Hormone replacement therapy and cognitive performance in postmenopausal women: a review by cognitive domain
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CRD summary
The authors concluded that there is no evidence of a consistent relationship between hormone replacement therapy (HRT) and performance in any cognitive domain. The only randomised evidence shows an increased risk of dementia associated with HRT. Although these conclusions appear well-supported by the data, methodological weaknesses in the review make it difficult to be certain of their reliability.

Authors' objectives
To assess the effects of hormone replacement therapy (HRT) on cognition and risk of dementia in postmenopausal women.

Searching
MEDLINE and PsycINFO were searched from 1966 to June 2004; the search terms were reported. The reference lists of reviews and retrieved articles were checked. The search was restricted to articles in English.

Study selection
Studies of oestrogen replacement in postmenopausal women were eligible for inclusion. Studies were required to report objectively-measured cognition or rates of dementia as outcomes, and to include at least 50 participants.

The participants in the included studies were current, past and/or ‘ever’ users of HRT. They were recruited from population, organisational, out-patient or general practice settings, or were volunteers. The mean age of the participants in the majority of included studies was 68 to 72 years (mean range: 51 to 87) and in most studies (where reported) the women were predominantly Caucasian. In some studies inclusion was restricted to women with, or without, coronary disease.

The intervention in most of the included studies (where stated) was oral conjugated equine oestrogen. The proportion of women reported to be using progesterone varied in the studies from nil to 100%, and the mean reported duration of therapy varied from 0.75 months to 22 years. Cognitive outcomes were measured using a wide range of neuropsychological tests and tools, which were listed in a table in the review. The review included randomised controlled trials (RCTs), longitudinal observational studies and cross-sectional studies.

The lead author selected the studies.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Cognitive data were grouped by domain (verbal memory, visual memory, speed, executive performance/concept formation) and performance on cognitive screening instruments. Mean differences (MDs) and 95% confidence intervals (CIs) were calculated for continuous outcomes, with effect sizes defined as small, medium or large (0.20, 0.50 and 0.80, respectively). Risk ratios (RRs) and 95% CIs were calculated for binary outcomes. Where studies included different timeframes of HRT use, data for current users were preferred for the review. Where a study used more than one outcome measure for a single cognitive domain, the mean effect size for that domain was used. Attempts were made to contact study authors for additional data, as required.

The lead author extracted the data.
Methods of synthesis
MDs for individual studies were presented in forest plots, grouped by outcome and study design. Data were pooled and tested for statistical heterogeneity using the \( \chi^2 \) test (level of significance p<0.1). Meta-regression was used to investigate the effects of participant age and duration of HRT therapy. Other study differences (related to the type of testing used) were investigated in subgroup analyses. Publication bias was assessed using funnel plots and Egger’s test. An a priori decision was made not to proceed with meta-analysis if the data were heterogeneous.

Results of the review
Forty-one studies were included. There were 26 studies on HRT and cognition: 4 RCTs (n=8,603), 5 longitudinal observational studies (n=21,933) and 17 cross-sectional studies (n=23,649). There were 18 studies on HRT and risk of dementia: one RCT (n=7,428), 11 cross-sectional studies (n=3,302) and 6 longitudinal studies (n=8,250).

Verbal memory (22 studies): effect sizes were calculable for 17 studies (50 comparisons). RCTs (n=3) and longitudinal studies (n=3) found no consistent evidence of a benefit related to HRT use. There was some evidence of a benefit related to HRT use in cross-sectional studies (n=11), with seven reporting positive results, but there was significant heterogeneity (p=0.000).

Visual memory (10 studies): effect sizes were calculable for 6 studies (one RCT and 5 cross-sectional studies; 15 comparisons). The results were inconsistent.

Cognitive speed (8 studies): the pooling of 2 RCTs showed no significant effect; the findings of the other studies (one longitudinal and 5 cross-sectional) were inconsistent.

Executive performance/concept formation (22 studies): effect sizes were calculable for 16 studies. The findings of RCTs (n=3) and longitudinal studies (n=3) were inconsistent. There was some evidence of a benefit associated with HRT in cross-sectional studies (n=10), with nine reporting positive results, but there was significant heterogeneity (p=0.000).

Cognitive test screening (16 studies): effect sizes were calculable for 11 studies (3 RCTs, 4 longitudinal studies and 5 cross-sectional studies examined). Findings were inconsistent, with a wide range of effect sizes. One RCT (n=2947) reported a small but statistically significant negative effect in the HRT group (MD -2.63, 95% CI: -2.69, -2.56). Overall, there appeared to be no positive effect related to HRT and possibly a small negative effect.

Risk of dementia (18 studies): the findings were inconsistent. The only RCT (n=7,428) found a significantly increased risk in the HRT group (RR 1.38, 95% CI: 1.02, 1.88). Four of the 6 longitudinal studies and two of the 11 cross-sectional studies reported a significantly reduced risk of dementia associated with HRT.

Heterogeneity: effect sizes and directions of effect varied widely across the forest plots, and nearly all analyses had statistically significant heterogeneity which precluded pooling of the data. Meta-regression analyses found no significant associations between effect size and either age or duration of therapy, and subgroup analyses did not in most cases explain the heterogeneity. There was no statistically significant evidence of publication bias.

Authors’ conclusions
There is no evidence of a consistent relationship between HRT and performance in any cognitive domain. The only randomised evidence shows an increased risk of dementia associated with HRT.

CRD commentary
The review objectives and inclusion criteria were clear. The search was limited to two databases and to studies in English, and there is no indication that unpublished studies were sought, which means that studies might have been missed. It appears that the studies were selected and data extracted by a single author, which increases the risk of subjectivity and error in the review process. Moreover, study validity does not appear to have been systematically assessed, though the studies with more robust designs were clearly highlighted in the interpretation of findings. The authors presented the available data clearly in forest plots, and appropriately chose not to report summary statistics unless the studies were homogeneous. Potential heterogeneity and publication bias were assessed with suitable tests, and thoroughly investigated where they occurred. Although the data presented appear to support the authors’ conclusions,
methodological weaknesses in the review make it difficult to be certain of their reliability.

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

Practice: The authors state that cognitive improvement or maintenance should not be claimed as a secondary benefit of HRT.

Research: The authors stated that, as future RCTs of HRT use are unlikely, observational studies should longitudinally monitor representative samples of women from perimenopause onwards. Outcomes should include neuropsychological measures in multiple domains, particularly verbal memory and executive function.

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