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REVIEW ARTICLE

Reproductive Lifespan as a Proxy for Estrogen Exposure and Alzheimer's Disease Risk in Women: A Multisystem Perspective

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ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disorder in which nearly two-thirds of cases occur in women. This literature review examines how reproductive lifespan serves as an important proxy for cumulative estrogen exposure, which helps regulate the risk of AD in women. Here, I will investigate the interactions of various biomarkers, including tau pathology and amyloid beta deposition, genetic predisposition, and brain bioenergetics. Estrogen plays a crucial role in protecting the brain by decreasing amyloid beta deposition while interacting with various genetic factors, such as the *APOE4* gene. Research shows that a longer reproductive lifespan, or a greater cumulative estrogen exposure, is associated with slower cognitive decline and reduced AD risk. A proposed solution to a shorter reproductive period is Hormone Replacement Therapy (HRT), although it has complex factors, such as the timing of HRT and genetics. Here, I will propose a cohesive framework using reproductive lifespan as a proxy for AD risk, combining multiple biological systems. This review aims to outline the connection between lifetime estrogen exposure and multiple different AD biomarkers, highlighting the importance of reproductive history in AD research and treatment.

KEYWORDS: Biology, Alzheimer's Disease, Reproductive Lifespan, Menopause, Estrogen, Cognitive Decline, Women's Brain Health, Hormone Replacement Therapy.

Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that is the most common type of dementia, affecting millions worldwide. Of all AD cases, two-thirds occur in women.[1] Traditionally, this gender disparity was associated with a longer female lifespan.[2] However, recent research points out that several gender-specific factors, such as hormonal, genetic, and structural differences in the female brain, play a major role in their higher AD risk.[3]

Recent research has discovered that estrogen exhibits neuroprotective effects in the brain, including regulating brain glucose metabolism and reducing AD-related biomarkers such as amyloid-beta (Aβ) buildup.[2] During the menopausal transition, estrogen levels drop quickly, ceasing its protective pathways. Additionally, interactions between genetics and estrogen have been explored, such as the increased expression of apolipoprotein E4 (*APOE4*), an AD-inducing gene.[1] Past research has a growing focus on estrogen's role in AD, though interactions between multiple AD biomarkers, Hormone Replacement Therapy (HRT), Aβ, and brain energetics have not been fully understood.

Reproductive lifespan is an understudied but important element that measures the time between menarche (the first occurrence of menstruation) and menopause (the cessation of menstruation). This measure has been proposed as a proxy for cumulative estrogen exposure, capturing a critical time period that can be used to demonstrate how hormonal shifts impact AD risk, tau and Aβ deposition, and cognitive decline.[4] Past research has suggested a link between AD and earlier or premature menopause, or a shorter reproductive lifespan.[5]

This paper investigates how reproductive lifespan correlates to the onset and severity of AD through several key biomarkers, such as hormone levels, brain metabolism, and genetic expression. This is a crucial question as it evaluates the disproportionate effect of AD on women, and may help guide the way to the development of more personalized, sex-specific treatment strategies. By measuring reproductive lifespan rather than menopause alone, or hormone levels at a single point in time, a more indicative and general medical evaluation can be drawn, one that sums up a lifetime of estrogen exposure. Capturing a woman's entire hormonal arc can be beneficial to achieve a more comprehensive approach to assessing AD risk and informing the therapeutic approach. While past research has studied the connection of AD risk to menopause, estrogen, HRT, tau buildup, Aβ deposition, and brain energetics separately, reproductive lifespan has not been fully established as a unifying measure combining multiple biological systems.

This review will argue that using an integrative approach like reproductive lifespan can serve as a meaningful proxy for cumulative estrogen exposure, which regulates the risk of AD in women through various biomarkers. To support this thesis, the paper first explores the relationship between reproductive lifespan and tau buildup, amyloid-beta deposition, brain structure, bioenergetics, and genetic individuality. This includes estrogen's function in all of the underlying factors, which makes women more vulnerable to the debilitating disease. Further, current treatment proposals, such as HRT, are evaluated, and the key contributors to its effectiveness, i.e., timing and genetics, are analyzed. Finally, these connections are brought

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together to propose a unified model to understand women's unique risk of AD.

Discussion

Reproductive Lifespan:

Reproductive lifespan is a measure of the period between menarche and menopause, which may be used as a proxy for cumulative estrogen exposure, a reproductive hormone that has regulatory neuroprotective benefits.[4]

Estrogen has a wide range of effects aside from its reproductive role: this includes important functions that relate to the brain and aging. Its neuroprotective role ranges from its effects on Aβ and tau deposition to synaptic and metabolic homeostasis. Estrogen plays a major role in neuronal survival, synaptic plasticity, and brain energetics, all of which are important to brain health and protection.[2] The hormonal fluctuations that take place during menopause have a critical effect on the female brain, changing the functionality of intracellular signalling, neural health, and mitochondrial metabolism. This sudden neurovulnerability makes the brain greatly susceptible to cognitive decline upon the hormonal transition.[2]

In recent research, later menopause has shown a correlation to slower cognitive decline and improved memory performance.[4] Conversely, an earlier age at menopause has been associated with greater AD risk, brain atrophy, and a quicker buildup of amyloid and tau pathology.[5] These findings indicate that a shorter reproductive lifespan due to early menopause, delayed menarche, or oophorectomy can lead to neurodegeneration and eventual AD development. This demonstrates how reproductive lifespan can be utilized as a useful proxy in predicting AD risk in women through linking estrogen's wide range of protective brain mechanisms to its cumulative exposure.

Estrogen's Role in Neuroprotection:

Estrogen is a key neuroprotective hormone in women, playing a critical role in maintaining cognitive function and influencing susceptibility to Alzheimer's Disease. It plays a crucial role in synaptic plasticity, brain structure and metabolism, and gene expression.[2] Various studies have demonstrated the protective effects of estrogen, contributing to cognitive benefits in women. Tang *et al.* provided evidence that the use of estrogen was linked to lower AD risk. The study established that estrogen "promotes the growth of cholinergic neurons" and "stimulates the secretase metabolism of the amyloid precursor protein."[3] Given estrogen's role in regulating neuromechanisms, its loss during menopause may trigger the amyloid cascade, prompting the onset of amyloid-beta accumulation, one of the earliest detectable biomarkers of AD.

Amyloid-beta accumulation is a key biomarker in AD, contributing to cognitive decline caused by interrupting neural communication between brain cells. The buildup leads to plaques and tangles, which in turn interfere with synaptic function and consequently can impair cognition.[2] Women, when compared to men of the same age group, were found to have greater Aβ buildup after menopause, when estrogen receptors are dismantled and lost.[6] The amyloid cascade hypothesis theorizes that Aβ accumulation happens early in AD development, concurrent with an upstream of oxidative stress.[7] This upstream takes place during the bioenergetic crisis in the menopausal brain when estrogen levels drop, indicating that earlier menopause is associated with greater cognitive decline.[2]

According to the Alzheimer's disease amyloid cascade, changes in cerebrospinal fluid (CSF) and tau pathology precede Aβ deposition during cognitive decline, with an increased tau pathology translating to faster cognitive decline.[7] During menopause, the depletion of estrogen has been shown to increase tau pathology and neuroinflammation.[6] While Aβ deposition in the endorhinal cortex is similar in both genders, after menopause, women were found to have much higher levels of tau pathology than age-matched males. Together, these factors show that tau pathology may be used as a predictive AD biomarker, particularly in relation to estrogen loss.

Research has demonstrated estrogen's role in activating a network of genes contributing to neuroprotection and AD pathology.[1] In a multi-species study done on both humans and macaques, it was found that estrogen upregulates thousands of different genes contributing to aging and cognition.[1] In the macaques, estrogen activated 504 genes important to neuron and brain health, while increasing the expression of the APOE. While the *APOE* gene is protective in most cases, those with the APOE e4 rare gene variant are negatively affected by its activation.[8] 140 of the 504 genes activated by estrogen were linked to synapse health and bioenergetic metabolism, creating another link between the cognitive AD biomarkers. Ultimately, this study emphasized the importance of genetic individuality in estrogen treatments combating cognitive decline.

Menopause triggers various metabolic and structural brain shifts upon estrogen loss, many of which contribute to cognitive decline.[2] With the influence of the estrogen receptor network, located in the nucleus of cells and associated with the plasma membranes and mitochondria, the brain effectively responds at proper times to regulate brain energy metabolism. During menopause, the loss of estrogenic regulation destabilizes the brain's glucose metabolism, dismantling ketogenic pathways and promoting hypometabolism. In a study of rats that had undergone oophorectomy, rats given estrogen did better on memory tasks than those without the treatment. Those treated with estrogen also showed further preservation of neurons in the brain, associated with better cognition, providing further evidence that greater estrogen exposure, or a longer reproductive lifespan, is associated with cognitive enhancement and AD protection.[9]

Menopause and Brain Changes:

Menopause is a major turning point regarding female brain health, during which estrogen levels drop, initiating numerous metabolic and structural brain changes, resulting in an elevated risk for AD.

Estrogen plays a critical role in the brain, balancing metabolism and maintaining healthy neuronal pathways, reducing vulnerability to AD. In particular, estrogen receptors are responsible for regulating cerebral metabolic rates and avoiding hypometabolism– a reaction that has been linked to Aβ deposition.[2] The brain's glucose metabolism is responsible for

providing the energy for the brain to function and maintain its neuronal pathways, along with a variety of other essential brain processes. Upon the reduction of estrogen and the slowing of the cerebral glucose metabolism, the body reacts by inducing a state of starvation, dismantling ketogenic pathways, and increasing fatty acids, a substitute form of energy.[2] This metabolic shift can lead to oxidative stress, mitochondrial damage, and potential neurodegeneration. In a study of ovariectomized rats, estrogen-treated rats showed increased expression of neuronal signalling and the cholinergic system– a process crucial for brain function, attention, and memory.[9] This suggests that estrogen benefits the brain and its mechanisms, especially in reducing AD risk, indirectly corroborating the benefits of late menopause and extended exposure.

The female brain shows signs of numerous structural changes in volume and atrophy during the menopause transition.[2] This includes changes in various cortical and subcortical structures such as the hippocampus, thalamus, and amygdala– especially regarding Grey Matter Volume (GMV) and White Matter Volume (WMV) changes.[10] In a study conducted by Lisa Mosconi, results suggested a direct correlation between peri- and post-menopausal brain and grey and white matter volume loss, connected to cognitive impairment and decline. Other research also showed that earlier menopause was linked with a greater reduction of GMV, increasing the likelihood of AD development.[5] Crucially, this change was not observed in age-matched males, indicating that menopause and hormonal shifts are significant contributors to the specified structural changes. Overall, these menopause-related patterns highlight the importance of estrogen-regulated systems in the brain.

At the molecular level, amyloid beta, one of the main pathological hallmarks of AD, plays an important role in the brain, being responsible for plaque buildup and neurofibrillary tangles, leading to eventual cognitive decline.[2] Moreover, tau pathology is even more closely associated with cognitive decline than Aβ.[11] In particular, individuals with widespread Aβ buildup demonstrated greater tau pathology than those with regional Aβ buildup.[10] This is especially relevant to menopause, as earlier menopause has been linked to the acceleration of the transition from regional to widespread Aβ buildup (Figure 1). These connections highlight the potential benefit of using spatial mapping of Aβ deposition with reproductive lifespan in order to predict AD susceptibility and cognitive decline.

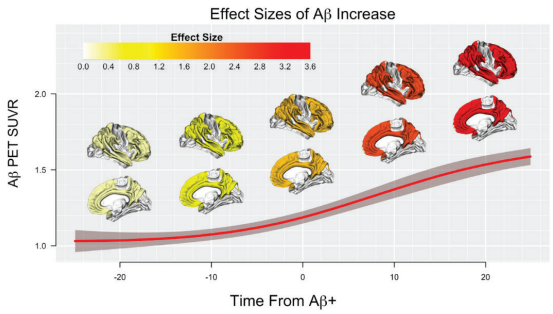

Figure 1: Effect sizes of Aβ PET SUVR (Standardized Uptake Value Ratio), an indicative measure of Aβ build-up, are displayed as a function of time, starting from initial Aβ positivity. The x-axis represents the time from the beginning of Aβ deposition, corresponding with the beginning of menopause, and the y-intercept represents the effect size of the Aβ based on the PET SUVR scores. The graph is color-coordinated, with lighter yellow indicating early regional deposition, while darker reds indicate severe, widespread Aβ deposition.[7] The graph illustrates the change in Aβ volume in relation to lifetime, emphasizing the role of time in protein buildup.

The above evidence supports the conclusion that menopause represents a critical transition point of estrogen decline in which the brain alters in structure, glucose metabolism rate, and Aβ and tau pathology. Based on the biological mechanisms outlined in this section, these changes can potentially drive neurovulnerability, cognitive decline, and AD pathology.

Genetic Importance:

Apolipoprotein E is a protein designated for lipid transport, playing a major role in neuronal repair and cholesterol metabolism.[1] It comes in various isoforms, such as APOE ε2, APOE ε3, and APOE ε4. Compared to the others, APOE ε4 is the most dangerous gene variant, being one of the strongest genetic risk factors of AD.[2] Women with *APOE4* have shown greater cognitive decline and AD pathology, such as greater tau buildup and Aβ spread. Importantly, estrogen decline has been linked to increased expression of the APOE ε4 gene, suggesting that reproductive lifespan may play a role in the cause of this gender disparity.[1]

While estrogen is important for regulating the brain, it also plays a major role in gene expression related to cognition and AD. As discussed earlier in the review, a study conducted by Abhirami Ratnakumar indicated that estrogen activated 504 genes important for brain and neuron health (Figure 2). While it had many positive effects on the brain, it also activated APOE-related genes. This meant that those with the *APOE4* gene variant had an increased expression of its negative effects, making them more susceptible to AD. The study identified rare genetic mutations such as MCM8, ASPM, and SORL1, showing how they were influenced by the presence of estrogen. Specifically, ASPM was determined to be a protective gene, activated by estrogen, while SORL1 and MCM8 were identified as AD-inducing genes.[1] These findings suggest that *APOE4* carriers may experience a variety of protective and harmful effects from estrogen, demonstrating the importance of genes in relation to reproductive lifespan.

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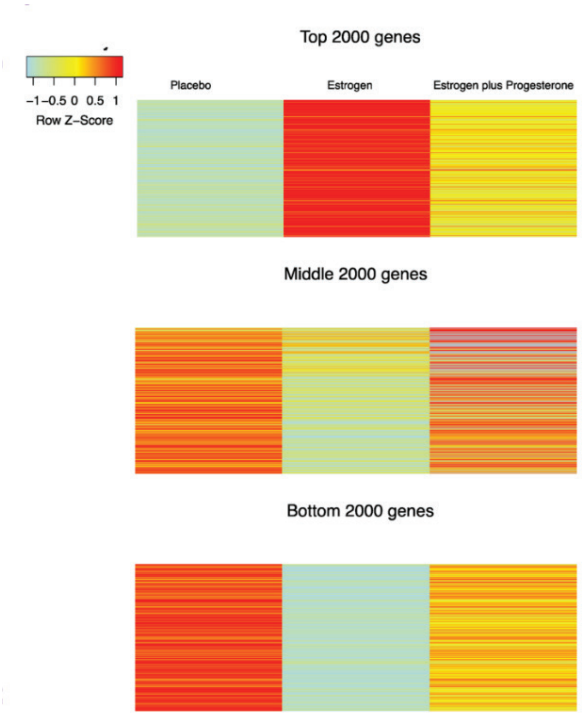

Figure 2: The expression levels of various treatments (Estrogen, Estrogen + Progesterone, and Placebo) are shown in a color scale (row z-score). The Top 2000 genes (top row) show that the highest expression was from the estrogen group. The Bottom 2000 genes (bottom row) were the least affected by estrogen. Each row is a gene (15,517 genes). Cooler colors indicate lower expression, and warmer colors indicate higher expression.[1] The data highlights that estrogen exposure facilitates greater gene expression, suggesting estrogen's role in enhancing neuroprotective genes.

Genetic individuality may also explain the conflicting results that have been reported on the effects of HRT, some leading to increased AD risk and some to neuroprotection.[8] People with specific genetic characteristics may respond differently to exogenous estrogen use, leading to different outcomes. In particular, it can be hypothesized that women without the *APOE4* gene may benefit from HRT use, slowing cognitive decline, Aβ deposition, and tau pathology, while those with the rare genetic variant may experience adverse effects.

In retrospect, reproductive lifespan may play a role in genetic expression, with possibilities including *APOE4* amplifying the effects of cumulative estrogen exposure. Women with *APOE4* and a shorter reproductive lifespan may exhibit faster progression and earlier onset, due to the deprivation of estrogen's protective effects. In contrast, a longer reproductive lifespan may enhance neuroprotection, sustaining estrogen's protective effects, although offset by the prolonged activation of the harmful *APOE4* genes. With further research, reproductive lifespan may be employed as a proxy for genetic expression, used to consider personalized treatment plans such as HRT.

Hormone Replacement Therapy and Window Period:

HRT has become increasingly common in women approaching menopause, used as a replacement for the hormones lost during the menstrual transition. It uses exogenous estrogen, sometimes combined with progesterone, to mimic the body's natural hormone production.[2] Aside from alleviating menopause symptoms such as hot flashes, insomnia, and depression, HRT may prolong estrogen's protective effects. In women with a naturally shorter reproductive period, estrogen replacement therapy can be a useful treatment to protect the brain from the vulnerability that comes with early menopause.[8]

Women taking estrogen post-menopause have been shown to experience the onset of AD significantly later than those who do not.[3] This was attributed to the protective effects of estrogen that were prolonged upon the use of estrogen replacement therapy. Conversely, another study found that HRT use post-menopause had an adverse impact on AD risk, causing brain atrophy and lowering hippocampus and brain volume.[13] These conflicting results raise the question: Is HRT beneficial or harmful in delaying the onset of AD?

The critical window hypothesis is an idea that HRT is only beneficial when given during the perimenopausal and early menopausal stage.[13] During this "window of opportunity," tau buildup and Aβ spread can be slowed, decreasing the risk of AD. In contrast, according to a study conducted by Rachel A. Whitmer, HRT taken in late life will have detrimental effects on the brain, accelerating AD pathology with a 48% elevated risk of AD. Based on the above, the effects of HRT may be altered by cumulative estrogen exposure, with a shorter reproductive period compressing the length of the window period, while a longer reproductive period would extend it. After the window period closes, the estrogen will exacerbate Aβ deposition and other AD biomarkers, rather than ameliorating cognitive function.[13] Timing is unique to every individual, and being able to pinpoint and adjust the most effective time period in which to administer HRT would advance therapeutic approaches to AD.

As discussed previously, estrogen plays a major role in regulating various AD-related mechanisms. During the window, the exogenous estrogen reduces the deposition of Aβ in the brain, improves synapse formation, and enhances glucose metabolism and cerebral blood flow.[13] The effectiveness of HRT may depend on when these biomarkers begin to shift. Personalized timing may be the key to maximizing therapeutic effects.

Genetics is also an important factor when considering HRT use, as certain gene carriers may respond differently to estrogen replacement therapy. For example, women with the *APOE4* gene variant would have adverse effects upon HRT use, even within the "window of opportunity."[8] This highlights the importance of considering genetics when prescribing medications, or in this case, when HRT is undergone. In contrast, individuals not carrying the *APOE4* gene would potentially benefit from HRT, depending on timing. Overall, gene-hormone interactions may potentially be an explanation for the conflicting results regarding HRT research. Exploring these interactions in future research would be beneficial to inform the effectiveness of treatment options.

Overall, the success of HRT usage is dependent on individualized factors, such as genetics and timing, thus leading to inconclusive findings on the usefulness of its application. This makes room for progress in the future. Here, I suggest that using reproductive lifespan and genotype as crucial factors for

personalizing HRT treatment can contribute to its effectiveness, ultimately delaying AD progression.

A Unified Model:

A unified model is crucial for integrating all the AD-related mechanisms that have been individually researched to create a comprehensive picture that utilizes reproductive lifespan as a proxy for AD risk. By capturing temporal dynamics across a woman's lifetime, the model can capture the evolution of various biomarkers and crucial factors in terms of reproductive lifespan in order to better combat the disease.

As discussed earlier, many variables contribute to the onset of AD, several of which have a network of links between one another. Reproductive lifespan serves as a common factor among various AD-related systems, linking a short vs. long lifespan with differences in cumulative estrogen (Figure 3). The hormonal decline at menopause has been connected to cognitive decline, such as the slowing of glucose metabolism and the decline of cerebral blood flow. Upon this shift, amyloid beta and tau dynamics change, accelerating their accumulation due to the loss of estrogen's protective effects.[10] Together, these alterations influence brain structure, prompting brain atrophy and a decrease in hippocampal volume.[5] Genetics also plays an important role, as people carrying the *APOE4* gene have an altered brain response to estrogen withdrawal, making them more vulnerable to cognitive decline compared to non-carriers.[1]

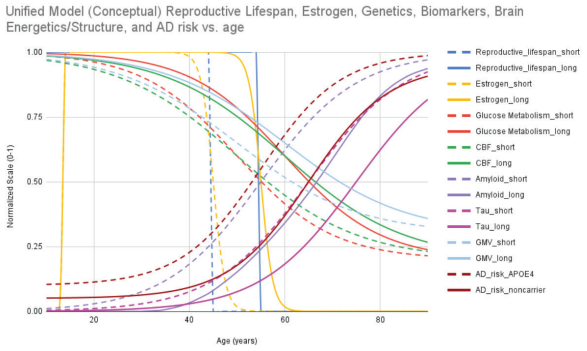

Figure 3: A conceptual graph using synthetic data to illustrate the unified model. This model uses a normalized scale (0-1) in relation to age in years to compare various important AD-related biomarkers and factors. It uses reproductive lifespan as a proxy, outlining the difference in the variables depending on cumulative estrogen exposure. The variables include estrogen, glucose metabolism, cerebral blood flow, Aβ burden, tau pathology, grey matter volume, and *APOE4*. The chart highlights the individual factors' relativity to one another, providing a comprehensive perspective of multiple AD biomarkers in relation to reproductive lifespan.

Rather than viewing these brain changes individually, it is more effective to look at them as interdependent (Figure 3). For example, a shorter reproductive lifespan signifies earlier estrogen withdrawal, causing energetic decline; in turn, this causes earlier vulnerability to amyloid and tau pathology, creating an increased risk of AD, which is amplified in *APOE4* carriers. Conversely, a long reproductive lifespan predicts delayed cognitive decline, with protection for brain energetics and postpones biomarker accumulation.

Overall, this unified model explains why women with shorter reproductive lifespans are more vulnerable to cognitive decline. This also explains the importance of the "critical window," as it integrates several factors to demonstrate the effects of HRT depending on whether it is started before or after major brain changes. The model shows that HRT not only affects hormones but also various significant brain mechanisms related to AD. By incorporating genetic, hormonal, and biomarker trajectories, this framework illustrates how different women need different treatments depending on their reproductive history.

■ Conclusion

Overall, this review addresses a gap in the literature by analyzing the interactions between reproductive lifespan, genetics, and brain biomarkers, providing an integrative foundation for personalized women's brain health and AD prevention. Current medicine and research fail to account for women's unique biology, leaving room for error and limiting the effectiveness of AD prevention. Leaving this gap under-researched risks leaving women behind in both understanding and treatment. This review lays the groundwork for possible future research, such as: a) longitudinal studies tracking the interactions between reproductive lifespan and genotype, b) critical window testing relative to menopause, and c) exploration of how to use individual differences to guide personalized HRT use.

Recognizing the unique trajectory of AD risk in women is not just a refinement of existing models; it's the next measure in preventing one of the most detrimental neurodegenerative disorders of our time.

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