRT.

Table 2. Relative Hazards for Alzheimer Disease in Women Estimated From Discrete-Time Logistic Regression Models

	Relative Hazard (95% Confidence Interval)					
Terms*	Model 1†	Model 2†	Model 3	Model 4	Model 5‡	Model 6
Female sex	1.82 (1.24-2.73)	. . .	. . .	. . .	. . .	. . .
Any HRT		0.33 (0.21-0.52)	0.59 (0.36-0.96)	0.63 (0.38-1.02)	0.49 (0.22-1.04)	0.66 (0.34-1.23)
Calcium supplements				0.85 (0.52-1.39)	. . .	. . .
Multivitamins				1.08 (0.62-1.83)	. . .	. . .
HRT by age					1.03 (0.94-1.12)	. . .
HRT by 1 *APOE* ϵ4 allele						1.01 (0.36-2.81)
HRT by 2 *APOE* ϵ4 alleles						0.25 (0.01-1.85)

*Reference group for each term shown includes women nonusers of the compound represented by that term, except for sex where the reference group is men. HRT indicates hormone replacement therapy.
†Models 1 and 2 are simple unadjusted bivariate models; models 3-6 are built on a "base model" that includes terms (not shown) for age, age-squared, years of education, dummy-coded terms for the presence of 1 or 2 *APOE* ϵ4 alleles, and interactions between age and the dummy-coded *APOE* terms.
‡The HRT term in model 5 with the HRT-by-age interaction was estimated at the mean age of 76 years.

Figure 2. Estimated Discrete Annual Hazard of Alzheimer Disease for Men and Women by Age, and by Duration of Hormone Replacement Therapy Use for Women



Both figures indicate risks estimated for an individual with the mean value of 13 years of education and no ϵ4 alleles at *APOE*. A, The curves depict the annual hazards predicted by fitting the base model including an age-by-sex interaction term. The annual hazard for Alzheimer disease (AD) appears similar for men and women before 80 years of age but diverges rapidly afterward with an excess risk found in women. B, The curves depict the annual hazards predicted by fitting model 7 of Table 3 to the women with available hormone replacement therapy (HRT) exposure information and, in filled circles, the corresponding annual hazards for men after omitting the terms for HRT. There were 35 instances of incident AD among 1357 men. Ordinate values for women differ slightly from those in panel A due to omission of women lacking HRT exposure information, several of whom experienced incident dementia.

Table 3. Relative Hazards of Alzheimer Disease (AD) in Women With Different Degrees of Duration and Recency of Hormone Replacement Therapy (HRT) Use, as Estimated From Discrete Time Logistic Regression Models

Terms*	Total No. (No. With AD)	Age, Mean (SD), y	Relative Hazard (95% Confidence Interval)		
			Model 7†	Model 8†	Model 9†
HRT use, y					
<3	310 (10)	73.6 (5.8)	0.82 (0.38-1.57)	. . .	. . .
3-10	319 (8)	72.3 (5.8)	0.60 (0.26-1.22)	. . .	. . .
>10	427 (7)	72.8 (5.7)	0.41 (0.17-0.86)	. . .	. . .
HRT use					
Former	490 (9)	74.5 (5.9)		0.33 (0.15-0.65)	. . .
Current	576 (17)	71.9 (5.4)		1.08 (0.59-1.91)	. . .
HRT use, y					
Former					
<3	252 (6)	73.8 (5.7)			0.58 (0.22-1.27)
3-10	146 (1)	74.9 (6.0)			0.32 (0.08-0.68)
>10	83 (1)	75.4 (6.3)			0.17 (0.01-0.80)
Current					
<3	58 (4)	73.0 (6.2)			2.41 (0.70-6.34)
3-10	173 (7)	70.9 (5.0)			2.12 (0.83-4.71)
>10	344 (6)	72.1 (5.3)			0.55 (0.21-1.23)

*All models are built on a "base model" that includes terms (not shown) for age, age-squared, years of education, dummy-coded terms for the presence of 1 or 2 *APOE* ε4 alleles, and interactions between age and the dummy-coded *APOE* terms.
†Reference group for each analysis is nonusers of HRT.

We observed a distinct relation between AD risk and duration of HRT use. Two previous studies reported a similar result on dichotomizing duration at 1 year of use.[10,16] We observed considerably stronger effects with longer duration of usage. Compared with nonusers, Cache County women who had used HRT for more than 10 years experienced 2.5-fold lower incidence, comparable with the risk observed in men. Others have speculated that the lower rates in older men may reflect their greater availability of circulating testosterone, which may be converted in the central nervous system by aromatase to estradiol.[26] Taken to their logical conclusion, our findings suggest that if women were to use long-term postmenopausal HRT, their excess risk of AD over that of men in late old age might disappear.

A new finding in this study is an apparent limited window of time during which sustained HRT exposure seems to reduce the risk of AD. We found that, in contrast with earlier use, HRT exposures within 10 years of AD onset yielded little, if any, apparent benefit. These results are in accord with prior findings of reduced cognitive decline in elderly women who initiated HRT at menopause, but not in those with more recent exposures.[27] In fact, our results and those of all prior observational studies are consonant with a loss of HRT effect from exposures near the onset of dementia. A similar finding was reported recently for NSAIDs.[28] The results with both HRT and NSAIDs suggest that potentially neuroprotective agents may be useful only in the latent pathogenetic stages of AD, before there is extensive damage to the integrity of the brain. Limitation of the benefit of HRT to the latent stages of AD is also consistent with recent randomized treatment trials that suggest HRT is not effective in mitigating the progression of cognitive decline in women with established AD.[29-31]

Some have suggested that HRT may be most beneficial at menopause, when a precipitous depletion of endogenous estrogens may have greatest deleterious effect on neurons.[30] We were unable to test this hypothesis directly, but our findings are consistent with it: many women who had used HRT for more than 10 years before our wave I interview would likely have been exposed many years prior to the time when they became vulnerable to the onset of dementia. Furthermore, we found a reduced risk with HRT among former users but not among current users unless the latter had used HRT for more than 10 years. This last observation may explain the contrast in the findings of the 2 prior prospective studies[16,17] with those of 2 well-designed case-control studies that evaluated the relation of AD onset to prescription records within a 10-year interval.[14,18]

Our study capitalized on several characteristics of the Cache County population. Its residents are well educated and relatively homogeneous in their sociodemographic characteristics, including their tendency toward healthy lifestyles. They offer high response rates in research, and they enjoy remarkably long lives. Consequently, the current study may be less susceptible than some to response or healthy user biases. Further, we attempted to control for the latter bias in our analyses by testing a model with terms for multivitamin and calcium supplement use. Only those who took HRT showed a significantly reduced risk of AD.

Among potential limitations, the unusual sociocultural attributes of the Cache County sample may suggest a lack of generalizability of our findings to other populations, although this is less worrisome with biological measures than with social or cultural ones. Another potential limitation is that we observed a relatively short period of follow-up between wave I and wave II.

A common difficulty in pharmacoepidemiologic studies is incomplete recall of drug exposures. Faulty recall that is not related to the later occurrence of incident AD (*nondifferential exposure misclassification*) would reduce the observed strength of any real association between HRT and incident AD. Of greater concern is biased recall, in which exposures are underreported by women who are destined subsequently to develop AD (*differential exposure misclassification*). This form of bias may be of particular concern for the 18 women whose AD was detected in the later stages of wave I. However, the threat of incomplete recall should be lower with HRT than with most other medicines, because the use of HRT after menopause is a major life

decision for most women, almost always made in consultation with a physician. Furthermore, because HRT is typically used for several years, it is less likely to be forgotten than other, more transient drug exposures. Also, regarding possible differential or biased recall, we found no relationship between AD incidence and recollection of several other control exposures, including calcium and multivitamin supplements. It seems unlikely that women who later develop dementia would selectively forget their carefully considered decision to use HRT, but would accurately recall their use of these other compounds.

An important limitation of this and all other observational studies is unsuspected confounding. We cannot exclude the possibility that HRT users differ from nonusers in other attributes related to health in general and to AD in particular. Specifically, we considered whether current HRT users of short duration might have initiated use because they were concerned about mild (possibly prodromal) memory difficulties and had learned of other recent evidence for possible neuroprotective benefits of HRT. We discount this possibility, however, because all current users were taking oral estrogen preparations, available only by prescription. Numerous conversations over several years with the county's physicians failed to reveal any practitioner prescribing HRT for this indication. Nonetheless, the only way definitively to avoid this sort of difficulty is to conduct large-scale randomized prevention trials. Two such trials are currently in progress.[30,32] Our observations suggest that the benefits of HRT, if any, may take years to appear, and a considerable latency period may intervene between treatment and perceptible effect. Thus, caution would be in order when interpreting null or disappointing early trial results. Our findings, along with other recent work, suggest that HRT may be effective for the primary prevention of AD—if not for its treatment—and that patience in awaiting definitive trial results is indicated.

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