



1998 Curt P. Richter Award

The effect of hormone replacement therapy on cognitive function in elderly women

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Received 14 August 1998

Abstract

Although evidence seems to indicate favorable effects of hormone replacement therapy (HRT) on cognitive functions and mood in elderly healthy and demented women, some questions remain. For instance, the nature of the long term effect of HRT, e.g. in preventing cognitive decline is still unclear. In this respect, the addition of progestagens in combined HRT has been mentioned to oppose some of the beneficial effects of estrogens. The present paper aims to illuminate these questions and presents two studies. In the first study, the long term effects of combined HRT in healthy postmenopausal women was investigated using a parallel groups (HRT-users vs. controls) design. HRT subjects were always tested during the estrogen–progestagen phase. Results indicated that after 6 and 12 months, women in the HRT-treatment group had higher scores on several indicators of the subjective feeling of well being (sleep, physical and psychological complaints) than matched controls, although at baseline both groups were not severely impaired. Effects of HRT on memory functions were seen when HRT treated subjects were compared with their own baseline functioning, but not when compared with controls. Hence, the addition of progestagen did not oppose the effects of estrogens on subjective feelings of well being or on memory. Our second (case-control) study involved women of middle-age who were unaware of the purpose of the experiment. No positive effects of HRT use on subjective scales of well being or on memory were found. However, women with HRT were faster on basic sensorimotor speed tasks as compared with

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controls. It should be kept in mind that double blind testing in an experimental study is difficult due to withdrawal bleeding and the reduction of flushes. Expectancy effects may have confounded the results of the first study. However, our findings indicate that the use of a particular design and type of memory test can explain the controversial results of studies into the effect of HRT on cognitive function. Furthermore, it was concluded that HRT has a global activating, instead of specific direct effect on cognitive functions. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Estrogens; Progestagen; Elderly women; Cognition; Mood

1. Introduction

Some neurons or groups of neurons are functionally dependent on estrogen levels (Fillit, 1994). Following this premise, low estrogen levels may lead to a decline in neuronal plasticity and structural neuronal loss (Toran-Allerand et al., 1992). It has been suggested that estrogen replacement therapy (ERT) in postmenopausal women could be a protective factor against age-related cognitive decline (ARCD) and Alzheimer's Disease (AD) (Simpkins et al., 1994; Halbreich et al., 1995; Lopes et al., 1995). For instance, ERT may decrease the risk for developing AD or delay the onset of the disease (Henderson et al., 1994; Mortel and Meyer, 1994; Paganini-Hill and Henderson, 1994; Tang et al., 1996). Also, ERT treatment has shown positive effects on the cognitive functions of women afflicted with AD (Fillit et al., 1986; Honjo et al., 1993, 1995; Ohkura et al., 1995) and healthy postmenopausal women (Vanhulle and Demol, 1976; Campbell and Whitehead, 1977; Fedor-Freyberg, 1977; Hackman and Galbraith, 1977; Sherwin, 1988; Sherwin and Phillips, 1990; Sherwin, 1991; Phillips and Sherwin, 1992; Kampen and Sherwin, 1994).

There are three main questions yet to be answered with regard to the relationship between ERT and cognitive function. The first is concerned with the possible long term protective effect of ERT. Although the epidemiological findings suggest a possible protective effect of estrogen, several studies did not find a significant negative association between ERT use and Alzheimer's disease (Amaducci et al., 1986; Broe et al., 1990; Brenner et al., 1994). Also, in a prospective study (Barrett-Connor and Kritz-Silverstein, 1993) no protective effect of ERT use was detected in preventing age-related cognitive decline. Furthermore, case-control studies only found marginal effects of ERT use on cognitive functions in normal postmenopausal women (Kampen and Sherwin, 1994; Robinson et al., 1994).

Second, it is unclear at which behavioral levels ERT exerts its effects and whether this effect is clinically relevant. The experimental studies into the effect of ERT on dementia only involved small numbers of subjects measuring global changes in cognitive functioning over a relatively short period of time. Yet some investigators (Sherwin, 1994) claimed that the experimental studies with healthy subjects have rendered sufficient evidence to support the contention that estrogens influence cognitive functioning in women and that this is a specific effect (e.g. on verbal memory and fine motor skills but not on attention) which is independent of changes in mood (Kampen and Sherwin, 1994; Sherwin, 1994).

However, Vanhulle and Demol (1976) found no effects on memory, but did find effects on alertness and attention in women using ERT when compared with controls. Fedor-Freyberg (1977) also found non-specific improvements on the performance of attention tests. Similarly, others only found global changes in well being without an effect on memory (Ditkoff et al., 1991). These findings suggest that there may be a global improvement in functions such as alertness, or subjectively experienced activation and attention, which in turn may affect memory performance. Methodological issues, such as differences in the populations sampled, cognitive tests and hormone preparations (estrogens and/or progestagens, duration of use) hamper clear cut conclusions difficult.

The third question is concerned with the effect of hormone replacement combination therapy (HRT: estrogens and progestagens) on cognitive function and mood. The addition of progestagens in the second half of the cycle phase, to eliminate the risk of endometrium hyperplasia due to unopposed estrogens, has been mentioned to reduce the positive effect of estrogens on cognitive function and mood (Sherwin, 1991; Ohkura et al., 1995). Again, others did not find a negative effect of the addition of progestagens (Kampen and Sherwin, 1994; Limouzin-Lamothe et al., 1994). In vitro studies have shown that there are many actions through which estrogens may affect brain physiology, e.g. in affecting neurotransmitter synthesis and activity (Luine et al., 1975; Luine and McEwen, 1977; Luine et al., 1980; Simpkins et al., 1994); in preserving cholinergic neurons (Rainbow et al., 1980; Janowski and Rausch, 1985); and in enhancing cerebral perfusion (Funk et al., 1991). However, progestagens have been found to oppose most of the effects of estrogens in the brain (Sarrel, 1989, 1990; Woolley and McEwen, 1993).

In this paper, we will present two studies of the effect of HRT on cognitive functions in healthy middle-aged women, in terms of short and long term effects, in specific or global effects and in terms of the effects of the addition of a progestagen. The first study describes a long term follow-up experiment. HRT users were always tested during the estrogen–progestagen phase of the cycle. A carefully matched group of postmenopausal women, who did not receive therapy was used as a control group. The monthly withdrawal bleeding in the HRT group precluded the use of a placebo-treated control group. Effects of HRT on memory function and aspecific changes in subjectively experienced activation and well being were assessed with a follow up period of 1 year. Therefore, the hypothesis was tested that HRT in postmenopausal women would improve subjectively experienced activation, general well being and memory functions.

In order to rule out the possibility of expectancy effects in these experiments, we also investigated the effect of HRT use in a population sample of which the women were unaware of the purpose of the experiment. In this second study, we tested the hypothesis that HRT users have better cognitive performance scores (memory, cognitive flexibility and sensorimotor speed) than non users. In addition, we tested the hypothesis that these effects would be independent of age, education, health risk factors and perceived health.

2. Method study 1

2.1. Subjects

A group of 11 healthy postmenopausal women who were elected to receive HRT were matched with 11 women who were drawn from the same outpatient subclinical population, but who had decided not to enter the treatment study. Matching was performed for age, postmenopausal complaints and social class (Table 1). The social class system has five subclasses (1-high and 5-low) which are based on the level of education and highest job level held by the subject (MEMIC, 1996). This study was part of a larger study into the effect of HRT on vessel wall properties.

Women were recruited through a meeting where information was supplied with regard to perimenopausal complaints. The study was approved by the medical ethical committee of the Academic Hospital and the University of Maastricht. Subjects were informed before the start of the study about all possible adverse effects of HRT and signed an informed consent form.

Before entering the study all subjects underwent a complete medical screening. Inclusion criteria were: age > 45 years, good health, last menstruation between 1 and 6 years ago and a weight within 10% of population norm for their age. Exclusion criteria were: participation in other medication studies, using 'yellow label' medication (medication inducing drowsiness/sleepiness), using > six alcoholic beverages per day and any sensory or motor handicaps which may have interfered with test performance. Three women dropped out of the study before the end of the study. One subject of the HRT group dropped out because of side effects occurring after 6 months. The other two women (one of the HRT group, one of the control group) dropped out of the cognitive study but continued with the larger study.

2.2. Procedure

The HRT group received the first 16 days of the cycle 2 mg 17- β -estradiol, followed by 12 days of estradiol with additional 2.5 or 5 mg progestagen, during 1 year. Subjects received cognitive testing when estrogen and progestagen levels were both elevated (day 16–28). At baseline (t_0) subjects were examined by a medical doctor and, after blood samples were taken, subjects underwent the memory test and filled in the questionnaires. At all following test sessions (6 and 12 months), a similar procedure was followed. Subjects were also tested after 2 weeks, 1 month

Table 1
Mean age \pm S.D. and social class (1–5) of HRT users and controls (CON)

	HRT	CON
Age	53.3 \pm 3.6	54.2 \pm 3.1
Social class	2.9 \pm 1.0	2.9 \pm 1.0
<i>n</i>	11	11

and 3 months to eliminate the effect of procedural learning. Data of these test sessions are not shown. At 0, 2 and 52 weeks subjects were examined completely by the medical doctor. Plasma samples showed that all women complied to the treatment.

2.3. Design

This study had a mixed, repeated measures, parallel group design. The within subjects factor was time and had three levels. The between factor was HRT use and had two levels (HRT and controls). Subjects were tested at baseline (t_0), 6 months (t_6) and 12 months (t_{12}).

2.4. Cognitive tests

2.4.1. Primary variables

2.4.1.1. Visual verbal learning test with distraction. A list of 15 monosyllabic, unrelated words was shown by the computer. Every 2 s a new word was presented during 1 s on a computer screen (Brand and Jolles, 1985). At the same time a list of 15 other words was auditory presented. Subjects were asked to recall verbally as many words seen on the screen as possible as soon as the presentation stopped. The first immediate recall was followed by two more trials where the same words were repeated in the same order. When the third trial was completed, the subjects filled in the lists and underwent an interview. After 20 min, subjects were asked to recall as many of the previously learned words without prompting (delayed recall). The number of correctly recalled words was noted after each trial. The trials yielding the total and the maximum number of recalled words were taken as the dependent measures of immediate recall. The number of words correctly recalled after 20 min was the dependent measures of long-term memory.

2.4.1.2. Activation–deactivation checklist (AD-ACL). A questionnaire consisting of 20 items, divided in two core dimensions: energy/positive subjectively experienced activation (activation, 10–40) and tension/negative subjectively experienced activation (stress, 10–40) (Thayer, 1986).

2.4.2. Secondary variables

2.4.2.1. Neurovegetative complaints list (NVL) (Bohnen et al., 1992). A questionnaire consisting of 26 items which could be scored 1 (never) to 4 (often). These items were grouped into five clusters: (1) emotional vulnerability which consisted of the items: depression (I find that life is too much of a burden for me); crying spells; loss of libido; irritability; defeated; insecurity; and tiredness. These items had a cronbachs alpha of .90; (2) psychosomatic—or tension related physical complaints, which consisted of the items: headaches; tension; chest pain; dyspnea; heart palpitations; dizziness; wet hands; problems falling asleep. These items had a cronbachs alpha of

.79; (3) cognitive complaints which consisted of the items: effort; slowness of working; concentration; difficulty in doing two simultaneous tasks; and initiative. These items had a cronbachs alpha of .73. The last two items were (4) flushes; and (5) quality of sleep which were analyzed separately.

2.5. Statistical analysis

First, dependent variables were analyzed with non-parametric Friedman analyses to assess the effect of the factor time which had three levels (0, 6, 12 months) per group. If these were significant, with non parametric Wilcoxon analyses, the location of the effect of time was tested (baseline vs. 6 and vs. 12 months, 6 vs. 12 months) separately per group. Third, at each test moment, the HRT users were compared with controls to investigate the effect of HRT use at baseline, after 6 and after 12 months with Mann–Whitney non parametric analyses. p -Values < 0.05 were considered significant.

3. Results

3.1. Primary variables

Non parametric Friedman analyses revealed that total immediate recall showed a significant effect of time for both HRT users ($\chi^2 = 6.17$, $p < .05$) and controls ($\chi^2 = 9.05$, $p < .05$). HRT use increased the total number of words immediately recalled after 6 ($Z = -2.31$, $p < .01$ one-tailed) and after 12 months ($Z = -1.82$, $p < .05$, one tailed) as compared with baseline (Fig. 1(A)). On average, two more words were recalled after 6 months of HRT use. However, also for controls, an increase in the number of words immediately recalled was seen after 6 ($Z = -2.55$, $p < .01$, two-tailed) and after 12 months ($Z = -1.99$, $p < .05$, two-tailed) indicating learning effects (Fig. 1(A)).

For delayed recall, non parametric Friedman analyses showed a trend effect of time in HRT users ($\chi^2 = 5.06$, $p = .08$), but not in controls ($\chi^2 = .67$, $p = \text{ns}$). Wilcoxon analyses revealed that HRT users recalled more words from long term memory after 6 ($Z = -1.89$, $p < .05$, one-tailed) and 12 months ($Z = -1.86$, $p < .05$, one tailed) as compared with baseline. No significant differences were found between HRT users and controls at the different test moments with Mann–Whitney tests (Fig. 1(B)).

On the activation subscale of the AD-ACL, no effect of time was seen after HRT use ($\chi^2 = .72$, $p = \text{ns}$) or in controls ($\chi^2 = 2.40$, $p = \text{ns}$) with non parametric Friedman tests. However, Mann–Whitney analyses revealed that at 6 and 12 months, HRT users reported to feel significantly more vigorous and activated as compared with controls ($Z = -2.13$, $p < .05$, two-tailed; $Z = -2.26$, $p < .05$, two tailed) (Fig. 2). The stress subscale showed similar effects (Fig. 2), as no effect of time was seen after HRT use ($\chi^2 = 1.06$, $p = \text{ns}$) or in controls ($\chi^2 = .15$, $p = \text{ns}$). Yet, Mann–Whitney tests showed that subjects which used HRT were significantly

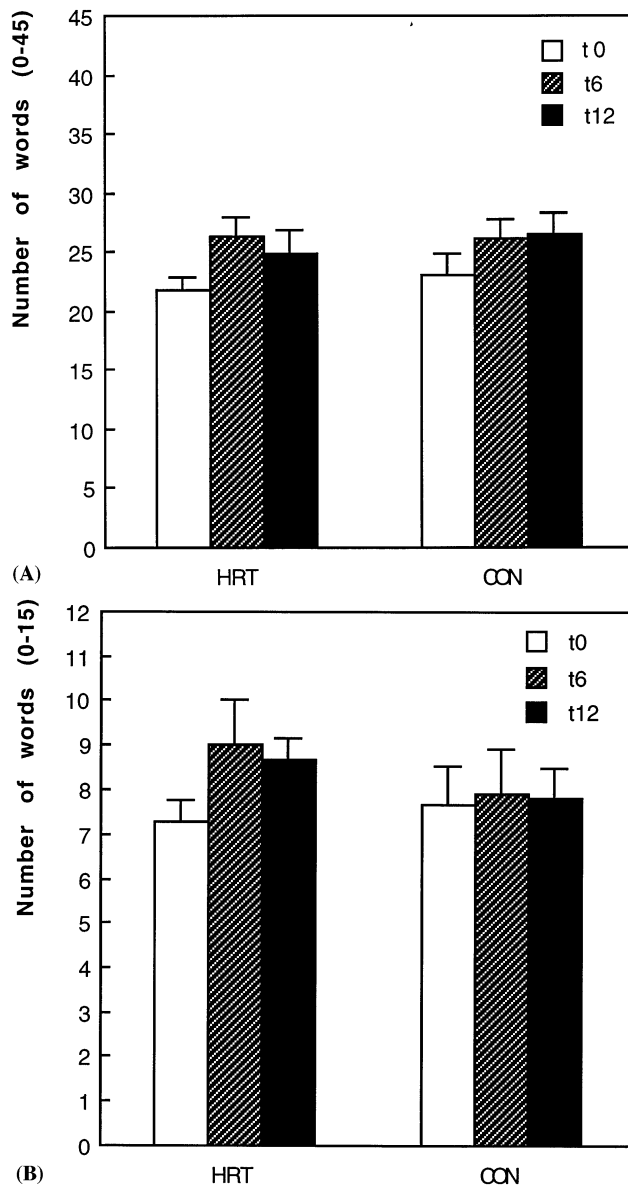


Fig. 1. (A) Total of number of words immediately recalled over three trials of the VVLT in HRT users and controls at baseline (t_0), after 6 (t_6), and after 12 months (t_{12}). (B) Number of words recalled after a delay of 20 min in HRT users and controls at baseline (t_0), after 6 (t_6), and after 12 months (t_{12}).

less stressed as compared with controls after 6 ($Z = -2.05$, $p < .05$, two-tailed) but not at 12 months ($Z = -1.52$, $p = \text{ns}$).

3.2. Secondary variables

On the neurovegetative scale no differences on the subscales were detected between groups at baseline as separate Mann–Whitney tests revealed. For emotional vulnerability (Fig. 3) no significant change in scores was seen with Friedman analyses over time for both groups (HRT, $\chi^2 = 1.79$, $p = \text{ns}$; CON, $\chi^2 = .89$, $p = \text{ns}$). However, HRT users had a significantly lower score on the emotional vulnerability subscale as compared with non users after 12 months as Mann–Whitney tests showed ($Z = -1.94$, $p < .05$), while no differences effects between groups were apparent at baseline ($Z = -.62$, $p = \text{ns}$) or after 6 months (-1.33 , $p = \text{ns}$). Psychosomatic complaints (Fig. 4) and cognitive complaints (Fig. 5) also did not show a significant change over time in either group (psychosomatic: HRT, $\chi^2 = 3.5$, $p = \text{ns}$, CON: $\chi^2 = 1.5$, $p = \text{ns}$; cognitive: HRT, $\chi^2 = 2.64$, $p = \text{ns}$, CON: $\chi^2 = 1.9$, $p = \text{ns}$). However, after 6 months HRT users had trend significantly less cognitive

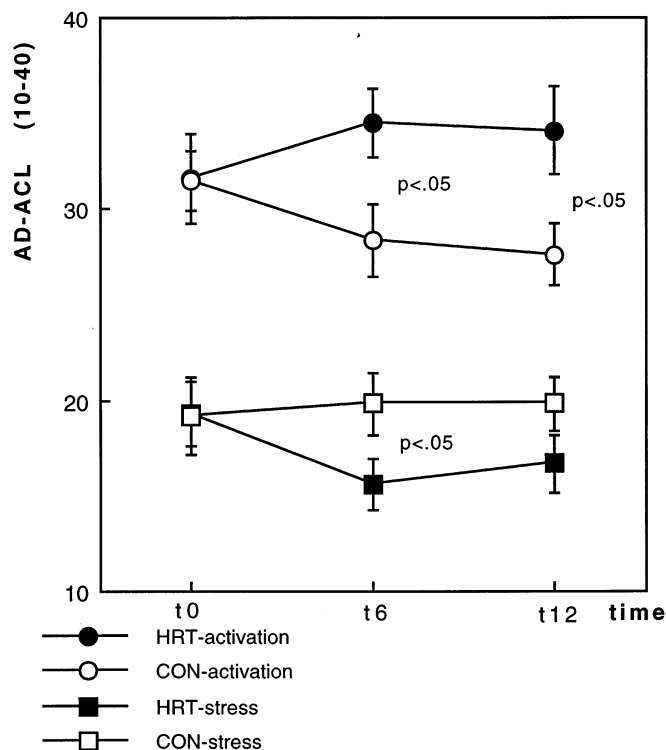


Fig. 2. Subjectively experienced activation and stress in users (HRT) and non users (CON) at baseline (t_0), after 6 (t_6) and after 12 (t_{12}) months.

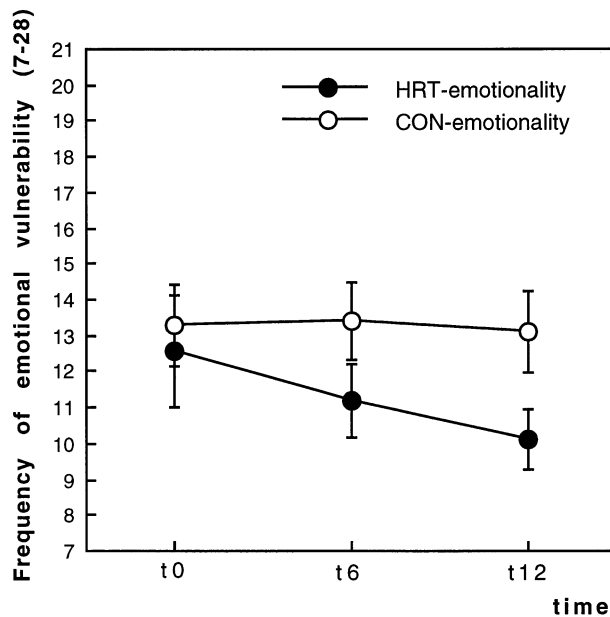


Fig. 3. Frequency of emotional vulnerability (7 = never, 14 = sometimes, 21 = regularly, 28 = very often) over time in HRT users and controls.

complaints as compared with non users as Mann–Whitney analyses revealed ($Z = -1.65$, $p = .10$) which became significantly different between groups after 12 months ($Z = -2.19$, $p < .05$). There was no effect of time on the frequency of flushes (Fig. 6) in HRT users ($\chi^2 = .86$, $p = \text{ns}$) or controls ($\chi^2 = 3.56$, $p = \text{ns}$). Mann–Whitney analyses indicated that the frequency of flushes was similar at baseline ($Z = -.95$, $p = \text{ns}$), but was significantly increased in non users as compared with HRT users after 6 months ($Z = -2.85$, $p < .005$) from sometimes (2) to regularly (3) on average, a difference that still was apparent after 12 months ($Z = -2.39$, $p < .05$). Sleep quality (Fig. 7) showed a trend for improvement over time in HRT users as Friedman analyses showed ($\chi^2 = 4.5$, $p = .10$) while in non users no difference was seen over time ($\chi^2 = .72$, $p = \text{ns}$). HRT subjects had a better sleep quality after 6 and 12 months as compared with baseline as Wilcoxon analyses revealed (respectively $Z = -1.83$, $p < .05$ (one-tailed); $Z = -2.02$, $p < .05$). There was no significant difference between groups, however, as Mann–Whitney tests revealed, only after 12 months, a trend significant difference was seen for a better sleep quality in HRT users as compared with non users ($Z = -1.75$, $p = .08$).

4. Discussion

In the present study, long term memory functions were seen to be enhanced with the combined use of estrogen and progestagen after 6 and 12 months. Also, both

subjectively experienced activation and the general feeling of well being were improved in HRT users as compared with controls as measured with the AD-ACL and the Neurovegetative questionnaire. HRT users were less stressed and more activated. Furthermore, after 1 year of use, HRT users showed less emotional vulnerability and had less cognitive complaints. HRT users showed trends for experiencing less psychosomatic complaints and a better quality of sleep. As expected, they had much less hot flushes. Hypotheses were thus confirmed in that women using HRT had improvements in long term memory functions, but also reported global effects in an increase in subjectively experienced activation and general well being.

There are several possible problems in the present study. First, the drop-out of several subjects can be suspected to have confounded statistical effects. However, the analyses concerned with within subjects effects, over time, only compared the subjects that remained in the sample. Hence, this argument does not hold for the effects on the memory task. Also, reanalyzing the ADACL and neurovegetative data without the drop-outs still revealed no significant difference for the baseline values. Second, learning effects may have been responsible for the results found. On the immediate recall performance over time, indeed procedural learning effects were detected. It may be expected that the women in both groups employed better strategies in learning the word lists. Yet, the learning effect did not affect the delayed recall parameter. However, effects on the delayed recall (long term mem-

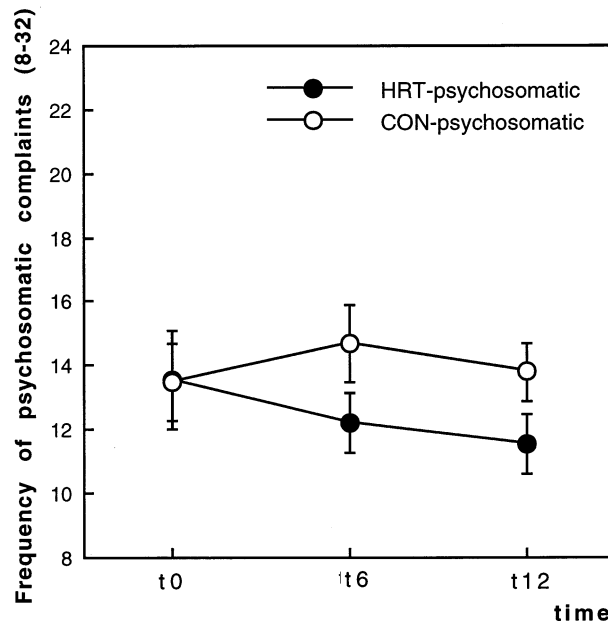


Fig. 4. Frequency of psychosomatic complaints (8 = never, 16 = sometimes, 24 = regularly, 32 = very often) over time in HRT users and controls.

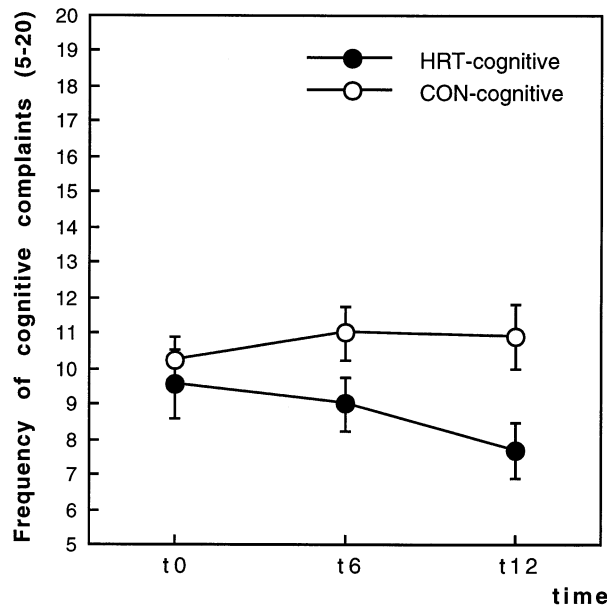


Fig. 5. Frequency of cognitive complaints (5 = never, 10 = sometimes, 15 = regularly, 20 = very often) over time in HRT users and controls.

ory) performance were only seen when HRT users were compared to their own baseline performance, but not as compared with controls.

Hence, third, the small number of subjects investigated in the present study could explain the absence of significant differences between groups. In this respect, Robinson et al. (1994) suggested that the larger variability in estrogen using women was responsible for their lack of significant findings on a memory test (object recall). Again, the memory test (word recall) used in the present study has earlier been shown to be very sensitive to small age-differences, which explains why slight changes within subjects could be detected (Hogervorst et al., 1998).

Another explanation for differences in findings could lie in the designs employed in the studies. In the study by Robinson et al. (1994), in which no or little effect of HRT use on memory were found, a case-control design was used. Similar to the present study, no effects could be detected between groups. However, using a cross-over design with a within subjects comparison, as was done by Sherwin (1988), may be a more sensitive method to detect effects on memory. Thus, it is likely that the between subjects effects of HRT are quickly overruled by non specific interindividual variation in performance. Since within subjects design are more sensitive to slight change, minor changes are more easily detected. If this hypothesis is right, we would expect no effects of HRT use on memory performance on the second study.

The literature describes that progestagens reverse some of the effects of estrogens when both are given together. Progestagens are reported to dampen mood (Sher-

win, 1991; Ohkura et al., 1995). Further, progestagens are suspected to have anaesthetic properties, since they can act upon the GABA system, which decreases the activity of excitatory neurotransmitters. Bäckström et al. (1985) reported that progestagens decrease the brain excitability. Furthermore, Merryman found that progestagens may induce sleepiness (Sherwin, 1991). However, in the present study, progestagen did not oppose the effect of estrogens or made subjects worse, since subjectively experienced activation and well being were not decreased. Similarly, others did not find a negative effect of the addition of progestagen on well being (Limouzin-Lamothe et al., 1994). However, it should be kept in mind that the increase in subjectively experienced activation and the decrease in stress experienced was rather small and non significant as compared with baseline. Furthermore, the frequency of occurrence of the other subjective complaints was on average 'less than sometimes' in both groups. Hence, also controls did not show severe clinical impairment.

Lastly, the expectancy of positive HRT effects may have confounded results. When investigating naturally postmenopausal women, double blind procedures cannot be maintained. The studies carried out by Sherwin usually included relatively young groups of women which had undergone hysterectomy, which enabled her to study the effects of estrogens double blind. Yet, we hypothesized that in the present study, the repeated testing ($6 \times$ in total) may have decreased the expectancy effect. Also, the standardized, mainly computerized testing and the no-nonsense

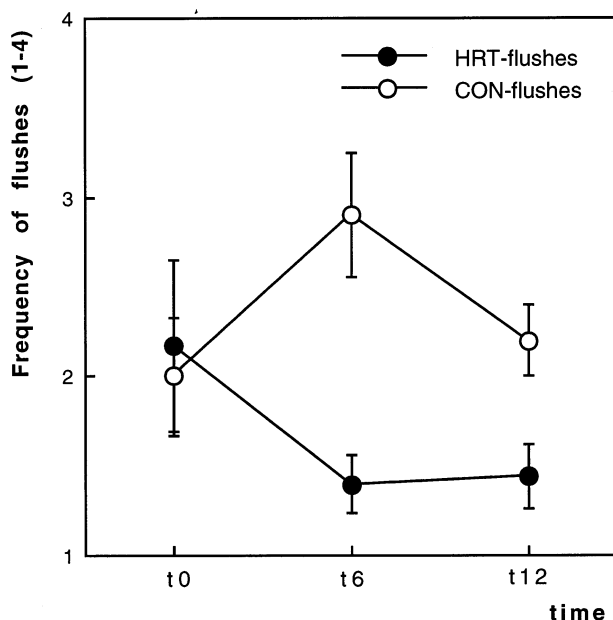


Fig. 6. Frequency of flushes (1 = never, 2 = sometimes, 3 = regularly, 4 = very often) over time in HRT users and controls.

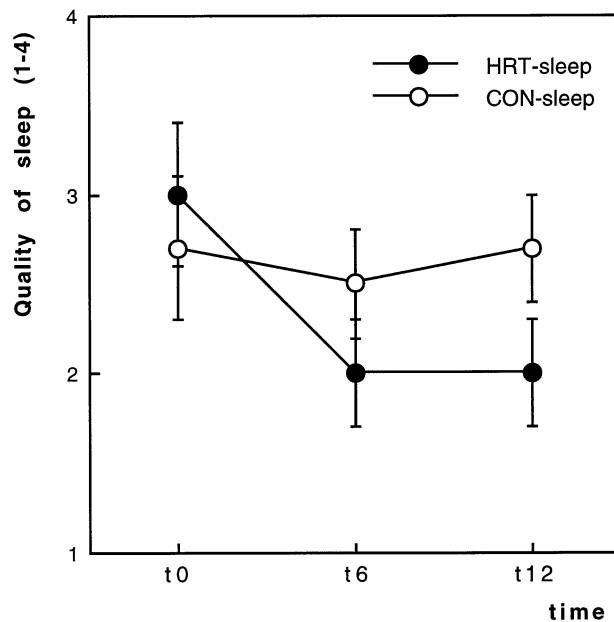


Fig. 7. Awakening at night (1 = never, 2 = sometimes, 3 = regularly, 4 = very often) over time in HRT users and controls.

attitude of the women investigated did not give rise to the suspicion of strong effects.

One method to investigate expectancy effects is to include women who use HRT and are unaware of the purpose of the study. For this purpose we also studied the effects of HRT in a large population sample.

5. Method study 2

5.1. Subjects

The Maastricht Aging Study (MAAS) consists of four separate cross sectional panel studies which were randomly drawn from a patients registration of a network of family practices (RNH). These studies shared the same methodology with respect to sample frame, subject inclusion and stratification criteria and basic measurement protocol. Briefly, each subject panel was stratified for age, sex and an equivalent of general ability: the level of occupational ability (LOA). The four panels comprised a total number of 1874 subjects (Jolles et al., 1995).

Medical exclusion criteria for the subject sampling procedure were defined as those active or inactive medical conditions in the RNH problem list that may interfere with normal cognitive function. This definition includes the following

conditions: coma (only active), cerebrovascular pathology, all tumors of the nervous system, congenital malformations of the nervous system, multiple sclerosis, parkinsonism, epilepsy (all types), dementia, organic psychosis (other than dementia), schizophrenia, affective psychosis and mental retardation. In addition, before participation in the test program all participants were screened by means of a semi-structured interview to update RNH exclusion criteria and to check for the following exclusion criteria not coded in the RNH data base: history of transient ischemic attacks (TIA), brain surgery, hemodialysis for renal failure, electroconvulsive therapy and regular use of psychotropic drugs.

In the MAAS database, 23 out of 342 women in the same age range were identified as HRT users. They were born between 1929 and 1949. The date of the actual menopause was not available. On average subjects had taken HRT for 4.3 years. In Table 2 the different HRT therapies and user frequencies are listed. A selection of females of the population sample was made based upon the age-range of the HRT group (range: 45–65 years of age). This selection yielded a group of 319 control subjects (controls). Thus, the HRT users comprised 6.7% of the total sample of 342 subjects. All subjects were females. Of the HRT users, medical histories were checked by inspecting the status for medical conditions associated with HRT-use, such as hysterectomy and ovariectomy. Unfortunately, these data were not readily available for controls. In Table 3, relevant subject characteristics are listed.

5.2. Procedure

Test sessions were scheduled on work days and Saturdays, in the morning, afternoon, or evening hours. Participants were tested at the neuropsychological test laboratory of the University Hospital, Maastricht. Four separate sound proof rooms permitted three parallel test sessions to be carried out at the same time. Completion of a test session took 2.5 h on average. In general, the time required to test elderly subjects was substantially longer than 2.5 h. Each session consisted of two test clusters, spaced by a rest period of 20 min. The block order was balanced within all ‘age class \times gender \times LOA’ stratification cells, to control for possible fatigue effects. However, analysis of the tests showed neither significant differences due to cluster order, nor trends in the direction of poorer performance when test clusters were administered later. Five test assistants carried out the MAAS data collection. All test assistants received intensive training in test administration and data documentation from the neuropsychologists and physician on the project staff. All assistants carried out a complete test session under close supervision of a member of staff at the start of the study and again after 3 months.

5.3. Assessments and tests

In the MAAS data base, measurements are derived from tests and questionnaires, respectively. The survey was carried out using questionnaires and yielded the variables briefly described subsequently. In Table 4 an overview of dependent and possibly confounding variables is given.

Table 2
Type and prevalence of hormone replacement therapies used

Trade name	Generic name	Contents and usual dosage	No. of subjects (n = 23)
<i>Estrogens</i>			
Premarin	Conjugated estrogens (CEE)	E: 0.625 mg/1.25 mg (28 d, E converts to E1 + E2)	9
Estraderm	Estradiol (E2)	E2: 4/8 mg (50/100 µg/24 h, transdermal system)	4
Prodynova	Estradiol (E2)	E2: 1/2 mg/d, 21 d/month	2
Synapause-E3	Estrinol (E3)	E3: 1/2 mg/d, 21 d/month (applied locally)	1
<i>Combination therapy</i>			
Premarin +	CEE + Medrogestron (P)	E: 0.625 mg/1.25 mg, + (d 17–28) P: 5 mg	9
Prempak C	CEE + Norgestrel (P)	E: 0.625 mg/1.25 mg, + (d 17–28) P: 0.15 mg	1
Estracomb TTS	Estradiol + Norethisteron (P)	E2: 4 mg/d (14 d), E2: 10 mg + P: 30 mg (14 d)	3
Trisequens	Estradiol + Norethisteron (P)	E2: 2 mg (12 d) E2: 2 mg + P: 1 mg (10 d) E2: 1 mg (6 d)	2
Livial	Tibolon	Progestagen and weak estrogen effects (2.5 mg/d)	2
<i>Other combinations</i>			
Premarin (E) +	Conjugated estrogens (E) +	E: 0.625 mg/1.25 mg (28 d)	5
Provera (P)	Medroxyprogesteron (P)	P: 5/10 mg (10 d)	2
Estraderm (E) +	Estradiol (E2) +	E2: 4/8 mg (50/100 µg/24 h)	
Orgametril (P)	Lynestrenol (P)	P: 5 mg (12/15 d)	1
Synapause-E3 (E)	Estrinol (E3) +	E3: 2 mg (12 d)	
+ Trisquens	Estradiol (E2) + Norethisteron (P)	E2: 2 mg + P: 1 mg (10 d), E2: 1 mg (6 d)	1
	Estrogens		1

Table 3

Subject characteristics: menopausal history, years of education and HRT use

	Years of education			Medical history possibly related to HRT use			
	Mean	S.D.	<i>n</i>	Ovariectomy	Hysterectomy	Sterilized	Other
HRT users	10.8	2.8	23	4	8	5	6
	9.8	2.3	318				
	Years of HRT use						
	Mean	S.D.	<i>n</i>		< 1 year	2–4 years	6–23 years
HRT non users	4.3	5.1	23		8	9	6

5.4. Cognitive performance

Three cognitive performance tests, the Verbal Learning Test, the Concept-Shifting Test and the Stroop-Color-Word Test, were taken to yield the main dependent variables: memory, sensorimotor speed and cognitive flexibility.

5.4.1. Verbal learning test (VLT)

The ‘Groningen Fifteen Words Test’ (Deelman et al., 1980; Brand and Jolles, 1985), which is well known in the Netherlands, is an improved version of a test originally devised by Rey (1964). Briefly, 15 words were presented, one after another, separated by short time intervals. Then the subject was asked to recall as many words as he or she could. This procedure was repeated $5 \times$, so that a learning curve can be plotted. The total number of words and the maximum number of words recalled over five trials were taken as dependent measures of learning and short term memory. After 20 min, a delayed recall trial was carried out without presentation of the list. The score at this delayed recall comprised the long-term memory score.

5.4.2. Concept shifting test (CST)

The CST consisted of three parts. On each test sheet, 16 small circles (diameter = 15 mm) were grouped in a larger circle, with a radius of 8 cm. In the smaller circles, the test items (numbers (A), letters (B), or both (C)) appeared in a fixed random order. Subjects were requested to cross out the items in the right order. In part A and B, the subjects had to connect the numbers (1–2–3–etc.) and letters (A–B–C–etc.) respectively. In part C, the subject was required to alternate between these sequences (1–A–2–B–etc.). An exact estimate of the slowing due to the shifting between concepts can be obtained by comparing part C (digits and letters) with part A and part B (letters). Furthermore, there is a so-called null-version of the CST which contains only empty circles which have to be connected as fast as possible.

5.4.3. The Stroop-Color-Word Test (SCWT)

The SCWT has often been used to test selective attention (Houx et al., 1993). The test involved three cards displaying a hundred stimuli each: color names, colored

patches and color names printed in incongruously colored ink. The amount of extra time needed to discard irrelevant but very salient information (verbal), in favor of a less obvious aspect (color naming) was recorded in milliseconds. Three outcome measures were derived from these tests: memory, sensorimotor speed and cognitive flexibility. Total, maximal and delayed recall scores on the Verbal Learning Task (VLT) made up the memory score. The null, digit and letter versions of the CST and the Stroop-Color-Word Test yielded an index of sensorimotor speed and the letter-digit version of the Concept Shifting Task (CST) and the Stroop interference were combined to give the cognitive flexibility score (Van Boxtel et al., 1996). These measures are compound scores that were calculated from the Z-transformed raw test scores, using the formulae:

$$\text{memory} = (Z_{\text{vlttot}} + Z_{\text{vltmax}} + Z_{\text{vltldel}})/3$$

$$\text{sensorimotor speed} = -(Z_{\text{cst}_0} + Z_{\text{cst}_A} + Z_{\text{cst}_B} + Z_{\text{scwt}_1})/4$$

$$\text{cognitive flexibility} = -(Z_{\text{cst}_C} + Z_{\text{scwt}_{III}})/2$$

Table 4
Overview of all dependent variables

Variables	Scale	Range	Categories
<i>Cognitive function</i>			
Memory compound score	Interval	Cont	Z-scores
Sensorimotor speed compound score	Interval	Cont	Z-scores
Cognitive flexible compound score	Interval	Cont	Z-scores
Subjective forgetfulness	Nominal	2	Yes, no
<i>Socio-demographic variables</i>			
Age	Ratio	Cont	45–65
Years of education	Ratio	Cont	5–18
Marital status	Nominal	4	Never married, married, divorced, widow
Offspring	Nominal	2	No, yes
<i>Health risk factors</i>			
History of general anesthesia	Nominal	2	No, yes
Use of psychoactive medication	Nominal	2	No, yes
History of tranquilizer use	Nominal	2	No, yes
Perinatal complications	Nominal	2	No, yes
History of brain trauma	Nominal	2	No, yes
History of brain disease	Nominal	2	No, yes
Exposure to neurotoxins	Nominal	2	No, yes
Hospital admission (ever)	Nominal	2	No, yes
Smoker (present)	Nominal	2	No, yes
<i>Perceived health</i>			
Number of physical complaints	Interval	21	0–21
Subjectively experienced health	Ordinal	5	Very bad, reasonable, good, very good
Anxiety score	Interval	41	10–50
Depression score	Interval	65	16–80
Insomnia score	Interval	13	3–15

5.5. *Subjective complaints about memory*

Subjectively reported memory complaints were obtained by a questionnaire in the postal survey and were derived from the question: ‘do you consider yourself forgetful?’ The answer could be ‘no’ (1), ‘yes’ (2) or ‘don’t know’ (3).

5.6. *Questionnaires survey*

5.6.1. *Sociodemographic variables*

This section contains questions about subject parameters. The number of years of full-time education was recorded. Information was also collected about marital status and offspring of the respondents. Data of the onset of the menopause were not available. Only age and years of education were included as confounders in the analysis of the weight of the association of the HRT-use with cognitive performance.

5.6.2. *Health risk factors*

Questions covering past and present morbidity that might have relevance for cognitive functioning were selected from a widely used medical screening questionnaire (LHV, 1981). Items were adapted to include information about the type of medical consultation resulting from the illness or complaint. Medication use (including over-the-counter drugs) was recorded and classified according to its pharmacological characteristics and side-effects (custom classification, based on Dukes and Dijke (1984) and Dukes (1988)). The sum of the variables ‘history of perinatal complications’, ‘general anaesthesia’, ‘brain trauma’, ‘brain disease’, ‘exposure to neurotoxins’, ‘hospital admission’, ‘use of psychoactive medication’, ‘current use of tranquilizers’ and ‘current tobacco use’ was entered as the ‘health risk’ variable in the analysis of the weight of HRT-use with cognitive performance, since these factors were earlier found to have a negative effect on cognitive functions (Houx et al., 1990).

5.6.3. *Perceived health*

The subjects were asked to rate their health on a five-point scale (range: very bad to very good). The VOG (Vragenlijst Omtrent Ervaren Gezondheid—Inventory of subjective Health) was included as an index of subjective health. It was originally developed by Dirken (1967) to measure stress in industrial situations. It has been used in several Dutch surveys to determine subjective health status. The 21-item version administered in this study probes health complaints of a somatic and psychosomatic nature. The VOG-21 was included because of the expected relationship between subjective measures of memory and memory-related functions and subjective health. Because of the expected relationship between mood and memory complaints, three subscales of the Symptom-Check-List 90 (SCL-90) were included (subscales depression, anxiety and insomnia). The SCL-90 is a widely used multidimensional checklist for psychopathological complaints (Arrindell and Ettema, 1986). The sum of the variables ‘physical complaints’, ‘anxiety’, ‘depression’,

‘insomnia’ and ‘subjective health’ (reversed) was entered as the ‘perceived health’ variable in the analysis of the weight of HRT use with cognitive performance.

5.7. Statistical analyses

The statistical analyses were carried out in two steps. The first step was a straightforward comparison of the cognitive, sociodemographic, health risk and perceived health variables, between HRT users and controls. HRT users were compared with controls with respect to sociodemographic background variables: age, years of education, marital status and offspring. Furthermore, HRT users were compared with controls on health risk factors. Dependent variables were the variables: history of general anaesthesia, use of psychoactive medication, history of tranquillizer use, perinatal complications, history of brain trauma, history of brain disease, exposure to neurotoxins, hospital admission (ever) and smoking and the sum of these variables (‘health risk’). Also, HRT users were compared with controls on perceived health variables. Dependent variables were the variables: number of physical complaints, subjectively experienced health and the anxiety, depression and insomnia scores of the SCL-90 and the sum of these variables (‘perceived health’). Lastly, HRT users were compared with controls on memory complaints and cognitive performance. Dependent variables were: subjective memory complaints, memory compound score, sensorimotor speed compound score and cognitive flexibility compound score. Nominal variables are tested using χ^2 -tests, ordinal variables are tested using Mann–Whitney-tests, whereas variables measured on interval and ratio level are tested using Student’s *t*-tests.

The second step comprised post-hoc logistic and linear multiple regression analyses. First, HRT use was entered separately. Then, HRT use was entered followed by a stepwise forward entering of the age, education, general health risk—and perceived health variables to assess the association of these variables, as compared with the weight of the effect of HRT use, on cognitive function. Independent variables were: HRT use, age, years of education, health risk factors (sum of history of general anaesthesia, use of psychoactive medication, history of tranquillizer use, perinatal complications, history of brain trauma, history of brain disease, exposure to neurotoxins, hospital admission and smoking) and perceived health (sum of number of physical complaints, subjectively experienced health and the anxiety depression and insomnia score of the SCL-90). Dependent variables were: subjective memory complaints, memory compound score, sensorimotor speed compound score and cognitive flexibility compound score. In the logistic regression analyses, the OR (observed risk) is given as an estimator of the relative risk (RR) to assess the strength of the association between HRT and the other variables and subjective memory complaints. A summary of the results is shown in Table 5, which includes the descriptive statistics of the comparisons between HRT-users and controls.

6. Results

HRT users had had more years of education (10.78 y) than controls (9.79 y) ($t_{(23,318)} = -1.94$, $p = .05$). Unexpectedly, there was a trend for HRT users to

Table 5

Summary of results of all dependent variables (mean \pm S.D.)

Variables	HRT (<i>n</i> = 23)	CON (<i>n</i> = 319)	Statistic	<i>p</i> <
<i>Cognitive function</i>				
Memory compound score	0.13 \pm 0.94	−0.01 \pm 0.93	<i>t</i> = −.72	
Cognitive flexibility compound score	0.30 \pm 0.59	−0.02 \pm 0.86 ^b	<i>t</i> = −1.73	
Sensorimotor speed compound score	0.33 \pm 0.60	−0.03 \pm 0.78 ^b	<i>t</i> = −2.16	0.05
Subjective forgetfulness (yes)	59% ^a	38%	χ^2 = 3.84	0.05
<i>Socio-demographic variables</i>				
Age	54.3 \pm 5.8	55.2 \pm 6.3	<i>t</i> = 0.66	
Years of education	10.8 \pm 2.8	9.8 \pm 2.3 ^b	<i>t</i> = −1.94	0.05
Marital status (yes)	82.6%	83.1%	χ^2 = 0.10	
Offspring (yes)	87.0%	88.6% ^c	χ^2 = 0.06	
Health risk factors (present) Σ	2.96 \pm 1.4	2.68 \pm 1.3	<i>t</i> = 0.98	
History of general anaesthesia	100%	86.2%	χ^2 = 3.64	
Use of psychoactive medication	8.7% ^a	6.9%	χ^2 = 0.11	
History of tranquillizer use	17.4%	11.9%	χ^2 = 0.60	
Perinatal complications	13.0%	16.3%	χ^2 = 0.17	
History of brain trauma	17.4%	19.7%	χ^2 = 0.08	
Exposure to neurotoxins	9.1% ^a	4.8% ^c	χ^2 = 0.77	
Hospital admission (ever)	95.7%	88.7% ^b	χ^2 = 1.08	
Smoker	26.1%	27.2% ^b	χ^2 = 0.01	
Perceived health Σ	43.1 \pm 16.4	49.8 \pm 16.9	<i>t</i> = −1.84	0.07
Number of physical complaints	7.4 \pm 3.9	6.3 \pm 4.5 ^d	<i>t</i> = −1.08	
Subjectively experienced health	3.7 \pm 0.5	3.8 \pm 0.5 ^b	<i>Z</i> = −0.21	
Anxiety score	15.5 \pm 4.9 ^a	13.3 \pm 4.9 ^d	<i>t</i> = −2.02	0.05
Depression score	25.0 \pm 7.4	21.8 \pm 7.4 ^c	<i>t</i> = −1.99	0.05
Insomnia score	5.6 \pm 2.9 ^a	5.8 \pm 2.9 ^c	<i>Z</i> = 0.31	

^a *n* = 22 (RT).^b *n* = 318.^c *n* = 317.^d *n* = 316.^e *n* = 315.

report a lower perceived health as compared with non-users ($t_{(22,311)} = -1.84$, $p = .07$). HRT users were also more likely to consider themselves forgetful ($\chi^2(1) = 3.84$, $p = .05$) and had higher anxiety ($t_{(22,316)} = -2.02$, $p = .05$) and depression ($t_{(23,315)} = -1.99$, $p = \text{Wald}_{(1)} = 4.30$, $p < .05$, OR = .62). Entering the other variables stepwise forward revealed that women who considered themselves as forgetful, perceived their health as less favourable ($\chi^2(1) = 22.24$, $p < .0001$, $B = .03$, S.E. = .01, $\text{Wald}_{(1)} = 19.27$, $p < .0001$, OR = 1.04). The effect of HRT was partialled out in these analyses ($B = -.38$, S.E. = .24, $\text{Wald}_{(1)} = 2.43$, $p = \text{ns}$, OR = .69). Age, education and health risk factors were also not entered in analysis.

Further, the results of regression analysis of sociodemographic, health risk and perceived health variables on the memory compound score showed that the HRT had a non significant contribution in explaining the variance on this score ($R^2 = .001$, $F(1, 319) = .41$, $p = \text{ns}$, $B = .13$, S.E. = .21, $\beta = .04$, $t = .64$, $p = \text{ns}$). HRT was partialled out of analyses when education was entered with stepwise forward

analyses ($B = .07$, S.E. = .21, $\beta = .19$, $t = .34$, $p = \text{ns}$). Women who performed better on memory tests were higher educated, since years of education was seen to explain 9% of the variance ($= R^2$, $F(2, 318) = 8.11$, $p < .0005$) on the memory compound score ($B = .09$, S.E. = .02, $\beta = .22$, $t = 3.98$, $p < .0001$) while the other variables, age ($B = -.06$, S.E. = .06, tolerance = .95, $t = -1.12$, $p = \text{ns}$), health risk factors ($B = .01$, S.E. = .01, tolerance = .98, $t = .17$, $p = \text{ns}$) and perceived health ($B = -.10$, S.E. = .10, tolerance = .98, $t = -1.84$, $p = .07$) were not included in the equation.

The results of regression analysis of sociodemographic, health risk and perceived health variables on the cognitive flexibility compound score revealed a non significant contribution of HRT use ($R^2 = .01$, $F(1, 318) = 2.5$, $p = \text{ns}$, $B = .30$, S.E. = .19, $\beta = .09$, $t = 1.58$, $p = \text{ns}$). When variables were entered stepwise forward with HRT, age and education were seen to explain 17% of the variance ($F(3, 316) = 21.77$, $p < .0001$) and the effect of HRT was partialled out ($B = .21$, S.E. = .18, $\beta = .06$, $t = 1.19$, $p = \text{ns}$). Women who performed better on cognitive flexibility tests were younger ($B = -.04$, S.E. = .01, $\beta = -.29$, $t = -5.56$, $p < .00001$) and higher educated ($B = .08$, S.E. = .02, $\beta = .31$, $t = 4.37$, $p < .00001$). Health risk ($B = -.08$, S.E. = .09, tolerance = .94, $t = -1.64$, $p = \text{ns}$) and perceived health ($B = -.06$, S.E. = .07, tolerance = .95, $t = -1.19$, $p = \text{ns}$) were not entered in the equation.

The results of regression analysis of sociodemographic-, health risk and perceived health variables on the sensorimotor speed compound score showed that HRT use explained only 1% of the variance when entered alone ($R^2 = .11$, $F(1, 318) = 4.11$, $p < .05$, $B = .35$, S.E. = .17, $\beta = .11$, $t = 2.03$, $p < .05$). Age explained 12% of the variance when entered stepwise forward with HRT. Explained variance was raised to 16% when years of education was entered on the next step ($F(3, 316) = 20.17$, $p < .00001$). Women who performed better on sensorimotor speed tests were younger ($B = -.03$, S.E. = .006, $\beta = -.29$, $t = -5.45$, $p < .00001$) and higher educated ($B = .07$, S.E. = .02, $\beta = .21$, $t = 3.89$, $p < .0001$). The contribution of HRT use approached significance ($B = .27$, S.E. = .16, $\beta = .09$, $t = 1.70$, $p = .09$). Health risk factors ($B = -.07$, S.E. = .08, tolerance = .94, $t = -1.36$, $p = \text{ns}$) and perceived health ($B = -.04$, S.E. = .04, tolerance = .95, $t = -.77$, $p = \text{ns}$) were not entered in the equation. Hence, women who scored higher on sensorimotor speed were somewhat more likely to be HRT users. The performance of women using HRT on sensorimotor speed tasks was comparable with the performance of women that were 9 years younger (B age divided by B HRT).

7. Discussion

As to the main purpose of this exploratory analysis, the hypothesized effects of HRT on cognitive performance could not be confirmed in statistical analyses, although basic sensorimotor processing speed did appear to be affected positively by HRT use. We also found that HRT users had had more years of education, similar to the findings of others (Tang et al., 1996). Since education is known to affect the performance on cognitive tests and may be a protective factor in

age-related cognitive decline, this means that the effect of education can confound the effect of HRT use. However, the trend towards the expected independent positive association of HRT use with performance on sensorimotor speed tasks was independent of both age and education.

Some of the findings were quite contrary to expectations. For instance, women in the HRT group were shown to complain more of anxiety and depression. In earlier studies the positive effect of estrogens on mood were extensively described. In fact, it was even considered to be an alternative antidepressant for post menopausal women (Klaiber et al., 1982; Bäckström et al., 1985). An explanation could be that HRT users were more anxious and depressed due to one of the most likely candidates of indication for estrogen use, namely hysterectomy and/or ovariectomy due to endometrial cancer. Cultural differences may explain these findings. In the United States of America, more women are reported to use estrogens. For instance, the 15 year prospective, cross-sectional study by Barrett-Connor and Kritz-Silverstein (1993) showed that of 800 women (aged 65–95 years), almost half of the cohort had used estrogen at some time after the menopause and one third were current users. Other studies in the USA (Salamone et al., 1996), the UK (Griffiths and Convery, 1995) and Australia (MacLennan et al., 1993) report current use incidences of 17, 20 and 14% respectively. In the cohort of the present study only about 7% of the women used HRT. HRT in the MAAS-database was mainly prescribed for strict medical reasons. These findings are compatible with the notion that clinicians in The Netherlands are more reluctant in prescribing estrogens to post menopausal women.

Subjects using HRT were also seen to complain more of forgetfulness, contrary to the earlier findings by, for instance, Campbell and Whitehead (1977) and Schneider and Brotherton (1982). Again, another double-blind study by Paterson (1982) also showed no improvement on self-report measures of memory function. It should be kept in mind that in the studies mentioned, subjects were conscious of participation in scientific research and were informed of the scientist's expectations. Since double blind testing of HRT is difficult (due to withdrawal bleeding) subjects might have been influenced by expectancy effects in the earlier studies. The tentative overall explanation of the results would be that HRT users in the MAAS-database probably are women with a pattern of related subjective complaints, i.e. of depression, anxiety and forgetfulness irrespective of whether these are determined by the climacterial syndrome. In this line, another study in which women were not aware of the purpose of the study HRT users reported a lower level of activation as compared with controls. Also in this study no effect of HRT on memory and complex speed tasks was found (Schmidt et al., 1996).

Yet, in contrast to the study by Schmidt et al. (1996) and the present study, most experimental studies did find an effect of HRT on memory. One explanation for the lack of findings on the memory task could be the large diversity in hormonal preparations that were used by the women investigated in this study. However, our first study showed that the addition of a progestagen does not decrease memory functions. Also others found no effect of the addition of a progestagen (Kampen and Sherwin, 1994; Limouzin-Lamothe et al., 1994).

Alternatively, it is possible that the type of test (immediate and delayed free word recall) used in the present study was not sensitive to the effect of HRT. For instance, Sherwin and Phillips (1990), Phillips and Sherwin (1992) and Kampen and Sherwin (1994) found effects of HRT on paragraph recall, while no effects were found by Kampen and Sherwin (1994) on immediate or delayed word recall. Similarly, Szklo et al. (1996) found no effects of HRT use on delayed word recall. Also, no effects of HRT on the immediate recall of digits (digit span) was found (Vanhulle and Demol, 1976; Ditkoff et al., 1991). Craik and Byrd (1982) stated that elderly subjects perform most poorly on tasks that contain little environmental or contextual support and that have high processing demands, such as free recall as compared with paragraph recall. The present data suggest it is possible that the more difficult memory tasks which require more processing capacity are not sensitive to the effect of HRT. In this line, cognitive flexibility was also not influenced by HRT in the present study. Yet, an independent positive association of HRT use with performance on sensorimotor speed tasks was detected. Similarly, other investigators found an effect of HRT in improving alertness and attentional functions as measured with sensorimotor speed tasks (Vanhulle and Demol, 1976; Fedor-Freyberg, 1977). Possibly, this general alerting effect of HRT explains why memory tasks with more environmental contextual support (e.g. paragraph recall) can be positively affected, while difficult tasks, which require more processing capacity (e.g. free recall of word lists) are not as sensitive to the effects of HRT.

In sum, the findings of the present study point towards a trend in the direction of a general activating effect of HRT use, rather than a specific association between HRT use and memory or cognitive performance. The general activating effect of HRT was found to be independent of age, education, perceived health and health risk factors. These findings are relevant for age-related memory impairment and Alzheimer's dementia. However, two early studies suggested that the cognition enhancing effects of estrogens are not maintained after 12 months of treatment (Caldwell and Watson, 1952; Kantor et al., 1973). Similarly in our first study, a slight non significant reversal of effects of HRT on memory functions was seen after 12 months. Hence, longer term studies involving a larger number of older subjects (between 65 and 80 years) are needed to investigate the possible protective actions of combined HRT in attenuating cognitive decline.

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