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How would we combat menopause as an Alzheimer's risk factor?

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1. Alzheimer's disease: sex matters

Late-onset Alzheimer's disease (AD) is the most common form of dementia and the sixth leading cause of death in Western societies, affecting over 50 million people worldwide, and projected to nearly triple by the year 2050 [1].

Women are at the epicenter of the AD epidemic. For most regions of the world, two-thirds of patients living with AD-dementia are women, with postmenopausal women accounting for >60% of those affected [2]. These findings are independent of age, ethnicity, and women's greater longevity relative to men [2].

Currently, there are no therapeutics to prevent, delay or reverse AD, leading to a host of potential reasons for failed clinical trials, including sex-specific genetic and hormonal factors known to contribute to variance in clinical efficacy [3]. For example, the improved response to acetylcholinesterase inhibitor treatment in female AD patients was attributed to polymorphisms of the estrogen receptor (ER) α gene (ESR1) [3]. Additionally, ER splice variant changes following estrogen depletion have been implicated in altered responses to hormonal therapies [3].

There is growing consensus that to stem the epidemic of Alzheimer's, interventions earlier in the course of the disease will be required. It is now accepted that the pathophysiological

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Declaration of interest

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mechanisms of AD are activated years to decades prior to clinically detectable symptoms and form the basis of a prodromal (preclinical) stage of disease [4]. While the biological mechanisms underlying the increased AD risk in women are not fully understood, changes in estrogen levels during the *menopause transition* is implicated in a later life vulnerability to AD.

2. Menopause: a bioenergetic brain crisis

The menopause transition is a midlife neuroendocrine transition state unique to the female that ends with reproductive senescence. However, symptoms are largely neurological in nature, including disruption of estrogen-regulated systems such as thermoregulation, sleep, and circadian rhythms, as well as depression and impairment in multiple cognitive domains [3].

Recent brain imaging studies with Magnetic Resonance Imaging (MRI) and Positron Emission tomography (PET) have shown that perimenopausal and postmenopausal women exhibit an early AD-endophenotype characterized by brain hypometabolism, gray and white matter loss, and increased brain amyloid-beta (Aβ) deposition (a hallmark of AD pathology) as compared to premenopausal women and to age-matched men [5 6]. Additionally, Aβ deposition was exacerbated in postmenopausal women positive for apolipoprotein E (APOE) epsilon 4 status, a major genetic risk factor for AD known to affect women earlier and in higher numbers than genotype-matched men [6].

These findings are consistent with mechanistic preclinical pathway evidence of a bioenergetic crisis in female brain that emerges specifically during the menopause transition [3]. In animal studies, estrogenic control of cerebral metabolic rates of glucose (CMRglc) is disassembled during the menopause transition, leading to an adaptive activation of ketone body metabolism to generate ATP [7]. Over time, continued reliance on ketone bodies can lead to white matter catabolism, compromised mitochondrial energetic function, and cellular apoptosis [7], with an increased risk of cognitive decline and AD later in life.

Altogether, these findings indicate a progressively increased risk of AD in females undergoing the menopause transition, and suggest that endocrine aging outweighs the effects of chronological aging in the female's brain several years, if not decades, before possible clinical AD symptoms emerge.

Consistent with the impact of endocrine aging, menopause-associated dysregulation of other HPG axis hormones, such as luteinizing hormone, has also been implicated in the etiology of AD [8]. Chronologically, age of menopause maps onto the time course for initiation of the prodromal phase of AD, which typically begins 15–20 years before clinical symptoms emerge [4]. Menopausal changes therefore coincide with the timespan between average age of menopause, in the mid-50s, and average age of AD diagnosis, in the seventies.

3. How can we combat menopause-related risk of AD?

Evidence of sex-specific differences in endocrine aging and AD risk provides earlier biomarkers to clinical evaluations in women and indicate that women would benefit from

targeted medical attention and care in their 40's, well in advance of any neurological symptoms. This also supports the notion that the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process.

Currently 850 million women worldwide are either entering perimenopause or are already menopausal [3]. On a national, global, and policy level, greater focus on risk of AD for women would impact the burden of AD worldwide.

On a drug discovery level, investigating the endophenotype of AD risk that emerges early in the prodromal phase when intervention can potentially slow or reverse the trajectory of AD progression is critical. Identifying sex differences in the initiating mechanisms underlying the prodromal phase of AD will enable identification of systems biology sex-specific targets for prevention and or delay of AD. If, as recent research suggests, the underlying mechanisms of vulnerability to AD are different for women and men [5 6], then therapeutic targets should also be different for women and men. Further, testing for the effects of APOE as well as other genes implicated in dementias by sex, rather than pooling data for both sexes, would speed efforts to discern new directions for personalized treatment and management.

On a clinical level, we strongly urge deeper research to test the efficacy and safety of hormonal therapies (HT) during early menopause. Clinical trials reported mixed evidence of beneficial effects of HT on dementia risk, which may depend on differences in timing, length of administration, and type of estrogens used [9]. Trials using estradiol (the physiological form of estrogen) as opposed to conjugated equine estrogen (CEE), found that treatment helped stabilize or improve cognition in women with AD [9]. There is also evidence that HT may promote preservation of brain metabolic function [10], while lowering risk of dementia and cardiovascular disease [9–11], if instituted before menopause or within five years of menopause onset. Recent biomarker results support further investigation of the potential efficacy of HT in mitigating bioenergetic declines in middle-aged women [5 6]. Development of safe and effective alternatives to hormone therapy to promote estrogen action in the brain is underway [12].

At the same time, leading a healthy lifestyle in combination with strategies to reduce vascular disease risk is increasingly viewed as preventative against cognitive decline and dementia. Findings from population-attributable risk models estimate that one in every three AD cases may be accounted for by *modifiable* risk factors such as midlife hypertension, obesity, diabetes, as well as a poor diet, lack of intellectual activity, and being sedentary [13]. The role of lifestyle intervention in women at risk for AD is supported by findings indicating that APOE4 positive women at risk for metabolic syndrome have significant cognitive deficits relative to metabolically healthy women [14]. Thus, while it is not possible to alter either chromosomal female sex or APOE4 genotype, it may be possible to alter bioenergetic phenotype and thus the trajectory of risk for late life AD.

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