Hormone replacement therapy and cognition
Leblanc E, Chan B, Nelson H D

Authors’ objectives
To review and evaluate studies of hormone replacement therapy (HRT) for preventing cognitive decline and dementia in healthy postmenopausal women.

Searching
MEDLINE (from 1966 to December 2000), HealthSTAR (from 1975 to December 2000), PsycINFO (from 1984 to December 2000) and the Cochrane Library were searched; the search strategy was reported. The reference lists of relevant reviews were also checked. Only peer-reviewed full papers were included in the review. Foreign language papers were excluded, unless deemed a ‘key article’ (not defined).

Study selection
Study designs of evaluations included in the review
To assess the association between HRT and cognitive testing, randomised, double-blind placebo-controlled trials (RCTs) and cohort studies were eligible for inclusion. To assess the association between HRT and dementia, case-control studies were also eligible for inclusion.

Specific interventions included in the review
Studies of HRT were eligible for inclusion. The types of HRT evaluated were not stated. However, a previous publication reported that the included studies evaluated the following types of HRT: conjugated equine estrogen (0.625 to 1.25 mg), transdermal oestrogen, intramuscular oestrogen, oral estradiol (2 to 4 mg), oral estropipate (3 mg), unopposed oestrogen, or oestrogen with or without progesterin.

Participants included in the review
Studies of healthy postmenopausal women were eligible for inclusion. Studies of women with pre-existing dementia were excluded from the review.

Outcomes assessed in the review
Studies providing data on tests of cognition or memory, or any type of dementia diagnosis, were eligible for inclusion. The reported outcomes included changes in memory recall, attention or concentration, concept formation, reasoning, motor speed, verbal functioning, mental status, learning ability, and the risk of Alzheimer disease and other forms of dementia.

How were decisions on the relevance of primary studies made?
A single reviewer assessed all English abstracts. The authors did not state how full articles were assessed for relevance to the review, or how many reviewers performed the assessment.

Assessment of study quality
The validity of the RCTs was assessed using the Jadad scale (see Other Publications of Related Interest no.1). For other study designs, the quality was assessed based on a quality score created by a work group of the U.S. Preventive Services Task Force (see Other Publications of Related Interest no.2).

Case-control studies were assessed with regards to: the selection of cases and controls; the response rate; diagnostic testing procedures applied equally to each group; accurate and equal measurement of exposure for each group; and attention to potential confounding factors.

Cohort studies were assessed for comparability of the groups, loss to follow-up, consistency of measurements, definition of interventions, outcomes reported, and adjustment for potential confounders.
Two reviewers independently assessed study quality, with any disagreements resolved by consensus.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Age, menopausal type and symptoms, type of HRT and duration of use, compliance and follow-up rates were extracted. Confounders controlled for in the cohort studies were also extracted.

**Methods of synthesis**

*How were the studies combined?*
Cognitive function: the data were combined in a narrative because of clinical heterogeneity among the studies.

Dementia: adjusted odds ratios (ORs) or relative risks and 95% confidence intervals (CIs) were calculated using both random-effects and fixed-effect models. The results from the random-effects model were presented. The Bayesian data analytic framework was used for the meta-analysis.

Selection bias was assessed using funnel plots, while publication bias was assessed using trim and fill.

*How were differences between studies investigated?*
Cognition: some study details were tabulated, grouped according to the cognitive tests measured (memory, attention, reasoning, mental status, motor speed, verbal function). Studies in the narrative synthesis were also grouped by the cognitive test used. Dementia: statistical heterogeneity was assessed using the chi-squared test. Sensitivity analyses were performed to determine the effect of different study design and quality, proxy bias, uncertain CIs, type of dementia assessed, and criteria for measuring dementia.

**Results of the review**
Nine RCTs (n=263), three of which were of a crossover design (n=148), and 8 cohort studies (n not reported) assessed the effect of HRT on cognitive testing. Ten case-control studies (n=4,261) and 2 cohort studies (n=1,596) assessed the effect of HRT on dementia.

Some asymmetry was detected in the funnel plots. No results were reported for the trim and fill analysis.

**Memory.**
Two RCTs and 4 cohort studies assessed immediate verbal recall. The 2 RCTs reported that women receiving estradiol performed better than those not in receipt of HRT. A cohort study of elderly women showed no significant difference in verbal recall between long-term users and nonusers. Another cohort study showed no significant difference in verbal recall between users and non-users of HRT; however, this had included women of a wide age range and showed younger women to have better recall. Another cohort study reported significantly better verbal recall in users of HRT.

**Attention.**
Ten studies (8 RCTs and 2 cohort studies) evaluated aspects of attention. Three RCTs evaluating working memory reported no effect of oestrogen. Six of the 7 studies (4 RCTs and 2 cohort studies) evaluating complex attention reported no effect of oestrogen. Mental tracking was evaluated by 9 studies, with four (3 RCTs and 1 cohort study) reporting improvement in 2 out of 13 variables; one RCT reported an improvement on digit span.

**Concept formation.**
Three studies evaluated concept formation. One randomised crossover trial and a cohort study reported improvements in abstract reasoning scores in women taking oestrogen compared with a placebo. However, another cohort study found no significant difference in women that had taken HRT and those that had not.

**Motor speed.**
Three studies evaluated motor speed. One RCT reported improved reaction time in women taking oestrogen, whereas a larger RCT reported no effect of HRT. The third trial reported an improvement in clerical speed and accuracy in women taking HRT.

Verbal function.

Four studies evaluated verbal function, but only one found an improvement in women taking HRT.

Dementia.

Twelve studies (10 case-control and 2 cohort studies) evaluated dementia. When all the studies were pooled, there was a significant reduction in the risk of dementia in women taking HRT (OR 0.66, 95% CI: 0.53, 0.82). There was still a significant reduction in the risk of dementia in women taking HRT when case-controlled (OR 0.71, 95% CI: 0.56, 0.91) and cohort studies (OR 0.50, 95% CI: 0.30, 0.80) were analysed separately. However, when only high-quality studies were analysed, the point estimate remained similar, but the confidence intervals widened to include 1, so that there was no longer a significant reduction in risk in women taking HRT.

Five studies evaluated dementia screening measures. Three studies using either the mini-mental status exam or the cognitive capacity screening exam, reported no significant improvement in mental status in women taking oestrogen. Two cohorts using multidimensional tests reported that women taking HRT performed better than those that were not.

**Authors’ conclusions**

HRT may have specific cognitive effects in women with menopausal symptoms. The authors also stated that the meta-analysis found a decreased risk of dementia in HRT users, but that most studies reporting on this outcome had methodological limitations.

**CRD commentary**

The review question and inclusion criteria were clearly stated. Relevant electronic databases were searched, but the inclusion of only peer-reviewed papers and 'key' foreign language papers means that language and publication bias might have been introduced into the review. The authors reported asymmetry in the funnel plots, which may indicate selection bias. No results for the trim and fill analysis for publication bias were presented. The study selection and data extraction methods were not reported, therefore the introduction of error and bias cannot be ruled out. The methods used to combine the data were appropriate, and the authors highlighted limitations of their review. Given the lack of methodological detail, and the potential for selection and publication bias, the authors’ cautious conclusions are appropriate.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors advised large, long-term, double-blind placebo-controlled trials with intervention arms containing oestrogen, with and without progestins, in older symptomatic women instead of perimenopausal women. They stated that studies should control for health status, health behaviour, education and the psychological effects of oestrogen. In addition, future cognitive studies should focus on domains most consistently affected in previous studies, such as verbal memory, vigilance, complex attention, mental tracking, concept formation and reasoning, and motor speed. Such studies should also include measures of the ability to care for oneself, live independently and complete activities of daily living.

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