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# Precision hormone therapy: identification of positive responders

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## Abstract

Since the introduction of menopausal hormone therapy (MHT) in the 1940s, randomized clinical trials and observational studies have been performed to determine the benefits and risks of MHT. However, MHT therapeutic impact remains under debate as multiple factors including genetic biomarkers and medical history contribute to inter-individual variations in neurodegenerative diseases. Herein, we review the characteristics of women who participated in clinical studies and methodological approaches for study analyses to assess the critical variables influencing an association between MHT and risk of neurodegenerative diseases. Outcomes of the review indicated that: (1) observational studies assessed outcomes of MHT in symptomatic women whereas MHT clinical trials were conducted in asymptomatic postmenopausal women not treated for menopausal symptoms, (2) in asymptomatic postmenopausal women, late MHT intervention was of no benefit, (3) different MHT treatments and regimens between observational studies and clinical trials may impact outcomes, and (4) observational studies may provide greater predictive validity for long-term neurological health outcomes as MHT was introduced in symptomatic women and administered over a long period of time. Going forward, achieving precision hormone therapy will require a priori identification of symptomatic women appropriate for MHT and the type and dose of MHT appropriate for their genetic profile and health risks.

### Keywords

Precision medicine; menopausal hormone therapy; Alzheimer's disease; cognitive decline; menopause; estrogen; progesterone

## Introduction

Women are at a higher risk of developing Alzheimer's disease (AD) than men[1] and this risk can be associated with decreased estrogen levels after menopause[2]. Multiple studies provide evidence that menopausal hormone therapy (MHT) may reduce risks of cognitive/memory decline and AD after the onset of menopause[3–10]. The National Health and Nutrition Examination Survey indicated that 10.9 million US women aged 45–74 years used a form of

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MHT in 1999–2000[11]. However, the number of MHT users decreased to 6 million in 2003–2004[11] after the release of reports from the Women's Health Initiative (WHI) studies[12,13].

The initial WHI reports[12,13] served as a basis for substantial analyses of multiple types of MHT that included randomized clinical trials and their ancillary studies, observational studies, and meta-analyses of the benefits and risks of MHT[14–26]. Ancillary studies were designed to investigate the effect of MHT on cognition, memory, and/or dementia[16,18,27,28] while observational studies addressed the impact of MHT on AD risk[3,9] (Table 1). Although outcomes from clinical trials failed to support a protective effect of estrogen therapy against cognitive and memory decline[20,27,29], some observational studies including the Cache County Study and the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) study reported a potential benefit of MHT to prevent AD, depending on the timing and duration of therapy[3,9]. Variations in study outcomes could be associated with different characteristics of study participants and design. Thus far, randomized clinical trials (intervention) have consisted of postmenopausal women without severe menopausal symptoms and the study participants were treated with a single dose, duration, and type of estrogen and/or progestin[15,17,30]. In contrast, observational studies utilized data obtained from women who were treated with more personalized MHT based on clinician advice at the time of the perimenopause to menopause transition[3,4,6,7]. Thus, the health and medical conditions of study participants could be reflected in treatment outcomes.

Multiple factors can influence the association between MHT and risks of cognitive decline, dementia, and AD, which include the patient's baseline health condition (e.g. body mass index, comorbidities, and family history of neurodegenerative diseases), age, race, genetic factors (e.g. apolipoprotein E [APOE]), and life condition (e.g. smoking, alcohol, and exercise)[31]. It is critical to adjust for these factors when interpreting results, particularly from observational studies since non-adjustment of differences in variables between non-users and MHT users may lead to heterogeneity of study outcomes regardless of a treatment effect by different doses, durations, and types of estrogen and/or progestin[32].

The disparity of outcomes between randomized clinical trials and observational studies suggests a substantial difference in study populations and design that could serve as a foundation on which to explore a precision medicine (personalized) approach to MHT to provide optimal and safe therapy to women. Because MHT is broadly used worldwide, has extensive safety and efficacy data, and can be investigated through public health data and electronic medical records, MHT offers a unique opportunity to capitalize on the current personalized approach to advance precision MHT.

Herein, we consider the characteristics of women who participated in clinical studies and the varied study design to identify critical variables relevant to an association between MHT and risks of cognitive decline, dementia, and AD.

## Timing of menopausal hormone therapy

Analysis of discovery mechanistic and clinical science led to the proposition of a healthy cell bias of estrogen action which posits that women will benefit from estrogen therapy

when treated at the time of perimenopause to menopause transition, before neurological health is compromised[33].

Varied outcomes from clinical trials and observational studies stress the importance of estrogen therapy within the 'critical window' of the perimenopause to menopause transition. To date, no clinical trials have included perimenopausal symptomatic women to determine the benefits of MHT on preventing or delaying age-associated neurodegeneration. Critically, clinical trials included asymptomatic postmenopausal women who would have not generally required MHT (Table 2). Women experiencing severe menopausal symptoms who could not tolerate the wash-out period or randomization to placebo were excluded from the WHI and the Kronos Early Estrogen Prevention Study (KEEPS) trials[17,30]. In the Early vs. Late Intervention Trial with Estradiol (ELITE), women receiving MHT within 1 month of screening were also excluded[15]. Thus, participants in the clinical trials did not represent women at perimenopause to menopause who require MHT to tolerate menopausal symptoms.

The WHI Memory Study (WHIMS) reported that conjugated equine estrogen (CEE) treatment was associated with greater brain atrophy in women aged 65 years and older[34]. In particular, the CEE-associated reductions in hippocampal volume were most apparent in women with lower cognitive function prior to initiating MHT[34], which is consistent with the healthy cell bias hypothesis, a potential benefit of estrogen therapy initiated when neurological health is not compromised. However, findings from the WHIMS of Younger Women (WHIMS-Y) indicated that there was neither a beneficial nor a harmful effect of MHT on long-term cognitive function in postmenopausal women when receiving CEE at earlier ages of 50–55 years[29].

In contrast to randomized clinical trials, several observational studies imply a positive association between MHT and reduced risk of AD and cognitive/memory decline[3,4,7,9,10]. These studies used data collected from women who initiated MHT during the menopausal transition to treat menopausal symptoms that occurred prior to study enrollment. Data from the Cache County Study indicated that the AD risk was reduced in former MHT users, but not in current users unless the therapy had been used for more than 10 years[3]. A study by Tang *et al.* reported a significantly reduced risk of AD in estrogen users compared with non-users and the risk reduction was greater if the therapy was continued for longer than 1 year[4]. Consistently, the MIRAGE study indicated that a protective effect of MHT on reduced AD risk was significant in younger women, implying the beneficial effect of MHT initiated in the early phase of menopause[9].

On the other hand, there are observational studies indicating no effect or an adverse effect of MHT on cognitive decline or AD risk[35–37]. A case–control study reported an increased risk of AD for those using systemic MHT, even with long-term use (10 years and more), which differed from the results in observational studies already described[35]. Further, the Nurses' Health Study reported that neither current nor long-term MHT users showed better cognitive performance or verbal memory than never users, although current MHT users showed better verbal fluency than never users[36]. However, as discussed in the report, all study participants were relatively healthy and educated women, which might be a potential reason for no

difference in cognitive function among never and MHT users[36]. In addition, a prospective cohort study presented no significant association between MHT and cognitive functions[37]. In particular, an increased risk of cognitive decline was high in women who initiated MHT at older ages compared with never users[37], which is consistent with no benefit of MHT if initiated after passing the 'critical window'. In this study, there was no significant change in results after adjustment for a wide range of potential confounding factors associated with cognitive decline and hormone use[37]. However, the follow-up time for testing cognitive functions was short (2 years), potentially contributing to the lack of significant association between MHT and cognitive function[37].

Collectively, the results from randomized clinical trials and observational studies indicate that MHT initiated after menopause or if neurological health is impaired exerts no benefit on cognitive function or reduction in AD risk.

## Genetic biomarkers

The APOE genotype, specifically APOE4, is widely recognized as a critical biomarker of higher risk of AD in women[38–42]. The role of APOE in cholesterol transport is key to maintenance of myelin and neuronal membranes in the central and peripheral nervous systems[38,43]. The impaired cholesterol transport in APOE4 carriers is associated with increased blood cholesterol, low-density lipoprotein, triglyceride levels, and risk of heart disease[42,44]. An observational multimodality brain imaging analysis indicated that amyloid-β (Aβ) deposition was exacerbated in APOE4-positive postmenopausal women compared to premenopausal or perimenopausal women and men[45]. Further, APOE4 carriers have lower brain glucose uptake and more rapid decline in brain glucose metabolism than non-carriers[46,47].

However, the impact of APOE4 status on an association between MHT and cognitive function remains uncertain in clinical studies[21,37,48–50]. On average, approximately 30% of participants in the Cache County Study and 66% of AD patients among MIRAGE participants were identified with APOE4 (Table 2)[7,9]. However, the association between APOE4 status and MHT on risk of AD was not determined. In contrast to the Cache County Study and the MIRAGE study, an observational study indicated that APOE4-positive women had a greater hazard ratio of cognitive impairment compared with APOE4-negative women[48]. Further, current estrogen use reduced the risk of cognitive impairment in APOE4-negative women, but not in APOE4-positive women, compared with never users[48]. This study specifically excluded women who received progestins (both alone and combination with estrogens), which might result in different outcomes, as women with an intact uterus in the KEEPS, ELITE, Cache County Study, and MIRAGE study were treated with progesterone combined with an estrogen. It is known that estrogen modulates APOE expression[51,52], but further studies are required to determine whether an interaction between combination therapy and APOE genotype exists.

The importance of the APOE4 genotype and metabolic health was investigated using nine metabolic biomarkers derived from ELITE baseline data (glucose, the homeostatic model assessment score, ketones, high-density and low-density lipoprotein cholesterol,

triglycerides, HbA1c, and systolic and diastolic blood pressures)[53]. Outcomes of these analyses indicated that women with a poor metabolic phenotype had significantly lower performance on executive functions, global weighted cognition, and verbal memory compared with healthy metabolic phenotypes among APOE4 carriers[53]. These data indicated the importance of metabolic health on the impact of the APOE4 genotype and the risk of cognitive/memory decline and AD pathogenesis.

In addition to the APOE genotype, polymorphism in genes relevant to estrogen synthesis and metabolism may increase the AD risk[54] and may contribute to an unpredictable impact of MHT. An illustrative case is women with Down syndrome as they are at higher risk for early-onset AD[55]. A prospective community-based cohort study including 235 women with Down syndrome aged 31–67 years showed that variants in CYP17 and CYP19, two key genes relevant to peripheral synthesis of estrogens, increased the risk of AD[56].

## Type and duration of menopausal hormone therapy

### Type of hormone therapy

The effect of MHT can vary by treatment regimens including the dose, duration, and type of estrogens/progestins[57]. To date, there are 39 MHT products approved by regulatory agencies in the USA (US Food and Drug Administration), Canada (Health Products and Food Branch of Health Canada), and Europe (European Medicines Agency) composed of 13 different estrogen or progestogen types of steroids, 12 different dosage forms, and four different routes of administration[31]. Randomized clinical trials were intervention studies in which all participants were treated with the same dose (0.625, 0.45, and 1 mg/day for the WHI, KEEPS, and ELITE), duration, and type of estrogen (CEE for the WHI and KEEPS, and 17β-estradiol for the ELITE) regardless of the individual's age, status of menopausal symptoms, and health conditions[15,17,30]. In contrast, women in observational studies were prescribed MHT based on physician's advice to treat menopausal symptoms. Thus, the dose, type, and duration of MHT were likely to be more personalized and provided at the time of the menopause transition. Treatment during this 'critical window' is hypothesized to result in increased benefits against AD pathogenesis.

Further, women with an intact uterus in these clinical trials were prescribed combination therapy of an estrogen and progestin. There are two different treatment regimens for progestin administration, cyclic and continuous. In the WHI trials, women with an intact uterus were treated with continuous medroxyprogesterone acetate, but the KEEPS and ELITE used cyclic progesterone for 12 days/month (Table 2)[15,30,58]. The benefit of cyclic over continuous progesterone has been demonstrated in preclinical studies[59]. 17β-Estradiol combined with cyclic progesterone is nearly identical to natural female hormone secretion patterns and induced gene expression profiles consistent with the ovary-intact rat brain[59].

In the WHIMS, CEE combined with continuous medroxyprogesterone acetate increased the risk of probable dementia and did not prevent mild cognitive impairment in postmenopausal women[27]. The KEEPS – cognitive trial reported no effect of 17β-estradiol combined with cyclic progesterone on cognitive or mood status[20]. Because multiple variables influenced study outcomes and the baseline characteristics of study participants varied among the

randomized clinical trials, it was difficult to evaluate a sole effect of progesterone treatment regimen on cognitive status.

The KEEPS was the first randomized clinical trial addressing a comparison between two different routes of administration, oral and transdermal, for estrogen therapy[58]. In APOE ε4 carriers, transdermal 17β-estradiol was associated with reduced Aβ plaque load compared with either placebo or oral CEE-treated women[60]. A mechanistic pathway underlying estrogenic reduction in Aβ load in brain is via estrogen-induced insulin degrading enzyme, a protease involved in Aβ degradation[61]. The MHT-associated reduction in Aβ burden was most evident in APOE ε4 carriers, not in non-carriers[60]. Reduced Aβ deposition was not associated with cognitive function[60]. Further, the age of women who received transdermal estradiol was 52–65 years when participating in the positron emission tomography scan[60]. The protective effect of reduced Aβ deposition on cognitive function may become apparent in older age[60]. Other analyses of the KEEPS data also indicated no difference in cognitive function among women who received placebo and MHT[20,62]. Follow-up time was limited to 4 years and the sample size was small[60,62], which might be other potential reasons for no difference in cognitive function.

## Duration of hormone therapy

An association between duration of MHT and risks of cognitive/memory decline and AD has been widely discussed, although its impact on the risks is still under debate[4,5,10,21,35,63,64]. Optimal duration of MHT should be achieved by personalizing a prescription because individuals have different previous contraceptive or MHT records and medical histories including hysterectomy/oophorectomy, diabetes, hypertension, and cardiovascular disease that may influence the effect of estrogen-based therapy[65–69].

Compared with randomized clinical trials, observational studies may be a more relevant assessment of the effect of MHT duration, because analyses were mostly performed using records of women who received MHT for menopausal symptoms and continued for varying duration. Findings from the Cache County Study indicated that women who initiated MHT within 5 years after menopause had reduced AD risk and the reduction was greater if therapy was sustained for 10 years or more[7]. Interestingly, the sex-specific increase in AD risk in women was attenuated with MHT for more than 10 years[3].

In contrast, study outcomes in randomized clinical trials were derived based on the duration of intervention treatment after randomization without taking previous MHT records into the analysis. Durations of treatment were 4 years in the KEEPS and 2–5 years with an additional 2.5 years in the ELITE[15,17,70], which might not be sufficient to determine the impact of MHT on cognitive function. Moreover, some proportion of participants had previous MHT records prior to their enrollment and wash-out period (21.2% in the KEEPS, and 50.9% and 86.3% in the early and late ELITE groups, respectively; Table 2)[16,17], which were not accounted for in the study analysis. As presented in randomized clinical trials, there might be no benefits of MHT for intervention treatment. However, the lack of beneficial or adverse effects of MHT on cognitive function observed in the randomized clinical trials might be related to short follow-up time to examine a difference in cognitive function and a potential risk of estrogen exposure at older age.

## Younger women with a history of hysterectomy or oophorectomy

Unlike the WHI and ELITE, the KEEPS excluded women who underwent hysterectomy (Table 2)[70]. Thus, the KEEPS could not evaluate MHT effects on cognitive function for women with hysterectomy. In the WHI and ELITE, women who had undergone hysterectomy received estrogen-alone therapy[15,30]. WHI participants were treated with oral CEE at 0.625 mg/day, but the ELITE used 17β-estradiol at 1 mg/ day[15,30]. Based on previous clinical studies, 17β-estradiol compared better than CEE on verbal memory performance[71,72]. Results from the WHI and WHIMS indicated no significant impact of CEE on cognitive function in women with prior hysterectomy[73]. These reports indicated that different type of estrogens may distinctly impact cognitive function or risks of AD and dementia in women who receive estrogen-alone therapy. In addition, optimization of estrogen therapy may be more critical for women who need the therapy due to surgical menopause at earlier age, prior to the onset of natural menopause.

Previous cohort studies have reported that oophorectomy before the onset of natural menopause increased risks of age-associated neurodegeneration including cognitive impairment, dementia, and AD[66,74,75], whereas MHT initiated within a 5-year perimenopausal window and continued for at least 10 years was associated with less global cognitive decline in those who underwent surgical menopause[74]. A case–control study indicated that oophorectomy with or without hysterectomy after the onset of natural menopause was not associated with AD risk in older women[76]. These findings imply that risks of cognitive impairment, dementia, and AD increase when the surgery occurs before the onset of menopause; however, the risks may be reduced when estrogen therapy is initiated within the ‘critical window’ and continued for an extended period of time.

## Women with comorbidities

Comorbidities including type 2 diabetes and hypertension may adversely influence the effect of MHT on cognitive decline, dementia, and AD in postmenopausal women. Data from the WHIMS indicated that the combination of diabetes and higher estrogen levels increased risks of dementia and cognitive impairment in postmenopausal women[77]. The use of MHT was associated with lower gray matter volumes in women with type 2 diabetes aged 65 years or older[78]. Although there was no statistical significance due to the small number of women in subgroups, risk of dementia in estrogen-alone users was greater in women with a history of hypertension than those without a history of hypertension in the WHIMS[79]. These findings indicate that a woman’s baseline medical condition can distinctly influence MHT effects on risks of cognitive decline, dementia, and AD. Risk factors associated with MHT may differ between women with and without a history of the comorbidities.

## Distinct analytical methodology and variations in study outcomes

Variations in outcomes from clinical studies might be associated with diverse analytical methods when adjusting for differences in life and health conditions for the comparison of MHT effects between control and treatment groups (Table 3). There are multiple conditions associated with MHT effects on risks of cognitive/memory decline, dementia, and AD[31].

These include age, body mass index, alcohol, smoking, education, socioeconomic status, number of births, type of menopause, cancer, cardiovascular disease, hypertension, diabetes, hypercholesterolemia, and family history of neurodegenerative diseases. These variables were not uniformly adjusted when comparing MHT effects between control and treatment groups in clinical studies, which might confound study outcomes (protective, harmful, or no effect). Adjusting for or not adjusting for variables will impact outcomes of observational studies moderately or significantly[32]. Illustrative cases are two case–control studies that reported no benefit of MHT on AD risk[35,64]. One case–control study investigated the effect of MHT use, age at MHT initiation, and type and duration of MHT on AD risk in postmenopausal women[35]. The outcomes of this study indicated that long-term use of systemic MHT might be associated with increased risk of AD[35]. In this study, women with and without a diagnosis of AD were matched in terms of age and hospital district; however, other medical and health conditions that potentially influence AD risk were not matched in data analyses between the case and control groups[35]. Another case–control study indicated increased risk of AD when using MHT less than 10 years both prior to and after adjusting for participant socioeconomic status, comorbidities, surgery, and gynecological cancer in study analyses[64]. Although they could not account for previous MHT records prescribed prior to the first year of their data period, participant's age at first estrogen use in this study was between 58 and 69 years, indicating that the results might be derived from women who started estrogen therapy in late postmenopause[64]. Moreover, they could not account for APOE status or family history of AD, which are potential factors influencing AD risk[64]. In contrast to the case–control studies described, results from the Cache County Study indicated a reduced risk of AD in women who received MHT within 5 years of menopause, especially for long-term use (10 or more years)[7]. In the analysis, potential confounders that might be associated with AD risk or MHT use including age at baseline, APOE status, years of education, and propensity to MHT use did not change their outcomes[7]. However, there might be other confounders potentially influencing the outcomes.

In addition, non-intervention observational studies enable analysis of the impact of diverse types and durations of MHT. However, in general, women who receive MHT may be healthy, well-educated, and of higher socioeconomic status compared to never users[80,81], which may cause unexpected bias during analyses and variations in study outcomes.

## Conclusion

Data from randomized clinical trials have been utilized to advance our understanding of the effect of MHT on cognitive function and AD pathogenesis. However, existing clinical trials were late intervention studies that included asymptomatic postmenopausal women or those who did not have severe menopausal symptoms[15,17,30]. These women did not represent those who need MHT in the real world. Lessons from randomized clinical trials include the following: (1) intervention treatment of asymptomatic women who have passed the 'critical window' may provide no benefit for cognitive improvement and prevention of dementia and AD; (2) the beneficial effect of MHT initiated at perimenopause was not determined; (3) benefits of MHT may be underestimated due to other covariables relevant to an individual's health conditions, including obesity, diabetes, hypertension, and cardiovascular disease, which can affect risks of cognitive decline, dementia, and AD; and

(4) the effects of various doses, durations, and types of MHT were not addressed because all participants were treated with a single dose, duration, and type of estrogen therapy. In contrast, some observational studies (non-intervention) indicate a potential positive association between MHT and reduced AD risk[3,4,7,9]. In observational data sets, women have been treated with MHT based on symptoms, with the potential of clinically based personalized MHT. Symptom-based MHT during the 'critical window' of symptomatic perimenopause to menopause potentially identifies positive responders to MHT (Table 3). However, variables associated with MHT effects should be cautiously taken into account when interpreting results from observational studies. Gaps between positive estrogen action in the brain demonstrated in preclinical studies and varied outcomes in clinical studies imply that precision MHT is key to provide the most optimal and safe therapy to women and to advance women's health.

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## References

1. Brookmeyer R, Gray S, Kawas C. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. Am J Public Health 1998;88:1337–42 [PubMed: 9736873]
2. Paganini-Hill A, Henderson VW. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol 1994;140:256–61 [PubMed: 8030628]
3. Zandi PP, Carlson MC, Plassman BL, et al. Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. JAMA 2002;288:2123–9 [PubMed: 12413371]
4. Tang M-X, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429–32 [PubMed: 8709781]
5. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. Arch Intern Med 1996;156:2213–17 [PubMed: 8885820]
6. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore longitudinal study of aging. Neurology 1997;48:1517–21 [PubMed: 9191758]
7. Shao H, Breitner JC, Whitmer RA, et al. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. Neurology 2012;79:1846–52 [PubMed: 23100399]
8. MacLennan AH, Henderson VW, Paine BJ, et al. Hormone therapy, timing of initiation, and cognition in women aged older than 60 years: the REMEMBER pilot study. Menopause 2006;13:28–36 [PubMed: 16607096]
9. Henderson VW, Benke K, Green R, MIRAGE Study Group, et al. Postmenopausal hormone therapy and Alzheimer's disease risk: interaction with age. J Neurol Neurosurg Psychiatry 2005;76:103–5 [PubMed: 15608005]
10. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry 2001;158:227–33 [PubMed: 11156805]
11. Hsu A, Card A, Lin SX, et al. Changes in postmenopausal hormone replacement therapy use among women with high cardiovascular risk. Am J Public Health 2009;99:2184–7 [PubMed: 19833984]
12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33 [PubMed: 12117397]

13. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701–12 [PubMed: 15082697]
14. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 2013;310:1353–68 [PubMed: 24084921]
15. Hodis HN, Mack WJ, Shoupe D, et al. Methods and baseline cardiovascular data from the Early versus Late Intervention Trial with Estradiol testing the menopausal hormone timing hypothesis. Menopause 2015;22:391–401 [PubMed: 25380275]
16. Henderson VW, John JAS, Hodis HN, et al. Cognition, mood, and physiological concentrations of sex hormones in the early and late postmenopause. Proc Natl Acad Sci 2013;110:20290–5 [PubMed: 24277815]
17. Miller VM, Black D, Brinton E, et al. Using basic science to design a clinical trial: baseline characteristics of women enrolled in the Kronos Early Estrogen Prevention Study (KEEPS). J Cardiovasc Transl Res 2009;2:228–39 [PubMed: 19668346]
18. Wharton W, Gleason CE, Miller VM, et al. Rationale and design of the Kronos Early Estrogen Prevention Study (KEEPS) and the KEEPS cognitive and affective sub study (KEEPS Cog). Brain Res 2013;1514:12–17 [PubMed: 23603409]
19. Wharton W, Gleason CE, Dowling NM, et al. The KEEPS-cognitive and affective study: baseline associations between vascular risk factors and cognition. J Alzheimers Dis 2014;40:331–41 [PubMed: 24430001]
20. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. PLoS Med 2015;12:e1001833 [PubMed: 26035291]
21. Matyi JM, Rattinger GB, Schwartz S, et al. Lifetime estrogen exposure and cognition in late life: the Cache County Study. Menopause 2019;26:1366–74 [PubMed: 31613825]
22. Mosconi L, Rahman A, Diaz I, et al. Increased Alzheimer's risk during the menopause transition: a 3-year longitudinal brain imaging study. PLoS One 2018;13:e0207885 [PubMed: 30540774]
23. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. J Steroid Biochem Mol Biol 2014;142:90–8 [PubMed: 23770320]
24. Hogervorst E, Bandelow S. Sex steroids to maintain cognitive function in women after the menopause: a meta-analyses of treatment trials. Maturitas 2010;66:56–71 [PubMed: 20202765]
25. Imtiaz B, Tuppurainen M, Rikkonen T, et al. Postmenopausal hormone therapy and Alzheimer disease: a prospective cohort study. Neurology 2017;88:1062–8 [PubMed: 28202700]
26. Song Y-j, Li S-r, Li X-w, et al. The effect of estrogen replacement therapy on Alzheimer's disease and Parkinson's disease in postmenopausal women: a meta-analysis. Frontiers Neurosci 2020;14:157
27. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 2003;289:2651–62 [PubMed: 12771112]
28. Vaughan L, Espeland MA, Snively B, et al. The rationale, design, and baseline characteristics of the Women's Health Initiative Memory Study of Younger Women (WHIMS-Y). Brain Res 2013; 1514:3–11 [PubMed: 23578696]
29. Espeland MA, Shumaker SA, Leng I, et al. Long-term effects on cognitive function of postmenopausal hormone therapy prescribed to women aged 50 to 55 years. JAMA Intern Med 2013; 173:1429–36 [PubMed: 23797469]
30. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. Controlled Clin Trials 1998;19:61–109 [PubMed: 9492970]
31. Kim YJ, Brinton RD. Precision hormone therapy: gaps and opportunities. Gynecol Reprod Endocrinol Metab 2020;1:80–8
32. Patel CJ, Burford B, Ioannidis JP. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. J Clin Epidemiol 2015;68:1046–58 [PubMed: 26279400]

33. Brinton RD. The healthy cell bias of estrogen action: mitochondrial bioenergetics and neurological implications. Trends Neurosci 2008; 31:529–37 [PubMed: 18774188]
34. Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI Study. Neurology 2009;72:135–42 [PubMed: 19139364]
35. Savolainen-Peltonen H, Rahkola-Soisalo P, Hoti F, et al. Use of postmenopausal hormone therapy and risk of Alzheimer's disease in Finland: nationwide case-control study. BMJ 2019;364:l665 [PubMed: 30842086]
36. Grodstein F, Chen J, Pollen DA, et al. Postmenopausal hormone therapy and cognitive function in healthy older women. J Am Geriatr Soc 2000;48:746–52 [PubMed: 10894312]
37. Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 2004;63:101–7 [PubMed: 15249618]
38. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: triad of risk of Alzheimer's disease. J Steroid Biochem Mol Biol 2016;160: 134–47 [PubMed: 26969397]
39. Wang Y, Brinton RD. Triad of risk for late onset Alzheimer's: mitochondrial haplotype, APOE genotype and chromosomal sex. Front Aging Neurosci 2016;8:232 [PubMed: 27757081]
40. Mahoney-Sanchez L, Belaidi AA, Bush AI, et al. The complex role of apolipoprotein E in Alzheimer's Disease: an Overview and Update. J Mol Neurosci 2016;60:325–35 [PubMed: 27647307]
41. O'Donoghue MC, Murphy SE, Zamboni G, et al. APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: a review. Cortex 2018;104:103–23 [PubMed: 29800787]
42. Salameh TS, Rhea EM, Banks WA, et al. Insulin resistance, dyslipidemia, and apolipoprotein E interactions as mechanisms in cognitive impairment and Alzheimer's disease. Exp Biol Med (Maywood) 2016;241:1676–83 [PubMed: 27470930]
43. Leduc VJasmin-Bélanger S, Poirier J. APOE and cholesterol homeostasis in Alzheimer's disease. Trends Mol Med 2010;16: 469–77 [PubMed: 20817608]
44. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA 2007;298:1300–11 [PubMed: 17878422]
45. Mosconi L, Berti V, Quinn C, et al. Sex differences in Alzheimer risk: brain imaging of endocrine vs chronologic aging. Neurology 2017;89:1382–90 [PubMed: 28855400]
46. Wang Y, Mishra A, Brinton RD. Transitions in metabolic and immune systems from pre-menopause to post-menopause: implications for age-associated neurodegenerative diseases. F1000Res 2020;9:68
47. Mosconi L, Nacmias B, Sorbi S, et al. Brain metabolic decreases related to the dose of the ApoE e4 allele in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004;75:370–6 [PubMed: 14966149]
48. Yaffe K, Haan M, Byers A, et al. Estrogen use, APOE, and cognitive decline: evidence of gene–environment interaction. Neurology 2000;54:1949–54 [PubMed: 10822435]
49. Kang JH, Grodstein F. Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline. Neurobiol Aging 2012;33: 1129–37 [PubMed: 21122949]
50. Ryan J, Carrière I, Scali J, et al. Characteristics of hormone therapy, cognitive function, and dementia: the prospective 3C study. Neurology 2009;73:1729–37 [PubMed: 19933973]
51. Stone DJ, Rozovsky I, Morgan TE, et al. Increased synaptic sprouting in response to estrogen via an apolipoprotein E-dependent mechanism: implications for Alzheimer's disease. J Neurosci 1998; 18:3180–5 [PubMed: 9547226]
52. Srivastava RAK, Srivastava N, Averna M, et al. Estrogen up-regulates apolipoprotein E (ApoE) gene expression by increasing ApoE mRNA in the translating pool via the estrogen receptor alpha-mediated pathway. J Biol Chem 1997;272:33360–6 [PubMed: 9407129]
53. Karim R, Koc M, Rettberg JR, et al. Apolipoprotein E4 genotype in combination with poor metabolic profile is associated with reduced cognitive performance in healthy postmenopausal women: implications for late onset Alzheimer's disease. Menopause 2019;26:7–15 [PubMed: 29975287]
54. Xing Y, Jia J, Ji X, et al. Estrogen associated gene polymorphisms and their interactions in the progress of Alzheimer's disease. Prog Neurobiol 2013;111:53–74 [PubMed: 24096044]

55. Mann DM. The pathological association between Down syndrome and Alzheimer disease. Mech Ageing Dev 1988;43:99–136 [PubMed: 2969441]
56. Chace C, Pang D, Weng C, et al. Variants in CYP17 and CYP19 cytochrome P450 genes are associated with onset of Alzheimer's disease in women with down syndrome. J Alzheimers Dis 2012;28: 601–12 [PubMed: 22057025]
57. Hogervorst E, Williams J, Budge M, et al. The nature of the effect of female gonadal hormone replacement therapy on cognitive function in post-menopausal women: a meta-analysis. Neuroscience 2000;101:485–512 [PubMed: 11113299]
58. Miller VM, Naftolin F, Asthana S, et al. The Kronos early estrogen prevention study (KEEPS): what have we learned? Menopause 2019;26:1071–84 [PubMed: 31453973]
59. Zhao L, Morgan TE, Mao Z, et al. Continuous versus cyclic progesterone exposure differentially regulates hippocampal gene expression and functional profiles. PLoS One 2012;7:e31267 [PubMed: 22393359]
60. Kantarci K, Lowe VJ, Lesnick TG, et al. Early postmenopausal transdermal 17β-estradiol therapy and amyloid-β deposition. J Alzheimers Dis 2016;53:547–56 [PubMed: 27163830]
61. Zhao L, Yao J, Mao Z, et al. 17β-Estradiol regulates insulin-degrading enzyme expression via an ERβ/PI3-K pathway in hippocampus: relevance to Alzheimer's prevention. Neurobiol Aging 2011;32: 1949–63 [PubMed: 20053478]
62. Kantarci K, Tosakulwong N, Lesnick TG, et al. Effects of hormone therapy on brain structure: a randomized controlled trial. Neurology 2016;87:887–96 [PubMed: 27473135]
63. Waring SC, Rocca WA, Petersen RC, et al. Postmenopausal estrogen replacement therapy and risk of AD: a population-based study. Neurology 1999;52:965–70 [PubMed: 10102413]
64. Imtiaz B, Taipale H, Tanskanen A, et al. Risk of Alzheimer's disease among users of postmenopausal hormone therapy: a nationwide case-control study. Maturitas 2017;98:7–13 [PubMed: 28274328]
65. Schwartz J, Freeman R, Frishman W. Clinical pharmacology of estrogens: cardiovascular actions and cardioprotective benefits of replacement therapy in postmenopausal women. J Clin Pharmacol 1995;35:314–29 [PubMed: 7608324]
66. Rocca WA, Bower JH, Maraganore D, et al. Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. Neurology 2007;69:1074–83 [PubMed: 17761551]
67. Maric-Bilkan C, Gilbert EL, Ryan MJ. Impact of ovarian function on cardiovascular health in women: focus on hypertension. Int J Women's Health 2014;6:131–9 [PubMed: 24493934]
68. Rocca WA, Ulrich LG. Oophorectomy for whom and at what age? Primum non nocere. Maturitas 2012;71:1–2 [PubMed: 22079872]
69. Karvonen-Gutierrez CA, Park SK, Kim C. Diabetes and menopause. Curr Diab Rep 2016;16:20 [PubMed: 26879303]
70. Harman S, Brinton E, Cedars M, et al. KEEPS: the Kronos early estrogen prevention study. Climacteric 2005;8:3–12
71. Wroolie TE, Kenna HA, Williams KE, et al. Differences in verbal memory performance in postmenopausal women receiving hormone therapy: 17β-estradiol versus conjugated equine estrogens. Am J Geriatr Psychiatry 2011;19:792–802 [PubMed: 21873835]
72. Silverman DH, Geist CL, Kenna HA, et al. Differences in regional brain metabolism associated with specific formulations of hormone therapy in postmenopausal women at risk for AD. Psychoneuroendocrinology 2011;36:502–13 [PubMed: 20810219]
73. Resnick SM, Espeland MA, An Y, et al. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J Clin Endocrinol Metab 2009;94:4152–61 [PubMed: 19850684]
74. Bove R, Secor E, Chibnik LB, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. Neurology 2014;82:222–9 [PubMed: 24336141]
75. Zeydan B, Tosakulwong N, Schwarz CG, et al. Association of bilateral salpingo-oophorectomy before menopause onset with medial temporal lobe neurodegeneration. JAMA Neurol 2019;76:95–100 [PubMed: 30326011]

76. Imtiaz B, Tuppurainen M, Tiihonen M, et al. Oophorectomy, hysterectomy, and risk of Alzheimer's disease: a nationwide case-control study. J Alzheimers Dis 2014;42:575–81 [PubMed: 24898656]

77. Espeland MA, Brinton RD, Hugenschmidt C, et al. Impact of type 2 diabetes and postmenopausal hormone therapy on incidence of cognitive impairment in older women. Diabetes Care 2015;38: 2316–24 [PubMed: 26486190]

78. Espeland MA, Brinton RD, Manson JE, et al. Postmenopausal hormone therapy, type 2 diabetes mellitus, and brain volumes. Neurology 2015;85:1131–8 [PubMed: 26163429]

79. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;291:2947–58 [PubMed: 15213206]

80. Jensen LB, Hilden J. Sociological and behavioural characteristics of perimenopausal women with an express attitude to hormone substitution therapy. Maturitas 1996;23:73–83 [PubMed: 8861089]

81. Progetto Menopausa Italia Study Group. General and medical factors associated with hormone replacement therapy among women attending menopause clinics in Italy. Menopause 2001;8: 290–5 [PubMed: 11449088]

82. Lautenschlager N, Cupples L, Rao V, et al. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? Neurology 1996;46:641–50 [PubMed: 8618660]

83. Stefanick ML, Cochrane BB, Hsia J, et al. The Women's Health Initiative postmenopausal hormone trials: overview and baseline characteristics of participants. Ann Epidemiol 2003;13:S78–S86 [PubMed: 14575940]

84. Henderson VW, John JAS, Hodis HN, et al. Cognitive effects of estradiol after menopause: a randomized trial of the timing hypothesis. Neurology 2016;87:699–708 [PubMed: 27421538]

85. Espeland MA, Rapp SR, Shumaker SA, et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: women's Health Initiative Memory Study. JAMA 2004;291: 2959–68 [PubMed: 15213207]

**Table 1.**

Clinical trials and observational studies relevant to menopausal hormone therapy and cognition, memory, or Alzheimer's disease (AD).

| Study | NCT number (ClinicalTrials.gov) | Study type | Initiation year | Outcome | References |
|---|---|---|---|---|---|
| WHI | NCT00000611 | Randomized trial | 1992 | Cardiovascular disease, cancer, and osteoporosis | 30 |
| WHIMS | NCT00685009 | Randomized trial, ancillary study of WHI | 1996 | Memory | 27 |
| WHIMS-Y | NCT01124773 | Randomized trial, ancillary study of WHI | 2009 | Cognitive function | 28 |
| KEEPS and KEEPS-Cog (ancillary study of KEEPS) | NCT00154180 | Randomized trial | 2005 | Atherosclerosis (KEEPS) Cognitive function and mood (KEEPS-Cog) | 17,18,58,70 |
| ELITE and ELITE-Cog (ancillary study of ELITE) | NCT00114517 | Randomized trial | 2004 | Atherosclerosis (ELITE) Cognitive function (ELITE-Cog) | 15,16 |
| Cache County Study | | Observational | 1995 | AD | 3,7 |
| MIRAGE | NCT00239759 | Observational | 2002 | AD | 9,82 |

ELITE, Early vs. Late Intervention Trial with Estradiol; ELITE-Cog, ELITE study including cognitive change; KEEPS, Kronos Early Estrogen Prevention Study; KEEPS-Cog, KEEPS-Cognitive and Affective Study; MIRAGE, Multi-Institutional Research in Alzheimer's Genetic Epidemiology; WHI, Women's Health Initiative; WHIMS, WHI Memory Study; WHIMS-Y, WHIMS of Youngest Women.

**Table 2.**

Characteristics of study participants at baseline.

| Characteristic | WHI and WHIMS | KEEPS and KEEPS-Cog | ELITE and ELITE-Cog | Cache County Study | MIRAGE |
|---|---|---|---|---|---|
| Target disease | Cardiovascular disease, cancer, and osteoporosis (WHI)[30]<br>Cognitive function (WHIMS)[27] | Atherosclerosis (KEEPS)<br>Cognitive function and mood (KEEPS -cognitive)[17,18,58,70] | Atherosclerosis (ELITE)<br>Cognitive function (ELITE - cognitive)[15,16] | AD[3,7] | AD[9,82] |
| Study size | 27,347 enrolled (16,608 with a uterus and 10,739 with prior hysterectomy)[12,13] | 727 participants[58] | 643 participants (271 early and 372 late)[15] | 1768 participants (1105 MHT users and 663 non-users)[7] | 971 (426 probands with AD; 545 relatives without dementia)[9] |
| Age (years) | 50–79[12,13] | 42–58 (mean 52.7)[17] | 55.4 ± 4.1 (early group)<br>65.4 ± 6.0 (late group)[15] | 73.4 ± 5.6 (MHT users)<br>76.7 ± 6.9 (non-users)[7] | 71.1 ± 8.1 (probands)<br>65.0 ± 8.6 (relatives)[9] |
| Treatment during study period | CEE+MPA or CEE alone[12,13] | Oral CEE (Premarin®) or transdermal 17β-estradiol (Climara®) with prometrium[70] | 17β-Estradiol ± vaginal micronized progesterone for 10 days each month[15] | Not applicable | Not applicable |
| Wash-out period prior to randomization | 3 months before continuing screening[12,13] | Excluded MHT/phytoestrogen-containing supplement users within 6 months of randomization[70] | Excluded current MHT users within 1 month of screening[15] | Not applicable | Not applicable |
| Previous hormone therapy use | History of use:<br>Never, *n*=17,639 (64.6%)<br>Past, *n*=6804 (24.9%)<br>Current, *n*=2881 (10.5%)<br>Duration of use:<br><5 years, *n*=5971 (61.5%)<br>5–10 years,*n*=1778 (18.3%)<br>10+ years, *n*=1958 (20.2%)[83] | Never: 78.7%<br>Past: 19.3%<br>Current: 1.9%[17] | Past:<br>*n*=138 (50.9%) early<br>*n*=321 (86.3%) late[15] | Any type of MHT[7] | Estrogen use for more than 6 months:<br>Probands, *n*=87 (21%)<br>Relatives, n=192 (35%)[9] |
| Menopausal status | Natural or surgical[83] | All natural, within 6 months–3 years[58] | Median time since menopause:<br>Early, 3.5 years (1.9–5.0 years)<br>Late, 14.3 years (11.5–18.7 years)<br>Type of menopause:<br>Early, *n*=262 (96.7%) natural<br>Late, *n*=312 (83.9%) natural[15] | Age at menopause:<br>47.3 ± 6.8 years (MHT users)<br>48.2 ± 6.3 years (non-users)[7] | Natural or surgical[9] |
| Hysterectomy/ oophorectomy | Age at hysterectomy:<br><40 years, *n*=4249 (39.8%)<br>40–49 years, *n*=4556 (42.7%)<br>50+ years, *n*=1872 (17.5%)<br>Bilateral oophorectomy:<br>*n*=4102 (15.5%)[83] | Not included[70] | Surgical menopause:<br>Early, *n*=9 (3.3%)<br>Late, *n*=60 (16.1%)[15] | Partial oophorectomy:<br>*n*=91 (8.4%) MHT users<br>*n*=38 (5.8%) non-users<br>Bilateral oophorectomy:<br>*n*=344 (31.9%) MHT users<br>*n*=67 (10.2%) non-users[7] | *n*=141 (35%) probands<br>*n*=231 (42%) relatives[9] |
| APOE | Not applicable | APOE4, *n*=147 of 568 (25.9%) among KEEPS - cognitive participants[20] | Early:<br>*n*=36 of 120 (30.0%) treatment<br>*n*=36 of 112 (32.1%) placebo<br>Late:<br>*n*=50 of 161 (31.1%) treatment<br>*n*=55 of 169 (32.5%) placebo[84] | APOE4:<br>*n*=330 (30%) MHT users<br>*n*=208 (31.7%) non-users[7] | APOE4:<br>*n*=281 (66%) probands<br>*n*=201 (37%) relatives[9] |

| Characteristic | WHI and WHIMS | KEEPS and KEEPS-Cog | ELITE and ELITE-Cog | Cache County Study | MIRAGE |
|---|---|---|---|---|---|
| Health condition relevant to MHT at baseline | Treated diabetes: *n*=1555 (5.7%)<br>History of hypertension: *n*=2259 (9.1%) untreated *n*=6174 (24.9%) treated<br>Treated hypercholesterolemia: *n*=3366 (13.7%)<br>History of stroke: *n*=306 (1.1%)<br>Family history of breast cancer: *n*=4224 (16.4%)[83] | Without history of cardiovascular disease, stroke, thromboembolic disease, dyslipidemia, and hypertriglyceridemia<br>Without current or recent (6 months) use of lipid-lowing medications<br>Without uncontrolled hypertension[70] | Without CVD<br>Current hypertension medication: *n*=50 (18.5%) early *n*=107 (28.8%) late<br>Current lipid-lowering medications: *n*=40 (14.8%) early *n*=88 (23.7%)[15] late | Family history of AD: *n*=271 (27.8%) MHT users *n*=150 (26.6%) non-users<br>Diabetes: *n*=134 (12.2%) MHT users *n*=87 (13.1%) non-users<br>Hypertension: *n*=492 (44.6%) MHT-users *n*=307 (46.5%) non-users<br>Stroke: *n*=69 (6.3% MHT users) *n*=39 (5.9% non-users)<br>High cholesterol: *n*=323 (29.7%) MHT users *n*=209 (32.2%) non-users[7] | Non-steroidal anti-inflammatory drug for more than 6 months: *n*=20 (5%) probands *n*=86 (16%) relatives[9] |
| BMI (kg/m$^2$) | 29.1 ± 6.0[83] | 26.2 ± 4.3[17] | Early: 27.2 ± 5.4<br>Late: 27.4 ± 5.4[15] | 25.7 ± 4.4 (MHT users)<br>25.9 ± 4.5 (non-users)[7] | Not available |
| Smoking | Never: *n*=13,605 (50.3%)<br>Past: *n*=10,594 (39.2%)<br>Current: *n*=2831 (10.5%)[83] | Past or current: *n*=45 (6.5%) among KEEPS – cognitive participants (*N*=693)[20] | Never: *n*=171 (63.1%) early *n*=214 (57.5%) late<br>Past: *n*=89 (32.8%) early *n*=147 (39.5%) late<br>Current: *n*=11 (4.1 %) early *n*=11 (3.0%) late[15] | Never: *n*=876 (79.5%) MHT users *n*=527 (79.6%) non-users[7] | Current or past: *n*=149 (37%) probands *n*=196 (35%) relatives[9] |
| Alcohol | Never: *n*=3365 (12.4%)<br>Past: *n*=5354 (19.7%)<br>Current: *n*=18,394 (67.8%)[83] | Past or current: *n*=519 (74.9%) among KEEPS – cognitive participants (*n*=693)[20] | None *n*=135 (49.8%) early *n*=194 (52.2%) late[15] | None: *n*=931 (84.6%) MHT users *n*=557 (84.4%) non-users[7] | Past or current: *n*=106 (25%) probands *n*=163 (27%) relatives[9] |
| Outcomes | Neither benefit nor harm on cognitive function[29]; adverse effect on cognition in women aged 65 years or older[85] | No benefit on cognition[20] | Neither benefit nor harm on cognition[16,84] | Benefit of prior MHT on reduced risk of AD[3,7] | Reduced risk of AD[9] |

AD, Alzheimer's disease; APOE, apolipoprotein E; BMI, body mass index; CEE, conjugated equine estrogens; CVD, cardiovascular disease; ELITE, Early vs. Late Intervention Trial with Estradiol; ELITE-Cog, ELITE study including cognitive change; KEEPS, Kronos Early Estrogen Prevention Study; KEEPS-Cog, KEEPS-Cognitive and Affective Study; MHT, menopausal hormone therapy; MIRAGE, Multi-Institutional Research in Alzheimer's Genetic Epidemiology; MPA, medroxyprogesterone acetate; WHI, Women's Health Initiative; WHIMS, WHI Memory Study.

**Table 3.**

Factors addressed or not addressed in randomized clinical trials and observational studies.

| Study variable | Randomized clinical trials[15,17,30,58,70] | Observational studies[3,7,9] |
|---|---|---|
| MHT initiation at perimenopause | No | Yes |
| Status of symptoms at the time of MHT use | No symptoms/exclusion of women with severe symptoms | Yes |
| Duration of MHT | Duration for intervention treatment that varied across clinical trials | Personalized by clinicians |
| Type of MHT | Single type of therapy that varied across clinical trials | Personalized by clinicians |
| APOE genotype | Randomized treatment arms not based on APOE genotype | Requires further investigation |
| Adjustment of differences in medical comorbidity history among participants | Controlled through exclusion health exclusion criteria | Varied across studies |

APOE, apolipoprotein E; MHT, menopausal hormone therapy.