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Oophorectomy, estrogen, and dementia: A 2014 update

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Abstract

Current evidence suggests that estrogen may have beneficial, neutral, or detrimental effects on the brain depending on age, type of menopause (natural versus induced), or stage of menopause (early versus late), consistent with the timing hypothesis. Three studies have now compared women who underwent bilateral oophorectomy before menopause with referent women and consistently showed an increased risk of cognitive decline and dementia. These studies suggest a sizeable neuroprotective effect of estrogen naturally produced by the ovaries before age 50 years. In this article, we focus on neuroprotection as related to cognitive decline and dementia. Several case-control studies and cohort studies also showed neuroprotective effects in women who received estrogen treatment (ET) in the early postmenopausal stage (most commonly at ages 50–60 years). The majority of women in those observational studies had undergone natural menopause and were treated for the relief of menopausal symptoms. However, the clinical trials by the Women's Health Initiative showed that women who initiated ET alone or in combination with a progestin in the late postmenopausal stage (ages 65–79 years) experienced an increased risk of dementia and cognitive decline regardless of the type of menopause. Three observational studies have now formally tested the timing hypothesis, and showed that the neuroprotective or harmful effects of estrogen depend on age at the time of initiation of treatment and on stage of menopause. Therefore, women who undergo bilateral oophorectomy before the onset of menopause or women who experience premature or early natural menopause should be considered for hormonal treatment until the average age of natural menopause (around age 50 years). Recommendations for the use of ET by women who experience natural menopause at typical ages remain less certain, and more research is needed.

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Keywords

Oophorectomy; Menopause; Estrogen; Dementia; Cognitive impairment; Timing hypothesis

1. Introduction

Controversy about the long-term neurological consequences of bilateral oophorectomy in younger women and about the harm or benefit of postmenopausal estrogen treatment (ET) continues (Henderson and Sherwin, 2007; Henderson and Rocca, 2012; Rocca and Henderson, 2014). The study of women who undergo bilateral oophorectomy to treat an existing ovarian condition or to prevent ovarian cancer offer a unique window to explore the effects of estrogen on brain aging in women. Bilateral oophorectomy before the onset of natural menopause causes an abrupt cessation of estrogen production with a consequent drop in circulating levels of estrogen (primarily estradiol).

In this article, we trace the history of the studies that have explored the relationship between bilateral oophorectomy and cognitive decline. The intention is to provide a narrative review based on interpretation and historical development as experienced by the authors from the clinical (LTS) and the research (WAR, BRG) perspectives. We have not applied conventional meta-analysis techniques, and we selected the studies based on scientific quality and judgment. In the second part of the paper, we present the data on oophorectomy in a broader context, discussing evidence for the effects of postmenopausal ET on cognition in general. The studies of ET after menopause are divided into studies of early menopause and late menopause. Finally, we provide an update on the timing hypothesis, which suggests that the neuroprotective effects of estrogen depend on a woman's age, type of menopause, and stage in menopause. (Rocca et al., 2011) In this article, we focus on neuroprotection as related to cognitive decline and dementia.

2. Clarification of terminology

We have observed some confusion in the literature concerning the use of the term surgical menopause. To reduce this confusion, we suggest to first distinguish women who experienced natural menopause from women who underwent medically induced menopause primarily via surgery. Natural menopause is defined as cessation of menses for 12 continuous months or more in the absence of a medical or surgical cause (Utian, 2001), and the mean age at natural menopause in the United States is approximately 51 years (Armstrong et al., 2004; Shuster et al., 2010). The age at natural menopause varies across countries. For women who undergo natural menopause, the cessation of menses occurs approximately at the same time as the cessation of ovarian function because the ovaries control the cyclic changes in the endometrium. However, natural menopause is not an abrupt event, and the variability of age at natural menopause is quite broad. Some women experience premature natural menopause (before age 40 years) or early natural menopause (between ages 40 and 45 years) (Rocca et al., 2011; Shuster et al., 2010).

Women who undergo surgically induced menopause (i.e., surgical menopause) may be divided into those who had the uterus removed with one or both ovaries conserved and those

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who had bilateral oophorectomy with or without hysterectomy. For women who had the uterus or the uterus plus one ovary removed, there may be a long gap between cessation of menses and cessation of ovarian function. In these women, the time of cessation of ovarian function is difficult to determine in the absence of menstruation. By contrast, the time and age at menopause due to bilateral oophorectomy is easily determined because cessation of menses and cessation of ovarian function coincide. Therefore, the term “surgical menopause” is ambiguous from an endocrinological perspective and should ideally be avoided (Rocca et al., 2011).

The hormonal changes occurring after bilateral oophorectomy in premenopausal women are different from those occurring during natural menopause or after bilateral oophorectomy in women who already experienced natural menopause. In particular, bilateral oophorectomy before menopause causes an abrupt decline of estrogen as well as progesterone and testosterone, and a disruption of the hypothalamic-pituitary-ovarian axis (Morrison et al., 2006; Rocca et al., 2011). Therefore, important observations on the effects of estrogen in younger women can be derived from studies of women who underwent bilateral oophorectomy before reaching natural menopause. In this review, we will not address the issue of the possible modifying effects of hysterectomy alone or of hysterectomy plus unilateral oophorectomy on the remaining ovarian function (one or two conserved ovaries) (Farquhar et al., 2005; Phung et al., 2010; Rocca et al., 2007; Zhou et al., 2011).

3. Early studies of bilateral oophorectomy (before 2007)

The idea of a possible harmful effect of oophorectomy on cognition was introduced in Canada by Sherwin and colleagues as early as 1988. They conducted a series of small clinical trials which involved short-term treatment with estrogen after bilateral oophorectomy, and short-term follow-up (2–3 months). These trials consistently suggested a neuroprotective effect of estrogen given to women after bilateral oophorectomy (Phillips and Sherwin, 1992; Sherwin, 1988; Sherwin and Phillips, 1990).

The idea was further developed in Italy by Nappi and colleagues who reported that short-term verbal memory was reduced in women who underwent oophorectomy, and in Egypt by Farrag and colleagues who reported cognitive decline at 3 and 6 months after bilateral oophorectomy (Farrag et al., 2002; Nappi et al., 1999). These two studies focused on short-term consequences of oophorectomy and included only a small number of women. By contrast, some other studies did not find harmful effects of bilateral oophorectomy. A US cross-sectional study showed a lower performance on some cognitive tests in a small sample of women who underwent hysterectomy with bilateral oophorectomy compared with women whose ovaries were conserved (both groups were taking estrogen at the time of the study). However, these differences were considered not clinically significant (Kritz-Silverstein and Barrett-Connor, 2002). A UK cohort study of women aged 53 years at the time of cognitive testing did not reveal any effects of hormone therapy use or hysterectomy status. Unfortunately, women with hysterectomy were not stratified into women with or without concurrent bilateral oophorectomy, and the women were too young to study the long-term effects of bilateral oophorectomy (Kok et al., 2006).

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4. The Mayo Clinic Study of Oophorectomy and Aging (2007)

The first study to formally test the association between bilateral oophorectomy and neurological outcomes in a large-scale study with long-term follow-up was the Mayo Clinic Cohort Study of Oophorectomy and Aging, which was conducted in the United States and published in 2007. The study showed an almost doubled long-term risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause (Rocca et al., 2007). The study also showed a trend of increasing risk of cognitive impairment and dementia with younger age at the time of oophorectomy or younger age at the time of estrogen deficiency. Time of estrogen deficiency was defined as the time of oophorectomy if the woman was not given ET, or the end of ET if the woman was initially treated with estrogen but stopped (Rocca et al., 2007). The risk did not vary by indication for the oophorectomy (for a benign ovarian condition or for prophylaxis), but was eliminated if estrogen therapy was initiated after the surgery and continued up to age 50 years or longer. In most of the women, oophorectomy was performed along with hysterectomy (Rocca et al., 2007).

5. The Danish nationwide historical cohort study (2010)

Because the design of a historical cohort study of women who underwent bilateral oophorectomy and were able to be followed up long-term is extremely complex, the results of the Mayo Clinic study remained unconfirmed through 2010. A first replication came from a nationwide historical cohort study conducted in Denmark using several national disease registries (Phung et al., 2010). Despite limitations related to the detection and classification of dementia using unconfirmed routine diagnoses in the population, the study showed that women who underwent bilateral oophorectomy had an increased risk of dementia with onset before age 50 years. This study also confirmed the timing effect observed in the Mayo Clinic study. The risk increased with younger age at the time of bilateral oophorectomy (Phung et al., 2010).

6. The Religious Orders Study and the Memory and Aging Study (2014)

A second replication and extension of the Mayo Clinic study was published in 2014. Bove et al. reported the results of a cohort study on the association between surgical menopause and cognitive decline along with Alzheimer’s disease (AD) pathology in two US populations (Bove et al., 2014). They found that earlier age at self-reported surgical menopause was associated with faster decline in global cognition, specifically in the domains of episodic memory and semantic memory. Among women who underwent autopsy after death, earlier age at surgical menopause was also associated with increased burden of AD neuropathology, in particular neuritic plaques. Estrogen therapy initiated within 5 years of the surgery and continued for at least 10 years was associated with a lesser decline in global cognition, supporting the view that the effect of surgical menopause on cognitive decline was mediated by early loss of ovarian hormones. These associations were not observed for women who reported experiencing natural menopause.

The study was based on two large, well-characterized cohorts in the United States, the Religious Order Study and the Memory and Aging Project (Bove et al., 2014). Strengths of

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the study include the long duration of follow-up, the detailed assessment of cognitive function, and the large number of autopsies. Weaknesses include the lack of information needed to distinguish the type of surgical menopause (with or without removal of the ovaries), the lag time between surgery and enrollment in the study, and the reliance on self-reported information about gynecological surgeries and about age of menopause (Rocca and Henderson, 2014)

7. Interpretation of the oophorectomy studies

There is some disagreement on the interpretation of the association between bilateral oophorectomy and cognitive decline (Hogervorst and Bandelow, 2007; Rocca et al., 2009; Rocca and Henderson, 2014). Bilateral oophorectomy may be a true risk factor for the subsequent increased risk of cognitive impairment or dementia, or the association may be spurious and caused by confounding. For example, there may be confounding by genetic factors (e.g., genetic variants), confounding by non-genetic factors (e.g., smoking or obesity), and confounding by accelerated aging, as discussed in detail elsewhere (Rocca et al., 2011).

If the association is causal, the detrimental effects of bilateral oophorectomy may be mediated primarily by estrogen deficiency or also by other hormonal mechanisms (Morrison et al., 2006; Rocca et al., 2009). In support of a causal association mediated by estrogen, women in the Mayo Clinic study who underwent bilateral oophorectomy before age 49 years but received ET through age 50 years or longer did not experience an increased risk of cognitive impairment or dementia (Rocca et al., 2007). These analyses suggest that estrogen deprivation plays a key role in the detrimental effect of oophorectomy. A causal association mediated by estrogen is also supported by the study of Bove and colleagues in which hormone replacement therapy initiated within 5 years of the surgery and continued for at least 10 years was associated with a lesser decline in global cognition (Bove et al., 2014). Figure 1 shows our etiologic model involving a chain of causality linking bilateral oophorectomy to increased risk of dementia. The figure also illustrates how estrogen treatment initiated early after oophorectomy may interrupt the chain of causality and restore the risk of cognitive impairment or dementia to baseline.

Also against a confounding effect is the similar risk of cognitive impairment or dementia among women who underwent bilateral oophorectomy for benign conditions or for prophylaxis of ovarian cancer in the Mayo Clinic study. These findings suggest that the risk was independent of the indication for the oophorectomy (Rocca et al., 2009). Although the possibility that confounding is an explanation of the observed associations cannot be completely ruled out at this time, the evidence for a confounding mechanism is limited.

We suggest that genetic variants and non-genetic factors are involved in the association of bilateral oophorectomy with cognitive decline or dementia as effect modifiers (or interaction variables) rather than as confounders (Fig. 1) (Porta and International Epidemiological Association, 2008; Szklo and Nieto, 2007). Bilateral oophorectomy may be the key initial step in a chain of causality leading to accelerated brain aging, and variants of the apolipoprotein E (*APOE*) gene, the estrogen receptor 1 (*ESR1*) gene, the estrogen receptor 2

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(*ESR2*) gene, or of other genes, and smoking, alcohol consumption, obesity, education, diabetes mellitus, or other non-genetic factors may reduce or accelerate the causal process (Rocca et al., 2009). Under this causal model, ovarian conservation at the time of hysterectomy could reduce the risk of cognitive impairment or dementia in the general population (Rocca et al., 2009), even though the consequences of bilateral oophorectomy may vary in severity among women (Parker et al., 2009). Consideration of inter-individual variations in the response to estrogen deprivation is important but should not distract our attention from the primary public health objective of reducing the risk of cognitive decline. We propose that changing medical decision-making and surgical practices in favor of ovarian conservation in younger women is the most important step toward prevention of harmful sequelae (Parker et al., 2009). Unfortunately, none of the ongoing clinical trials of postmenopausal ET is focusing specifically on women who underwent bilateral oophorectomy before natural menopause or who experienced premature or early natural menopause (Lethaby et al., 2008).

8. Combining oophorectomy studies with estrogen treatment studies

The results of studies of bilateral oophorectomy contribute to the overall debate about the effects of estrogen deprivation or estrogen treatment on brain aging. Therefore, we combined in Figure 2 the data available from studies of bilateral oophorectomy with data from studies of estrogen treatment initiated after the onset of menopause. Case-control and cohort studies have consistently shown a beneficial effect of estrogen on cognition when ET is started in early postmenopause (most commonly at ages 50–60 years) as shown by three meta-analyses (Hogervorst et al., 2000; LeBlanc et al., 2001; Yaffe et al., 1998). The majority of women in these observational studies had undergone natural menopause and were treated for the relief of menopausal symptoms. However, some studies did not confirm the beneficial effect of ET (Petitti et al., 2008; Roberts et al., 2006).

Observational studies showing beneficial effects of estrogen for reducing the risk of dementia have been criticized because their findings could be due to confounding. It has been argued that other factors such as higher socioeconomic status, higher education, or better general health may be the real causes of neuroprotection, and that ET is only a surrogate marker. By contrast, we suggest that the observational findings are likely not due to confounding, and that the apparent contradiction between the results of observational studies and experimental studies is more likely due to the timing of initiation of ET (timing hypothesis).

The Women’s Health Initiative Memory Study (WHIMS) clinical trials showed an increased risk of dementia or mild cognitive impairment (MCI) among women who initiated treatment with estrogen alone or in combination with progestin at ages 65–79 years (Fig. 2) (Espeland et al., 2004; Rapp et al., 2003; Shumaker et al., 2003; Shumaker et al., 2004). These trials focused on the effects of ET initiated many years after the onset of natural or surgical menopause, and the discrepancy between WHIMS results and observational data may be explained by the timing of initiation of estrogen (Brinton, 2008; Henderson and Brinton, 2010; Henderson and Rocca, 2012; Manson et al., 2006; Rocca et al., 2008; Rocca et al., 2010; Siegfried, 2007).

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There is a fundamental problem with applying results of the WHIMS clinical trials to clinical decision-making for most women considering estrogen therapy. The WHIMS trials considered only women of ages 65–79 years at randomization because of statistical rather than biological considerations. The trials were designed to have sufficient power to detect a difference in dementia risk between women randomized to hormonal treatment versus placebo. Because the risk of dementia is relatively low before age 65 years, this design was justified from a statistical perspective but was not justified from a clinical perspective. The findings of the WHIMS trials for dementia are statistically correct but have no relevance to decision-making about estrogen therapy for the majority of women considering hormone therapy for menopausal symptom relief, typically before age 65 years, or as replacement therapy following bilateral oophorectomy before age 50 years (Rocca et al., 2011).

Indeed, the effects of estrogen on the brain are probably beneficial when initiated early after menopause, but when vascular or degenerative lesions have occurred estrogen cannot reverse the lesions or halt progression (Brinton, 2008; Rocca et al., 2009; Zhang et al., 2011). Detrimental effects of estrogen may predominate in older women and may increase the risk of cognitive impairment or dementia through thrombotic effects or other vascular effects (Mendelsohn and Karas, 1999; Mendelsohn and Karas, 2005; Mendelsohn and Karas, 2007; Shumaker et al., 2003; Shumaker et al., 2004).

9. The timing hypothesis

As a result of the heated debate that followed publication of the WHIMS studies, three observational studies have formally tested the timing hypothesis by comparing the incidence of dementia in women who took estrogen early after the onset of menopause with women who started estrogen later in life. The three studies are shown in Fig. 2 with two separate lines for the two age strata. In 2005, the Multi-Institutional Research on Alzheimer Genetic Epidemiology study (MIRAGE) showed that the risk of dementia was reduced in women who initiated hormonal therapy at age 50–63 years, but was not reduced in women who started hormonal treatment at ages 64–71 or 72–99 years (Henderson et al., 2005). In 2011, a Kaiser Permanente study showed that women who received estrogen treatment only in midlife (median age of 49 years) had a reduced risk of dementia, whereas women who took estrogen treatment only in late life (median age of 76 years) had an increased risk of dementia. The risk went down to 1.0 in women who took estrogen both early and late in life, suggesting that the two opposite effects cancelled each other (Whitmer et al., 2011).

Finally, in 2012, a study from Cache County, UT further substantiated the timing hypothesis. Compared with women who reported no use of hormone therapy, women who initiated therapy within five years of menopause had a 30% lower incidence of AD. Risk was unaltered among hormone users who began treatment more than five years after menopause. However, the risk was increased among women who started combined therapy (estrogen plus progestogen) when they were at least 65 years of age. This risk estimate was similar to that observed in women recruited in WHIMS who were allocated to a combined estrogen-progestin therapy (Shao et al., 2012).

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10. Conclusions

A combination of current scientific evidence from animal studies and from observational studies suggests that estrogen is neuroprotective against cognitive decline and dementia; however, the neuroprotective effects are dependent on age at the time of initiation, type of menopause, and stage in menopause. The apparent contradiction of results between observational studies and clinical trials may be explained by the timing hypothesis (Fig. 2) (Rocca et al., 2011).

The results from the Women's Health Initiative (WHI) clinical trials have been inappropriately extrapolated from women in the late postmenopausal stage to younger women in the early postmenopause, and even further to women who underwent bilateral oophorectomy before the onset of natural menopause or experienced premature or early natural menopause. Thus, after the publication of the WHI results, many women discontinued ET or avoided starting ET at all ages, including before age 50 years (Buist et al., 2004; Haas et al., 2004; Hersh et al., 2004). In agreement with the 2010 guidelines of the European Menopause and Andropause Society (EMAS), we suggest that women who undergo bilateral oophorectomy before the onset of natural menopause or experience premature or early natural menopause should be considered for hormonal treatment until the average age of natural menopause, and that the results from the WHI trials should not be applied to them (Shuster et al., 2010; Vujovic et al., 2010).

At this point, we cannot make general recommendations for the use of ET in the women who experience natural menopause in the typical age range. Although there is moderate evidence for a neuroprotective effect when ET is initiated early, this effect has not yet been confirmed in randomized clinical trials, and the beneficial effect observed may be due to confounding variables. More research is underway to address this question.

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Abbreviations

AD	Alzheimer's disease
APOE	apolipoprotein E
EMAS	European Menopause and Andropause Society
ESR1	estrogen receptor 1
ESR2	estrogen receptor 2
ET	estrogen treatment
MIRAGE	Multi-Institutional Research on Alzheimer Genetic Epidemiology study
WHI	Women's Health Initiative

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WHIMS Women's Health Initiative Memory study

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Highlights

- The effects of estrogen on the brain vary with age at the time of treatment.
- Estrogen naturally produced by the ovaries before age 50 years is neuroprotective.
- Estrogen treatment (ET) in early menopause may be neuroprotective (most commonly at ages 50–60 years).
- ET in late menopause (ages 65–79 years) is harmful regardless of the type of menopause.
- Women who experience premature or early menopause either naturally or after bilateral oophorectomy should receive ET.

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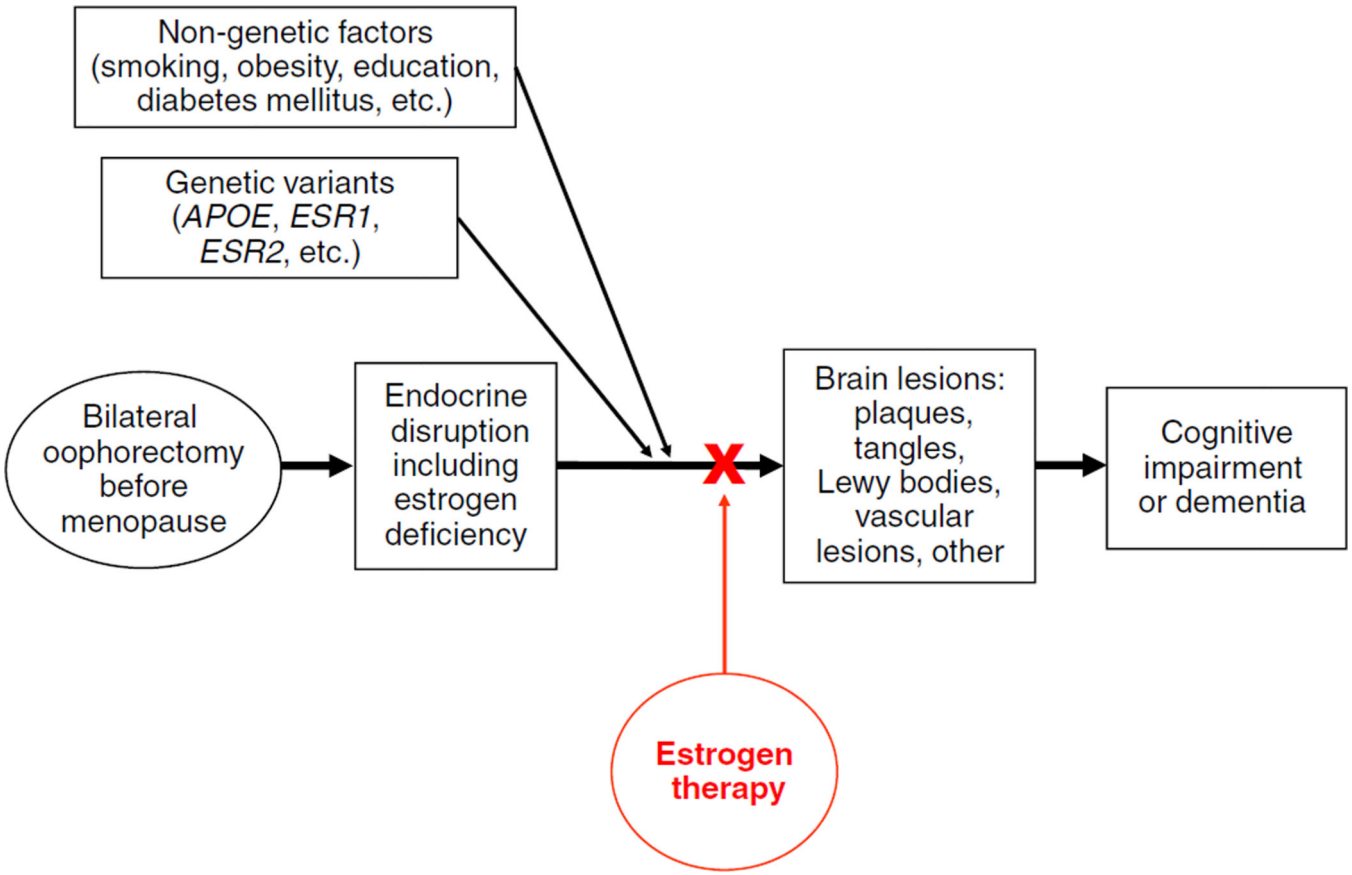

Fig. 1.

Proposed chain of causality linking bilateral oophorectomy to the increased risk of cognitive decline and dementia. In our etiologic hypothesis, genetic variants or non-genetic factors are effect modifiers (or interaction variables) rather than confounders. *APOE* = apolipoprotein E; *ESR1* = estrogen receptor 1; *ESR2* = estrogen receptor 2.

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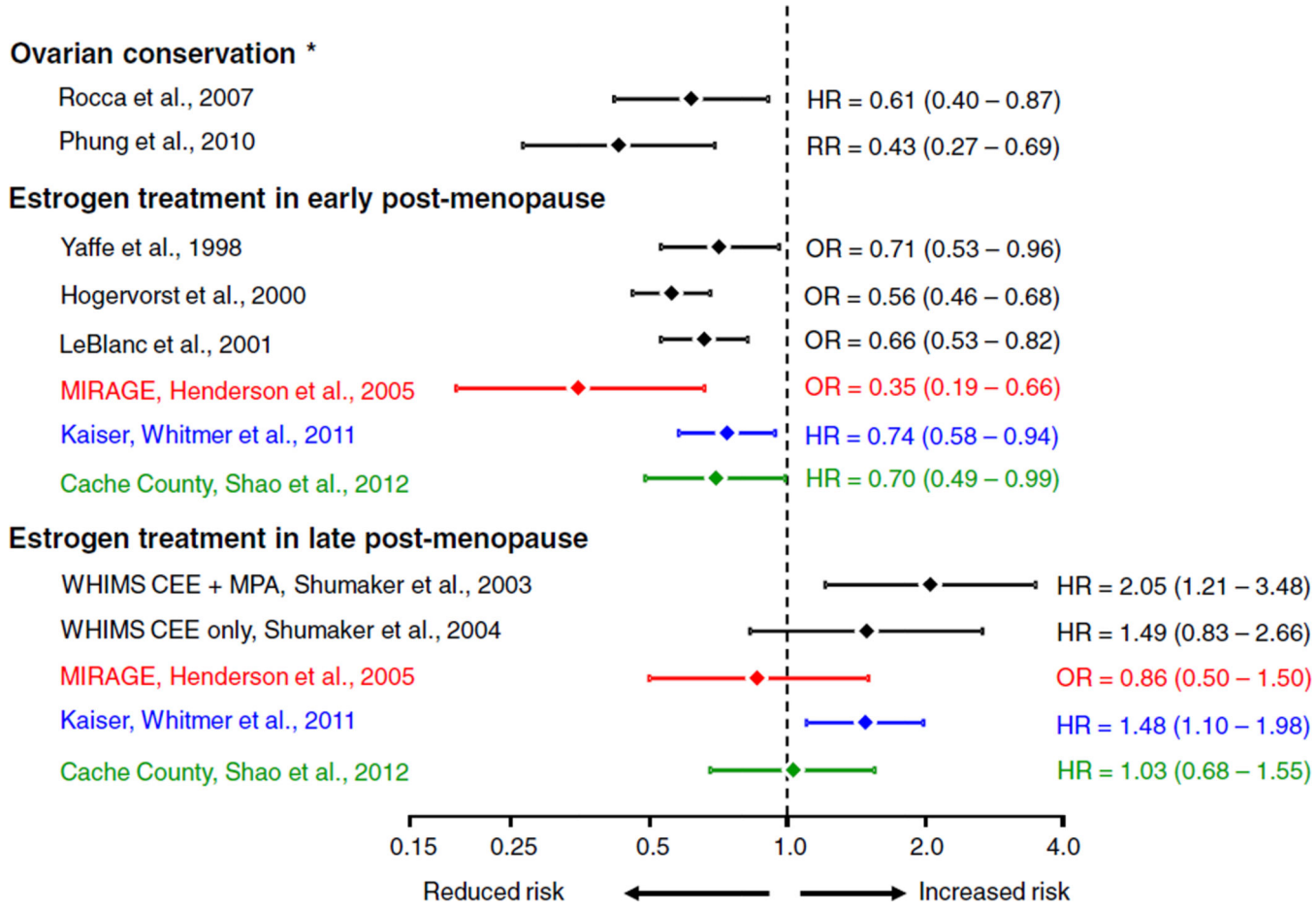

Fig. 2.

An update on the timing hypothesis. The effect of estrogen on the risk of cognitive decline or dementia varies with the age at which estrogen is removed (via bilateral oophorectomy) or added as pharmacological treatment. The figure shows the results of 13 studies expressed as relative risks (RR), odds ratios (OR), or hazard ratios (HR) and 95% confidence intervals (plotted on a logarithmic scale). Women with ovarian conservation have a reduced long-term risk of cognitive decline or dementia compared to women who underwent bilateral oophorectomy before menopause (most commonly before age 50 years). * One additional study confirmed the protective effect of ovarian conservation; however, the results were not reported using comparable relative risk estimates and could not be displayed (Bove et al., 2014). Treatment with estrogen in the early postmenopausal stage (most commonly at ages 50–60 years) is associated with a reduced long-term risk of cognitive decline or dementia in three meta-analyses. However, initiation of estrogen treatment in the late postmenopausal stage (ages 65–79 years) is associated with an increased risk of cognitive impairment or dementia. Three studies tested the timing hypothesis by conducting stratified analyses by age at the time of hormonal treatment. The two strata for the MIRAGE study are shown in red, for the Kaiser study are shown in blue, and for the Cache County study are shown in green. CEE = conjugated equine estrogen; MIRAGE = Multi-Institutional Research on Alzheimer Genetic Epidemiology study; MPA = medroxyprogesterone acetate; WHIMS=

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Women's Health Initiative Memory Study (Bove, 2014; Rocca, 2007; LeBlanc, 2001; Shumaker, 2004; Shumaker, 2003; Yaffe, 1998; Hogervorst, 2000; Phung, 2010; Bove, 2013; Whitmer, 2011; Henderson, 2005; Shao, 2012).
[Modified from Rocca et al., 2011(Rocca et al., 2011)].