REVIEW

Hormone Replacement Therapy and Cognition
Systematic Review and Meta-analysis

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Context Some observational data suggest that hormone replacement therapy (HRT) may reduce the risk of cognitive decline and dementia but results have been conflicting.

Objective To review and evaluate studies of HRT for preventing cognitive decline and dementia in healthy postmenopausal women.

Data Sources Studies with English-language abstracts identified in MEDLINE (1966-August 2000), HealthSTAR (1975-August 2000, PsychINFO (1984-August 2000); Cochrane Library databases; and articles listed in reference lists of key articles.

Study Selection Randomized controlled trials and cohort studies were reviewed for the effects of HRT on cognitive decline; cohort and case-control studies were reviewed for dementia risk. No randomized controlled trials regarding dementia risk were identified.

Data Extraction Twenty-nine studies met inclusion criteria and were rated. Two reviewers rated study quality independently and 100% agreement was reached on Jadad scores and 80% agreement was reached on US Preventive Services Task Force quality scores. A final score was reached through consensus if reviewers disagreed.

Data Synthesis Studies of cognition were not combined quantitatively because of heterogeneous study design. Women symptomatic from menopause had improvements in verbal memory, vigilance, reasoning, and motor speed, but no enhancement of other cognitive functions. Generally, no benefits were observed in asymptomatic women. A meta-analysis of observational studies suggested that HRT was associated with a decreased risk of dementia (summary odds ratio, 0.66; 95% confidence interval, 0.53-0.82). However, possible biases and lack of control for potential confounders limit interpretation of these studies. Studies did not contain enough information to assess adequately the effects of progestin use, various estrogen preparations or doses, or duration of therapy.

Conclusions In women with menopausal symptoms, HRT may have specific cognitive effects, and future studies should target these effects. The meta-analysis found a decreased risk of dementia in HRT users but most studies had important methodological limitations.

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OBSERVATIONAL DATA SUGgest a relationship between lifelong endogenous estrogen exposure and cognition.[1,2] Thus, as has been hypothesized, postmenopausal hormone replacement therapy (HRT) might prevent cognitive decline and dementia. To determine supporting evidence, we reviewed medical literature on HRT (estrogen alone or estrogen combined with progestins) (1) to prevent cognitive decline, or (2) to decrease dementia risk in healthy postmenopausal women. This review was conducted in conjunction with the US Preventive Services Task Force to update its recommendations on HRT use.

A review showing possible positive effects of HRT on overall cognition in perimenopausal women has been previously published.[3] What is not known is which cognitive domains might be most affected by estrogen. Cognition includes a variety of processes from memory to attention to motor speed, each mediated by different brain systems. Sex steroids might not affect various brain systems and cognitive processes equally. Indeed, performance on mental rotation and articulatory skills varies across the menstrual cycle, but other cognitive domains are unaffected.[4-6] Such neural and cognitive specificity is not surprising because estrogen receptors are not distributed uniformly throughout the brain. For example, the hippocampus, a brain area rich in estrogen receptors,[7-9] mediates verbal memory,[10,11] a function that some studies show is affected by estrogen.[4,12] We sought to determine whether HRT affects cognition and the cognitive specificity of any effects.

We also evaluated the effects of HRT on dementia risk. A previous meta-analysis found that HRT users had a decreased risk of dementia, and the overall risk reduction just reached significance.[3] However, when only case-control studies were combined, the risk reduction was no longer statistically significant. Since that time, 2 additional case-control studies have been performed.[13,14]

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Box 1. Criteria for Grading Quality of Randomized Controlled Trials: The Jadad Score[16]

Study received 1 point for each yes or 0 point for each no for each of the following questions:

1. Was the study described as randomized such as using the words randomly, random, and randomization?
   a. An additional point was given if method of randomization was described and it was appropriate (for example, table of random numbers, computer generated)
   b. A point was deducted if the method of randomization was inappropriate (for example, patients allocated alternately by birth date or hospital number)
2. Was the study described as double blind?
   a. A point was given if method of blinding was described and it was appropriate (for example, identical placebo)
   b. An additional point was deducted if method of blinding was inappropriate (for example, comparing placebo tablet with injection)
3. Was there a description of withdrawals and dropouts?

Maximum number of points is 5.

Box 2. Criteria for Grading the Internal Validity of Individual Studies

The Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria to determine how well individual studies were conducted (internal validity).[17] Presented below are a set of minimal criteria for case-control and cohort study designs. The Task Force also defined a 3-category rating of "good," "fair," and "poor," based on these criteria. In general, a good study is one that meets all criteria well. A fair study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known important limitation that could invalidate its results. A poor study has important limitations. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made.

Case-Control Studies

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- High response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Cohort Studies

- Initial assembly of comparable groups: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders

METHODS

We searched MEDLINE (1966-August 2000), HealthSTAR (1975-August 2000), PsychINFO (1984-August 2000) and the Cochrane Library databases. We combined the Medical Subject Headings *hormone replacement therapy* and *estrogens* with the headings *dementia*, *mental processes*, *cognition disorders*, and *memory disorders*. Additional articles were obtained from reference lists of relevant reviews. A single reader (E.S.L.) reviewed all 509 abstracts identified by the search and found 56 studies with primary data.

To identify which studies to include, a "best evidence" approach was applied.[15] For the question of the association between HRT and cognition, we included only randomized, double-blind, placebo-controlled trials and cohort studies. Cohort studies were included because they used older populations followed up for longer periods than did randomized controlled trials.

To address the association between HRT and dementia, we included only cohort and case-control studies. There were no randomized controlled trials about the association. For a case-control study to be included, the study methodology had to provide details about how Alzheimer disease or dementia was determined. If 2 studies were done on the same population, the study with the most recent data was included.

Jadad scores were used to measure the quality of the randomized controlled trials (BOX 1).[16] For the other studies, methodological limitations that could compromise the study's quality were recorded based on a quality score created by a work group of the US Preventive Services Task Force (USPSTF) (BOX 2).[17] Two reviewers (E.S.L. and H.D.N.) rated study quality independently; there was 100% agreement on Jadad scores and 80% agreement on USPSTF quality scores. When the reviewers disagreed, a final score was reached through consensus. We evaluated studies for selection bias using funnel plots.[18]

The original goal was to combine the results of the cognitive tests quantitatively; however, the study designs and

cognitive measures were too dissimilar. Instead, the cognitive tests were qualitatively combined according to what was measured (memory, attention, reasoning, mental status, motor speed, verbal function) using a reference guide[19] and expert opinion. When possible, we calculated the increment of effect and normalized the scores using a total of 100 points. In some cases, scores were estimated from figures.[12,20,21]

For studies of dementia, we performed a meta-analysis of the 2 cohort[22,23] and 10 case-control studies[13,14,24-31] meeting inclusion criteria. All reported either relative risk (RR) or odds ratio (OR) estimates. The logarithm of RR (logRR) was assumed to have a normal distribution. If confidence intervals (CIs) or *P* values were reported, SEs for the logRR were calculated. If neither was reported, SEs were calculated for studies that reported enough data. The logRR and the corresponding SEs were used as data points for the meta-analysis.

Fixed and random effects models were fit on the data. Mean RRs and CIs were estimated for a global HRT effect. The Bayesian data analytic framework was used to fit the model. Inference on the parameters was done via posterior probability distributions. The data were analyzed using WinBUGS software,[32] which uses a method of Markov Chain Monte Carlo called Gibbs Sampling to simulate posterior probability distributions.

Noninformative prior probability distributions were used. Inference was made on 5000 simulated draws (1000 draws from 5 chains) from the posterior distribution after adequate convergence. Sensitivity analysis was performed using different prior distributions, combining only studies with similar methods and excluding a study with uncertain CIs.

RESULTS

Effects on Cognition

The literature search identified 9 randomized controlled trials (TABLE 1), of which 1 had a quality score of five[34] and 3 had quality scores of four[35-37]; and 8 cohort studies (TABLE 2), 6 rated as fair and 2 as poor in quality, that used formal testing to measure the effects of estrogen on the cognition of women without dementia. The randomized controlled trials are dissimilar in several ways. Three used a cross-over design[12,34,35]; the rest used separate experimental and placebo groups. The mean age of the women in the studies ranged from 45 to 80 years. Three studies included women immediately after a total abdominal hysterectomy/bilateral salpingo-oophorectomy[12,36,37]; 6 other studies included only a small percentage of women with surgical menopause.[20,34,35,38,39,42] Some studies included women with menopausal symptoms[12,20,36,39]; one specifically excluded symptomatic women.[37] More than 40 different cognitive tests were used in these studies, and 30 of these tests were used by only 1 investigator. Only 7 tests were used in more than 2 studies, and even when tests were repeated by several investigators, the administration was not uniform.[12,35-37,39,42-45] Only 2 studies used the identical estrogen formulation and dose. Duration of use ranged from 21 days to 6 months. Because of these differences in design, results were not combined quantitatively. Instead, the tests were grouped according to the cognitive process they measured. Details of effects are summarized in TABLE 3.

Memory. Memory is the first process to be affected in Alzheimer disease; thus, memory tasks are often used to track dementia onset. Although cross-sectional studies suggest that HRT affects memory,[47-51] results from randomized controlled trials and cohort studies are conflicting.

Nine tests of verbal recall were used by 2 randomized controlled trials and 4 cohort studies.[12,36,40,42,44,45] In verbal recall tests, subjects are shown verbal stimuli such as lists of words, word pairs, or paragraphs and are asked to recall them either immediately or after a 15- to 60-minute retention interval.[19] The 2 randomized controlled trials and 1 cohort study found that users had better immediate verbal recall than nonusers. Users recalled 1 to 2 more words or word pairs from a paragraph or word list of 13 to 14 unrelated words or word pairs after the delay period.[36,42,44] However, no test was uniformly positive in all studies. Estrogen exposure was associated with improvement in at least 1 test of delayed verbal recall in 3 of 4 studies.[36,42,44,45] Users recalled 2 to 5 more words or word pairs from a paragraph or word list of 13 to 14 unrelated words or word pairs.[12,36,44] However, neither study using several measures of delayed verbal recall found a difference on more than 1 test.[36,42]Also, none of the tests were positive in all of the studies.[36,42,44,45]

On visual memory tests, subjects are shown shapes or figures and respond through drawing. One small cohort study[21] found that users performed better on 1 test of visual recall, but 5 other studies,[35,36,42,39,45] including 3 randomized controlled trials,[35,36,39] found no benefit.

Attention and Working Memory. Ten studies looked at the effects of HRT on attention or working memory: the ability to hold information in mind, to manipulate it, and to use it to guide behavior without external cues.[19] Three randomized controlled trials used 3 separate tests to measure working memory. No study found that users performed better than nonusers.[35,34,45] One study found that although there were no behavioral effects, the estrogen group, when performing working memory tasks, had increased activation of certain brain areas by functional magnetic resonance imaging.[34]

Digit span, the most commonly used test, was used in 6 studies.[12,35-37,39,42] On this test, subjects repeat a list of 2 to 8 numbers backward. Only 1 study, using women with symptoms of menopause, found that women randomized to estrogen performed better than nonusers.[12]

Women using estrogen showed improvement compared with nonusers on 1 of the 8 tests of mental tracking, such as arithmetic and repeating months backward.[20,35,39,45] Although 1 study found that women were better able to read a word or state its color despite distracting stimuli,[20] this was not confirmed by a larger study.[35]

Although quite varied, complex attention tasks typically require both visual attention and concentration. Five studies did not find estrogen users better able than nonusers to pair symbols and numbers or to connect consecutively numbered and lettered circles.[35,37,39,43,49] However, 2 randomized controlled trials found that women symptomatic from menopause had improvement on 2 other tests of complex attention when taking estrogen.[20,39]

Of the 3 studies measuring vigilance, 2 found that estrogen improved the ability to sustain attention. The women in both studies were symptomatic, with fatigue, sleep problems, hot flashes, and depression.[20,39] In contrast, a larger randomized cross-over trial did not find that women given estrogen performed better on 2 sensitive tests of vigilance.[35]

Concept Formation and Reasoning. Concept formation and reasoning refers to the quality or process of thinking and was tested in 3 studies with conflicting results. While a randomized cross-over study and cohort study found that subjects given estrogen improved in abstract reasoning scores compared with when they took placebo,[12,40] a New York-based cohort study did not find that scores for ever-users changed over 2.5 years compared with never-users.[44]

Motor Speed. Motor speed, as measured by simple reaction time, was improved by 150 milliseconds in symptomatic postmenopausal women given estrogen in 1 study[20] but not another.[35] Users had improvement in clerical speed and accuracy in a third study.[12]

Dementia Screening Measures. In 2 early studies, women given estrogen did not have improvement in mental status

Table 1. Hormone Replacement Therapy (HRT) and Cognition in Randomized Controlled Trials*

Author and Location	No. of Users	No. of Nonusers	Mean Age (Range), y	HRT Form and Dose	Menopausal Symptoms	Duration of Use	Main Results†	Quality Score‡
Janowsky and Chavez,[33] 2000, Portland, Ore	6	7	69 (61-75)	0.625 mg of CEE, orally	No	30 d	No improvement on a working memory task	2§‖¶
Shaywitz et al,[34] 1999, New Haven, Conn	46	46	50.8 (33-61)	1.25 mg of CEE, orally	Not stated	21 d	No improvement on 2 working memory tasks	5
Polo-Kantola et al,[35] 1998, Finland	62	62	56.3 (47-65)	Transdermal#	Not stated	3 mo	No improvement on 7 tests of attention or 2 tests of working memory	4‖
Phillips and Sherwin, 1992,[36] Canada	10	9	48.2 (+/- 4.7)	Intramuscular**	Yes	2 mo	Performance better on 3 out of 4 tests of verbal recall; no difference on working memory or visual recall tasks	4§
Ditkoff et al,[37] 1991, East Los Angeles, Calif	24	12	53 (45-60)	0.625 mg (12) or 1.25 mg (12) of CEE, orally	No	3 mo	No improvement on 2 tests of attention	4¶
Sherwin,[12] 1988, Canada	10	10	45.4	Intramuscular**	Probably††	3 mo	Improvement on all 4 tests of working memory, reasoning, speed of perception, and verbal recall	3§‖
Fedor-Freybergh,[20] 1977, Stockholm, Sweden	11	10	56.5 (47-70)	2 mg of estradiol, orally	Yes	3 mo	Improvement on all 4 tests of attention and reaction time	3§‖
Hackman and Galbraith, 1976,[38] England	9	9	29-68	3 mg of estropipate, orally	Yes	6 mo	Improvement on a memory battery	2§‖#
Vanhulle and Demol,[39] 1976, Belgium	11	15	57.8	4 mg of estriol, orally	Yes	3 mo	Borderline improvement on 2 of 5 tests of attention	3§‖

*CEE indicates conjugated equine estrogen.
†For magnitude of effect refer to Table 3.
‡Jadad Quality Score (see Box 1). Highest total score is 5.
§Points were deleted from quality score because the method of randomization was either not described or not appropriate.
‖Points were deleted from quality score because blinding was either not described or not appropriate.
¶Points were deleted from quality score because there was no description of withdrawals and dropouts.
#Women younger than 56 years received 0.6 mg/g (2.5 g/d) of estradiol gel transdermally and women older than 55 years received the estradiol patch at a dose of 50 µg every 24 hours.
**Each month 10 mg of estradiol valerate was administered.
††Most likely symptoms from recent oophorectomy.

Table 2. Hormone Replacement Therapy (HRT) and Cognition in Cohort Studies*

Author and Cohort by Estrogen Use	No. of Participants	Mean Age, y	HRT Definition	Average Duration of Use, y	Follow-up, y	Main Results†	Quality Score‡
Rice et al,[40] Kame Project							
Current	196	69.6	Use of any form of unopposed estrogen or estrogen combined with progestin	4.0 to 15.0	2.0	Current users of unopposed estrogen improved more than never and past users on a screening test of global cognitive function; current users of estrogen-progestin were the only group with a decline in cognitive scores	Fair§‖
Past	186	71.4					
Never	455	72.1					
Yaffe et al,[41] Cardiovascular Health Study							
Current	297	70.6	Use of unopposed oral estrogen	Not stated	7.0	Current users had a smaller average decline in modified Mini-Mental State Examination score vs never and past users	Fair§‖¶
Past	336	71.0					
Never	2083	72.5					
Carlson et al,[42] McGill University							
User	14	71.2	Current use of oral CEE#	19.5	1.5	Users performed better on 1 of 13 tests; they performed better on 1 of 6 tests of verbal memory but not better on visual memory tests, a working memory task, or a verbal fluency test	Fair§‖¶
Nonuser	41						
Matthews et al,[43] Study of Osteoporotic Fractures							
Current	1325	. . .	Ever use of any form of oral HRT	Current, 14.3; past, 5.2	4.0-6.0	Users did not perform better on 2 tests of attention or the Mini-Mental State Examination	Fair§‖¶
Past	2612	. . .					
Nonuser	5714	. . .					
Jacobs et al,[44] Manhattan Study of Aging							
User	81	73.8	Ever use of any form**	4.55	2.5	Users performed better on both tests of verbal memory but not on a test of concept formation or a verbal function task	Fair§‖¶
Nonuser	646	74.3					
Resnick et al,[21] Baltimore Longitudinal Study of Aging							
User	18	59.9	Never use at beginning of study and current use (oral or transdermal HRT) at end of study	6 mo to 10 y	Not stated	Users performed better on a visual recall test	Poor‖¶††
Nonuser	18	60.2					
Barrett-Connor et al,[45] Rancho Bernardo Cohort							
User	394	76.9	Ever use of oral HRT**	Current, 19.1; past, 7.7	15.0	Users did not perform better on 10 tests including attention, verbal function, motor speed, verbal recall, or visual recall	Fair§‖
Nonuser	406						
Funk et al,[46] Longitudinal Study of Aging							
User	30	67	Current use of mostly unopposed estrogen	Not stated	≤6.0	Users did not perform better on a screening test for dementia	Poor§‖¶††
Nonuser	77						

*Ellipses indicate that users were younger.
†For magnitude of effect, refer to Table 3.
‡Quality score created by US Preventive Services Task Force (Box 2).
§Study did not assemble comparable groups.
‖Study did not maintain comparable groups.
¶Study experienced important loss to follow-up.
#Seven participants used 0.625 mg of unopposed conjugated equine estrogen (CEE), 3 used 0.625 mg of CEE with 2.5 mg of medroxyprogesterone acetate, and 2 used 0.30 mg of unopposed CEE.
**Most used unopposed oral CEE.
††Study was not adjusted for potential confounders.

as measured by the Mini-Mental State Examination or Cognitive Capacity Screening Examination.[43,45,46] However, this is not unexpected, given that the simplicity of the Mini-Mental State Examination for cognitively intact women might preclude finding subtle differences (ceiling effect). Two recent cohort studies using more sensitive multidimensional tests of cognition found that over time users performed better than nonusers.[40,41]

Verbal Function. Only 1 study[40] of 4 found that users performed better than nonusers on tests of verbal functions and language skills.[42,44,45] Users of unopposed estrogen were more fluent in naming categories.[40]

Influence of Symptoms. In the randomized controlled trials, changes in cognitive measures were most likely to occur in symptomatic women (Table 1). In all 4 trials in women with somatic complaints, estrogen improved at least 1 cognitive function.[12,20,36,38,39] The cognitive processes that were most consistently improved were verbal recall[12,36,42,44] and vigilance,[20,39] although complex attention,[20,39] mental tracking,[12,20] concept formation and reasoning,[12] and motor speed[12,20] were also affected.

The 2 randomized trials in asymptomatic women found no enhancement of cognitive function.[33,37] Two trials that did not state the symptom profile of subjects also showed no improvement. One of these, a cross-over study of 62 women using transdermal estrogen for 3 months, used sensitive tests (outcomes measured in milliseconds) and had a power of 90%.[35]

Effects of Progestins. All of the randomized controlled trials used unopposed estrogen. The 4 cohort studies that looked at the type of HRT found that most (> 70%) of the women used unopposed oral conjugated equine estrogen.[42,44-46] One recent cohort study looked separately at users of unopposed and combined HRT regimens. Women currently using unopposed estrogen had more improvement in global cognition, abstract reasoning, and category fluency, compared with never-users. However, current users of estrogen combined with progestin had a decline in global cognition and mental tracking scores.[40]

Table 3. Summary of Cognitive Tests*

Cognitive Function	References	Positive/Total Tests†	Subject Profile Studies With Positive Tests	Explanation of Results and Magnitude of Effect‡
Memory				
Memory battery	38	1/1	Symptomatic	Increase of 8.0 with use
Immediate verbal recall	12§‖, 36, 40, 42, 44, and 45#	4/9	Symptomatic	Paragraph recall: increase of 2.2, 5.9¶, and 11.5¶ with use; selective reminding: increase of 2.4 and 2.8¶ with use; associate learning: increase of 1.7 and 14.0¶ with use
Delayed verbal recall	36, 42, 44, and 45#	3/8	Asymptomatic/ symptomatic	Paragraph recall: change of –5.4 and 1.52¶ with use; selective reminding: increase of 16.6¶ and 21.6¶ with use; associate learning: increase of 2.6 and 19.3¶ with use
Visual memory	21, 35, 36, 39, 42, and 45	1/9	Not stated	Fewer errors made by users in 1 study; 8 measures in 5 other studies were negative
Attention				
Working memory	33, 34, and 35#	0/5	. . .	Increase of 0.2**, 0.7**, and 3.2 with use
Complex attention	20§, 35, 37, 39#, 40, 43, and 45	2/9	Symptomatic	Positive findings were on 2 tests not repeated by other studies; 1 was only of borderline significance ($P = .08$); 4 studies found no effects on digit symbol; 2 studies found no effect on trail making
Mental tracking	12§, 20§, 35#, 36, 37#, 39#, 40, 42, and 45	2/14	Symptomatic	1 of 5 studies had improvement on digit span**: change of –1.67, 2.25, and 11.25¶ with use
Vigilance	20§, 35#, and 39#	3/5	Symptomatic	5 Different tests were used; in 1 study, visual search improved by 0.4 to 4 min¶ and sorting improved by 3 to 4 min¶ with use; other positive result was only of borderline significance ($P = .07$)
Concept formation and reasoning	12§, 44#, and 40	2/3	Asymptomatic/ symptomatic	Abstract reasoning: increase of 3.4¶ and 11.0¶ with use
Motor speed	12,§ 20,§ and 35#	2/3	Symptomatic	Clerical speed and accuracy: increase of 9.5¶ with use; reaction time: 160-millisecond improvement with use
Mental status	45#, 40, 41, 43#, and 46#	2/5	Asymptomatic	Dementia screening examinations**: increase of 0.89¶ and 0.90¶ with use
Verbal functions and language	40, 42, 44#, and 45#	1/4	Asymptomatic	Category fluency and retrieval: increase of 3.4¶ and 6.0 with use

*Ellipses indicate not applicable.
†Positive test indicates that women using estrogen scored significantly higher (at .10 significance level) than nonusers. Total tests refers to the total number of test sessions on that cognitive measure. The same test may have been used by more than 1 study, and some studies may have used more than 1 type of test to measure that cognitive function.
‡Scores normalized using a total of 100 points.
§Scores derived from figure and represent estimates of effect magnitude.
‖Denominator not reported so estimated by authors.
¶Significant ($P<.05$).
#No data given in study.
**Ceiling effect may have contributed to null findings.

Formulation, Dose, and Duration. Subjects in the randomized controlled trials used a variety of preparations and doses. Because the randomized controlled trials lasted only several months, information about duration comes from cohort studies. The 1 cohort study that looked at duration found that users of greater than 20 years scored slightly higher on 1 of 9 cognitive measures.[45] Although 1 cohort study looking at recency of use actually found that past users had more benefit than current users,[43] another study found that past users had scores intermediate between current and never-users.[40]

Effects on Dementia

Two cohort studies (TABLE 4) and 10 case-control studies (TABLE 5) on the association between postmenopausal estrogen use and risk of Alzheimer disease met inclusion criteria.

The strongest evidence for an association between HRT and Alzheimer disease comes from 2 cohort studies (Table 4). Because users tend to be healthier and have healthier lifestyles as well as other differences, the raters did not feel that comparable groups were assembled and therefore rated both studies as fair. In the Manhattan Study of Aging, 156 ever-users of postmenopausal estrogen and 968 nonusers were followed up for 1 to 5 years.[23] Users were significantly younger, more educated, less likely to be black, more likely to have undergone a hysterectomy, and younger at menopause. After controlling for education, age, and ethnicity, users were significantly less likely to develop Alzheimer disease (RR, 0.5; 95% CI, 0.25-0.9) and had a later age of onset. The Baltimore Longitudinal Study of Aging followed up 230 HRT users and 242 nonusers every 2 years for up to 16 years.[22] Loss to follow-up and maintenance of comparable groups was not described. After controlling for age and education, users were significantly less likely to develop Alzheimer disease than nonusers (RR, 0.46; 95% CI, 0.21-1.0).

Most of the case-control studies had important methodological limitations: 8 were rated poor, 1 was rated fair, and 1 was rated good. Several studies used self-report for controls and proxy for cases.[14,25,26] In these studies, the risk estimates could indicate a spurious protective effect of estrogen because proxy respondents might not be aware of previous HRT exposure.[52] (Although Watkins et al[53] believe proxys' responses are often correct, we still believe proxy bias is a potentially a significant limitation.) Some studies did not use blinded interviewers.[28-31] Other studies did not control for education.[24,25,28-31] Women who use HRT are generally more educated,[54-56] and formal education has been found to be protective against dementia.[57,58] Several of the studies only looked at current use of HRT.[25,26,31] Women with dementia might have been less likely to receive HRT because of concerns about compliance or potential interactions with complex medication regimens. Finally, the largest case-control study used self-administered questionnaires completed 5 years before death to define HRT exposure and did not exclude women with early dementia.[24] Women with early, subtle memory changes might be less likely to remember previous HRT use, causing a false-protective effect of HRT to be seen.

In the earlier case-control studies,[28-31] HRT use was only 1 of many risk factors evaluated. These early case-control studies did not find an association between HRT and Alzheimer disease (OR, 0.78-2.38). All but one[27] of the more recent case-control studies found significantly decreased risks of Alzheimer disease among users of postmenopausal estrogen (OR, 0.33-1.1) (Table 5).[13,14,24-27]

Two case-control studies[13,27] were rated fair and good because they used objective methods to determine estrogen use. In 1 study, HRT was determined through blinded record abstraction.[13] After controlling for age, education, and length of time in the linkage system, users of any form of postmenopausal estrogen for at least 6 months had a 58% risk reduction (OR, 0.42; 95% CI, 0.18-0.96). The second study used computerized pharmacy records to identify postmenopausal estrogen use.[27] After controlling for age and history of hysterectomy, this study found no decreased risk of Alzheimer disease among ever-users of HRT (OR, 1.1; 95% CI, 0.6-1.8).

Only 1 study looked at dementia other than Alzheimer disease and found that women exposed to HRT had a 50% decreased risk of developing dementia secondary to ischemic vascular disease, although the 95% CI did not reach significance (OR, 0.50; 95% CI, 0.26-1.20).[25]

Table 4. Hormone Replacement Therapy (HRT) and Dementia in Cohort Studies*

Author	Cohort	No. of Users	No. of Nonusers	With Dementia: No. of Users	With Dementia: No. of Nonusers	Mean Age, y	HRT Form	Average Duration of Use, y	Follow-up, y	Adjusted RR (95% CI)	Quality Score†
Kawas et al,[22] 1997	Baltimore Longitudinal Study of Aging	230	242	9	25	61.5	212 Oral; 12 patch	Not stated	Up to 16	0.46 (0.21-1.00)	Fair‡§
Tang et al,[23] 1996	Manhattan Study of Aging	156	968	9	158	74.2	Majority used CEE	6.8 (2 mo to 49 y)	1 to 5	0.50 (0.25-0.90)	Fair‖

*RR indicates relative risk; CI, confidence interval; and CEE, conjugated equine estrogen.
†Quality score created by US Preventive Services Task Force (Box 2).
‡Study did not maintain comparable groups.
§Study experienced important loss to follow-up.
‖Study did not assemble comparable groups.

Bayesian Data Interpretation. The results of these 2 cohort and 10 case-control studies were combined by meta-analysis. The test of heterogeneity indicated that the studies were not heterogeneous ($P>.10$). The fixed and random effects model did not differ, so we present only the random effects model.

The summary RR was 0.66 (95% CI, 0.53-0.82) (FIGURE). The estimates did not change substantially when case-control (RR, 0.71; 95% CI, 0.56-0.91) and cohort studies (RR, 0.50; 95% CI, 0.30-0.80) were analyzed separately or when poor quality studies were excluded (RR, 0.64; 95% CI, 0.32-1.06) although excluding poor quality studies made the result no longer significant. When studies with proxy bias were excluded (which was one of the factors considered in classifying a study as "poor") the RR was 0.72 (95% CI, 0.55-0.96). The summary RR was similar for studies looking only at Alzheimer disease or using only the strict clinical criteria of the work group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Using different prior distributions and excluding both a study with

Table 5. Hormone Replacement Therapy (HRT) and Dementia in Case-Control Studies*

Author and Location	No. of Cases	No. of Controls	No. of HRT Users		Mean Age, y		HRT Definition	Adjusted OR (95% CI)	Quality Score†
			Cases	Controls	Cases	Controls			
Waring et al,[13] 1999, Rochester, Minn	222	222	9	20	Not stated‡	Not stated	Use of any form for more than 6 mo§	0.42 (0.18-0.96)	Fair‖
Harwood et al,[14] 1999, Alzheimer Disease Center in Miami									
White	229	139	28	44	79.9	75.7	Ever use¶	0.6 (0.3-1.0)	Poor‖#
Hispanic	133	53	14	35	76.0	71.5	Ever use¶	0.4 (0.2-1.0)	
Paganini-Hill and Henderson,[24] 1996, nested in Leisure World Cohort	248	1198	96	568	87.7	87.3	Ever use of any form	0.65 (0.49-0.88)	Poor**††
Mortel and Meyer,[25] 1995, Houston and Waco, Tex									
All participants	93	148	18	29	74.0	72.3	Current use¶	0.53 (0.26-0.94)	Poor‖#**
Alzheimer disease	. . .	. . .	11	. . .	73.7	. . .	Current use¶	0.55 (0.26-1.16)	
Ischemic vascular disease	. . .	. . .	7	. . .	74.4	. . .	Current use¶	0.50 (0.20-1.2)	
Henderson et al,[26] 1994, Alzheimer Disease research center, California	143	92	10	17	76.0	76.3	Current use of any form§	0.33 (0.14-0.76)	Poor#‡‡
Brenner et al,[27] 1994, HMO, Washington	107	120	52	58	78.7	76.6	Ever use of any form§	1.1 (0.6-1.8)	Good
Graves et al,[28] 1990, Alzheimer disease referral center in Washington State	60	60	11	10	66.2	63.6	Ever use¶	1.15 (0.50-2.64)	Poor**‖
Broe et al,[29] 1990, Alzheimer disease referral center in Sydney, Australia	106	106	14	18	78.6	78.7	Ever use¶	0.78 (0.39-1.56)	Poor**
Amaducci et al,[30] 1986, neurology departments in Italy	60	50	6	4	51-80 (range)		Ever use¶	1.67 (0.39-6.97)§§	Poor**
Heyman et al,[31] 1984, Durham, NC	28	56	4	4	60.8		Current use¶	2.17 (0.5-9.41)‖‖	Poor**

*OR indicates odds ratio; CI, confidence interval; HMO, health maintenance organization; and ellipses, nonapplicable.
†Quality score created by US Preventive Services Task Force (see "Individual Studies" box).
‡Case matched to control ± 3 years.
§Majority (66%-90%) used oral conjugated equine estrogen.
‖Received a poor score because selection of controls was potentially biased.
¶Formulation not stated.
#Received a poor score for using self-report for controls and proxy for cases.
**Received a poor score for not controlling for education.
††Received a poor score for not excluding women with dementia at baseline.
‡‡Received a poor score because ascertainment of cases may be inaccurate.
§§Matched odds ratio and confidence intervals calculated from data provided in paper using Statistical Analysis Software (SAS).
‖‖Odds ratios and confidence intervals are unadjusted and calculated from data published in tables. Adjusted OR given in study is 2.38.

uncertain CIs[31] and a study with a low SE (thus, a high weight)[24] did not significantly change the risk estimate.

Formulation, Dose, and Duration. Where reported, 66% to 95% of women used oral conjugated equine estrogen.[13,26,27] Data on the relation of dose, duration, and recency of treatment to response are scant, and results of studies that examined these relationships had conflicting results.[13,22-24,27]

Only 1 study looked at the effect of progestins on Alzheimer disease risk. Adding progestin use to the logistic regression model did not significantly change the risk estimate.[27]

Finally, studies were evaluated for evidence of study selection bias. Some asymmetry was detected in the funnel plots, suggesting that study selection bias was possible although interpretation of the plots is subjective (data available from author on request).

COMMENT

Although the study populations and outcome measures differ and most of the studies have methodological shortcomings, the 9 randomized controlled trials and 8 cohort studies that we reviewed offer provisional conclusions about the effects of postmenopausal estrogen on cognition and risk of dementia. No deleterious effects on cognition have been reported. Estrogen does not appear to enhance asymptomatic women's performance consistently on formal cognitive testing; however, in symptomatic women, postmenopausal estrogen improved cognitive performance, especially in tests of verbal memory, vigilance, reasoning, and motor speed. There were not consistent effects on visual recall, working memory, complex attention, mental tracking, mental status, or verbal function. Symptomatic women taking estrogen might perform better on cognitive testing because they have fewer hot flashes and sleep better or have improved mood. However, affective changes would be expected to have broad effects on most cognitive functions, and this analysis showed that only some cognitive domains were affected by estrogen. Alternatively, the subtle effects of estrogen on cognition might only be apparent in subjects not performing at maximum cognitive ability because of sleep loss.

There is insufficient evidence about whether progestins attenuate these cognitive effects, the optimal estrogen formulation, or dose. Duration of use was not related to cognitive performance.

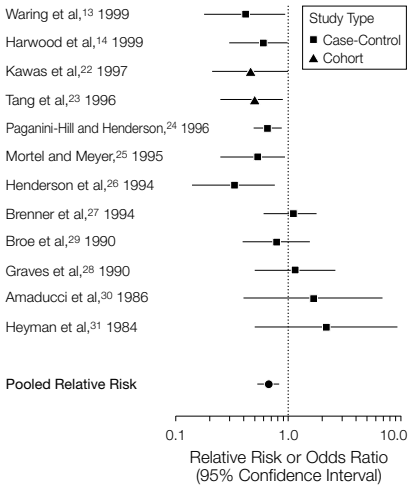
Two cohort and 10 case-control studies suggest that HRT users have a 34% decreased risk of Alzheimer disease (95% CI, 18%-47%). However, there are limitations in the studies on which this estimate is based. The risk estimates may have shown a spuriously larger protective effect of HRT if proxy respondents for women with dementia were not aware of HRT exposure, if women with undiagnosed mild memory changes did not remember previous HRT use, or if women with dementia were less likely to receive HRT due to concerns about compliance or medical complications.

Also, HRT users might be less likely to develop Alzheimer disease not because of postmenopausal estrogen exposure but because they are healthier and have healthier lifestyles ("healthy user bias").[59] Physical health status has been associated with cognitive changes with advancing age.[60] Finally, we cannot exclude that studies that did not find a protective effect of HRT on dementia risk were less likely to be published although statistical tests on the data did not reveal this bias.

Whether estrogen is also associated with a decreased risk of other forms of dementia is unknown. No conclusions can be drawn about progestins or whether specific dosages or formulations of estrogen are more protective.

It has been proposed that HRT decreases the risk of dementia by improving cognition and delaying clinical disease onset. However, the studies we reviewed do not show a consistent improvement in the cognition of older women. In addition, 3 recent randomized controlled trials found HRT did not improve the cognitive function of women with dementia.[61-63] Therefore, if the association between HRT and Alzheimer disease proves to be true and not the result of other variables such as education or health or mood, how HRT might prevent the neuropathological changes of Alzheimer disease will need to be explored further. Current theory suggests that HRT might promote the breakdown of β-amyloid precursors, thereby preventing the development of neurofibrillary tangles, or it might stimulate dendritic spine density, promoting neuronal circuitry.[3,64]

Figure. Results of Meta-analysis of Dementia Studies



Large double-blind, placebo controlled trials with intervention arms containing estrogen with and without progestins are needed and 2 such primary prevention trials are under way.[65,66] Of crucial importance in designing a study of cognition is deciding on cognitive measures. These must be sensitive to small differences because a subtle decline in cognitive function may have important clinical consequences, for instance reducing the quality of interpersonal or intellectual life. They should examine particular cognitive domains, such as verbal memory and vigilance, as the evidence indicates that estrogen has neural and cognitive specificity. This review demonstrates the need for a large standardized data set with a hierarchy of cognitive measures to distinguish which domains and neural systems are affected by HRT. Results for all cogni-

tive measures studied, not just those with statistical significance, should be reported in a way that the magnitude of the effect is clear. In addition, future trials should include functional outcome measures, such as activities of daily living or progression to nursing home care.

Clinicians are confronted with questions about the efficacy of HRT for cognitive health and dementia prevention. The analysis presented herein distinguishes these issues and should help physicians advise patients on what has become a complex body of evidence. From a clinical perspective, the most important conclusion is that HRT improves some cognitive functions in symptomatic women. However, it may not affect all cognitive processes equally. Which cognitive functions and the strength of HRT's effects cannot be determined from the current literature. Only future randomized trials can determine whether HRT use also prevents Alzheimer disease.

ADDENDUM

After this study was conducted, the literature search described herein was updated. In the period from August 2000 to February 2001, 1 additional study[67] that met selection criteria was published. Thirty-seven women (mean [SD] age 65 [4.9] years) without menopausal symptoms were randomized in double-blind fashion to 3 weeks of transdermal 17 β-estradiol or placebo. The women receiving estrogen performed worse than those receiving placebo at baseline and subsequently improved more on verbal and nonverbal memory and spatial cognition tasks. Although the improvement was not statistically significant in the primary analysis, an exploratory analysis combining multiple memory or spatial cognitive measures suggested a beneficial effect of estrogen. Estrogen did not enhance performance on working memory tasks. The additional study does not change our conclusions.

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Acquisition of data: LeBlanc and Nelson.
Analysis and interpretation of data: LeBlanc, Janowsky, Chan, and Nelson.
Drafting of the manuscript: LeBlanc, Nelson, and Chan.
Critical revision of the manuscript for important intellectual content: LeBlanc and Janowsky.
Statistical expertise: Chan.
Obtained funding: Nelson.
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