The Journal of Obstetrics and Gynecology of India (July–August 2019) 69(4):303–312
https://doi.org/10.1007/s13224-019-01223-5

REVIEW ARTICLE

Sex Hormones and Cognition: Where Do We Stand?

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Received: 14 December 2018 / Accepted: 12 March 2019 / Published online: 10 April 2019

Abstract
Hypothalamic–pituitary–gonadal axis regulates the reproductive system. The overall health and wellbeing of a woman is subject to fluctuations in the sex hormones throughout her lifespan. Menopause, either natural or surgically induced, is often associated with cognitive complaints, especially memory disturbances. Sex hormones, besides affecting the reproductive function, affect the central nervous system in many ways. Here, we aim to review the role of sex hormones in cognition and the current evidence on use of or against menopausal hormonal therapy as a cognition enhancer in women with cognitive disturbances, including those with Alzheimer's disease.

Keywords Alzheimer's disease · Cognition · Dementia · Estrogen · Estradiol · Hormone therapy · Menopausal hormonal therapy · Memory · Sex hormones

Memory, Cognition and Dementia

As populations age across the globe, the prevalence of neurodegenerative disorders increases. India is no exception [1, 2]. The Indian population is undergoing a demographic shift. The crude birth rates and crude death rates are dropping, and as a result, the existing population is aging. The average life span of Indian men and women has increased by almost a decade [3]. Thus, India expects increasing challenges in the care of elderly. Problems of memory, cognition and dementia affect this section of the population. So let us understand some of the concepts of these neurocognitive disorders (NCDs).

While deterioration of memory is perhaps the most common, other cognitive faculties are also affected in the aging population [4]. The Diagnostic and Statistical Manual of Mental Disorders details six cognitive domains—complex attention, executive ability, learning and memory, language, perceptual-motor-visual perception, praxis and social cognition, which may be affected in different grades of NCDs. Minor NCD differs from major NCD (formerly labeled as dementia) as the basic activities of daily living are compromised in the latter [5].

Dementia is a progressive neurodegenerative condition, caused by diverse etiologies, leading to decline in cognitive and functional abilities [6]. In 2016, about 43.8 million people lived with dementia globally [7]. Alzheimer's disease (AD) is the most common cause of dementia (about 60–80% of all cases); the other causes being vascular dementia, dementia with Lewy bodies, Parkinson disease dementia, mixed dementia, normal pressure hydrocephalus and frontotemporal degeneration [6, 7].The risk factors associated with AD are multifactorial. Age is the greatest risk factor, the others being genetic predisposition, and certain modifiable risk factors (cardiovascular disease, diabetes mellitus, hypertension, head injury, smoking and lower social engagement, sex hormone deficiency associated with menopause) [7–9].

Patients with dementia suffer from memory disturbances early in the course of their disease. Memory is characterized by the ability to store learned information presented either externally or internally and reproduce it later, when required [10]. Broadly, memory may be divided into immediate, short-term and long-term memory [4] (Table 1). Long-term memory is further divided into declarative memory (explicit memory) and non-declarative memory (implicit memory)

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Table 1 Types of memory and their anatomical localization

Type of memory	Anatomical localization
Immediate memory (working memory)	Prefrontal cortex
Short-term memory	Medial temporal lobe
Long-term memory	
Declarative memory (explicit memory)	
Episodic memory	Medial temporal lobe
Semantic memory	Anterior, lateral and inferior temporal lobes
Non-declarative memory (Implicit memory)	
Procedural memory	Basal ganglia, cerebellum
Priming	Neocortex
Classical conditioning	Amygdala, cerebellum

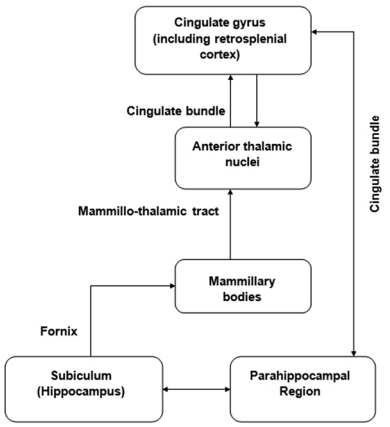

Fig. 1 Schematic representation of the Papez circuit

[11]. Declarative memory (consciously evoked memory) comprises episodic and semantic memory. "Episodic memory" denotes the memory related to past episodes/experiences, and "semantic memory" denotes memory pertaining to general knowledge concerning people, objects, words or concepts. Non-declarative memory (not consciously evoked memory) may be further divided into procedural memory, priming and classical conditioning [10].

Working memory is the ability to hold information for a short period of time after the inciting stimulus is no longer present in the environment and typically is a function of the prefrontal cortex. The declarative memory is a function of the temporal lobes (episodic memory by medial temporal lobe and semantic memory by the anterior, lateral and inferior temporal lobes). The entorhinal cortex and hippocampal formation help in the linking of information presented to different regions of the cortex and storage of memory (from short-term to long-term memory). After representation, memory is first encoded and later retrieved when required, which is a function of the medial temporal lobe [10]. The Papez circuit (memory circuit) is an intricate circuit composed of the hippocampus, thalamus and cingulum, involved in memory, learning and emotion [12] (Fig. 1).

The neuroendocrinology of cognition is complex [13, 14]. Fluctuations in the levels of sex hormones appear to affect sleep, appetite, cognition and memory [14, 15]. Sex hormones affect cognition in women through all ages, prenatally to postmenopausally [16]. In utero exposure to androgens is hypothesized to influence lateralization of brain and behavior in men as well as women [17]. Sex hormone levels across various phases of menstrual cycle do not seem to affect cognitive abilities significantly [18]. The suppression of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) by estrogen gets attenuated as women age [14]. Sex differences in cognitive abilities like verbal and spatial memory occur due to differential modulation of prefrontal and hippocampal function [13]. Sex hormone-binding globulin (SHBG) levels, too, are found to affect cognition, with varying effects [18, 19]. Besides sex steroids, insulin and leptin also seem to influence learning, memory and cerebral brain volume [14].

Age-related changes in sex hormones occur in both women and men. The fall in levels of sex hormones is more abrupt and rapid in women as compared to men [16]. The cognitive domains which are affected the most with aging are declarative memory, spatial learning and executive functions [20]. Cognition in women is influenced by many factors like aging, reproductive status, race, sleep quality, mood disturbances, stress, body mass index, metabolic status and past history of sexual abuse [21]. Menopause and andropause are associated with impairment in verbal episodic memory, attention/working memory and verbal learning [22, 23].

Aging is known to slow mental processing speed. The levels of bioactive sex steroids and gonadotropins acting on the hypothalamic–pituitary–gonadal (HPG) axis correlate with the various stages of cognitive decline. Postmenopausal women have lower performance on verbal memory and phonemic verbal fluency tasks. However, among women in the postmenopausal age, those with higher serum estradiol are likely to perform better [24]. Performance on verbal memory scores is a composite of many processes including mental processing speed, immediate recall, etc. When postmenopausal women with different ages and various stages of menopause were tested for cognitive scores, it was noted that menopause stage did not contribute independently to performance. Thus, cognitive changes that occur during menopause appear to be independent of that expected with normal aging [25].

We shall now review the role of sex hormones and menopausal hormonal therapy (MHT) in cognition and dementia.

What Does Animal Research Tell Us About Cognition and Sex Hormones?

Numerous studies on rodent and monkey models point toward the vital role of estradiol in brain development [26–32]. Estradiol influences synaptic signaling, dendritic arborization, protein synthesis, energy metabolism and neuronal survival [27]. Rodents exposed to exogenous 17β-estradiol were found to have enhanced learning and memory [28]. These actions seem to be mediated by the synaptic and nuclear estrogen receptors (ERs)—ERα, ERβ—and G protein-coupled estrogen receptor 1 (GPER1). Estrogenic receptors are found to be concentrated in the hippocampus and dorsolateral prefrontal cortex, which are the major areas concerned with memory and learning [27, 29].

Neuroprotective effects of progesterone have been observed both in cell and animal models. These are modulated by action of progesterone on its receptors, either directly or indirectly through the regulation of mitogen-activated protein kinase (MAPK) and brain-derived neurotrophic factor (BDNF) signaling pathways [33]. Progesterone has shown protective effect against ferrous sulfate and amyloid β-peptide-induced toxicity in primary hippocampal cultures [34]. Besides, it regulates long-term potentiation which has been linked to long-term memory [35]. Although combining estrogens and progesterones have shown to improve memory, a recent study on ovariectomized rats has questioned this beneficial effect [36].

Non-human primates in whom oophorectomy/ovariectomy had been performed, a more severe cognitive decline was observed when compared with natural menopause [37]. This observation points toward a potential role of gonadotropins in mediating cognitive performance. Additionally, in menopausal monkey models, where menopause was induced naturally or surgically, differences were noted in their estrogen receptor and aromatase levels [27]. Testosterone was found to enhance spatial memory in female rats and can rescue spatial memory when estradiol levels are low [38].

In animal models of Alzheimer's disease, estrogen reduces β-amyloid formation, diminishes hyperphosphorylation of tau protein and increases apolipoprotein expression [39]. 17 β-estradiol also reduces the level of amyloid precursor protein (APP) through enhanced alpha secretase processing resulting in marked reduction of APP-C terminal fragment, amyloid beta and plaque burden in rats [40]. It also enhances the level of transthyretin in the brain, which inhibits the aggregation of amyloid beta into plaque [41].

How Does Animal Research Translate into Clinical Practice?

Menopausal hormonal therapy and its effects on cognition in women have been a topic of interest for a long time. The data from animal studies led researchers to put forth the hypothesis that hormonal supplementation is potentially beneficial for enhancing cognition in aging women. However, the negative results from the initial studies like Women's Health Initiative Memory study (WHIMS) and Women's Health Initiative Study of Cognitive Aging (WHISCA) trials were a setback to this theory [42, 43].

The WHIMS was comprised of two parallel, randomized, double-blind, clinical trials ($n = 7510$) comprising women older than 65 years of age and concluded that conjugated equine estrogen (CEE) combined with medroxyprogesterone acetate (MPA) doubled the incidence of dementia, compared to placebo, and failed to reduce global cognitive decline. The later WHIMS CEE-alone trial reported a 49% increase in the incidence of dementia [24, 42, 44, 45]. Ancillary to the WHIMS study was the WHISCA study, which aimed to assess the efficacy of CEE-based postmenopausal hormonal therapy on age-related changes in cognition over time [43]. They found that CEE + MPA was associated with decrements in verbal memory after several years of treatment. CEE-alone was associated with lower spatial rotational ability at the initial assessment, but the association diminished with continued treatment.

The results from the Women's Health Initiative (WHI) and WHIMS trials aroused considerable debate on the potential health risks of MHT in women, especially occurrence of cardiovascular events, cancer and dementia [45, 46]. Largely, the limitations of these trials were older age at recruitment in the study, no differentiation of various types of dementia, and timing of initiation of MHT with respect to menopause [46, 47].

The concept of "healthy cell bias" came forth when the shortcomings of these trials were analyzed. As per this hypothesis, estrogens were more likely to be beneficial for cognition in a healthy environment rather than a diseased state [48]. Thus, the baseline cognitive function seemed to be a predictor of health benefits or risks after use of MHT. Women who were old, but "healthy" (having average or better baseline cognitive scores), did better with MHT. Those with a low baseline score, irrespective of the age, had worse cognitive outcome from MHT [48].

To determine whether clinically silent cerebrovascular disease on cerebral magnetic resonance imaging (MRI) may occur with use of MHT in aging women, a small proportion of women ($n = 1424$) from the WHIMS trial were enrolled for the WHIMS MRI study [49]. The investigators concluded that cognitive impairment in women who received conjugated estrogens was mediated through brain atrophy and not through subclinical ischemic disease. Thus, MHT may benefit younger postmenopausal women and not the older women [50].

Another concept which came forth was the "critical window" hypothesis, also known as the "timing hypothesis" or

the "critical period" hypothesis [42, 51]. It was based on the belief that the effects of MHT on cognition depend on the timing of initiation of treatment with respect to age and/or the onset of menopause. Thus, benefits might be limited to early initiation of MHT.

The concept of timing hypothesis arose probably much before the results from the WHIMS trials were available [51]. Observational studies like the Cache county study (from Utah) and Cardiovascular Risk factors, Aging and Dementia (CAIDE) cohort study (from Finland) concluded that long-term postmenopausal MHT may be beneficial for some cognitive domains in women [52, 53].

The Cache County Study (Utah) detected a reduced AD risk (hazard ratio [HR] 0.3, 95% CI 0.2–0.7) if MHT was started within 5 years of menopause and continued for more than 10 years [52]. CAIDE cohort was a population-based study from Eastern Finland in 731 cognitively normal women with self-reported hormone therapy. They concluded that use of estradiol alone among women having hysterectomy with bilateral oophorectomy was associated with better episodic memory at baseline, but not in 5–10-year follow-up of the original cohort [53]. A 20-year follow-up data from the Kuopio Osteoporosis Risk Factor and Prevention study cohort of about 8195 Finnish women (227 cases of incident AD) also found a protective association between long-term (> 10 years) self-reported use of MHT and AD [47].

Marder and colleagues, thus, observed that there was a discrepancy when results of effect of hormonal therapy on cognition in treatment trials (like WHIMS and WHISCA) were compared to those in observational studies [42, 43, 45, 47, 48, 51–54]. Hence, there appears to be a relationship between the timing of initiation of MHT with respect to age/onset of menopause and its potential cognitive benefit.

Surgical menopause in younger women due to procedures like bilateral oophorectomy [16] leads to a drastic decline in the levels of estrogens, increasing the risk of cognitive disturbances and dementia, as observed in large-scale cohorts [55–58]. The younger the age at menopause, the greater the impact. Both episodic memory and semantic memory are significantly affected [42]. Autopsy studies in this group showed an increased burden of AD neuropathology like the neuritic plaques [58].

Women's Health Initiative Memory Study of Younger Women (WHIMS-Y) tested whether randomized assignment to CEE + MPA and/or CEE-alone in younger postmenopausal women (50–54 years) may confer the proposed protection relative to placebo in their 1362 participants [59]. There was, however, no significant difference in treatment effects when these women's cognitive function was assessed 5 years following the termination of the trials. A recent post hoc analysis by Espeland and colleagues concluded that CEE-based hormone therapy delivered near the time of menopause provides neither cognitive benefit nor detriment. If administered in older women, it results in small decrements in several cognitive domains that remain for many years [59].

Kronos Early Estrogen Prevention Study (KEEPS), KEEPS Cognitive and Affective Sub Study (KEEPS-Cog) and Early versus Late Intervention Trial with Estradiol (ELITE) were designed to investigate effect of MHT as regards age of initiation around menopause [60, 61]. The KEEPS and KEEPS-Cog trials concluded that transdermal 17 β-estradiol was associated with a reduced amyloid-β deposition as seen on Pittsburgh Compound B (PiB) imaging, particularly in apolipoprotein E (APOE) ε4 carriers. There was, however, no cognitive benefit for either MHT compared to placebo [60]. Among 643 postmenopausal women stratified as "early" or "near menopause" (menopause within 6 years of a final menstrual period) and "late" therapy (more than 10 years postmenopause) in the ELITE trial, estradiol did not affect verbal memory, executive functions or global cognition, irrespective of timing postmenopause [61].

The precise role of estrogen in AD is as yet unclear.AD is about two to three times more prevalent in women. The cognitive decline is worse once diagnosis has been established in women as compared to men [6].This sex-specific predilection to AD seems to be a composite of hormonal influences on aging and genetics (APOE gene risk allele, Met66 allele of BDNF gene) [13]. Some observational and case–control studies have found that use of MHT may cause reduced risk of AD [48, 62, 63]. Whitmer and colleagues further found that use of MHT in mid-life may reduce risk of dementia (about 26%), while use in late-life may be deleterious [63]. When effect of MHT on older women who were already suffering from AD was studied, no benefit in cognitive symptoms was observed. MHT did not seem to halt or slow the cognitive decline in this group [64]. It is also worthwhile to note that "healthy cell bias" and additional risk factors like hypertension and vascular disease act as a confounding factor in such observations.

The observational studies of use of MHT show a reduced risk of AD. A meta-analysis of few observational studies that examined the timing of initiation and/or age supports the hypothesis that use of MHT early or near menopause was protective, and later use did not prevent occurrence of dementia or was detrimental [51].

The composition of MHT may also influence effects of the therapy on cognition [65]. Largely, differences exist in regimens as deleterious effects of unopposed estrogens need to be countered in women with an intact uterus. Various formulations of estrogens were compared for their efficacy on cognitive improvement. Thus, it was investigated whether estrogen alone was better than combined therapy. No statistically significant differences due to hormonal regimes were found after pooled data from WHIMS (CEE-alone and CEE/MPA groups) was compared [51]. The progestogenic compound used in WHIMS was MPA, which has been found to

have a negative impact on cognition in animal studies [33, 51]. The Finnish cohort was administered norethisterone or levonorgestrel and not MPA [47]. Using ultra-low-dose transdermal estradiol as well as CEE, or estradiol valerate combined with dienogest or norethindrone, may result in cognitive benefits compared to CEE + MPA combination [51].

Testosterone supplementation in elderly males (≥ 65 years) with memory impairment has shown no beneficial results [23]. Studies using testosterone in low dose in postmenopausal women, however, have found improvement in verbal learning and memory [66]. Selective estrogen receptor modulators (SERMs), such as raloxifene, have mixed agonist/antagonist action [67]. Raloxifene has been currently approved for osteoporosis in postmenopausal women. When these women on raloxifene were studied for cognitive effects of raloxifene, conflicting results have been found, some favoring, others not favoring use of the drug for improving cognition [67, 68].

The various clinical trials and observational studies regarding role of MHT in cognition in young as well as older postmenopausal women and women with Alzheimer disease are summarized in Table 2.

What is the Current Advice?

The consensus guidelines for the use of MHT mention that there is a greater safety profile with estrogen-only therapy versus combined therapy (estrogen and progesterone). In women with intact uterus who receive estrogen therapy, additional progesterone in adequate dose is advisable to negate the risk of endometrial cancer [69].

As per the critical timing hypothesis, it may be advisable to initiate MHT in less than 10 years postmenopause and earlier, that is, perimenopausally [45]. Hormone therapy provides some benefit on cognition in young postmenopausal women; those with vasomotor symptoms have an additional advantage with MHT [45, 64, 69].Women with surgical menopause at an early age may benefit more than those with natural menopause at an early age [69]. The baseline cognitive function is important, and more favorable effects may be seen in women with normal baseline cognitive function [69].The data from use of MHT in already demented women are scarce [70]. Regarding the formulation used, it appears that transdermal estradiol is more effective. Progesteronic preparations like levonorgestrel/micronized progesterone may be better than synthetic MPA [64, 69].

It has been accepted that MHT has a favorable role in preventing osteoporosis and ameliorating vasomotor symptoms in postmenopausal women. Women who have undergone hysterectomy seem to benefit more than those with intact uterus for the health outcomes with MHT [45]. Whether such recommendations shall extend to cognitive benefits of MHT in future will only be evident as more and more data become available.

Where Do We Go From Here?

The exact role of sex hormones like estrogens, progesterones, testosterone and newer selective agents in cognition is as yet unclear. The available data are largely from observational cohorts or small-scale trials, which fail to provide substantial level of evidence to support use of MHT for reducing dementia risk. With advent of newer selective agents like SERMs and tissue-specific estrogen complexes, growing knowledge of pharmacogenetics and concept of precision medicine, a tailor-made therapy for each woman may be a possibility in the future.

Learning Points

- As India undergoes demographic transition, the numbers of aging women are expected to increase in the coming years.
- Sex hormones affect the central nervous system in many ways and play a role in cognitive decline and dementias.
- Menopause, either natural or surgically induced, is often associated with cognitive complaints, especially memory disturbances.
- In animal models, estradiol and progesterone are shown to influence energy metabolism and neuronal survival.
- Estrogen reduces β-amyloid formation, diminishes hyperphosphorylation of tau protein and increases apolipoprotein expression in Alzheimer disease models of rats.
- There is a greater safety profile with estrogen-only therapy versus combined therapy (estrogen and progesterone). In women with intact uterus, additional progesterone in adequate dose is advisable.
- Menopausal hormonal therapy (MHT) may have some favorable cognitive effects in young postmenopausal women with vasomotor symptoms.
- The timing of initiation of MHT is critical for its effect. If there is a delay in starting MHT by more than 10 years postmenopause, therapy may cause detrimental results.
- Current evidence does not justify the use of MHT of any type to specifically enhance cognition or reduce dementia risk.

Table 2 Various clinical trials and observational studies on effect of menopausal hormonal therapy on cognition in postmenopausal women and those with Alzheimer dementia [42, 43, 47, 49, 52, 53, 59–61]

Trial name	Study type	Years	*N* (All)	Age (years)	Hormonal therapy used	Test of cognition used	Duration (time at assessment) (years)	Results
WHIMS	Two parallel, randomized, double-blind, clinical trials	1995–2002	*N* = 7510 CEE + MPA: 4532 participants	50–79	CEE + MPA or CEE-alone versus placebo	Modified mini-mental state examination (3MS) and CERAD battery	CEE + MPA: 4.05 (SD = 1.19) years	Pooled data: overall HR for probable dementia was 1.76 (95% CI 1.19–2.60, *P* = 0.005)
		1995–2004	CEE-alone: 2947 participants				CEE-alone: 5.21 (SD = 1.19) years	Mean (SD) decrement of 0.21 (0.08) units on the 3MS score (*P* = 0.006)
WHISCA	Two-armed, randomized placebo-controlled, clinical trial		*N* = 2304	66- 84	CEE + MPA or CEE-alone versus placebo	Modified mini-mental state examination (3MS) and WHISCA battery	CEE + MPA: 3 (SD = 0.7) years	CEE + MPA had a negative impact on verbal memory over time compared to placebo (*P* = 0.01)
		1999–2002	CEE + MPA: 1416 participants				CEE-alone: 3 (SD = 0.7) years	CEE-alone was associated with lower spatial rotational ability (*P* < 0.01) at initial assessment
		1999–2004	CEE-alone: 1361 participants					CEE-alone did not significantly influence change in other cognitive functions and affect
WHIMS-Y	Two-armed, randomized placebo-controlled, clinical trial	2009–2016	*N* = 1376	50–54	CEE + MPA or CEE-alone versus placebo	Telephone cognitive battery Dementia Questionnaire	7 years	No overall differences between CEE-alone and CEE +MPA therapy between women who had and had not used hormone therapy
WHIMS – MRI	Two-armed, randomized placebo-controlled, clinical trial	2005–2010	*N* = 1424	50–79	CEE + MPA or CEE-alone versus placebo	Total ischemic lesion volume	CEE + MPA 4.0 years	No differences in ischemic lesion volumes in the basal ganglia or in the white and gray matter outside the basal ganglia. Small but significant differences favored women originally assigned to placebo for frontal lobe volume (2.4 ml difference) and hippocampal volume (0.1 ml difference)
			CEE + MPA: 883 Participants			Total and regional brain volumes	CEE-alone 5.6 years	

Table 2 (continued)

Trial name	Study type	Years	*N* (All)	Age (years)	Hormonal therapy used	Test of cognition used	Duration (time at assessment) (years)	Results
			CEE-alone: 520 participants					
KEEPS-Cog	Randomized, double-blinded, placebo-controlled clinical trial	2005–2012	*N* = 727	Mean age: 52.6 y	Oral CEE + micronized progesterone	Modified mini-mental state four cognitive factors	2.85 years	Hormonal therapy did not improve cognition when initiated in healthy recently postmenopausal women compared to placebo
			CEE + micronized progesterone:220 participants		Transdermal Estradiol + micronized progesterone	Profile of Mood States		Results did not indicate adverse or beneficial cognitive effects associated with hormonal therapy
			Transdermal Estradiol + micronized progesterone: 211 participants		Versus placebo			
ELITE	Randomized, double-blinded, placebo-controlled trial	2005–2013	*N* = 643 2 postmenopausal strata: women near to menopause and further from menopause.	41 to 84 y	Oral micronized 17β-estradiol (with vaginal micronized progesterone gel) versus placebo	Standardized composite of neuropsychological test scores assessing verbal episodic memory, executive functions and global cognition	5 years	Class I evidence—estradiol initiated within 6 years of menopause does not affect cognition at 2.5 years differently than estradiol initiated 101 years after menopause
Cache county	Longitudinal, population-based study	1995–2013	*N* = 1889	65 – 105	Formulations varied among provinces	Modified mini-mental state examination (3MS)	8 years	Beneficial effects of HT among former users, with no effect among current users of < 10 years duration Risk of AD was reduced by 41% among women who ever used HT compared to women who never used

Table 2 (continued)

Trial name	Study type	Years	*N* (All)	Age (years)	Hormonal therapy used	Test of cognition used	Duration (time at assessment) (years)	Results
CAIDE Cohort	Population-based study	1998- 2005 and 2008	*N* = 731	65–79	Estradiol-based HT	MMSE immediate word recall test, Stroop test, Category fluency test, Bimanual Purdue Pegboard Test letter digit substitution test	Follow-up over 8 years	Improved global cognition among long-term users Long-term users also performed better in verbal expression test at baseline than short-term users
Finnish study(2017)	Population-based study	20-years follow-up (in 2009) of original cohort (1989)	*N* = 13,100 8195 women (227 cases of AD)	47–56	Estradiol only (in women with hysterectomy) estradiol + norethisterone or levonorgestrel (In women with intact uterus)	Clinically verified AD diagnosis by DSM-V and NINDS-ARDA criteria	20 years follow-up	Reduced AD risk among those with long-term self-reported HT use (No strong evidence for a protective association)

WHIMS Women's Health Initiative Memory Study; *WHISCA* Women's Health Initiative Study of Cognitive Aging; *WHIMS-Y* Women's Health Initiative Memory Study-Younger; *ELITE* Early versus Late Intervention Trial with Estradiol; *KEEPS-Cog* Kronos Early Estrogen Prevention Study-Cognitive; *CAIDE* Cardiovascular Risk factors, Aging and Dementia; *CEE* conjugated equine estrogen, *MPA* Medroxyprogesterone acetate, *HR* Hazard ratio; *CERAD* Consortium to Establish a Registry for Alzheimer's Disease

Author's Contribution SVK and VAP were involved in literature research, manuscript preparation, manuscript editing and revision. Both the authors have read the manuscript and approved the final version.

Compliance with Ethical Standards

Conflict of interest Both the authors declare that they do not have any conflict of interest.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

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