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Estrogen Receptor α: A Critical Role in Successful Female Cognitive Aging

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Abstract

Due to potential health risks, current recommendations are that individuals who wish to use hormone therapy to treat menopausal symptoms do so for the shortest period of time possible. In our investigation into how short-term use of estrogens in midlife following loss of ovarian function exerts long-term effects on female cognitive aging in rodents, we discovered a link between the ability of previous exposure to estradiol to enhance memory long-term and its ability to increase estrogen receptor (ER) α levels in the hippocampus, a brain area important for memory. Follow-up studies in model systems implicate a role for ERα in enhanced cognitive function independent of ovarian or exogenously administered estrogens. Results are consistent with clinical studies in which brain ERα levels in older women and men are related to cognitive functioning and risk of cognitive decline is associated with polymorphisms in the gene that transcribes ERα. Research in preclinical models reveals mechanisms through which ERα can be activated and affect cognition in the absence of ovarian estrogens including ligand-independent activation via insulin-like growth factor-1 signaling and activation by brain-derived neuroestrogens. This report reviews preclinical and clinical data that collectively point to the importance of ERα in cognition and highlights the need to differentiate the role of estrogen receptors from their classical ligands as we seek approaches to facilitate successful cognitive aging.

Keywords

Estrogen receptor α; estrogens; hippocampus; brain; cognition; aging; IGF-1; neuroestrogens; menopause; Alzheimer's

The loss of ovarian hormones during menopause coincides with cognitive decline and increased risk of age-related dementias including Alzheimer's Disease [1, 2]. Several decades of research provides convincing evidence that estrogens play a neuroprotective role in the brain [3, 4]. Thus, expectations were that menopausal hormone therapy would provide benefits to the brain and cognition. In fact, early reports indicated that estrogens used during

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or near menopause reduced the risk and severity of Alzheimer's disease (AD) [5, 6]. However, results of the large Women's Health Initiative Memory Study (WHIMS) conducted by the National Institutes of Health indicated that conjugated equine estrogens (CEE) therapy resulted in small long-term deficits in cognitive function, smaller brain volumes and increased risk of dementia [7, 8, 9]. Following these unexpected results, attention was focused on various factors related to experimental design including type of estrogen administered and tests used to assess cognition. Attention also focused on the importance of the timing of initiation of hormone therapy. In the WHIMS, hormone therapy was administered to women aged 65 years and older (mean age of 73) and well after ovarian hormone levels have declined at menopause. The critical period hypothesis, which proposes that cognitive benefits of estrogens may only be apparent if administered near the time of menopause, is viewed as a possible explanation for discrepant results across studies [10]. Although existing clinical data provide some support for the critical period hypothesis of estrogen effects in women [11], recent results of the Kronos Early Estrogen Prevention Study (KEEPS) indicate no harm, but also no benefit, of either oral CEE or transdermal 17β-estradiol (estradiol) in healthy recently postmenopausal women [12]. Ongoing clinical trials such as KEEPS should provide more insight as women enrolled in the study reach ages at which cognitive decline is more prevalent.

Following publication of the Women's Health Initiative study results, long-term use of menopausal hormone therapy dropped significantly [13]. Furthermore, because of concerns regarding putative health risks [14, but see 15], the Food and Drug Administration (FDA) now recommends that women who wish to use hormone therapy to treat menopausal symptoms should limit its use for the shortest time period possible [16]. Because hormone therapy is now recommended to be used for only a few years near menopause, understanding if and how short-term exposure to estrogens exert long-term effects on the brain and cognitive aging trajectory has become critical.

In our own work investigating the long-term impacts of short-term use of estrogens on the brain and memory in a preclinical rodent model, we have identified an intriguing role for brain estrogen receptors, in the absence of ovarian or exogenous estrogens, in successful cognitive and brain aging. Consistent with experimental evidence are clinical studies that point to a potential relationship between brain estrogen receptor and cognitive aging. The current report provides an overview of the research from across the translational science spectrum that points to estrogen receptor (ER) α as a vital mediator of cognitive function during aging and highlights the importance of the translational link between preclinical and clinical research, in which results from each can inform questions asked by the other.

Lasting impact for cognition of short-term estrogen use in midlife: A role for ERα

Based on current recommendations that women use hormone therapy, if needed, for a short time, we employed a rodent model to empirically test whether short-term previous exposure to estrogens in middle-age had lasting impact on cognition. We found that in rodents, short-term treatment with estrogens in midlife produce similar benefits for memory to that of

continuous estradiol treatment without the prolonged exposure to hormones (See Fig 1A). Rats that received 40 days of estradiol treatment (roughly comparable to 3.5 years in women) immediately following ovariectomy in midlife displayed enhanced performance on a hippocampal dependent radial-maze memory task up to seven months after hormone treatment had been terminated [17]. These rats previously treated with estradiol showed comparable performance on the radial-arm maze to animals continuously receiving estradiol treatment throughout the experiment, demonstrating that short-term exposure to estradiol near the start of loss of ovarian function can have similar cognitive benefits to ongoing estrogen use. More recently, similar results have been found in nonhuman primates. Ovariectomized rhesus monkeys that received 11 months of cyclic estradiol injections displayed enhanced memory when tested one year after hormone treatments had ended [18]. These results provide evidence across species that midlife estradiol use can impact the brain and cognition via mechanisms that persist long after hormone exposure is terminated. Identifying the long-term changes in the brain resulting from midlife estradiol use can therefore provide new avenues for combating age related cognitive decline that avoid traditional long-term hormone treatment.

In our exploration into how short-term exposure to estrogens can exert long-term impacts on the brain, we found that in parallel to effects on memory, previous exposure to estradiol in midlife results in increased levels of ERα, but not ERβ, in the hippocampus up to eight months after hormone treatment had ended [17]. Importantly, the effects of previous exposure to estradiol on ERα were identical to those of animals that received ongoing estradiol treatment. This lasting increase in ERα resulting from previous treatment with estradiol following loss of ovarian function has been replicated in several studies [19, 20]. In addition to the impact on hippocampal levels of ERα, previous estradiol treatment results in lasting increases in choline acetyltransferase (ChAT) expression [17, 19], phosphorylation of p42-MAPK [19], and estrogen receptor mediated transcriptional activity [21] in the hippocampus. The long-lasting elevation of ERα protein levels and downstream mediators of cognitive function in the hippocampus following previous exposure to estradiol in midlife provide mechanistic evidence for a role for ERα in enhancing cognition in the absence of ovarian hormones.

Impacts of ERα on cognitive and brain aging in the absence of ovarian or exogenously administered estrogens

Our findings in a preclinical rodent model of female cognitive aging of elevated brain ERα levels and lasting memory enhancements that persist long after termination of midlife estradiol treatment led us to examine the clinical literature for evidence of a role of ERα in cognitive aging in humans. An overview of that literature is provided in Table 1.

In brief summary, similar to what we found in our preclinical model, levels of ERα in brain areas important for cognition are associated with cognitive and/or brain function in humans. For example, in both men and women with Alzheimer's disease (AD), increased levels of the full-length 66-kD isoform of ERα in the frontal cortex is associated with better performance on cognitive tests [22], suggesting that levels of ERα in the brain may

modulate cognition in AD patients. Additionally, nuclear expression of ERα protein levels in the CA1 and CA2 regions of the hippocampus is decreased in brains of women with AD as compared to those of age-matched controls [23]. Similarly, mRNA expression of *Esr1*, the gene that encodes for ERα, is decreased in the brains of women with AD as compared to those of age-matched controls [24]. Further supporting a role for ERα in cognitive aging are results that implicate polymorphisms in *Esr1* in both pathological and non-pathological cognitive decline. For example, there are several reports of an increased risk of AD in men and women with certain *Esr1* polymorphisms [25, 26, 27], although not all studies agree on which specific *Esr1* polymorphisms are relevant. Additionally, *Esr1* polymorphisms may act as effect modifiers for risk of AD in carriers of the *APOE* ε4 allele [28] and interact with *APOE* polymorphisms to impact cognition [29]. However, in contrast to these results are data that show no association between estrogen receptor genotype and susceptibility to late-onset AD [30]. In addition to potential effects on risk of AD, *Esr1* polymorphisms have been implicated in non-pathological cognitive decline [31, 32]. Interestingly, the increased risk of cognitive decline associated with *Esr1* polymorphisms in women was found to be independent of menopausal estrogen use [33]. However, certain polymorphisms can modulate effect of estrogens on cognitive function [34], suggesting that variations in ERα expression might affect the efficacy of menopausal hormone treatments. Not all reports support the association between *Esr1* polymorphisms and cognitive decline. For example, in elderly women without dementia associations were found between cognition and polymorphisms in *Esr2*, the gene that encodes for ERβ, but for not *Esr1* polymorphisms [35, 36].

Although a more thorough and critical review of the clinical data related to the association of estrogen receptor and cognitive aging is warranted, collectively current data suggest a potential role for brain ERα in successful brain and cognitive aging in humans. To test for a causal relationship of this association, we turned to our preclinical model.

Experimental evidence implicating brain ERα as a mediator of cognitive function in the absence of ovarian estrogens

To determine if ERα can directly impact cognitive function in aged females following the loss of ovarian function, we used two approaches – increasing and decreasing availability of brain ERα in aging ovariectomized rats and assessing effects on memory (See Fig 1B). We first overexpressed ERα in the hippocampus of aged ovariectomized females using lentiviral delivery of the gene for the protein (lenti-ERα) [37]. Aged females that received lenti-ERα outperformed rats that received a control virus on a hippocampus-dependent spatial memory task. In a second experiment, we blocked brain ERs in ovariectomized aging females that had previously undergone midlife estradiol treatment [20]. Rats received chronic intracerebroventricular infusion via osmotic minipumps of the ER antagonist, ICI 182,780 (ICI) or aCSF vehicle beginning after estradiol treatment was terminated. Rats treated with ICI had significantly worse memory on a radial-maze task than controls. Results reveal that increased levels or availability of ERs in the hippocampus lead to enhanced memory in the absence of ovarian or ongoing administration of estrogens. They provide support for the hypothesis that treatments that increase or maintain levels of ERα in aging females help to

improve or maintain memory processes even in the absence of ovarian or exogenously administered estrogens.

In addition to its direct effects on memory, ERα plays a neuroprotective role in the brain. For instance, increased hippocampal ERα expression protects female neonatal mice following hypoxic ischemia [38], a time point before ovarian estrogen production begins but at which ERα can have a lasting impact on cognitive function through adulthood [39]. This finding is particularly interesting considering the several studies that have shown the neuroprotective impacts of estrogens acting specifically through ERα following stroke in the aging brain [40, 41]. The protective functions of ERα have also been demonstrated in other brain regions and as well as in males. In the nucleus accumbens, stress results in decreased levels of ERα and overexpression of ERα promotes resilience against chronic social defeat stress through transcriptional changes in both male and female mice [42].

Together, data from preclinical models indicates an important role for estrogen receptors—independent of ovarian estrogens—in maintaining cognitive health across the lifespan.

Mechanisms by which brain ERα can be activated in the absence of circulating estrogens

In order for ERα to continue to impact cognition after loss of ovarian function, it must be activated by mechanisms independent of ovarian estrogens. Based on work from our lab and others, we propose two mechanisms for sustained activation of ERα in the absence of ovarian estrogens: ligand-independent activation of ERα by growth factors including insulin-like growth factor-1 (IGF-1) and activation of the receptor by locally synthesized neuroestrogens (See Fig 1C).

Ligand-independent activation by IGF-1

Activation of estrogen receptor-dependent transcriptional activity in the absence of estrogens by growth factor was shown years ago *in vitro* [43]. Specifically, insulin-like growth factor-1 (IGF-1) is able to activate ERα through activation of the MAPK pathway resulting in phosphorylation of ERα at S118 [44]. More recently, work from our lab demonstrated a similar effect *in vivo* [45]. Acute infusion of IGF-1 to the lateral ventricle of ovariectomized rats results in increased levels of pS118-ERα in the hippocampus one hour after treatment, and increased levels of total ERα 24 hours after treatment Therefore, ligand-independent activation of ERα by IGF-1 provides a potential mechanism through which increased expression of ERα can enhance cognition in the absence of ovarian estrogens.

IGF-1 is a peptide hormone that acts as the major effector of the pituitary hormone growth hormone (GH). It is structurally very similar to insulin and can bind to insulin receptors in addition to its own IGF-1 receptor [46]. IGF-1 is necessary for neuronal development and regulates plasticity in the developing brain [47]. Because of the critical role it plays in development, levels of IGF-1 change over the lifespan and ultimately decline in the brain with aging [48]. Similar to the decline in estrogens following the loss of ovarian function, this decrease in IGF-1 coincides with increased risk of cognitive decline.

Studies in humans implicate IGF-1 signaling dysfunction in the pathology of age-related dementias including AD, although much debate remains about whether increased IGF-1 levels would be beneficial in combatting these disorders. For instance, IGF-1R expression levels were found to be decreased in the brains of patients with AD as compared to those of controls [49]. On the other hand, work in animal models suggests that increased IGF-1R signaling contributes to the pathological formation of proteins associated with AD [50]. Dysfunction in IGF-1 and insulin signaling likely plays a role in the pathology of Alzheimer's, although the specific mechanisms remain unclear.

Studies in model systems have demonstrated that the effects of IGF-1 signaling in the brain overlap greatly with the impacts of estrogen receptor signaling and indicate that these two systems closely interact. Most neurons and some astrocytes in the rat brain that express IGF-1R also express either ERα or ERβ, with particularly prevalent colocalization of IGF-1R and ERα in hippocampal neurons [51]. The interaction between these receptors goes beyond simply colocalization, however. ERα and IGF-1R have been shown to form estradiol dependent protein complexes in the brains of ovariectomized rats [52].

These interactions between ERα and IGF-1R are important for maintaining cognition in the aging brain. In ovariectomized rats treated with continuous exposure to estradiol, antagonizing IGF-1R with JB1 directed to the lateral ventricle blocked the ability of estradiol to enhance performance on the radial-arm maze and increase hippocampal expression of synaptic proteins PSD-95 and spinophilin [53]. Furthermore, JB1 blocks the memory enhancements and increased hippocampal expression of ERα, ChAT, and phosphorylated p42-MAPK in ovariectomized rats previously treated to estradiol during midlife [19]. These findings demonstrate that IGF-1R modulates the ability of ERα to impact memory and hippocampal function in both the presence and absence of circulating estrogens.

Neuroestrogen activation of ERα

In addition to ligand-independent activation, following loss of ovarian function, estrogen receptors may be activated by locally synthesized estradiol. These brain-derived neuroestrogens are capable of being synthesized throughout the human brain—including in the hippocampus, cerebral cortex, hypothalamus, and amygdala, among others—as indicated by widespread expression of aromatase, the enzyme that synthesizes estradiol from testosterone [54]. Because aromatase inhibitors are used in breast cancer treatments postmenopause, there are clinical insights into the role of neuroestrogens in cognition—presumably due to activation of estrogen receptors—in the absence of ovarian estrogens. Many, but not all, studies demonstrate that the use of aromatase inhibitors can negatively impact cognitive function in humans [for meta-analysis, see 55]. Interestingly, the use of aromatase inhibitors is associated with decreased hippocampal activity and impaired memory function in postmenopausal women [56]. However, the lack of randomized clinical trials investigating the role of aromatase inhibitors in cognitive function limits the ability to draw conclusions as to the role of neuroestrogens in estrogen receptor function in the absence of ovarian estrogens.

Preclinical model systems have been used to empirically test the effects of aromatase inhibitors on hippocampal memory and estrogen receptor function. Chronic systemic administration of the aromatase inhibitor letrozole, which blocks estradiol synthesis including neuroestrogens, was recently shown to impair spatial memory performance in male and female gonadectomized marmosets [57]. Additionally, we recently showed in a mouse model that neuroestrogens are able to impact estrogen receptor-dependent transcription in the brain for a short-term, but not a long-term following ovariectomy [58]. Further work is necessary to fully elucidate the long-term role of neuroestrogens in mediating estrogen receptor-dependent activity in the brain after loss of ovarian function. Interestingly, recent findings from our lab a potential interaction between neuroestrogens and IGF-1 in sustaining ERα activity in the absence of ovarian estrogens [59].

Conclusion

Across multiple species and paradigms, an increasing body of literature suggests an important role for ERα in maintaining cognitive function in aging females in the absence of ovarian or exogenously administered estrogens. Clinical studies have revealed that variability in expression of ERα in older women (and men) is associated with variability in risk of cognitive impairment. Ongoing work in preclinical model systems is providing valuable insight into the mechanisms through which ERα enhances memory in aging females. Moving forward, identification of factors that contribute to variability in levels of brain ERα during aging, likely including previous use of menopausal estrogen therapy in midlife and perhaps environmental factors such as stress [42], may lead to novel approaches to cognitive aging that capitalize on the potential of ERα to positively impact the aging brain.

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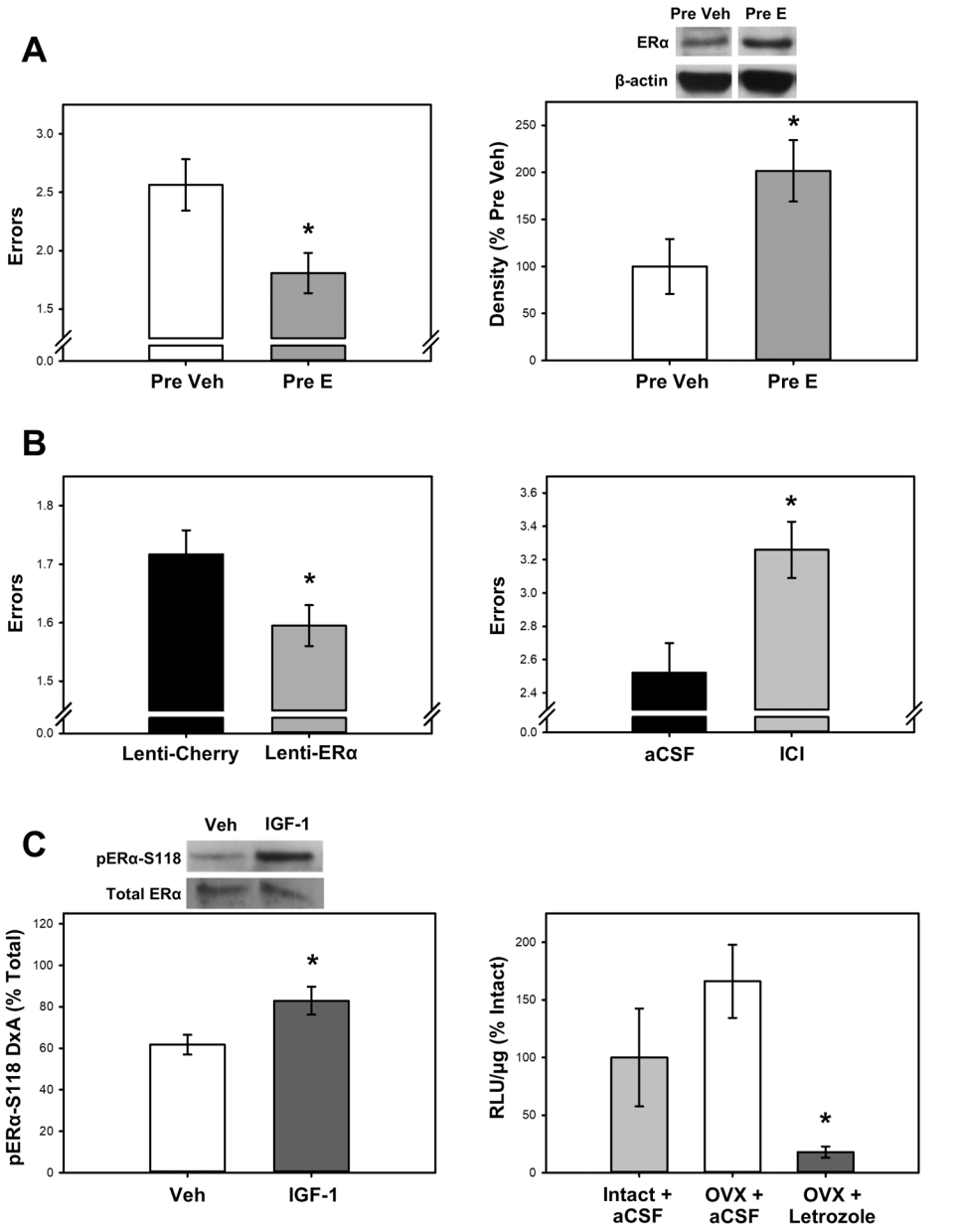

Fig 1. Evidence that ERα acts in the brain to enhance female cognitive aging in the absence of ovarian or exogenously administered estrogens.

(A) *Increased levels of brain ERα are associated with improved memory in the absence of ovarian or exogenous estrogens*. Previous midlife estradiol treatment (Pre E) as compared to vehicle treatment (Pre Veh) in aging ovariectomized rats enhances memory (decreased errors) on a radial-arm maze task (left) and increases protein levels of ERα in the hippocampus as measured by western blotting (right) seven months after termination of estradiol treatment. (B) *A causal relationship exists between increased levels or availability of brain ERα and enhanced memory in the absence of ovarian or exogenous estrogens*. Overexpressing ERα in the hippocampus of aging ovariectomized rats via lenit-viral delivery (Lenti-ERα; left) enhances memory (decreased errors) on a radial-maze task as compared to a control virus (Lenti-Cherry). Antagonizing brain ER via intraventricular (icv)

infusion of the ER antagonist ICI 182,780 (ICI; right) in aging ovariectomized rats impairs memory (increased errors) on the radial maze task as compared to infusion of aCSF vehicle. (C) *In the absence of ovarian or exogenous estrogens, ERα can be activated by at least two mechanisms*. Ligand-independent activation occurs by growth factor signaling (left) in which an icv infusion of insulin-like growth factor-1 (IGF-1) increases levels of phosphorylated ERα at S118 in the hippocampus of ovariectomized rats as compared to infusion of aCSF vehicle. Brain-derived neuroestrogens can activate the receptor (right) in which mice that were ovariectomized (OVX) 10 days prior had similar levels of hippocampal ER-dependent transcription (i.e. luciferase activity indicated by RLU/μg) as gonadally intact females. Chronic icv infusion of the aromatase inhibitor letrozole, which blocks brain estradiol synthesis, blocks ER-dependent transcription in the hippocampus. *p < .05; Adapted from [17, 20, 37, 45, 58].

Table 1.

Overview of results of clinical studies investigating the relationship between ERα and pathological and non-pathological age-related cognitive decline

Relationship	Authors	Reported Population	Measures	Summary of findings	PMID/doi
Studies supporting an association between ERα/*Esr1* and cognitive outcomes	Bojar et al. 2016	Middle-aged women without dementia	Cognitive tests; E2 levels; *Esr1* polymorphisms	*Esr1* polymorphism modulated the effect of E2 on cognitive function	PMID: 27680398
	Cheng et al. 2014	Meta-analysis of other studies	*Esr1* SNPs PvuII and XbaI; AD risk	*Esr1* PvuII SNP significantly increases risk of AD in Caucasian, but not Asian women	PMID: 25061285
	Corbo et al. 2006	AD patients and age-matched controls (men and women)	*Esr1* SNPs PvuII and XbaI; APOE plasma levels	*Esr1* SNPs PvuII and XballI increased risk of AD in men only; in women those SNPs increased rate of cognitive decline	PMID: 16699281
	Hu et al. 2003	AD patients and age-matched controls (women)	ERα localization in hippocampus	Decreased nuclear ERα staining in CA1 and CA2 of AD brains	PMID: 12819990
	Ishunina et al. 2007	AD patients and age matched controls (women)	*Esr1* mRNA and aromatase activity in hippocampus	Decreased *Esr1* mRNA (normal and splice variant) and decreased aromatase expression in AD hippocampi	PMID: 17010478
	Kelly et al. 2008	AD patients (men and women)	Cognitive tests; ERα protein levels	Increased nuclear ERα in frontal cortex associated with better cognitive performance	PMID: 18288931
	Ma et al. 2009	AD patients and age-matched controls (men and women)	*Esr1* SNPs; AD risk	Several *Esr1* SNPs associated with AD risk and age of onset	PMID: 19586561
	Ma et al. 2014	Elderly men and women	*Esr1* SNPs; Cognitive tests	Several *Esr1* polymorphisms associated with cognitive decline	PMID: 23567436
	Pinkas et al. 2018	Post-menopausal women	*Esr1* and *APOE* polymorphisms; cognitive tests	Interactive effects with certain *Esr1* and *APOE* polymorphisms on memory	doi.org/10.5114/aoms.2018.72972
	Ryan et al. 2014	Elderly men and women	*Esr1* polymorphisms; Risk of AD and dementia	*Esr1* polymorphism slightly assoc. with increased AD risk in women, but *Esr1* polymorphism + *APOE* ε4 allele increased risk of AD	PMID: 23491264
	Yaffe et al 2002	Elderly women	Cognitive tests; *Esr1* SNPs	*Esr1* SNPs increase risk of cognitive impairment, independent of estrogen use	PMID: 11955468
	Yaffe et al. 2009	Elderly men and women without dementia	Cognitive tests; *Esr1* and *Esr2* SNPs	*Esr1* and *Esr2* SNPs increased risk of cognitive impairment	PMID: 17889406
Studies not supporting an association between ERα/*Esr1* and cognitive outcomes	Fehsel et al. 2016	Elderly women without dementia	Cognitive tests; *Esr1, Esr2, APOE* SNPs	No association of *Esr1* SNPs with cognitive effects but did see effects for *Esr2* and some interaction of *Esr2* with *APOE* SNPs	PMID: 27629499
	Goumidi et al. 2011	AD patients and age-matched controls (men and women)	*Esr1* and *Esr2* SNPs; late onset AD risk	No association of *Esr1* or *Esr2* SNPs with late onset AD risk	PMID: 21673408

Relationship	Authors	Reported Population	Measures	Summary of findings	PMID/doi
	Ryan et al. 2013	Elderly women without dementia	Cognitive tests; Esr1 and Esr2 polymorphisms	Five common *Esr1* polymorphisms not associated with cognitive impairment, but some effect of *Esr2* polymorphisms	PMID: 23932494