

Review

# Endogenous Hormones and Cognitive Decline in Women: Unveiling the Complex Interplay

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**Abstract:** This narrative review delves into the area of endogenous hormones and their impact on cognitive function, with a focus on women transitioning through perimenopause. While artificial intelligence technologies have revolutionized cognitive research, the inclusion of hormonal biomarkers remains sparse. The review synthesizes findings from diverse studies exploring the relationships between estrogen, progesterone, testosterone, other sex hormones, and cognitive performance. The research question explores the potential for monitoring endogenous hormonal levels during perimenopause to predict cognitive decline and inform preventive strategies. An analysis of relevant studies reveals a complex relationship, with varying impacts on cognitive domains. Thus, high E2 levels correlate positively with verbal memory and retrieval efficiency, contrasting with lower levels associated with enhanced visual memory, and testosterone shows positive links to verbal fluency. The limitations of existing research, including heterogeneous methodologies and a dearth of premenopausal representation, emphasize the necessity for future studies. To achieve this objective, it is important to leverage data from studies implementing standardized methodologies for tracking endogenous hormonal levels while accounting for cycle phases and menopausal transition stages. Additionally, employing standardized assessments for cognitive decline and analyzing extensive datasets derived from real-world sources, such as hospital or outpatient clinic chains, and digital apps, is crucial.



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**Keywords:** estrogens; estradiol; progesterone; androgens; preventive care; cognitive decline; cognitive impairment; dementia; prediction; perimenopause

## 1. Introduction

As humans are living ever longer, concerns about cognitive decline and fears about the future are on the rise. Cognitive decline typically begins around midlife, which is often the peak of individuals' careers and social lives. Women are more affected by cognitive decline and dementia, both as patients and also as carers for people with these conditions [1]. While there are several causes of cognitive decline, this narrative review will focus on the impact of reproductive hormones and whether this impact is modifiable.

Decreased cognitive performance is associated with major increases in estrogen and progesterone hormones, such as those occurring during pregnancy and perimenopause [2,3]. The most substantial decline is observed during the postmenopausal period when the sex hormones reach their lowest levels [4,5]. Longer exposure to endogenous estrogens is positively associated with cognitive status later in life with early menarche and late menopause showing a positive impact on cognitive function in later life. Additionally, the late age of menarche has been identified as a risk factor for dementia [6,7].

Existing hypotheses exist that explain ovarian hormones' impact on cognitive functioning. These include alterations in the cholinergic [8–10] and dopamine [11–14] systems, along with the functioning of their receptors in the brain [15]. The impact of androgens on

cognitive function is less clear, whereas their receptors are widely distributed throughout the human brain and play a role in both reproductive and endocrine functions, but it is unclear whether they directly affect cognition [16].

A previous attempt to systematically analyze reproductive hormone levels in relation to cognitive decline was performed on a postmenopausal group and produced mixed results. Estradiol (E2) showed a positive effect on women's verbal learning and memory and episodic and semantic memory, while the effect of testosterone was ambiguous [17]. There remains a gap in the literature relating to the perimenopausal group.

Prior to exploring and synthesizing the findings from studies on perimenopausal groups, it should be mentioned that utilizing reproductive hormone thresholds for predicting cognitive decline is challenging for several reasons. Hormone levels fluctuate significantly during menstrual cycle phases and during perimenopause [3,18], making it difficult to establish a reliable baseline or reference range for prediction. In addition, individual responses to hormonal fluctuations vary widely [19], making it difficult to establish a direct causal relationship between specific hormone levels and any level of cognitive impairment. Additionally, cognitive decline is influenced by a multitude of factors beyond hormonal changes, including lifestyle [20], genetics [21], and overall health [22].

Artificial intelligence (AI) offers the potential to predict cognitive decline through the analysis of various data types, including imaging, genetic markers, and clinical assessments [23]. AI-driven predictive models can integrate these diverse data sources to identify patterns and markers associated with cognitive decline, aiding in early detection and intervention [23].

When considering the potential role of reproductive hormone levels in these estimations, AI could offer precision by leveraging hormone data to enhance the accuracy and comprehensiveness of predictive models [23,24]. Machine learning can overcome the limitations associated with monitoring due to its ability to process large and complex datasets: detecting patterns and trends in hormone fluctuations in different menstrual cycle phases during perimenopausal transition and associated symptoms that may indicate risk factors for cognitive decline [24,25]. In addition, machine learning models are capable of analyzing individual responses to hormonal fluctuations across diverse populations, allowing for the identification of subtle correlations and predictive markers that may not be evident through traditional analysis methods [24].

*Research question:* Can monitoring endogenous hormonal levels during perimenopause assist in predicting cognitive decline?

## 2. Materials and Methods

A literature search was conducted for the narrative review in three online libraries for original research and review papers: PubMed, Wiley, and Semantic Scholar. The following keywords were used: 'estrogens', 'estradiol', 'estrone', 'estrogen metabolites', 'progesterone', AND 'cognitive decline', OR 'cognitive impairment', OR 'dementia', OR 'Alzheimer's disease'. Only full-text manuscripts written in English and published after 1990 were chosen. After removing duplicate papers, the selected manuscripts' reference lists were manually revised and papers describing endogenous hormone levels, cognitive testing, and the risk of dementia in women were included. Manuscripts were excluded if they only had men in the study population (Table 1).

**Table 1.** PICOS criteria for manuscripts inclusion and exclusion.

| PICOS       | Inclusion                            | Exclusion                                          |
|-------------|--------------------------------------|----------------------------------------------------|
| Population: | Adults 30 and older, including women | Age less than 30, men only in the study population |

**Table 1.** *Cont.*

| PICOS         | Inclusion                                                                                                                                                                                                                                                            | Exclusion                                                                                                      |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Intervention: | Evaluation of endogenous reproductive hormone levels, such as estradiol and its metabolites, estriol, progesterone and its metabolites, testosterone, sex hormone globulin building but not limited to them, and cognitive assessment using neurophysiological tests |                                                                                                                |
| Comparators:  | Participant groups based on the hormone level detected                                                                                                                                                                                                               |                                                                                                                |
| Outcomes:     | Cognitive assessment score, risk of dementia, and Alzheimer’s disease                                                                                                                                                                                                |                                                                                                                |
| Study design: | Prospective cohort studies, retrospective cohort studies, cross-sectional studies, and randomized clinical trials                                                                                                                                                    | Case reports, expert opinions, letters to editors, conference reports, protocols, editorials, and commentaries |
| Other         | English language, publication since 1990                                                                                                                                                                                                                             | Publication before 1990                                                                                        |

**3. Results**

This review encompasses 56 papers: 15 studies that measured endogenous hormone levels and various aspects of cognitive function, and 5 studies that evaluated endogenous hormone levels and the risk of dementia. There are 18 manuscripts related to cognitive performance and 13 related to dementia.

*3.1. Cognitive Impairment*

Issues with attention, thinking, reasoning, and memory are related to cognitive impairment [26]. There are different neuropsychological and cognitive tests developed to assess cognition, which include executive functioning assessment, math skills, verbal recall and fluency, visual memory, and attention. When impairment is significant enough to interfere with social life and occupational functioning, dementia is diagnosed [27].

An individual’s own subjective perception of reduced cognitive function may be the first indication of age-related cognitive decline and dementia. However, correlating subjective perception of one’s own cognition with objective measures has proven complex, and clinical studies have not shown consistent results [3,9]. In a small study on perimenopausal women, it was found that memory complaints were not correlated with verbal memory and verbal learning, but were correlated with working memory and complex attention [28]. Using regression analysis, researchers were able to determine that depressive symptoms, somatic complaints, and working memory performance were the most reliable indicators of future memory complaints [28].

In Table 2, we summarized findings from studies that measured endogenous hormone levels and tested cognitive performance. The study population is pre-, peri- and postmenopausal women.

**Table 2.** Summary of findings from studies that measured endogenous hormone levels and tested cognitive performance in a study population of pre-, peri-, and postmenopausal women.

| Authors           | Year | Population                       | Hormone Tested         | Cognitive Function Measured            | Results                                                                                                                                                                                                                             |
|-------------------|------|----------------------------------|------------------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Yaffe et al. [29] | 1998 | 532 women aged 65 years or older | Estrone and E2 (serum) | Global measures of cognition (3 tests) | Initial cognitive performance did not correlate with E2 and estrone levels, as well as cognitive decline and E2 levels assessed in 5 years. However, women with elevated estrone levels had worse cognitive performance in 2 tests. |

Table 2. Cont.

| Authors                    | Year | Population                                       | Hormone Tested                                                                              | Cognitive Function Measured                                                                                                                                                                               | Results                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------|------|--------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Barrett-Connor et al. [30] | 1999 | 393 women aged 55 to 89                          | Bioavailable testosterone, total and bioavailable E2, and estrone (serum)                   | Global measures of cognition, mental control, verbal memory, mathematical skills, memory score, visuospatial tracking, and attention (12 standard tests of cognitive function)                            | Women with better cognitive performance demonstrated notably elevated mean total testosterone (TT) levels ( $p = 0.009$ ). Conversely, higher estrogen levels did not exhibit a statistically significant correlation with improved cognitive function test outcomes.                                                                                                                                                                 |
| Drake et al. [31]          | 2000 | 39 women (age range: 65 to 90, mean 78.8)        | Total E2, bioavailable E2, estrone, progesterone, testosterone, and androstenedione (serum) | Global measures of cognition, verbal fluency, semantic memory, semantic score, non-verbal skills such as visual memory and non-verbal attention, spatial perception, and executive functioning (17 tests) | Increased E2 concentrations corresponded with enhanced performance on delayed verbal memory and retrieval efficiency tests, while reduced levels were linked to improved immediate and delayed visual memory tests. Elevated testosterone levels demonstrated a positive correlation with verbal fluency. Conversely, cognitive performance exhibited no significant correlation with the levels of progesterone and androstenedione. |
| Yaffe et al. [32]          | 2000 | 425 women, 65+ years old                         | Free E2, bioavailable E2, free testosterone                                                 | Global measures of cognition (1 test)                                                                                                                                                                     | Women exhibiting elevated levels of non-protein-bound and bioavailable E2 in their serum were found to have a reduced likelihood of experiencing cognitive impairment, as opposed to those with lower concentrations. This discovery provides evidence in favor of the theory that increased levels of endogenous E2 play a role in preventing cognitive decline.                                                                     |
| Wolf et al. [33]           | 2002 | 38 women (median age: 68)                        | E2 and testosterone (blood)                                                                 | Stroop, verbal memory, mental rotation, spatial memory, and verbal fluency (5 tests)                                                                                                                      | Elevated E2 and testosterone concentrations demonstrated a connection with improved verbal memory performance. Specifically, E2 was linked to reduced susceptibility to interference.                                                                                                                                                                                                                                                 |
| Yonker et al. [34]         | 2003 | 36 participants, 18 women and 18 men, aged 35–85 | E2, free testosterone, and DHEA-S (blood)                                                   | Episodic memory, verbal memory, face recognition, semantic memory, spatial visualization, and problem-solving                                                                                             | A significant correlation between E2 levels and face recognition performance in women ( $p < 0.02$ ), but not in men, with a similar trend observed for episodic memory composite score, free recall, verbal recognition, and semantic memory.                                                                                                                                                                                        |

Table 2. Cont.

| Authors                | Year | Population                                                                                        | Hormone Tested                                             | Cognitive Function Measured                                                                                               | Results                                                                                                                                                                                                                                                                                                                     |
|------------------------|------|---------------------------------------------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hogervorst et al. [35] | 2004 | 145 participants (66 women) aged 61–91                                                            | TT and total E2 (serum)                                    | Global measures of cognition, verbal memory, and visuospatial memory functions (8 tests)                                  | A correlation was observed between the levels of TE2 in serum and verbal list recall in women, although no such correlation was found with other verbal memory tests. Conversely, serum TT levels were found to have a negative association with verbal recall.                                                             |
| Thrillers et al. [36]  | 2006 | 1276 women and 1107 men aged 35–90                                                                | Free testosterone (FT)                                     | Visuospatial, verbal fluency, semantic, and episodic memory tasks                                                         | In the case of women, FT showed a negative correlation with verbal fluency, semantic memory, and episodic memory, with only verbal fluency demonstrating statistical significance at standard alpha levels. These findings provide evidence for the assertion that FT has gender-specific effects on cognitive functioning. |
| Herlitz et al. [37]    | 2007 | Premenopausal: 45 ( $n = 129$ ), perimenopausal: 50 ( $n = 58$ ), postmenopausal: 55 ( $n = 55$ ) | Estrogen (serum)                                           | Episodic memory tasks, verbal fluency tasks, visuospatial tasks, face recognition tasks, semantic memory tasks (15 tests) | No significant distinction in cognitive activity among premenopausal, perimenopausal, and postmenopausal women in association with serum estrogen levels.                                                                                                                                                                   |
| Yaffe et al. [38]      | 2007 | 792 participants (45% are women) aged 70–79                                                       | Bioavailable E2 and free testosterone (serum)              | Global measures of cognition, verbal memory, and selective memory (3 tests)                                               | Women exhibiting lower serum E2 concentrations at the initial assessment were markedly inclined to manifest significant cognitive deterioration over a period of 2 years, reflecting impairments both in executive cognitive functioning and verbal memory. Men followed a similar trend.                                   |
| Hogervorst et al. [39] | 2010 | 521 participants (51% female) aged 64–94                                                          | Testosterone, sex hormone globulin building (SHBG) (serum) | Global measures of cognition (2 tests)                                                                                    | In older individuals without health issues, higher levels of testosterone were linked to improved MMSE scores at the beginning of the study. Further investigation revealed that in men, lower testosterone levels were identified as a potential risk factor for significant cognitive decline after a 2-year period.      |

Table 2. Cont.

| Authors               | Year | Population                                                                         | Hormone Tested                                                                         | Cognitive Function Measured                                                                            | Results                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------|------|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ryan et al. [40]      | 2011 | 147 women aged 56–64 (recent natural menopause, median age: 53)                    | SHBG, estrone, free E2, and free testosterone (serum)                                  | Executive functioning (visual scanning, working memory, attention, and response alternation) (5 tests) | Regression analysis revealed that out of 20 initial correlations, 2 displayed significance at $p < 0.05$ . Specifically, estrone levels exhibited a positive association with executive functioning performance ( $p = 0.02$ ), while the ratio of free testosterone to free E2 demonstrated a positive relationship with psychomotor speed ( $p = 0.04$ ). Subsequently, no hormone was identified as predictive of the change in cognitive function over a two-year period. |
| Henderson et al. [41] | 2013 | 643 healthy postmenopausal women. Two groups: early: median age 55.4 and late 65.4 | E2, estrone, progesterone, and testosterone (serum)                                    | Verbal episodic memory, executive functioning, and global cognition (17 tests)                         | Hormone concentrations did not show a correlation with verbal memory, executive functions, global cognition, or mood. However, among women in the early-stage group, higher progesterone levels were linked to improved memory and global cognition.                                                                                                                                                                                                                          |
| Koyama et al. [42]    | 2016 | 3044 women, aged 30–55 at the beginning of the study                               | Estrone, estrone sulfate, E2, androstenedione, testosterone, DHEA, and DHEA-S (plasma) | General measures of cognition, working memory, semantic memory, and verbal memory (6 tests)            | No association was observed between hormone levels and neuropsychological test performance. Additionally, the correlation between elevated plasma estrone levels and higher scores for both overall cognition ( $p = 0.1$ ) and verbal memory was found to be insignificant.                                                                                                                                                                                                  |

The evidence relating to sex hormones' effect on cognitive functioning is conflicting. In a study of 532 postmenopausal women 65 years and older, estradiol and estrone were not found to be correlated with cognitive performance at study initiation. A 5-year follow-up found that cognitive scores had significantly declined, but the age-adjusted odds of cognitive decline were not associated with estrone or estradiol [29]. The next study on the same population assessing levels of bioavailable estradiol found that women exhibiting elevated levels of non-protein-bound and bioavailable estradiol in their serum had a reduced likelihood of experiencing cognitive impairment, as opposed to those with lower concentrations [32,38]. This supports the theory that increased levels of endogenous estradiol play a role in preventing cognitive decline [32,38].

In addition, a positive correlation was found between estradiol and good verbal memory and retrieval efficiency [31]. Low estradiol levels were associated with higher scores in immediate and delayed visual memory [31], verbal memory [33], reduced susceptibility to interference [33], verbal list recall [35], and face recognition performance in women ( $p < 0.02$ ) [34], but not in men. A similar trend was observed for episodic memory composite score, free recall, verbal recognition, and semantic memory [34]. Conversely, another study showed that serum estrogen was not significantly associated with cognitive performance across 11 different measures of episodic memory, semantic memory tasks, verbal fluency, and face recognition tasks [37]. This is in line with later findings from a postmenopausal cohort which showed no significant predictive associations related to executive function

performance over a two-year period [40]. In this study, only estrone was positively associated with executive functioning measured using the Tower of London performance score [40].

Higher testosterone levels were positively associated with higher scores on the Mini-Mental State Examination (MMSE) [30,39], verbal fluency [31], verbal memory [33], and Symbol Digit Modalities scores [40]. Conversely, other studies found a negative correlation between total testosterone and verbal recall [35], free testosterone and verbal fluency, semantic memory, and episodic memory, with only verbal fluency demonstrating statistical significance at standard alpha levels [36].

A 2013 study measured cognition, mood, and physiological concentrations of sex hormones in 643 healthy postmenopausal women during early and late postmenopause, with a median age of 55.4 and 65.4, respectively. They found a correlation between verbal memory and sex-hormone-binding globulin (SHBG) [41]. All spectrum of hormones measured included free estradiol, estrone, progesterone, free testosterone, and SHBG. Cognitive measures included verbal episodic memory, executive functions, and global cognition. The results indicated that sex steroid levels were linked to cognitive composites, while SHBG was positively correlated with verbal memory [41]. Furthermore, progesterone was also positively linked to verbal memory and overall cognition [41].

These findings conflict with those of another study examining the relationship between endogenous hormones and cognitive function in older postmenopausal women, which found that plasma levels of estrone, estrone sulfate, estradiol, androstenedione, testosterone, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) showed little to no correlation with cognitive test performance, except for an insignificant ( $p = 0.08$ ) association between higher levels of estrone and higher scores for overall cognition and verbal memory [42]. Although it is the largest study included in this manuscript, it has its own limitations: researchers assessed cognition only on individuals older than 70 years, so the baseline was not established before the potential decline, and the assessment was performed via telephone [42].

Most of the studies were conducted on postmenopausal women. However, it is known that two years before the final menstrual cycle, levels of estrogen and progesterone drop dramatically [5,43]. Therefore, testing is required that is consistent in terms of the phase of the menstrual cycle of menopausal transition to draw specific conclusions about the relationship between endogenous levels and cognitive function [5,43]. Furthermore, studies that demonstrate borderline significance by measuring levels only once during reproductive years are insufficient, as hormone levels fluctuate during the menstrual cycle.

### 3.2. Dementia

According to the World Health Organization (WHO), dementia is a syndrome characterized by cognitive decline beyond that which is expected as a result of biological aging [44]. It is the seventh leading cause of death worldwide and causes significant disability. The most common type of dementia is Alzheimer's disease (AD), while others include vascular, frontotemporal, and dementia with Lewy bodies [44].

AD accounts for 60–70% of dementia cases, according to the WHO [44]. It typically starts after the age of 65 and affects women twice as often as men [45]. The initial common symptoms include memory loss and cognitive decline, which can result in deficiencies in language and visuospatial skills [46].

AD has a 20-year prodromal period during which pathological processes are already taking place, albeit with no visible or detectable signs. During this period, amyloid  $\beta$  is deposited around meningeal and cerebral vessels and gray matter [47]. The initial symptoms typically occur during the perimenopausal period and may be influenced by fluctuating estrogen levels. This was partially supported by studies on perimenopausal women who received hormone replacement therapy (HRT) during this time and experienced a reduced risk of AD [30]. Current AD treatment options primarily focus on alleviating symptoms rather than addressing pathophysiological mechanisms [47,48]. However, the extended

prodromal period underscores the importance of prevention, as neuronal loss is irreversible by the time clinical symptoms occur [48].

The primary hypotheses that describe the role of estrogens in AD development are their impact on neuromodulation, neuroprotection, and cerebrovascular regulation [48]. Studies that were used to confirm these hypotheses investigated the impact of exogenous estrogen and the role of endogenous levels, predominantly in perimenopausal and postmenopausal women [48]. Although epidemiological data supports the protective effects of estrogen, clinical trials that tested HRT showed mixed results [48].

A genomic approach, which is an investigation into whether low estrogen levels during menopause increase vulnerability to AD, showed that progesterone acts as an antagonist to estrogen on a genome-wide scale, which could explain why HRT administration shows different results in clinical studies [49]. According to their findings, estrogen upregulates synapse genes, with the loss of synapses most strongly correlating with the onset of the disease. These findings are consistent with imaging data. Furthermore, they confirmed the central role of mitochondria, as mutations in mitochondrial enzymes have been linked to amyloid  $\beta$  production in early menopause. However, there are several limitations in this research, primarily that macaque gene expression data were used rather than human, and the sample size was small [49].

Currently, the literature suggests variability in the extent to which androgens are responsible for neuroprotection. Their role is less prominent in women but more so in men, where testosterone depletion is a risk factor for developing AD. Some examples of neuroprotective actions of androgens in both women and men include promoting the growth of neurons, regenerating axons and enhancing synaptic function, protecting against neuron cell loss, and preventing plaque accumulation [50].

Table 3 summarizes findings from studies on peri- and postmenopausal women; the endogenous hormone levels were tested and the risk of developing dementia was assessed.

In a case-control study, the relationship between endogenous estrogen levels and AD in postmenopausal women not receiving HRT was investigated [51]. The authors found that patients with AD exhibited significantly lower estradiol levels ( $p = 0.005$ ) compared to controls [51]. The adjusted analysis revealed a four to six times higher likelihood of AD in women with estradiol levels below 20 pg/mL, highlighting a potential link between declining estradiol levels and the development of AD in this population [51].

**Table 3.** Summary of findings from studies on peri- and postmenopausal women, endogenous hormone levels were tested and risk of developing dementia was assessed.

| Authors               | Year | Population                                           | Hormone Tested                                                                 | Results                                                                                                                                                                                                                                                                                                                                               |
|-----------------------|------|------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Manly et al. [51]     | 2000 | 50 women, 93 controls (mean age: 75.4)               | E2 and estrone (serum)                                                         | Individuals diagnosed with AD had decreased E2 ( $p = 0.005$ ) concentrations compared to those in the control group. Similarly, patients also demonstrated lower estrone levels; however, this contrast did not fully meet the significance criteria ( $p = 0.06$ ). Women with AD were four to six times more likely to have levels below 20 pg/mL. |
| Geerlings et al. [52] | 2003 | 508 women (mean age: 72.1), 438 men (mean age: 69.8) | E2 (serum)                                                                     | Patients with elevated total E2 levels demonstrated an elevated risk of developing dementia. Furthermore, the age-adjusted hazard ratio of AD and vascular dementia were associated with heightened total E2 levels.                                                                                                                                  |
| Schupf et al. [53]    | 2006 | 119 (age range: 42–59)                               | Total E2, estrone, follicle-stimulating hormone (FSH), DHEAS, and SHBG (serum) | Women with initially low levels of bioavailable E2 demonstrated a fourfold increased likelihood of developing and an earlier onset of AD, with an average difference of 3 years compared to individuals with high levels of bioavailable E2, following appropriate adjustments.                                                                       |

Table 3. Cont.

| Authors              | Year | Population                                                             | Hormone Tested                         | Results                                                                                                                                                                                                                     |
|----------------------|------|------------------------------------------------------------------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ravaglia et al. [54] | 2007 | 433 women (mean age: 74),<br>376 men (mean age: 73)                    | Total E2 and free testosterone (serum) | There was no observed relationship between free testosterone and dementia in women, nor between E2 or free testosterone in men. Elevated E2, however, stands as an autonomous predictor for dementia and AD in older women. |
| Muller et al. [55]   | 2010 | 731 individuals (men and women),<br>65+ years old, mean age 77.4 years | SHBG (serum)                           | Elevated levels of SHBG were linked to a higher likelihood of AD and dementia in both males and females. These findings remained consistent regardless of vascular risk factors and levels of bioactive hormones.           |

The levels of endogenous estrogen were more extensively studied in postmenopausal women compared to premenopausal groups. In a case-cohort study conducted as part of the Rotterdam Study, which involved 7983 subjects aged 55 years or older, the authors investigated the relationship between endogenous estradiol levels and the risk of dementia in older men and women who were not using HRT [52]. Despite the prevailing hypothesis, the results indicated that heightened levels of total estradiol in women were correlated with an increased risk of dementia, displaying an age-adjusted hazard ratio (HR) of 1.38 per standard deviation increase (95% CI 1.04–1.84). Likewise, the age-adjusted hazard ratios for AD and vascular dementia connected with elevated total estradiol levels were 1.24 (95% CI 0.87–1.76) and 2.19 (95% CI 1.22–3.92), respectively. However, no distinct correlation emerged between estradiol levels and dementia risk in men [52].

In a longitudinal study exploring the correlation between endogenous estrogen concentrations and the risk of AD in postmenopausal women with Down syndrome (a risk factor for dementia), the authors ascertained that individuals who developed AD exhibited lower levels of bioavailable estradiol at the study's commencement [53]. Among women with an average age of 50.7 and diminished bioavailable estradiol levels, the likelihood of developing AD was fourfold (HR = 4.1, 95% CI: 1.2–13.9), with an onset of AD occurring roughly 3 years earlier compared to those with elevated bioavailable estradiol levels. This result remained after accounting for various factors such as age, cognitive disability level, ethnicity, BMI, history of hypothyroidism, or depression. These outcomes lend support to the notion that decreased estrogen levels in postmenopausal states may contribute to the pathological mechanisms underpinning AD [53].

These results were refuted by another study, where baseline serum total estradiol and free testosterone were examined in relation to the four-year risk of dementia in 433 women with a mean age of 74 and 376 men with a mean age of 73 [54]. High serum estradiol was identified as an independent predictor for dementia in women only, and no such association was observed for testosterone in this study [54].

A systematic review of the associations of reproductive factors with dementia in 22 observational studies unveiled a negative correlation between elevated postmenopausal estrogen levels and the likelihood of developing AD [56]. Additionally, their study suggests a negative correlation between an extended reproductive period (>35 years) and the onset of dementia. These results may imply a protective role of reproductive hormones in this process [56].

Given the importance of preventive strategies, further research is necessary to determine whether measuring estrogen and progesterone levels during reproductive years, long before the transition to menopause, could help with defining population groups at high risk.

#### 4. Discussion

As described above, establishing a clear relationship between endogenous hormone levels and cognitive decline is challenging and has been underrepresented in clinical

research, particularly for premenopausal and perimenopausal women. However, it is a promising approach that can offer valuable insights and be particularly beneficial for perimenopausal women by identifying populations that can benefit from early intervention with HRT. This could be carried out with the aim of optimizing cognitive function through personalized hormone therapy strategies tailored to their specific needs and hormonal profile. The current guidelines recommend using HRT for menopausal symptoms for the shortest duration possible due to health risks [15]. Preclinical studies on the effects of short-term estrogen use in midlife, after ovarian function loss, on long-term female cognitive aging revealed a connection between previous estradiol exposure enhancing memory in the long run and increasing estrogen receptor  $\alpha$  (ER $\alpha$ ) levels in the hippocampus—an area crucial for memory [15]. Thus, estrogen exposure in midlife increased the levels of estrogen receptor  $\alpha$  in the hippocampus for up to 8 months after HRT, but had no effect on estrogen receptor  $\beta$  [15]. These results are in line with clinical studies where cognitive functioning correlates with ER $\alpha$  expression [15]. Identifying and addressing factors that contribute to variability in levels of brain  $\alpha$  receptors during aging is believed to enhance the positive effects of estrogen receptors on the aging brain [15].

Research indicates that women with elevated levels of non-protein-bound and bioavailable estradiol are less likely to experience cognitive impairment, supporting the theory that higher endogenous estradiol levels may help prevent cognitive decline; however, this was found by only half of quoted studies, while others showed the opposite result [32]. Among women, positive correlations were found between higher estradiol levels and verbal memory and retrieval efficiency [31], whereas low estradiol levels were associated with better visuospatial memory only [31]. Notably, cognitive changes in perimenopausal women are intricately linked to depressive symptoms and working memory performance [28]. Perimenopausal women with low levels of bioavailable estradiol have a fourfold increased risk of an earlier AD compared to women with high levels of bioavailable estradiol [53]. Studies on postmenopausal women and the risk of dementia showed mixed results [51,52,54].

Testosterone levels showed positive associations with certain cognitive functions such as verbal fluency [31] and memory [33] but had negative correlations with other aspects of memory performance [35,36]. No influence on dementia risk has been detected [54].

#### 4.1. Limitations

Several limitations are associated with the studies described in this review. Firstly, the heterogeneity of cognitive testing methodology is evident, as studies use diverse cognitive assessment tools, thereby making it challenging to compare results across different investigations. The absence of standardized assessments may contribute to discrepancies in findings and hinder the establishment of robust correlations between hormonal levels and specific cognitive domains.

Secondly, the limited representation of younger premenopausal women leaves a notable gap in our understanding of the potential impact of hormonal fluctuations on cognitive health during reproductive and perimenopausal stages. The omission of reproductive cohorts limits the generalizability of findings and overlooks potential early indicators of cognitive changes.

Additionally, variation in methods of hormone level measurement introduces further challenges. Differences in assay techniques, sample types, and the timing of sample collection across studies may contribute to inconsistencies in hormonal data.

The majority of studies are observational and have relatively short follow-up periods. Longitudinal studies tracking hormonal fluctuations and cognitive changes over extended periods are key for capturing the dynamic nature of these relationships.

#### 4.2. Future Directions

Based on the advances in AI that have been achieved in recent years and described in the introduction, it is hard to imagine a future without it. We believe that it can help in

pushing forward research on hormonal impact on cognition and identifying risk groups that could benefit from early intervention with HRT.

Numerous experimental and observational studies have already been conducted to investigate the relationship between hormone levels and cognitive function. However, these studies are heterogeneous in the types of cognition tests administered, the hormone panels analyzed, and the laboratory methods employed for data analysis. To address these disparities and enhance the robustness of research in this field, using a large dataset derived from real-world data obtained from a hospital chain or a network of outpatient clinics could be considered a promising solution. By tapping into such a comprehensive dataset and utilizing machine learning for data analysis, researchers can access a wealth of diverse and standardized information. However, there is a limitation in this approach, as healthy women without any complaints will not be represented in those accessing secondary care. There are now solutions for home hormone monitoring with the help of lateral flow assays and digital tools for data collection, analysis, and storage. These technologies can help bridge the gap and improve the underrepresentation of data from healthy aging individuals.

## 5. Conclusions

In conclusion, the relationship between hormonal changes, cognitive abilities, and the risk of developing dementia in women is complex and still poorly understood. It is important to address the limitations of existing research and explore the potential of artificial intelligence in forecasting cognitive decline to allow early intervention. This can be achieved by utilizing data from studies that employ standardized methods for monitoring endogenous hormonal levels, considering cycle phase and menopausal transition stage, as well as using standardized assessments for cognitive decline. Analyzing a large dataset with real-world data obtained from a hospital or outpatient clinic chain, and digital apps that collect, process, and store this information would help fill the knowledge gap. Gaining an understanding of this connection is essential for optimizing interventions and prevention strategies for cognitive decline in women.

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## Abbreviations

|       |                                |
|-------|--------------------------------|
| AD    | Alzheimer's disease            |
| AI    | artificial intelligence        |
| CI    | confidence interval            |
| DHEA  | dehydroepiandrosterone         |
| DHEAS | dehydroepiandrosterone sulfate |
| E2    | estradiol                      |
| FT    | free testosterone              |
| HR    | hazard ratio                   |
| HRT   | hormone replacement therapy    |
| MMSE  | Mini-Mental Status Examination |
| MRI   | magnetic resonance imaging     |
| SHBG  | sex hormone globulin binding   |

TT total testosterone  
WHO World Health Organization

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