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Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause

Victor W. Henderson, MD, MS
Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, CA

Abstract

Hormonal changes associated with the menopausal transition and postmenopause have the potential to influence processes linked to Alzheimer's disease symptoms and pathogenesis, but effects of menopause on Alzheimer risk can be addressed only indirectly. Nine randomized clinical trials of estrogen-containing hormone therapy in Alzheimer's disease patients were identified by a systematic literature search. Findings suggest that hormone therapy does not improve cognitive symptoms of women with Alzheimer's disease. No clinical trials of hormone therapy address Alzheimer prevention, but one clinical trial provides moderate evidence that continuous, combined estrogen plus progestogen initiated at age 65 years or older increases the risk of dementia. The timing, or critical window, hypothesis suggests that hormone therapy initiated at a younger age in closer temporal proximity to menopause may reduce the risk of Alzheimer's disease. This hypothesis is supported by observational research but is not addressed by clinical trial data. Unrecognized confounding is of concern in interpreting observational results, and research that helps resolve this issue will have important public health implications. Well-designed cohort studies, convergent evidence from appropriate laboratory models, and long-term clinical trials using surrogate biomarkers of brain function and neural pathology could provide relevant answers. Other estrogenic compounds are of theoretical interest with respect to Alzheimer treatment and risk. Effects of selective estrogen receptor modulators such as raloxifene may differ from those of estrogens; potential effects of phytoestrogens are not well studied.

Keywords

Alzheimer's disease; estrogen; hormone therapy; menopause; selective estrogen receptor modulator

Correspondence: Victor W. Henderson, 259 Campus Drive, mc 5405, Stanford University, Stanford, CA 94305-5405, USA, vhenderson@stanford.edu, Tel 1-650-723-5456.

1. Introduction

Estrogens and progesterone are produced cyclically by the ovaries during a woman's reproductive years. The perimenopause is associated with fluctuations in the hormonal milieu. After menopause, the depletion in ovarian follicles culminates in permanent reductions in circulating levels of these sex steroids. In the postmenopause, low concentrations of estrone are derived from androstenedione, which is made in adipose tissue and from other peripheral sources [1]. Estradiol is derived in turn from estrone. Estradiol is the predominant estrogen before menopause, but in the postmenopause circulating concentrations of estrone exceed those of estradiol. Circulating levels of testosterone are largely unchanged after the natural menopause [2], derived from androgen precursors produced by the adrenal glands and stromal cells of the involuted ovary. The hormonal changes associated with the menopausal transition and postmenopause affect the brain and may modulate neural processes concerned with cognition and pathological processes linked to Alzheimer's disease. Effects of menopause on Alzheimer risk, however, cannot be assessed directly; it is obvious that menopause cannot be randomly allocated as an experimental intervention. The preponderance of research pertaining to Alzheimer's disease has therefore focused on potential therapeutic roles of estrogen-containing hormone therapy during the postmenopause. Androgen effects have also been explored, but particularly in men [3].

Estrogen receptors are part of a nuclear receptor superfamily whose main function is the regulation of the expression of genes involved in growth, differentiation, and sexual development. Other members include receptors for androgen, progesterone, glucocorticoids, and mineralocorticoids. Estrogen effects on the brain are mediated in part through two estrogen receptor isoforms, estrogen receptor alpha and estrogen receptor beta. Within the brain, human estrogen receptors are distributed in a topographic pattern unique to each isoform. Estrogen receptor beta is more abundantly expressed in the cerebral cortex and the hippocampus [4, 5]. For widely projecting magnocellular cholinergic neurons in the basal forebrain region, estrogen receptor alpha is the predominant subtype. Estrogen binding to the ligand-binding domain of the receptor induces receptor dimerization, which in turn enables binding to hormone response elements on the genome. Binding of the receptor complex stimulates or inhibits expression of nearby target genes. Putative G-protein-coupled estrogen receptors are associated with the plasma membrane and are likely involved in regulating intracellular signaling cascades and mediating rapid actions that do not involve genomic activation [6, 7].

The brain is affected secondarily by estrogens acting on non-neural tissues. Estrogen effects on the vascular endothelium and on inflammation may be especially germane to disorders such as Alzheimer's disease [8, 9].

2. Alzheimer's disease

Dementia represents major cognitive impairment, which substantially affects social or occupational function and interferes with independence. Dementia implies a decline from some premorbid level of independent functioning due to an underlying pathological

substrate. In most regions of the world, Alzheimer's disease is by far the most common cause of dementia [10]. It is rare before age 60 years, and both incidence and prevalence increase well into late old age.

The cognitive symptoms of Alzheimer's disease begin insidiously and progress gradually over a period of years. A consistent early symptom is a deficit in episodic memory, manifest by impaired recollection of recent events or poor recall of recently encountered information [11]. Other cognitive skills are also affected but typically less so early in the disease course. Women with Alzheimer's disease may have relatively greater difficulty with cognitive skills viewed as female-advantaged, for example, verbal fluency, naming, and verbal episodic memory [12, 13].

The microscopic hallmarks of Alzheimer's disease are neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles are located within cell bodies of affected neurons in the cerebral hemisphere and brainstem. They consist largely of paired helical filaments whose main constituent is tau, a cytoskeletal protein, which has been excessively phosphorylated.

The principal component of plaques is amyloid-beta, or Aβ, a peptide derived from the amyloid precursor protein. When strands of Aβ line up next to one another, they assume a beta-pleated structure, which aggregate to form insoluble amyloid sheets. These accumulate within extracellular spaces between nerve cell bodies. Over time, these diffuse plaques become associated with microglia, reactive astrocytes, and the deposition of complement, together with distended neurites (usually axons), which may contain paired helical filaments. At the center of these neuritic plaques is a dense amyloid core. The amyloid hypothesis suggests that Aβ formation or Aβ deposition is the central initiating event in Alzheimer's disease pathogenesis. However, the relation between amyloid burden and cognitive symptoms by no means clear, and therapeutic approaches to reduce Aβ production or Aβ aggregation have thus far been disappointing. Aggregates of hyperphosphorylated tau may precede amyloid accumulation. The relation between tangles and plaques has yet to be fully elucidated, but Aβ fibrils can promote tangle formation [14].

The onset of Alzheimer symptoms before about age 60 years is associated with autosomal dominant mutations that lead to excessive accumulations of Aβ in the brain. The late onset of Alzheimer's disease is much more common, and the incidence increases with age [15, 16]. Dominantly inherited mutations do not play an important role in this older age group, but a common polymorphism in the gene that encodes apolipoprotein E (the ε4 allele) increases risk, more so for women than men [17, 18]. Estrogen influences apolipoprotein E expression in the brain in a regionally specific manner [19]. Apolipoprotein E is a lipid carrier protein that regulates the transport of lipids during dendritic growth, synaptogenesis, and neuronal repair [20]. It forms complexes with Aβ and may be involved in amyloid trafficking [21, 22]. In Alzheimer's disease the ε4 allele is associated with greater Aβ deposition in the brain [23, 24].

The hippocampus and adjacent structures of the medial temporal lobes are affected early by pathological changes of Alzheimer's disease, as are cholinergic neurons of the basal forebrain. Cholinergic deficits are prominent in Alzheimer's disease [25], and the current

mainstay of treatment is directed toward increasing brain levels of acetylcholine. Association areas of the cerebral cortex are increasingly involved as the illness progresses. Pathological features of Alzheimer's disease may be found decades before clinical manifestations emerge [26]. Increasingly, it is appreciated that Alzheimer pathology usually does not occur in isolation. Often, there is coexisting evidence for vascular changes and other abnormalities. Not surprisingly, multiple pathologies appear to reduce the threshold at which Alzheimer changes are clinically manifest as cognitive impairment [27]. Improving vascular health might, for example, reduce the likelihood of later developing symptoms of Alzheimer's disease.

Estradiol reduces the formation of Aβ [28] and reduces tau hyperphosphorylation [29]. It can enhance neurogenesis within the dentate gyrus of the hippocampus [30]. Further, estradiol facilitates long-term potentiation in the hippocampus [31]. This physiological process is believed to be important in the formation of episodic memories. Estradiol has other attractive properties. It is neuroprotective in laboratory models of oxidative stress, excitatory neurotoxicity, apoptosis, and ischemia [32–34]. Estradiol promotes neurite growth and synapse formation [35, 36] and it enhances glycolytic metabolism in the brain [37].

3. Estrogens and Alzheimer's disease treatment

3.1. Approach

Among women with Alzheimer's disease, current use of hormone therapy is associated with better cognitive skills [38–40]. In one clinical trial of an Alzheimer therapeutic agent, where the randomized intervention was a cholinesterase inhibitor, women using hormone therapy at baseline and assigned to active treatment achieved significantly better cognitive endpoints than non-users who were assigned to active treatment and also better than women in the placebo group [41]. These observations suggest that starting estrogen-containing hormone therapy might improve Alzheimer symptoms. Indeed, small uncontrolled and nonrandomized studies raised early hope that initiating an estrogen or an estrogen plus a progestogen would benefit cognition in this disorder [42–44]. However, a potential causal relation between hormone therapy and cognitive symptoms of Alzheimer's disease is better addressed by clinical trials that examine this association directly.

3.2. Randomized trials

Studies considered for review were identified in the PubMed electronic database by the author using medical search heading terms for estrogens or estrogen replacement therapy or hormone replacement therapy combined with Alzheimer's disease or dementia and publication types randomized controlled trial or clinical trial. There were no restrictions with regard to publication date or language. Titles, abstracts and text were reviewed to identify randomized, double-blind (investigator and participant), placebo-controlled trials of systemic estrogen with or without progestogen, in women with dementia due to Alzheimer's disease, of at least 4 weeks duration, and including an objective cognitive endpoint based on neuropsychological testing. Extracted data included, study design, country, subject number, treatment duration, type of menopause (surgical or natural), participant age, active

intervention, cognitive endpoints, functional endpoints, and global endpoints. A quantitative synthesis was not undertaken. The PubMed search was augmented by a search of the Cochrane central register of controlled trials and by a manual search of article bibliographies from topic reviews and identified trials.

Nine trials met selection criteria (Table 1), involving 489 women of mean age 75 years [45–53]. In all but one trial, the mean age of participants was 72 or older. Sample sizes were small (12 to 120 women per trial), and trials ranged in duration from 8 weeks to 12 months.

Endpoints in most trials indicated no overall cognitive benefit or harm. The three smallest trials — also among the shortest — reported cognitive benefit on a subset of measures [45–47] (Table 1). The intervention in each included transdermal estradiol. These studies were undertaken by the same investigative team, and authors suggested that transdermal estradiol selectively benefits aspects of selective attention and either verbal or visual memory. A study of women with early-onset Alzheimer's disease implied cognitive benefit with oral conjugated estrogens, but methodological details are missing [52]. The largest two trials — one using conjugated equine estrogens and the other using transdermal estradiol — discerned no cognitive, functional, or global effect [48, 49]. Overall findings seem to indicate no substantial cognitive benefit or substantial harm of initiating hormone therapy in women with Alzheimer's disease. This conclusion is supported by another recent review, which included six trials shown in Table 3 and three trials [54–56] not meeting Table 1 selection criteria. Authors of this review concluded that hormone therapy is not indicated for cognitive improvement or maintenance in women with Alzheimer's disease [57].

The hypothesis that starting estrogen-containing hormone therapy improves cognitive symptoms of Alzheimer disease is thus poorly substantiated by clinical trial results. Caveats are that trials have been relatively small, generally lack statistical power to detect moderate treatment effects if present, and provide insufficient evidence to discern whether outcomes are modified by variations in hormone preparation (e.g. oral versus transdermal estrogen formulations).

4. Menopause and dementia risk

For women, menopause is a universal physiological process, occurring at a mean age of about 51 years. In rodent models, loss of ovarian function is unfavorably linked to altered cerebral metabolism and increased oxidative stress, which can culminate in Aβ accumulation [58]. Perimenopause may be a time of increased cognitive vulnerability, during which menopausal hormone therapy might have cognitive benefit [59–61]. It is controversial, however, whether women face greater risk for Alzheimer's disease than men [62, 63].

Several studies have examined links between age at menopause and dementia risk. In cohorts of older women, age at menopause was unrelated to Alzheimer risk [64–67]. Other reports are not fully congruent.

In the US, about one woman in seven undergoes oophorectomy prior to natural menopause, and surgical menopause is the most common cause of early menopause. There are

suggestions that surgically menopausal women could be more vulnerable to dementia. Oophorectomy in Olmsted County, Minnesota, was associated with cognitive impairment or dementia later in life [68]. Danish women who had undergone hysterectomy — with our without oophorectomy — were at elevated risk for early-onset dementia [69]. Other studies have not linked hysterectomy with oophorectomy as a risk factor for poor cognitive function [70, 71]. As a caveat, surgical menopause differs from natural menopause in other ways apart from age at menopause, and cognitive consequences of surgical menopause may differ from those of natural menopause [72].

5. Estrogens and Alzheimer's disease prevention

5.1. Approach

If early menopause does in fact increase dementia risk, one inference is that menopausal hormone therapy might reduce risk. The relation between hormone therapy and dementia risk has been assessed to a limited extent in clinical trials and more extensively in observational research.

5.2. Randomized trials

Search terms given in Section 3 yielded no trials that addressed effects of estrogen-containing hormone therapy on Alzheimer's disease risk.

One trial, the Women's Health Initiative Memory Study (WHIMS), was identified as examining the effects of hormone therapy on all-cause dementia risk [73]. WHIMS participants were recruited from among participants in the Women's Health Initiative trials, who were ages 65 to 79 years and without dementia at baseline. Women without a uterus were assigned to daily conjugated equine estrogens (0.625 mg) or placebo. Women with a uterus received conjugated estrogens plus medroxyprogesterone acetate 2.5 mg/day in a continuous combined formulation or placebo. Sixty-one women with a uterus (mean follow-up of 4 years) and 47 women without a uterus (mean follow-up of 5 years) developed dementia. For women with a uterus, the incidence of dementia was doubled among women in the hormone group (hazard ratio [HR] 2.1, 95% confidence interval 1.2 to 3.5, $p = 0.01$) [73]. For women without a uterus, the incidence of dementia did not differ significantly between women in the two treatment groups (HR 1.5, 0.8 to 2.7, $p = 0.2$), but dementia risk was significantly elevated in a combined analysis of women with and without a uterus [74]. Secondary analyses considered mild cognitive impairment as an endpoint; mild cognitive impairment is conceptualized as an early stage of cognitive decline for pathologies that lead eventually to dementia. The effect on this endpoint was not significant for women with (HR 1.1, 0.7 to 1.6, $p = 0.7$) or without (HR 1.3, 0.95 to 1.9, $p = 0.1$) a uterus. Alzheimer's disease was not reported as a separate trial endpoint because of the small number of Alzheimer cases: 32 in the estrogen plus medroxyprogesterone trial (women without a uterus) and 22 women in the estrogen trial (women with uterus).

Another randomized trial in postmenopausal women assessed similar endpoints, comparing raloxifene to placebo. Raloxifene is a selective estrogen receptor modulator with tissue specific effects that can be estrogenic or antiestrogenic. The Multiple Outcomes of Raloxifene Evaluation trial recruited postmenopausal women with osteoporosis [75]. After

three years, results implied that a higher dose of raloxifene (120 mg/day), but not a standard dose (60 mg/day), reduced the incidence of Alzheimer's disease (HR 0.5, 0.2 to 1.2, p = 0.1). However, the number of events was small. Only 8 women in the raloxifene group and 15 women in the placebo group developed Alzheimer's disease, and the difference may have occurred by chance. The reduction in mild cognitive impairment, however, was significant (HR 0.7, 0.5 to 0.98, p = 0.04), and a combined endpoint for mild cognitive impairment and dementia approached significance (HR 0.7, 0.5 to 1.0, p = 0.05) [75].

5.3 Observational research

Over 20 case–control and cohort studies have examined the relation between menopausal hormone therapy and Alzheimer's disease. In most, the observed association was one of lower Alzheimer risk, and meta-analyses suggest risk reductions of about one-third [76, 77]. However, these findings have been challenged. Among other criticisms, it is difficult to exclude exposure misclassification due to recall bias, since cognitively impaired women may less often remember prior hormone use. Recall bias is less likely in studies where information on hormone use was collected before the onset of dementia [64, 65, 67, 78–83], and here most reports still suggest protective associations (Table 2). Another challenge pertains to unrecognized confounding by the healthy user effect, which suggests that hormone users may be healthier or may differ in other relevant ways from nonusers. It is difficult to exclude the possibility that these other factors account for at least some of the apparent benefit of hormone therapy rather than hormone use per se [84].

5.4. The potential importance of timing

Participants in the WHIMS clinical trials differed from many women in observational studies. Among other differences, trial participants initiated hormone therapy between the ages of 65 and 79 years [84]. Because hormone therapy is most often started during the perimenopause or early postmenopause for vasomotor symptoms, hormone use in observational studies more often than not occurred at a relatively young age. WHIMS findings might be valid for women with characteristics similar to those of trial participants but may not generalize to much younger women who initiated hormone therapy much closer to the time of menopause [84]. This conjecture — often referred to as the timing, or critical window or window of opportunity, hypothesis [85–87] — is supported by follow-up analyses of middle-age participants in Denmark from three randomized trials of hormone therapy. In these osteoporosis prevention studies, women in active treatment groups received hormones for two or three years. After a mean interval of 11 years, women originally randomized to hormone therapy were significantly less likely to have cognitive impairment than women in the placebo groups [88]. The mean age at follow-up was 65 years. This intriguing finding implies that short-term hormone use during midlife may have a cognitive benefit a decade later.

Three observational studies offer evidence for an early temporal window during which hormone therapy might reduce risk of Alzheimer's disease or dementia (Table 3). First, in the large Multi-Institutional Research on Alzheimer Genetic Epidemiology (MIRAGE) case-control study, the effect of hormone therapy was significantly modified by age [89]. Reductions in Alzheimer risk were evident only among younger postmenopausal women,

where hormone use necessarily occurred at a younger age. Second, in the Kaiser Permanente integrated health care system, self-reported hormone use at midlife (mean age 49 years), coupled with no record of hormone therapy prescriptions in a pharmacy database during a 5-year period nearly three decades later, was associated with a significant reduction in risk of all-cause dementia [90]. Late life hormone prescriptions without midlife use was associated with significantly increased risk. Third, in the Cache County cohort study of healthy postmenopausal women age 65 years and older, self-reported initiation of hormone therapy within five years of menopause was linked to a significant reduction in incident Alzheimer's disease, whereas later initiation did not alter risk [83].

6. Phytoestrogens

Dietary estrogens derived from plants (phytoestrogens) occur in high concentrations in certain foods. The most often studied phytoestrogens are isoflavones found in soy food products and sometimes consumed as soy-derived dietary supplements. Like other phytoestrogens, isoflavones have selective affinity for estrogen receptor beta [91]. These micronutrients may affect human cognition [92, 93], although the magnitude, and even the direction, of the effect remains controversial. There are no clinical trials of phytoestrogens for the treatment or prevention of Alzheimer's disease. (Articles screened for this search were identified by the author using search terms of phytoestrogens or isoflavones combined, as described in Section 3.2, with Alzheimer's disease or dementia and publication types randomized controlled trial or clinical trial.)

7. Conclusions

Estrogens affect brain tissues and brain processes in ways that might improve Alzheimer symptoms or might reduce the risk of developing Alzheimer's disease. Human research described above, however, thus far fails to demonstrate convincing roles for these compounds in Alzheimer treatment or prevention, but these studies also delineate areas of uncertainty and suggest research opportunities.

For older women with dementia due to Alzheimer's disease, inferences from clinical trial results are constrained by small sample sizes and short treatment durations; findings thus far suggest no important cognitive benefit of estrogen initiation in this setting (Table 1). Laboratory investigations and some human evidence indicate that relevant hormone effects might vary by dose, type of estrogen, type of progestogen, mode of administration, and cyclicity [94–97]. The continuous–combined hormone preparation used in WHIMS for women with a uterus differed from preparations used by women in many of the observational studies. In aged, ovariectomized non-human primates, cyclic estradiol enhances synaptic plasticity but not continuous treatment or combined treatment with progesterone [96]. It is possible, but still largely conjectural, that some approaches (for example, low dose transdermal estradiol with cyclic micronized progesterone, rather than a continuous oral estrogen–progestin preparation) might lead to better cognitive outcomes than thus far achieved. It is also possible that related compounds such as selective estrogen receptor modulators could be effective where estrogens are not [75].

Regarding prevention, clinical trial data from the WHIMS trials provide moderate evidence that conjugated equine estrogens combined with medroxyprogesterone acetate increase dementia risk; unopposed estrogens may elevate risk as well but the level of evidence is low. These results pertain to hormone initiation at age 65 years or older, the age group of women studied in the WHIMS trials. Treatment effects in the raloxifene prevention trial trended in the opposite direction. The number of events in both trials was modest, and either result could be due to chance, but the net effect of estrogen–progestogen initiation among older women may be to promote processes leading to dementia. Raloxifene, which has the potential to act as an estrogen receptor antagonist as well as an agonist, may have the opposite net effect on dementia risk [75], but data are too limited for valid inferences.

For younger postmenopausal women, issues are more complicated. WHIMS clinical trial results may or may not generalize to midlife women, who were by design ineligible for WHIMS protocols, and may or may not generalize to Alzheimer's disease, which was not reported as a separate study endpoint. Observational studies (Tables 2 and 3), indirectly bolstered by follow-up results of small Danish osteoporosis trials [88], imply that midlife hormone therapy could indeed reduce Alzheimer risk, although recall bias and unrecognized confounding by the healthy user effect are formidable concerns in observational research on hormone therapy.

Most drug effects are not substantially modified by age, and one must be cautious in concluding that estrogen effects might vary according to age or temporal proximity to menopause. Hormone effects on the vascular endothelium, which appear to be modified by endothelial health, offer one plausible model for this scenario [8, 98, 99]. Estrogens and progestogens have multifaceted, competing effects on pathways involved in thrombosis and thrombolysis, fibrinolysis, inflammation, atherosclerotic plaque formation, and atherosclerotic plaque rupture. The net vascular effect might thus be protective or harmful and might differ in different clinical settings [100, 101]. Estradiol protects the healthy vasculature endothelium but effects are deleterious in the presence of atherosclerotic lesions [8]. While it is clear that hormone therapy increases coronary heart disease in the late postmenopause, there may be no effect on coronary risk for women initiating treatment close to the time of menopause [102] or the effect may be protective [103].

These findings are directly relevant to Alzheimer's disease. The emergence of dementia symptoms in the presence of Alzheimer tangles and plaques depends in part on the health of the cerebral vasculature and on concomitant brain pathologies [27]. An age-related reduction in Alzheimer risk by estrogens could stem from age-related differences in vascular risk. Other competing mechanisms would likely play a role as well. Anticipated results from the Early versus Late Intervention Trial with Estradiol (ELITE; ClinicalTrials.gov identifier NCT00114517), a randomized controlled trial of oral estradiol compared to placebo — conducted in two strata of postmenopausal women: within six years of menopause or at least 10 years after menopause — will be informative.

It is perhaps not surprising that clinical consequences are difficult to predict from laboratory models. Still, a firmer understanding of basic mechanisms is needed before large scale clinical trials might be devised to exploit the inference that specific processes modulated by

estrogens and selective estrogen receptor modulators have the potential to reduce Alzheimer's disease risk. Given the need for large sample sizes and lengthy follow-up, and given recognized health risks of hormone therapy, it is difficult to envision primary prevention trials for Alzheimer's disease that begin in midlife. Well-designed cohort studies, convergent findings from appropriate laboratory models, and long-term clinical trials using surrogate biomarkers of brain function and neural pathology could help provide less ambiguous answers to vexing questions that remain [104].

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Highlights

- Hormone therapy has no substantial role in Alzheimer's disease treatment.
- Estrogen–progestogen therapy begun after about age 65 years probably increases dementia risk.
- For hormone therapy used near the time of menopause, effects on risk could differ.
- Selective estrogen receptor modulator risks may differ from hormone therapy risks.

Table 1

Randomized clinical trials of estrogen therapy in women with Alzheimer's disease

Authors, country, year[a]	Country	Number	Duration, weeks	Type of menopause[b]	Mean age, years	Active intervention	Endpoints[c]		
							Cognition	Function	Global
Asthana et al., 1999 [45]	US	12	8	Natural	79	TD E2	+/0[d]	NE	NE
Henderson et al., 2000 [50]	US	40	16	Both	78	CEE	0	0	0
Mulnard et al., 2000 [48]	US	120	52	Surgical	75	CEE	0	0	0/−[d]
Wang et. al., 2000 [51]	Taiwan	50	12	Natural	72	CEE	0	NE	0
Asthana et al., 2001 [46]	US	20	8	Both	80	TD E2	+/0[d]	0	0
Rigaud et al., 2003 [49][e]	France	117	26	Both	76	TD E2	0	0	0
Zhang et al., 2006 [52][f]	China	41	16	NE	55	CEE	+	+	0
Valen-Senstad et al., 2010 [53]	Norway	55	52	NE	81	E2	0	0/−[d]	0
Wharton et al., 2011 [47]	US	34	12	Both	77	TD E2	+/0[d]	NE	NE

Randomized placebo-controlled trials in postmenopausal women with dementia due to Alzheimer's disease, with a treatment duration of at least 4 weeks and reported objective cognitive endpoints. See text for details. All trials used a parallel groups design.

[a] Three trials from a recent review [57] are not included in Table 1 because participants were not characterized as having dementia or Alzheimer's disease [54], trial duration was less than 4 weeks [55], or reported analyses did not include cognitive endpoints [56].

[b] Surgical menopause includes women who underwent hysterectomy, with or without oophorectomy.

[c] Functional endpoints refer to activities of daily living; global endpoints refer to formal ratings of overall, or global, change.

[d] Asthana et al. [45] reported significant between-group differences on 5 of 14 cognitive endpoints (pertaining to attention and verbal memory). In the study of Mulnard et al. [48], the primary global endpoint did not differ between treatment groups; a secondary global outcome suggested worsening among women in the estrogen group. Asthana et al. [46] reported significant between-group differences on 4 of approximately 15 cognitive endpoints (pertaining to attention, verbal memory, and visual memory). In subgroup analyses, women without the apolipoprotein E4 allele in the study of Valen-Senstad et al. [53] performed better on 1 of 12 cognitive tasks (pertaining to verbal memory). Wharton et al. [47] reported significant between-group differences on 3 of 18 cognitive endpoints (pertaining to naming and visual memory).

[e] Both groups also received, a cholinesterase inhibitor, viewed as standard therapy for Alzheimer patients.

[f] Comparisons performed within — not between — groups implied estrogen benefit on a cognitive and functional endpoints [52]. The trial was reported as double-blind, but estrogen was given once daily and placebo (oral vitamin B12) was given three times daily.

+ between-group difference(s) favored estrogen; −, between-group difference(s) favored placebo; 0, no significant between-group difference(s).

CEE = oral conjugated equine estrogens, 0.625 mg/d [48] or 1.25 mg/d [48, 50–52, 55]; E2 = oral estradiol 1 mg/d with 0.5 mg norethisterone [53]; NE = not examined or not reported by study authors; TD E2 = transdermal estradiol, 0.05 mg/d [45], 0.10 mg/d [46], 0.05 or 0.10 mg/d with or without medroxyprogesterone acetate 2.5 mg/d [47], or 0.05 mg/d with micronized progesterone 100 mg/d [49]; US = United States.

Table 2

Associations between hormone therapy and Alzheimer's disease risk, where hormone exposure was ascertained prior to dementia onset

Study, authors, year	Number of Alzheimer's disease cases	Number of non-demented controls	Source of exposure information	Relative risk	95% confidence interval
Group Health, Brenner et al., 1994 [78][a]	107	120	Pharmacy records[a]	1.1	0.6–1.8
Leisure World, Paganini-Hill & Henderson, 1996 [64][b]	248	1193	Self-report	0.65	0.5–0.9
North Manhatten, Tang et al., 1996 [65]	167	957	Self-report	0.5	0.25–0.9
Baltimore Longitudinal Study of Aging, Kawas et al., 1997 [80]	34	438	Self-report	0.5	0.2–1.0
Rochester, MN, Waring et al., 1999 [79][c]	222	222	Medical records	0.4	0.2–0.96
Rochester, MN, Roberts et al., 2006 [67][c]	245	245	Medical records	1.1	0.6–1.9
United Kingdom, Seshadri et al., 2001 [81][a]	59	221	Pharmacy records[a]	1.2	0.6–2.4
Women's Health Initiative Memory Study, Henderson, Espeland et al., 2007 [82][d]	53	7047	Self-report	0.4	0.2–0.85
Cache County, Shao et al., 2012 [83][b,e]	176	1768	Self-report	0.8	0.6–1.1

[a] Pharmacy records for studies of Brenner et al. [78] and Seshadri et al. [81] were available from approximately the preceding 10 years. Earlier hormone use would not have been captured.

[b] Prior reports from Leisure World [105] and Cache County [106] include cases in these reports.

[c] Case-control studies from the same population for cases identified 1980–1984 [79] and 1985–1989 [67]. The latter analysis found no overall association between hormone therapy and Alzheimer risk, but there was a significant interaction with smoking such that hormone use plus smoking (ever) was associated with elevated risk (odds ratio 4.6, 95% confidence interval 1.3 to 15.5) and hormone use without smoking was associated with diminished risk (0.7, 0.4 to 1.3) [67].

[d] Meeting report. Note that hormone therapy increased all-cause dementia risk during the Women's Health Initiative Memory Study clinical trial irrespective of prior hormone exposures [74].

[e] Hazard ratio for women initiating hormone therapy within 5 years of menopause was reduced; see Table 3.

Table 3

Observational studies with information on timing of menopausal hormone therapy in relation to risk of Alzheimer's disease or dementia

Study, authors, year	Case type	Number of cases	Number of non-demented controls	Basis of timing	Interaction probability	Relative risk	95% confidence interval
MIRAGE, Henderson et al., 2005 [89]	Alzheimer's disease	426	525	Age	0.03[a]		
Youngest age tertile (50 to 63 years)						0.35	0.19 to 0.66
Middle age tertile (64 to 71 years)						0.86	0.50 to 1.5
Oldest age tertile (72 to 99 years)						0.97	0.57 to 1.6
Kaiser Permanente, Whitmer et al., 2011 [90]	All-cause dementia	1525	2454	Reported or observed hormone use[b]	0.03[c]		
Only midlife use						0.74	0.58 to 0.94
Both midlife and late life use						1.02	0.78 to 1.34
Only late life use						1.48	1.10 to 1.98
Cache County, Shao et al., 2012 [83]	Alzheimer's disease	176	1768	Reported hormone initiation	NE		
Initiation <5 years of menopause						0.70	0.49 to 0.99
Initiation ≥5 years after menopause						1.03	0.69 to 1.55

[a] Age analyzed as a continuous variable

[b] Use based on self-report at midlife (mean age 49 years) and late life review of pharmacy prescriptions during a 5 year window (mean age 76 years).

[c] Interaction probability based on comparisons between only midlife and only late life strata.

MIRAGE = Multi-Institutional Research on Alzheimer Genetic Epidemiology; NE = not examined or not reported by study authors