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Review

Hormone replacement therapy and cognitive performance in postmenopausal women—a review by cognitive domain

Lee-Fay Low*, Kaarin J. Anstey

Centre for Mental Health Research, Australian National University, Building 63, Eggleston road, Canberra, ACT 0200, Australia

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Abstract

Laboratory, animal and neuroimaging evidences suggest that hormone replacement therapy (HRT) may be beneficial to human cognition. This systematic review includes 26 studies on the association between HRT and cognition and 17 studies on HRT and risk of dementia. It was hypothesised that HRT would have a positive association with cognitive speed and verbal memory and possibly visual memory but not with executive functioning, and would be associated with a decreased risk of dementia. Evidence for HRT's neuroenhancing and neuroprotective properties was also evaluated. There was significant statistical and clinical heterogeneity among studies precluding meta-analysis. Results showed no consistent relationship between HRT and performance in any cognitive domain. Cross-sectional studies tended to report more positive results than longitudinal studies and randomised-controlled trials, particularly in the areas of verbal memory and executive functioning. HRT was associated with decreased risk of dementia in observational studies, but with increased risk in one randomised-controlled trial. Cognitive improvement or maintenance are not secondary benefits of HRT.

Keywords: HRT; Estrogen; Cognition; Dementia; Memory

Contents

* Corresponding author. Tel.: +61 2 6125 3132; fax: +61 2 6125 0733.
E-mail address: lee-fay.low@anu.edu.au (L.-F. Low).

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1. Introduction and aims

Hormone replacement therapy (HRT) consists of estrogen therapy alone or with the addition of progesterone, and was originally used to relieve symptoms of menopause such as hot flushes and genitourinary changes. Additional benefits were subsequently observed including reduced risk of osteoporosis, coronary heart disease and Alzheimer's disease (Fillit, 2002; Genazzani and Gambacciani, 1999; Lip et al., 1995).

The objective of this review is to systematically examine the evidence for a relationship between hormone replacement therapy and cognition. There have been several recent reviews in the area, including a Cochrane review of randomised-controlled trials (Hogervorst et al., 2004), a review of observational and experimental studies in postmenopausal women (Zec and Trivedi, 2002) and a meta-analysis of HRT and dementia risk (LeBlanc et al., 2001). This paper adds to this literature by asking more detailed questions about the HRT–cognition relationship. Specifically, this paper aims to review the evidence that HRT improves or maintains cognition in the domains of verbal memory, visual memory, speed, executive functioning and concept formation. Additionally, the evidence that HRT improves or maintains performance on cognitive screening instruments and reduces risk of dementia is systematically reviewed. Results are examined in relation to cognitive domains because if the effect of HRT is specific to one cognitive ability, pooling data across cognitive domains may dilute the observable effect of HRT on that specific ability. It is also likely that other variables, particularly those that affect exposure, such as duration of use, influence the observed associations between HRT and cognition. Further, this study will investigate whether age is associated with the effect of estrogen on cognition in human studies, as the animal literature suggests a differential effect of estrogen treatment with age (Adams et al., 2002; Lacreuse et al., 2002; Rapp et al., 2003a). Hence this paper aims to investigate whether age at assessment and duration of HRT have a moderating effect on the influence of HRT on cognition.

Gender differences have been observed on cognitive performance, with women generally performing better than men on verbal abilities and on tests of perceptual speed and accuracy, and men generally performing better than women in visuospatial tasks (Lezak et al., 2004). These differences suggest that estrogen may enhance verbal abilities. Human neuroimaging studies also report changes associated with HRT in the hippocampus (see below for details), an area associated with verbal and visual memory and learning. Hence it is hypothesised that estrogen will improve or maintain cognitive function in the domains of verbal memory and speed, and possibly on visual memory but not in the domain of executive function and concept formation.

A secondary objective of this review is to examine the evidence supporting estrogen's role as a neuroenhancer or a neuroprotector. If estrogen acts as a neuroenhancer, then it would be expected that at sufficient doses HRT would improve cognition, in one or more domains. This beneficial effect would be apparent whenever HRT was being taken, but not after HRT use was terminated. Whereas estrogen's neuroprotective effect would only be expected when non-HRT users are observed to be declining longitudinally while HRT users maintain their cognitive status. Hence HRT's neuroprotective effect may only be evident on cognitive testing in cohorts where cognitive aging is evident. HRT may only offer neuroprotection if estrogen levels are maintained through the menopausal and postmenopausal periods. If HRT does act as a neuroprotectant, it is plausible that both long-term current and past HRT use may have beneficial effects on cognition, and that HRT will be associated with better performance on cognitive screening instruments and with reduced risk of dementia.

1.1. Estrogen and the brain

HRT may impact on cognition through two pathways: by acting directly on brain systems and structure, or by acting indirectly on the brain through the cardiovascular system.

Laboratory and animal studies suggest that estrogen stimulates neurogenesis in the temporal lobes and prefrontal cortex (Lee and McEwen, 2001; Murphy et al., 1998; Murphy and Segal, 2000; Ormerod and Galea, 2001; Tanapat et al., 1999; Tang et al., 2004), and is involved in maintaining the function of the cholinergic system (Gibbs, 1998; Kompoliti et al., 2004; Kritzer and Kohama, 1999; Singh et al., 1994, 1995). Estrogen has also been shown in animal studies to protect against a variety of neurotoxic insults such as cell death induced by inhibition of mitocondrial function, suppression of glucose metabolism, alteration of nitric oxide production, induced stroke,

administration of substances such as beta-amyloid peptide, excitatory amino acids and free radicals (Wise, 2003a,b). However, there are circumstances under which estrogen does not offer neuroprotection such as when cerebral injury is severe, and in animal models of epilepsy (Wise, 2003a). Laboratory and animal study results are not directly generalisable to the use of HRT in humans.

The impact of HRT on human brains has been examined using neuroimaging technology, although most studies to date have been limited by small sample size and cross-sectional design. Observational studies have published evidence that HRT users have better brain structure as quantified by the area of white matter hyperintensities (Schmidt et al., 1996), anterior and posterior ventricular CSF (Cook et al., 2002), hippocampal volumes (Eberling et al., 2003), 5-HT2a receptor binding in the prefrontal region (Kugaya et al., 2003), and blood flow in the hippocampus, parahippocampal gyrus and temporal lobe (Maki and Resnick, 2000). But other studies (including one with over 2000 subjects) found no association between HRT and ventricular volume, total brain, grey and white matter volumes, or frontal, parietal, temporal and occipital volumes (Resnick et al., 1998), cortical atrophy, sulcal widening and white matter disease (Luoto et al., 2000). Lower levels of choline (a marker of inflammation) (Robertson et al., 2001) and less central atrophy (Luoto et al., 2000) have been found in women taking HRT compared with women not taking HRT.

1.1.1

Laboratory and animal studies support the theory that estrogen enhances brain structure and systems important in memory and has neuroprotective properties. Human neuroimaging studies have reported inconsistent results regarding the association of HRT with brain structure.

1.2. Indirect effects of estrogen on the brain via the cardiovascular system

It is possible that HRT may influence cognition and dementia risk indirectly via its effects on the cardiovascular system (Clinical Synthesis Panel on HRT, 1999; Gorelick et al., 1999). Clinically defined vascular disease, including heart failure, stroke, coronary heart disease, plaques in the carotid arteries, and peripheral arterial atherosclerotic disease, have been associated with poorer cognitive performance and risk of dementia (Breteler et al., 1994; de la Torre, 2004; Verhaegen et al., 2003). Cardiovascular risk factors such as cholesterol, diabetes, blood pressure and homocysteine have also been linked to cognitive function in old age (Coker and Shumaker, 2003; Lithell et al., 2003; Teunissen et al., 2003; Yaffe et al., 2002).

Randomised-controlled trials of HRT have shown that HRT lowers LDL cholesterol, raises HDL cholesterol (Espeland et al., 1998; Herrington et al., 2000; Shlipak et al., 2003) and reduces the risk of diabetes (Kanaya et al., 2003; Margolis et al., 2004; Rossi et al., 2004). Some, but not all randomised trials have reported that estrogen replacement reduces blood pressure in subjects not treated with antihypertensives (Angerer et al., 2001b; The Writing Group for the PEPI Trial, 1995) and decreases homocysteine (Evio et al., 2000; Farag et al., 2003; Hak et al., 2001; Mijatovic et al., 1998; Os et al., 2002; van Baal et al., 1999; Ventura et al., 2001; Walsh et al., 2000).

None of the seven published randomised-controlled trials of HRT of the secondary prevention of coronary heart disease have reported a positive result (Angerer et al., 2001a; Clarke et al., 2002; Grady et al., 2002; Herrington et al., 2000; Hulley et al., 1998; Schulman et al., 2002; Viscoli et al., 2001; Waters et al., 2002). There have been two published randomised-controlled trials using HRT for the primary prevention of CHD (Hodis et al., 2001; The Women's Health Initiative Steering Committee, 2004; Writing Group for the Women's Health Initiative Investigators et al., 2002). The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) found that the average rate of progression of subclinical atherosclerosis was lower in those taking HRT than placebo after 2 years in women who did not receive lipid-lowering medication (Hodis et al., 2001). The Women's Health Initiative Study reported that subjects in the estrogen and progestin arm had increased rates of coronary heart disease, stroke and blood clots compared to placebo after 5 years (Writing Group for the Women's Health Initiative Investigators et al., 2002) and women in the estrogen only arm had increased risk of stroke and no change in risk of coronary heart disease (The Women's Health Initiative Steering Committee, 2004). This increase in stroke and cardiovascular disease was accompanied by an increased risk of cognitive decline and dementia (Espeland et al., 2004; Rapp et al., 2003b; Shumaker et al., 2004, 2003).

1.2.1

HRT has some beneficial effects on LDL and HDL cholesterol and diabetes risk. But with one exception, randomised-controlled trials of HRT consistently found no effect or a negative effect when treating or preventing coronary heart disease. This suggests that HRT may not have a positive effect on the cardiovascular system, and hence does not influence cognition through improvement of cardiovascular health.

1.3. Methodological considerations of HRT and cognition studies

There are limitations to both observational studies and randomised trials in the study of the association between HRT and cognition. In observational studies, 'healthy user' and socio-economic bias may confound the relationship between hormone use and cognition (Finley et al., 2001; Grodstein, 1996). Women who commence

HRT are better educated, healthier and more self-aware of feelings, motives and symptoms *before* HRT use than women who do not commence HRT (Matthews et al., 1996). Women with more severe symptoms of menopause are more likely to be prescribed HRT (Bardel et al., 2002), and these symptoms of menopause may also have a negative influence on cognition. Estrogen may alleviate symptoms of depression associated with menopause (Campbell and Whitehead, 1977; Ditkoff et al., 1991), and this may confound cognitive test results, although the estrogen-mood association has not been firmly established (Stephens and Ross, 2002). Many observational studies are cross-sectional, making it impossible to infer causality. Detailed information on type, dose and duration are usually not obtained in larger observational studies and the accuracy of self-report data cannot be ascertained. Compliance with hormone replacement use is also not known. Cohort effects may influence results as the proportion of women using HRT use is increasing (Bakken et al., 1997; Lawrence et al., 1999; MacLennan et al., 2002; North and Sharples, 2001) as are the rates of risk factors for 'lifestyle-related' diseases (Galobardes et al., 2003; McMichael et al., 2004). Publication bias towards significant results, particularly in cross-sectional population studies, may create an overall positive bias.

Randomised-controlled trials provide a higher level of evidence on the effectiveness of a treatment than observational studies (National Health and Medical Research Council, 2001), nonetheless, such trials have their own limitations. Randomised-controlled trials allow better control for confounders, exact knowledge on dose, type and compliance, and can involve more detailed neuropsychological assessment. But such trials are expensive, so many include smaller samples. Randomised trials recruit volunteers who may not be representative of general populations. Many trials tend to be short (less than 1 year), therefore not allowing the examination of the long-term effect of hormone replacement therapy. Several of the larger trials of estrogen therapy have had the primary aim of treatment or prevention of coronary heart disease, and only administered short cognitive screening instruments designed to detect dementia and that are not sensitive to subclinical cognitive change. Other criticisms of randomised HRT and coronary heart disease trials are that their samples are dissimilar to the women who begin taking HRT for the amelioration of menopausal symptoms as they are selected to have heart disease, or had been postmenopausal for some time before commencing HRT (Grady et al., 2002; Naftolin et al., 2004). Trials tend to only use one type and mode of estrogen therapy, not informing on the effects of other hormone regimens. The large randomised-controlled trials have orally administered conjugated equine estrogen, and there have been arguments that other less tested forms of estrogen (such as 17β-estradiol) may have beneficial effects on cognition (Asthana, 2004).

2. Methods

2.1. Search strategy

Articles examining the relationship between hormone replacement therapy and cognition were obtained by searching Medline and Psychinfo databases from 1966 to June 2004 using the keywords 'estrogen' or 'oestrogen' and 'cognition' or 'memory' or 'dementia' or 'Alzheimer$'. Articles were included if they reported original data on the relationship between estrogen replacement and cognition or dementia, involved postmenopausal females, objectively measured cognition or a diagnosis of dementia, and were in English. Reference lists of articles obtained and other review papers were also searched for appropriate articles. Studies that had a sample size below 50 were excluded, as they were most likely to produce spurious results through biased subject selection.

Where insufficient data were available in the published article, a request was made for this data from the corresponding author by email. Efforts were made to obtain the most up-to-date email address and a reminder was sent after a month if no response was obtained. Data were grouped by cognitive domain and study design as there was variability between studies in terms of design (observational cross-sectional data, observational longitudinal data, randomised-controlled trials) and cognitive domains tested (verbal memory, visual memory, speed, executive performance and concept formation, and cognitive screening instruments). Other differences between studies such as sample characteristics (age, type and duration of HRT use, cardiovascular disease status) were also noted.

2.2. Categorising data

There were several ways of defining 'HRT users'. Some studies included only *current* HRT users, some included women who had *ever* used HRT and some also analysed data for *past* HRT users. Where HRT users were defined in several ways in one paper, data for current users were included here.

The types of neuropsychological tests grouped by cognitive domain are listed in Table 1. If a study reported more than one neuropsychological measure for a cognitive domain (e.g. list learning and paragraph recall), the mean effect size for that cognitive domain for that study was used so as to not to over-represent those studies that employed multiple tests. Verbal memory tests were those involving learning of lists of words, or digits, and the content of stories, with or without reminding of forgotten words. Visual memory tests were those involving memory for visual stimuli including, faces, figures and spatial locations. Speed tests were reaction time tasks, and timed tasks involving simple pattern matching or joining. Executive function and concept formation tests involved the manipulation of either visual or verbal information.

Table 1
Neuropsychological tests grouped under each cognitive domain

Verbal memory	Visual memory	Speed	Executive function/ concept formation	Cognitive screening instruments
Digit span forwards and backwards	Spatial working memory	Simple and complex reaction time	Block design	MMSE
Paired verbal associates	Memory for faces	Trails A	Trails B	3MSE
Word list recall	Memory for figures	Digit symbol substitution	Wisconsin card sort	TICS
Paragraph recall	Corsi block-tapping	Figure and letter cancellation	Card rotations	Cognitive abilities screening instrument
Selective reminding test			Similarities	Short Blessed score
			Number letter sequencing	
			Abstract reasoning	
			Mental rotation	
			Word generation by letter and category	

Cognitive screening instruments were tests usually used for the detection of cognitive impairment. These tests are brief, and usually involved several simple tasks in multiple cognitive domains.

2.3. Data analysis

Data were analysed using STATA 7.0 software. Effect sizes were calculated for cognitive outcome measures and risk ratios were calculated when dementia was the outcome. Effect sizes were calculated as the standardised mean difference between groups, i.e. taking the difference between HRT and non-HRT groups, then dividing by the pooled standard deviation. Risk ratios were calculated by taking the proportion of subjects who developed dementia in the HRT group and dividing by the proportion who developed dementia in the non-HRT group. Effect size magnitude was described according to criterion set out by Cohen with $d=0.20$, 0.50 and 0.80 representing small, medium and large effect sizes, respectively (Cohen, 1988).

Chi-squared tests for statistical heterogeneity of studies in each cognitive domain by study design were performed. Tests of statistical heterogeneity check whether the variation between study results is greater than would be expected with chance if there was a single treatment effect underlying all studies (Thompson, 1994). Since heterogeneity tests for meta-analysis are conservative, a p-value of 0.10 for significance was used (Petitti, 2001). If data in a group were statistically heterogeneous, sources of heterogeneity were explored through meta-regression and subgroup analysis. Clinical heterogeneity, the differences between studies in terms of subject selection and outcome measures were subjectively examined.

Meta-regression examines the association between effect size and one or more characteristics of the studies, similar to the way linear regression examines the relationship between a dependent variable and one or more independent variables (Thompson and Higgins, 2002). Meta-regression was used to test the hypothesis that sample age at assessment and duration of HRT affected the relationship between HRT and cognition. Where appropriate, heterogeneity was also explored using sub group analysis, e.g. only including studies using similar neuropsychological tests.

Publication bias was assessed using funnel plots in which study sample sizes (y-axis) were plotted against the effect sizes (x-axis). In the absence of bias, the graph will resemble an upside down funnel with the smaller studies scattered across the bottom of the graph (Deeks et al., 2002; Egger et al., 1997). Additionally, the Egger regression asymmetry test was performed (Egger et al., 1997). The Egger test regresses standardised effect sizes against their precision (1/standard error) and tests whether the intercept deviates significantly from zero.

Data are presented in forest plots, which graphically represent the mean, 95% confidence interval and size of each study. An a priori decision was made that if data were heterogenous, meta-analysis would not be performed. If clinical and statistical heterogeneity are present, the assumption that a single common ‘fixed’ effect underlies all studies is violated and fixed-effects meta-analysis should not be performed (Poole and Greenland, 1999). Random effects meta-analysis does not require heterogeneity, but assumes that the effects estimated by the studies follow some distribution, usually a normal distribution. Random effects analyses are more unpredictable than fixed effect models and do not always produce more conservative results (Deeks et al., 2002; Poole and Greenland, 1999). The lead author performed all literature searching and data analysis.

3. Results

In total one hundred and five full-text articles were obtained. Thirty-two articles did not meet the inclusion criteria of presenting original data, including postmenopausal women, or objectively measuring cognition or dementia status. Three cross-sectional studies (Keenan et al., 2001; Miller et al., 2002; Resnick et al., 1998), three longitudinal studies (Hogervorst et al., 1999; Maki and Resnick, 2000; Verghese et al., 2000), and nine randomised trials were excluded because of small sample sizes (Caldwell, 1954;

Ditkoff et al., 1991; Duka et al., 2000; Hackman and Galbraith, 1976; Janowsky et al., 2000; Phillips and Sherwin, 1992; Sherwin, 1988; Vanhulle and Demol, 1976; Wolf et al., 1999). There were four articles each published on the cognitive and dementia outcomes for one study, the Women's Health Initiative (Espeland et al., 2004; Rapp et al., 2003b; Shumaker et al., 2004, 2003).

The final sample for this review consisted of 17 cross-sectional (Carlson and Sherwin, 1998; Carlson et al., 2001; Duff and Hampson, 2000; Galen Buckwalter et al., 2004; Grodstein et al., 2000; Jacobs et al., 1998; Kimura, 1995; Luoto et al., 2000; Maki et al., 2001; Matthews et al., 1999; Resnick et al., 1997; Robinson et al., 1994; Schmidt et al., 1996; Steffens et al., 1999; Szklo et al., 1996; Whitmer et al., 2003), five longitudinal observational (Carlson et al., 2001; de Moraes et al., 2001; Jacobs et al., 1998; Kang et al., 2004; Matthews et al., 1999; Rauramo et al., 1975; Resnick et al., 1997; Rice et al., 2000) and four randomised-controlled trials (Binder et al., 2001; Goebel et al., 1995; Grady et al., 2002; Rapp et al., 2003b; Shaywitz et al., 2003; Shumaker et al., 2004, 2003) published on the relationship between HRT and cognition in cognitively intact post-menopausal women with data from which effect sizes could be calculated. Studies for which there were insufficient data to calculate effect sizes are described separately for each cognitive domain.

Descriptive data for these studies are presented in Tables 2–4 listed by sample age. Sample sizes for cross-sectional studies ranged from 54 to 9651 and in total included 23,649 subjects. The mean age of subjects was 68.9 years (range 55.6–80 years). Ten of the studies recruited participants from population or organisational samples; six of the smaller studies recruited volunteers. The percentage of HRT users in the different studies ranged from 11 to 65%. Where data on HRT type and administration were available, most women were taking oral conjugated equine estrogens. There was also clinical heterogeneity in terms of race, duration of HRT use and percentage also using progesterone, though these data were not available for all studies.

Sample sizes for longitudinal studies ranged from 88 to 13,807 women and included 21,933 women in total. The mean age of women in longitudinal studies was 71.5 (range 56.6–74.7 years). One study recruited the members of a nurses' organisation (Kang et al., 2004), and all others recruited from population samples. Similar to cross-sectional studies, there were differences in race, proportion of HRT users, and progesterone users, and duration of use.

Sample sizes for randomised trials ranged from 52 to 4481 subjects and included 8603 women in total. Their mean age was 72.6 (range 51.2–81.0). All women were volunteers, one study exclusively recruited women with coronary disease (Grady et al., 2002) and another recruited women without clinically established coronary disease (Espeland et al., 2004; Rapp et al., 2003b). Coronary disease status was not specified in the other studies.

Eighteen studies were identified that published data on the relationship between HRT use and risk of dementia (1986; 1998; 2003; 1994; 1990; 2004; 1990; 1994; 1984; 1997; 2002; 1995; 1996b; 2001; 1999; 1996; 1999; Zandi et al., 2002). Characteristics of these studies are presented in Table 5. A total of 18,980 women were studied (sample size ranged from 84 to 7428) with an overall mean age of 73.5 years (mean age ranged from 58 to 87 years). The percentage of cases differed by design, with samples followed longitudinally having lower proportions of dementia cases than case-controlled studies. Nine studies defined HRT users as 'ever' users, and the other nine defined HRT users as 'current' users.

3.1. HRT and verbal memory

Twenty-two studies reporting results relating to verbal memory and HRT were identified. There was insufficient data to calculate effect sizes for five studies. Of these one reported a positive relationship (Kimura, 1995) and the others reported no relationship between HRT and verbal memory (Barrett-Connor and Kritz-Silverstein, 1993; Lokkegaard et al., 2002; Polo-Kantola et al., 1998; Rauramo et al., 1975). Hence data from eleven cross-sectional, three longitudinal and three randomised trials were examined which reported results of 50 tests of verbal memory. Test results were averaged for each study. Tests of statistical heterogeneity were significant for cross-sectional ($\chi^2 = 961.52$, df = 11, $p = 0.000$), longitudinal ($\chi^2 = 38.96$, df = 2, $p = 0.000$) and randomised ($\chi^2 = 8.22$, df = 2, $p = 0.016$) trials.

Meta-regression revealed that neither age (coefficient = −0.0005, $p = 0.972$) nor duration (coefficient = 0.0026, $p = 0.890$) had a significant effect on standardised mean difference between groups. On visual inspection, the funnel plot appeared asymmetrical but Egger's test of funnel plot asymmetry was non-significant ($p = 0.683$).

The standardised mean difference between HRT and control groups on verbal memory for cross-sectional, longitudinal and randomised trials are shown in Fig. 1. The effect sizes ranged from small to large, but most are in the small range. Of cross-sectional studies, two found a negative relationship, two found no relationship and seven reported a positive relationship. Of longitudinal studies, one large trial reported a negative relationship, one reported no relationship and one reported a positive effect of HRT on cognition. Of the three randomised trials, two found no relationship and one reported a positive association.

To investigate whether this heterogeneity was due to differences in the tests of verbal memory, analyses were performed for results pertaining to specific tests in the cross-sectional studies where there were a sufficient number of studies to permit such sub-analysis. These included verbal list and story learning data (eight studies), digits forwards (five studies) and digits backwards (five studies). There was still significant

Table 2
Cross-sectional observational studies

Lead author	Study name	Total sample size	Mean age (±SD)	Race	Sample source	HRT groups	Users (%)	Mean duration (years)	Progesterone use (%)
Kimura (1995)		54	–	–	Volunteers	Current	39	–	24
Duff (2000)		96	55.6±5	–	Volunteers	Current	40	5.8	–
Tivis (2003)		214	56	–	Volunteers	Current	65	–	52
Szklo (1996)	ARIC	6100	58 ± 0.1	74.5% Caucasian	Population	Current	23	–	–
Schmidt (1996)	Australian Stroke Prevention Study	210	60±6	Caucasian	Population	Current	33	4.4±5	24
Kampen (1994)		71	64.3±5	Caucasian	Volunteers	Current	64	–	57
Resnick (1997)		288	65±10	Caucasian	Population	Ever	40	55% between 1 and 5	–
Maki (2001)		184	67±10	Caucasian	Population & Organisation	Current	56	Median 1–4	42
Robinson (1994)		144	67.2±6.5	–	Volunteers	Current	50	13.4±7.5	45
Whitmer (2003)	SALSA	1041	70.3	Latino	Population	Current	21	–	–
Matthews (1999)	Epidemiology of Hearing Loss Study	9651	71.7±5.3	Caucasian	Population	Current	14	14.3±9.9	21
Carlson (1998)		55	72.1±5	–	Volunteers	Current	25	19.1	21
Grodstein (2000)	Nurses Health study	2138	74	Mixed	Organisation	Current	33	12.8	28
Jacobs (1998)		727	74.2±6.9	Mixed	Population	Ever	11	4.6±8.6	–
Luoto (2000)	Cardiovascular Health Study	2133	74.8	Mixed	Population	Current	15	–	14
Steffens (1999)	Cache County Study	2338	75.1±6.8	Caucasian	Population	Current	28	–	–
Galen Buckwalter (2004)	Women's Memory Study	105	77.8±2.1	98% Caucasian	Organisation	Current	55	22.7±10.9	24

heterogeneity within these verbal memory subsets ($\chi^2=209.82$, df=7, $p=0.000$; $\chi^2=104.69$, df=4, $p=0.000$; $\chi^2=104.69$, df=4, $p=0.000$, respectively). Using verbal list and story learning tests, seven studies reported no association and one study reported a positive association (data not shown). Using either digits forwards tests or digits backwards tests, two studies reported no association, and three reported positive associations between HRT and performance (data not shown).

3.1.1

There is some evidence for a positive association between HRT and verbal memory in cross-sectional data, though not in longitudinal or randomised-controlled trials. Clinical and statistical heterogeneity complicate interpretation.

3.2. HRT and visual memory

Ten of the studies reviewed reported results on the relationship between HRT use and visual memory. Of these, there was insufficient data to calculate effect sizes for four studies (Barrett-Connor and Kritz-Silverstein, 1993; Kampen and Sherwin, 1994; Lokkegaard et al., 2002; Polo-Kantola et al., 1998). These four reported no significant association between HRT use and visual memory. Data were analysed for five cross-sectional and one randomised-controlled trial that reported the results of 15 tests of visual memory. There was significant heterogeneity among cross-sectional trials ($\chi^2=204.4$, df=4, $p=0.000$). Neither age nor duration had a significant effect on standardised mean difference on meta-regression (coefficient=0.0627, $p=0.752$; coefficient=−0.670, $p=0.765$, respectively). On visual inspection, the funnel plot appeared asymmetrical, but Egger's test of asymmetry was non-significant ($p=0.457$).

The standardised mean difference between HRT and control groups on visual memory for cross-sectional, longitudinal and randomised trials are shown in Fig. 2. Two cross-sectional studies reported significant negative associations, one reported no association and two studies

Table 3
Longitudinal observational studies

Lead author	Study name	Total sample size	Mean age	Race	Sample source	HRT group	No. of users (%)	Mean duration (years)	Progesterone use (%)	Follow-up (years)
de Moraes (2001)	ARIC	2859	56.6±5.5	78.6% Caucasian	Population	Current	32	–	–	6
Rice (2000)	Kame project	895	71.4±5.4	Asian	Population	Current	16	15±11.7	32	2
Yaffe (2000)	Cardiovascular Health Study	2380	72.3	Mixed	Population	Current	11	–	–	
Kang (2004)	Nurses Health Study	13,807	74.0±2.2	–	Organisation	Current	36	–	28	2
Carlson (2001)	Cache County Study	1992	74.7±6	Caucasian	Population	Current	38	–	–	3

reported positive associations. The randomised-controlled trial found no effect of HRT on visual memory. Effect sizes ranged from small to large. It is notable that the study with the largest effect size of 2.27 (95% CI 1.97–2.57) was the only one in this domain to categorise HRT use as 'ever' use.

3.2.1

There was no consistent association between HRT use and visual memory.

3.3. HRT and cognitive speed

Eight studies contained results relating to HRT and cognitive speed and all included enough data to calculate effect sizes. Five studies were cross-sectional, one was longitudinal, and two were randomised-controlled trials. There was significant heterogeneity among cross-sectional trials ($\chi^2=3077.90$, df=4, $p=0.000$) but the heterogeneity statistic between the two randomised-controlled trials was non-significant ($\chi^2=0.39$, df=1, $p=0.531$). When a meta-regression was performed, neither age nor duration were predictors of standardised mean difference (coefficient=0.0021, $p=0.877$, coefficient=0.0111, $p=0.427$, respectively). Publication bias was not detected using Egger's test of funnel plot asymmetry ($p=0.860$).

The standardised mean differences for studies of HRT and speed are displayed in Fig. 3. Three cross-sectional studies reported no significant association between HRT and speed, and two cross-sectional studies both with large effect sizes reported a positive association, one longitudinal study reported no association. The two randomised trials found no association, with an overall non-significant effect between those two randomised trials.

3.3.1

HRT does not have a consistent association with speed of performance.

3.4. HRT and executive function and concept formation

Twenty-two studies were identified that published evidence relating HRT and executive function and concept formation. There were insufficient data to calculate effect

Table 4
Randomised trials

Lead author	Study name	Sample size (HRT, controls)	Mean age	Race	Duration (months)	ERT mode	ERT type	Progesterone use (%)
Shaywitz (2003)		31, 29	51.2±5	Caucasian	0.75	Oral	Conjugated equine estrogen	0
Grady (2002)	HERS	517, 546	71±6	Most Caucasian	48	Oral	Conjugated equine estrogen	100
Rapp (2003b), Espel (2004)	WHI—estrogen and progesterone arm	2145, 2336	73±7.1	90% Caucasian	54	Oral	Conjugated equine estrogen	100
	WHI—estrogen only arm	1464,1483	Range 65–79	Most Caucasian	63	Oral	Conjugated equine estrogen	0
Binder (2001)		34, 18	81±3.5	85% Caucasian	9	Oral	Conjugated equine estrogen	58

Table 5
HRT and risk of dementia

Lead author	Study name	Total sample	Mean age	Race	Sample source	Groups	# Users (%)	Mean duration (years)	% Dementia cases	Follow-up (years)
Amaducci (1986)		220	–	Mediterranean	Outpatients (case-controlled)	Ever	11	–	50	–
Heyman (1984)		84	–	–	Volunteers (case-controlled)	Current	10	–	33	–
Slooter (1999)		218	58±6	Caucasian	Population (case-controlled)	Current	16	–	48	–
Kawas (1997)	Baltimore Longitudinal Study of Aging	514	61.5	92% Caucasian	Population	Ever	45	–	7	16
Graves (1990)		260	63	Caucasian	Outpatients (case-controlled)	Current	17	–	50	–
Seshadri (2001)	UK GP research database	280	65.5	Caucasian	Population (case-controlled)	Current	24	All ≥1	21	–
Shumaker (2004, 2003)	WHI	7428	Range 65–79	Most Caucasian	Volunteers (RCT)	Current	49	4.8	2.1	5
Mortel and Meyer (1995)		306	73.2±8	–	Volunteers (case-controlled)	Current	15	–	51.6	–
Lindsay (2002)	Canadian Study of Health and Aging	2079	73.3	Caucasian	Population	Ever	6	–	5	5
Baldereschi 1998	Italian Longitudinal Study on Aging	2046	74±6	Mediterranean	Population	Ever	12	–	5	–
Tang et al., (1996)	Northern Manhattan	1145	74.2±7.0	Mixed	Population	Ever	13	6.8	15	1–5
Zandi (2002)	Cache County Study	1889	74.5	Caucasian	Population	Ever	56	11.6	6.5	3
Barnes (2003)	Religious Order Study	577	76.1±7.0	Most Caucasian	Organisation	Ever	36	9.2	16	5.8
Henderson (1994)		235	76±9	–	Volunteers (case-controlled)	Current	12	–	60.9	–
Brenner (1994)		227	77±7	95% Caucasian	Population (case-controlled)	Current	23	7.9	47	–
Broe (1990)	Sydney Older Persons Study	340	78.1±7	Caucasian	General practice (case-controlled)	Current	9	–	50	–
Waring (1999)	Rochester Epidemiology project	444	82	Caucasian	Population (case-controlled)	Ever	18	41% ≥0.5	50	–
Paganini-Hill and Henderson (1996b)	Leisure World Cohort	688	87±6	Caucasian	Population (case-controlled)	Ever	44	–	20	1–11

sizes in two studies that reported a positive association (Lokkegaard et al., 2002; Paganini-Hill and Henderson, 1996a), and in four studies that reported no association (Barrett-Connor and Kritz-Silverstein, 1993; Kampen and Sherwin, 1994; Polo-Kantola et al., 1998; Rauramo et al., 1975). Ten cross-sectional, three longitudinal and three randomised trials were examined and statistical heterogeneity was detected among cross-sectional trials ($\chi^2 = 868.57$, $df = 9$, $p = 0.000$), longitudinal studies ($\chi^2 = 3099.18$, $df = 2$, $p = 0.000$), and randomised-controlled trials ($\chi^2 = 8.42$, $df = 2$, $p = 0.015$). To investigate whether heterogeneity was due to differences in the tests of executive functioning, analyses were performed for verbal fluency tests only. This did not improve heterogeneity among the five cross-sectional, and three longitudinal studies that included verbal fluency tasks ($\chi^2 = 839.45$, $df = 4$, $p = 0.000$; $\chi^2 = 3759.61$,

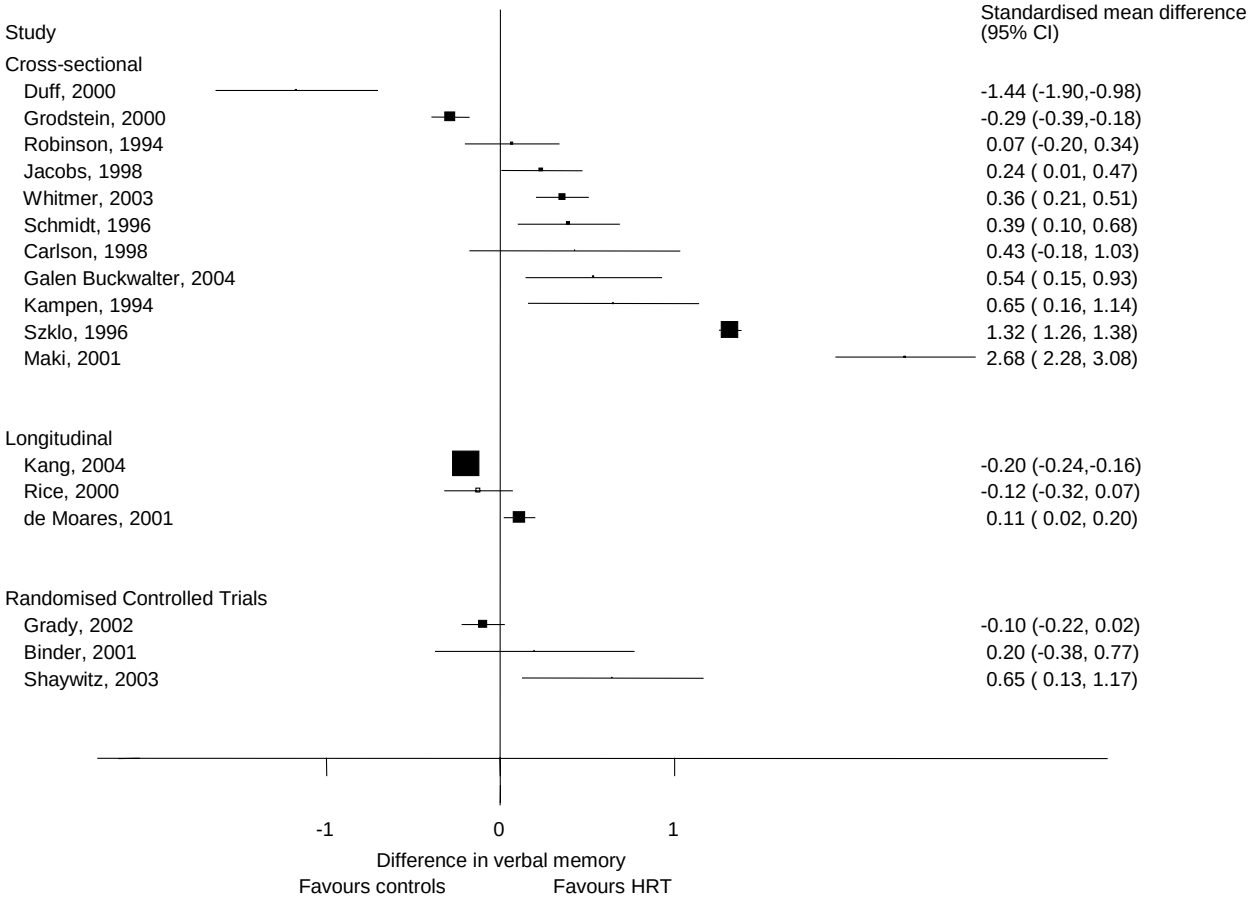

Fig. 1. The association between HRT and verbal memory performance.

df = 2, $p = 0.000$), though the two randomised-controlled trials were not significantly heterogeneous ($\chi^2 = 0.39$, df = 1, $p = 0.533$, respectively).

A meta-regression found no influence of age or duration of HRT use on the standardised mean difference between groups (coefficient = −0.0514, $p = 0.213$, coefficient = 0.0712, $p = 0.118$, respectively). Egger's test for funnel plot asymmetry was non-significant ($p = 0.888$).

The effect sizes from studies reporting data on the relationship between HRT and executive function and

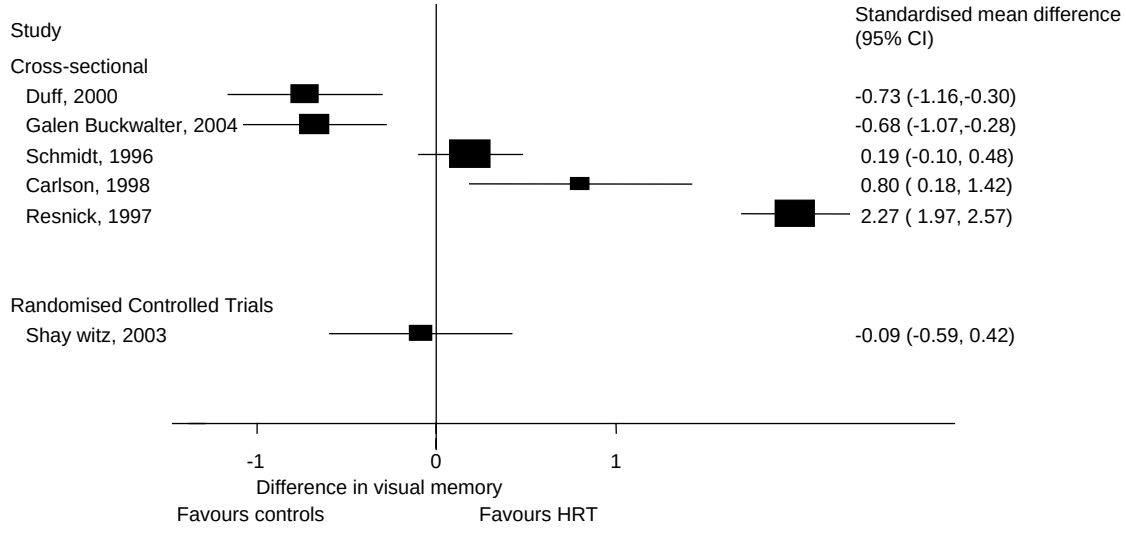

Fig. 2. The association between HRT and visual memory performance.

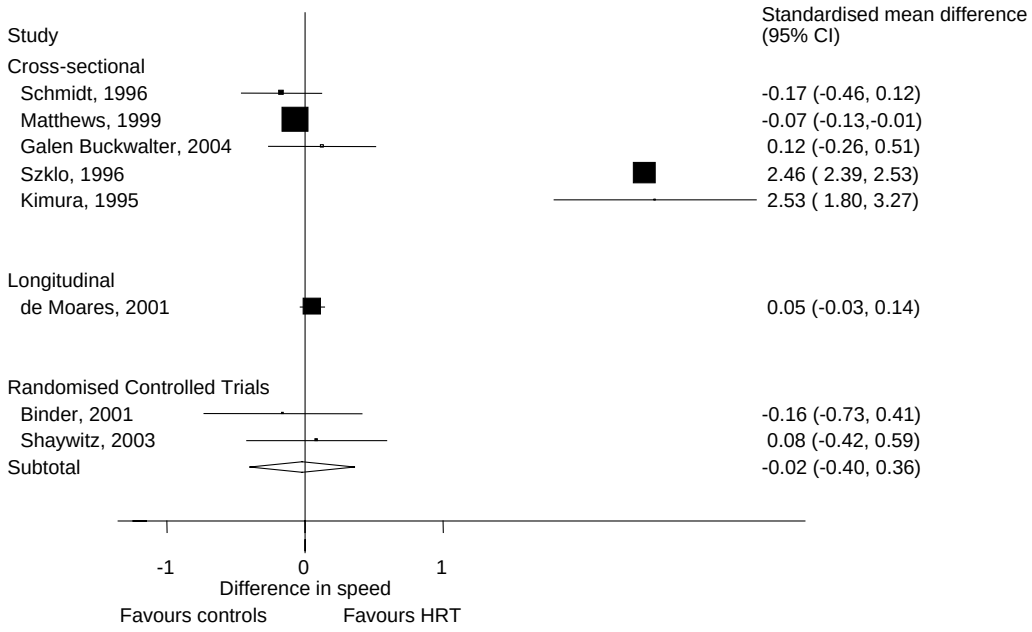

Fig. 3. The association between HRT and speed.

concept formation are presented in Fig. 4. Nine of the 10 cross-sectional studies reported a positive effect of HRT, and one reported no significant association. Of the three longitudinal studies, one reported a positive association, one a negative association and one no significant association. Two of the three randomised trials reported no association, and one reported a negative association. Most effect sizes were large for cross-sectional and longitudinal studies and small for randomised studies.

3.4.1

Cross-sectional studies reported a positive association between HRT and executive function that was not detected in longitudinal and randomised trials. This does not allow conclusions to be drawn on the relationship between HRT and executive function.

3.5. HRT and cognitive screening test scores

Sixteen papers measured the relationship between HRT and performance on cognitive screening instruments. There was insufficient information published in five of these papers to calculate effect sizes, two of these reported no significant relationship (Polo-Kantola et al., 1998; Robinson et al., 1994), and three reported a positive association (Barrett-Connor and Goodman-Gruen, 1999; Fillenbaum et al., 2001; Funk et al., 1991; Matthews et al., 1999). There was significant statistical heterogeneity between the five cross-sectional, four longitudinal and three randomised-controlled trials examined ($\chi^2 = 4582.80$, df = 4, $p = 0.000$; $\chi^2 = 1837.46$, df = 3, $p = 0.000$; $\chi^2 = 1430.69$, df = 2, $p = 0.000$, respectively). A meta-regression revealed no significant influence of age or duration of HRT use on differences between groups effect size (coefficient = 0.117, $p = 0.586$, coefficient = 0.222, $p = 0.155$, respectively). On visual inspection, the funnel plot appeared asymmetrical, but Egger's test of funnel plot asymmetry was non-significant ($p = 0.070$).

Effect sizes from studies of the relationship between HRT and performance on cognitive screening instruments are presented in Fig. 5. There was a large range in results, with two cross-sectional studies reporting no relationship and three reporting a positive relationship (one with a very large effect size), one larger longitudinal study reporting no relationship and two reporting a positive relationship. Two randomised-controlled trials reported no relationship and one reported a negative relationship.

3.5.1

There is contradictory evidence between observational and randomised trials on the effects of HRT on performance on cognitive screening instruments. Overall it would appear that there is no positive effect and there may even be a small negative effect of HRT on cognitive screening instruments.

3.6. HRT and risk of dementia

Eighteen studies were identified that presented data on the risk of dementia associated with HRT use (Amaducci et al., 1986; Baldereschi et al., 1998; Barnes et al., 2003; Brenner et al., 1994; Broe et al., 1990; Graves et al., 1990; Henderson et al., 1994; Heyman et al., 1984; Kawas et al.,

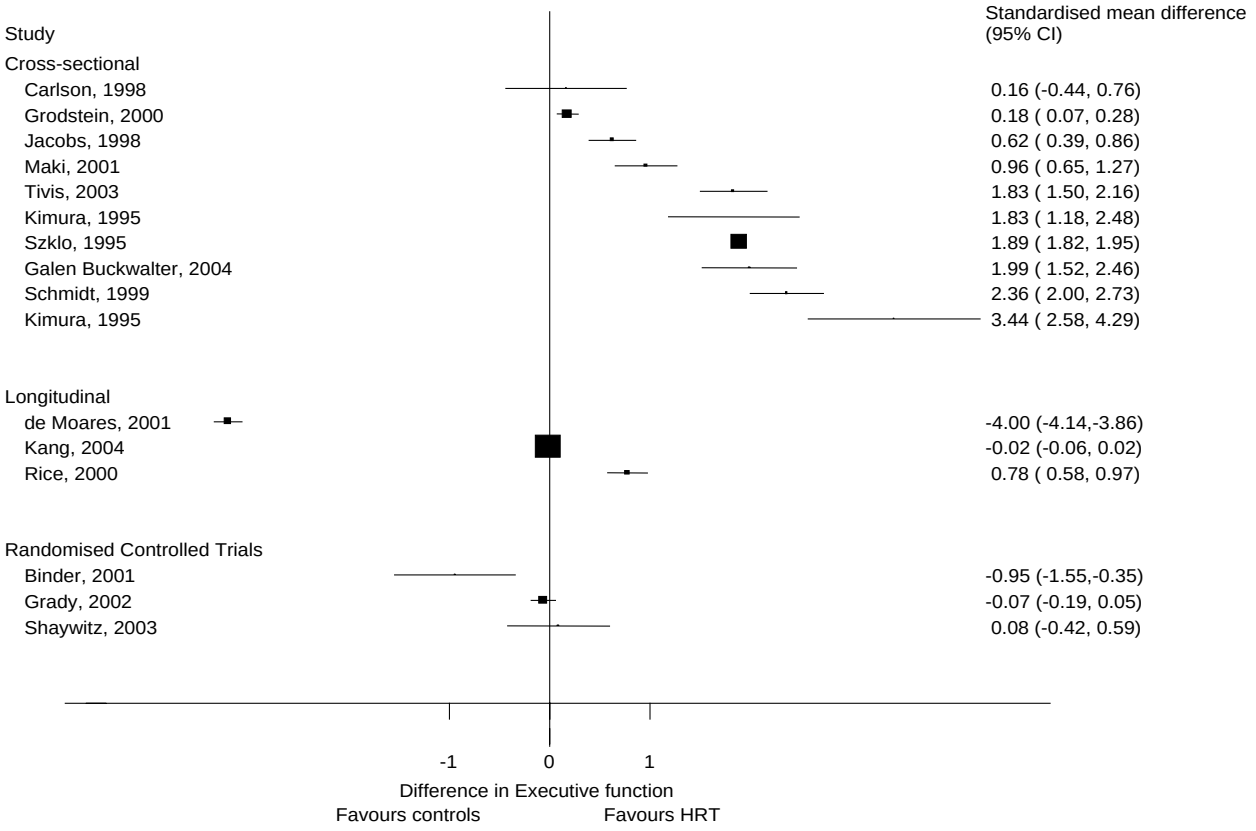

Fig. 4. The association between HRT and executive function and concept formation performance.

1997; Lindsay et al., 2002; Mortel and Meyer, 1995; Paganini-Hill and Henderson, 1996. Seshadri et al., 2001; Shumaker et al., 2004; Shumaker et al., 2003; Slooter et al., 1999; Tang et al., 1996; Waring et al., 1999; Zandi et al., 2002). Of these, 11 studies were cross-sectional, six were longitudinal and one was a randomised-controlled trial. There was significant statistical heterogeneity among cross-sectional, but not longitudinal studies ($\chi^2 = 17.72$, df = 10, $p = 0.060$; $\chi^2 = 15.00$, df = 5, $p = 0.010$, respectively). Egger's test of asymmetry was non-significant ($p = 0.400$).

Risk ratios from the studies of HRT and dementia are presented in Fig. 6. Two cross-sectional, and four longitudinal studies reported significantly reduced risk of dementia with HRT use, nine cross-sectional and two longitudinal studies reported no significant difference in risk, and the single randomised-controlled trial found significantly increased risk.

3.6.1

The observational studies, particularly longitudinal studies, provided evidence that HRT reduced risk of dementia, but this was in contradiction to the results of the randomised-controlled trial that found increased risk of dementia.

4. Discussion

Contrary to hypotheses and evidence from laboratory and animal studies showing neurogenesis and neuroprotection, this review did not find consistent positive associations between HRT use and cognition in any cognitive domain. There may be negative effects of HRT on performance on cognitive screening instruments. Similar to the review by Zec and Trivedi (2002) we found that there were many non-significant results, although positive results tended to favour HRT users over controls. Notably, these data suggest an inverse relationship between study design and effect size, with most studies reporting positive relationships between HRT and cognition being cross-sectional. Longitudinal observational studies and randomised-controlled trials reported fewer positive relationships and several reported significant negative effects. Cross-sectional studies are most vulnerable to confounding through subject selection. Observational cross-sectional and longitudinal studies of dementia risk suggested that HRT is protective against dementia, but one randomised-controlled trial found increased risk. This pattern of results was similar to that found in cardiovascular disease where positive effects of HRT detected in observational studies were not substantiated in randomised-controlled trials (Yaffe, 2003).

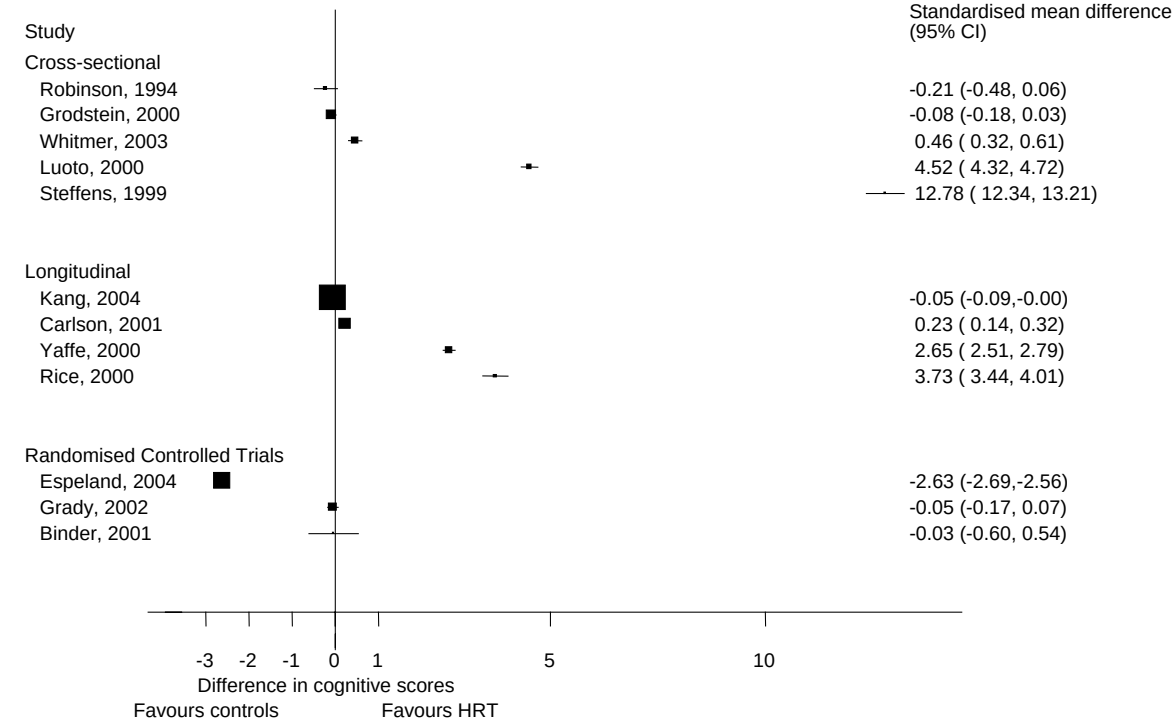

Fig. 5. The association between HRT and cognitive screening test scores.

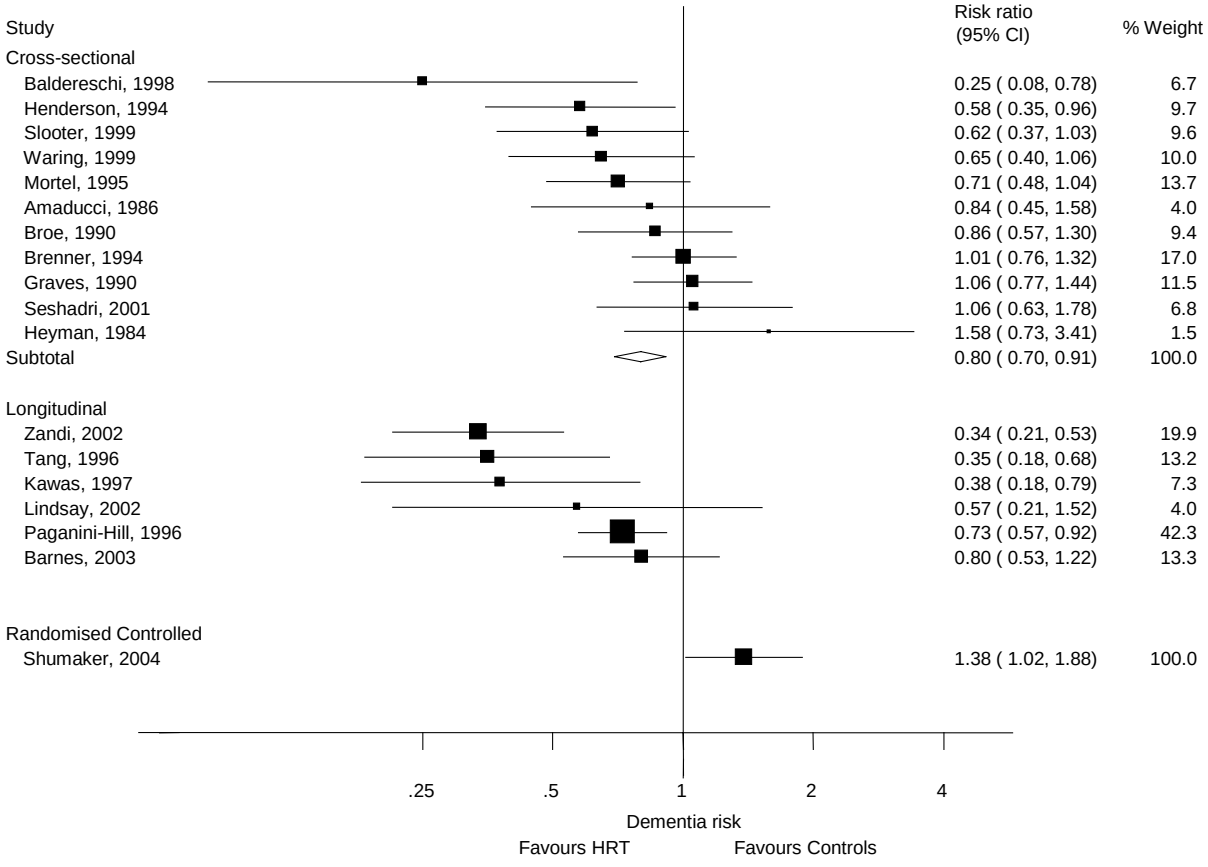

Fig. 6. The association between HRT and risk of dementia.

One interpretation of these results is that there are no true cognitive enhancing or protective effects of HRT and that positive results reported were due to other possibly pre-existing differences between HRT users and non-users.

The data in this review could not address the question of whether the age at which HRT is commenced affects its impact on cognition. It may be that HRT only has a positive effect when commenced during the perimenopause or shortly after menopause (Sherwin, 2005). There have been suggestions that randomised-controlled trials of HRT here were commenced too long post menopause to have a positive effect on either cognition or cardiovascular disease (Naftolin et al., 2004; Studd, 2004). For instance in the Women's Health Initiative study, the mean age of subjects was 73, 22 years above the average age of menopause of 51 in the USA. If HRT provides neuroprotection sustaining levels of estrogen through HRT from menopause onwards may help prevent decline, but if commenced some time after menopause, neuronal health may already have deteriorated to a level where estrogen is no longer efficacious. This theory is supported by post hoc analysis from the Women's Health Initiative study that found that the risk of dementia for women who had never taken HRT was greater than for women who had previously used HRT, though this difference was non-significant (Shumaker et al., 2004). One observational study also found higher risk of cognitive decline in women who were older when they began HRT (Kang et al., 2004). Although in this review meta-regressions did not find that subjects' age at assessment or average duration of HRT influenced effect sizes, this could have been because all studies recruited postmenopausal women. If HRT is neuroprotective, then absolute age or duration of HRT may not be as important as whether estrogen levels are maintained through menopause and postmenopausally.

The theory that estrogen is neuroprotective was supported by the results of observational studies showing that HRT may decrease risk of dementia, and this decreased risk was observed both in current and ever users of HRT. However, the WHI randomised trial showed that HRT was associated with *increased* risk of dementia when commenced at age 60 years and older. This has led to suggestions that there is a critical period around menopause in which estrogen levels should be maintained in order to achieve this neuroprotection (Resnick and Henderson, 2002; Schneider, 2004; Sherwin, 2005).

The estrogen type most used by women in observational studies was oral conjugated equine estrogen. This was also the estrogen type tested in most randomised trials, with the most common dose at 0.625 mg/day. Different hormone regimens result in different levels of bioavailable estrogen in the blood (Nachtigall et al., 2000), so other hormone regimens may prove more efficacious (Welty, 2003), though there is only limited evidence to support this. For instance, two trials excluded from this review because of small sample sizes administered injections of estradiol valerate at menopause and reported positive effects on cognition (Phillips and Sherwin, 1992; Sherwin, 1988). Two other small excluded trials studying transdermal estradiol in patients with Alzheimer's disease also reported positive effects on cognition (Asthana et al., 1999, 2001). Addition and type of progestin may also influence the effect of HRT, although there were no significant differences in cognitive outcomes between the estrogen and progestin and estrogen only arms of the Women's Health Initiative study (Shumaker et al., 2004).

Co-administration of other medications such as statins may impact on HRT. Statins alter the relationship between HRT and cardiovascular disease (Herrington et al., 2002; Hodis et al., 2001; Wakatsuki et al., 2002). But their interaction with HRT in regards to cognition is not known. Genetics may also change the impact of HRT on cognition. Some studies have found that HRT reduced the risk of cognitive impairment and improved episodic memory in women without the apolipoprotein 4 allele, but had no impact on women who were apolipoprotein 4 positive (Burkhardt et al., 2004; Yaffe et al., 2000). Race and other factors appear to affect the estradiol levels achieved during HRT, with one study finding non-Caucasian women, moderate drinkers and longer HRT users reached higher doses with oral HRT (Gavaler, 2002). Most studies were performed on samples where the majority of subjects were Caucasian; HRT may have larger effects on non-Caucasian women.

Ideally the relationship between HRT and cognitive function should be investigated further with several long-term randomised-controlled trials of women taking HRT from menopause, but given that the risks appear to outweigh the benefits from HRT (US Preventive Services Task Force, 2002), such trials would be considered unethical, and are unlikely in the future (MacLennan and Sturdee, 2002). Instead, observational studies should follow representative samples longitudinally from perimenopause to reduce possible confounding of other health and lifestyle variables. Both observational and experimental research should include neuropsychological tests in multiple cognitive domains, particularly verbal memory and executive functioning. Baseline confounding variables such as physical health, cardiovascular health, education and socio-economic levels should be controlled for as well as examining the interaction with other medications, such as statins. Negative results in this area should also be submitted for publication.

In conclusion, the evidence suggests that while there have been many studies reporting positive results, HRT use does not have a consistently positive effect on improving or maintaining cognition in any cognitive domain. Cognitive improvement or maintenance should not be listed as a secondary benefit of HRT. There was no evidence that HRT has a neuroenhancing effect resulting in overall improvement in cognition in humans. HRT may have a neuroprotective effect under certain circumstances, such as when HRT is

taken from menopause onwards, or when taken by apolipoprotein 4 negative women, although exact circumstances, dose, administration route and duration of HRT use are not known. One possible reason no clear effect of HRT on cognition was detected is that HRT is neuroprotective rather than neuroenhancing. If this was the case, then in order for the effects of HRT to be detected, subjects have to be of sufficient age so that cognitive decline is observed in control subjects. Neuroimaging may reveal neuroprotective effects of HRT that are not yet detectable on cognitive testing.

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