

BACKGROUND

Alzheimer's disease (AD) is the leading cause of dementia worldwide, characterized by progressive cognitive decline, extracellular amyloid- β plaque deposition, and intracellular neurofibrillary tangles composed of hyperphosphorylated tau.

Women account for approximately two-thirds of AD cases and exhibit greater lifetime risk than men. Sex-specific genetic, hormonal, metabolic, and neuroimmune mechanisms contribute significantly to this disparity.

~67%

of AD cases are women

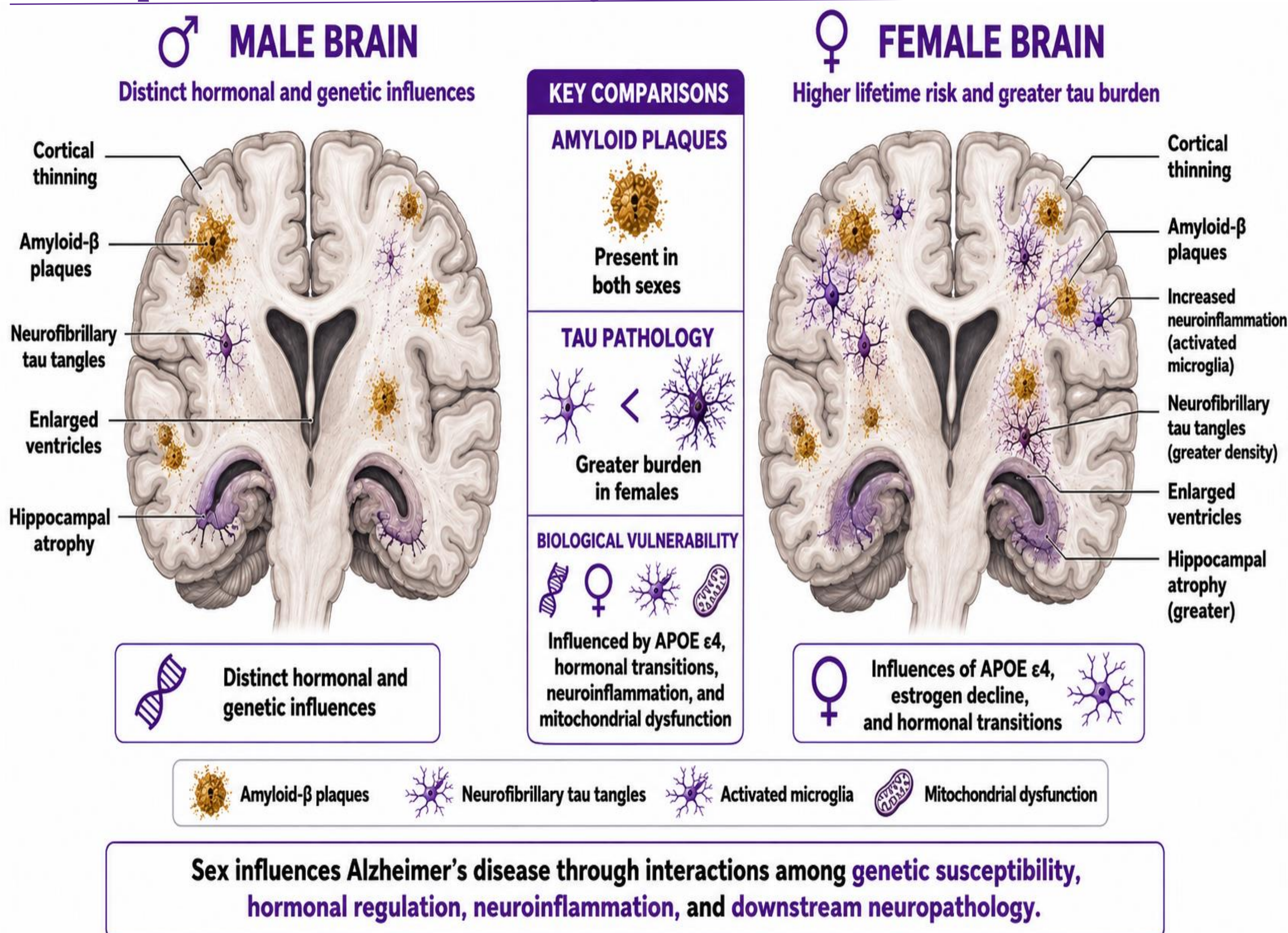
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APOE ϵ 4 risk amplification in females vs. males

OBJECTIVE

To synthesize current evidence on the biological mechanisms underlying sexual dimorphism in Alzheimer's disease, with emphasis on genetic susceptibility, hormonal regulation, neuroinflammation, mitochondrial dysfunction, and implications for precision medicine.

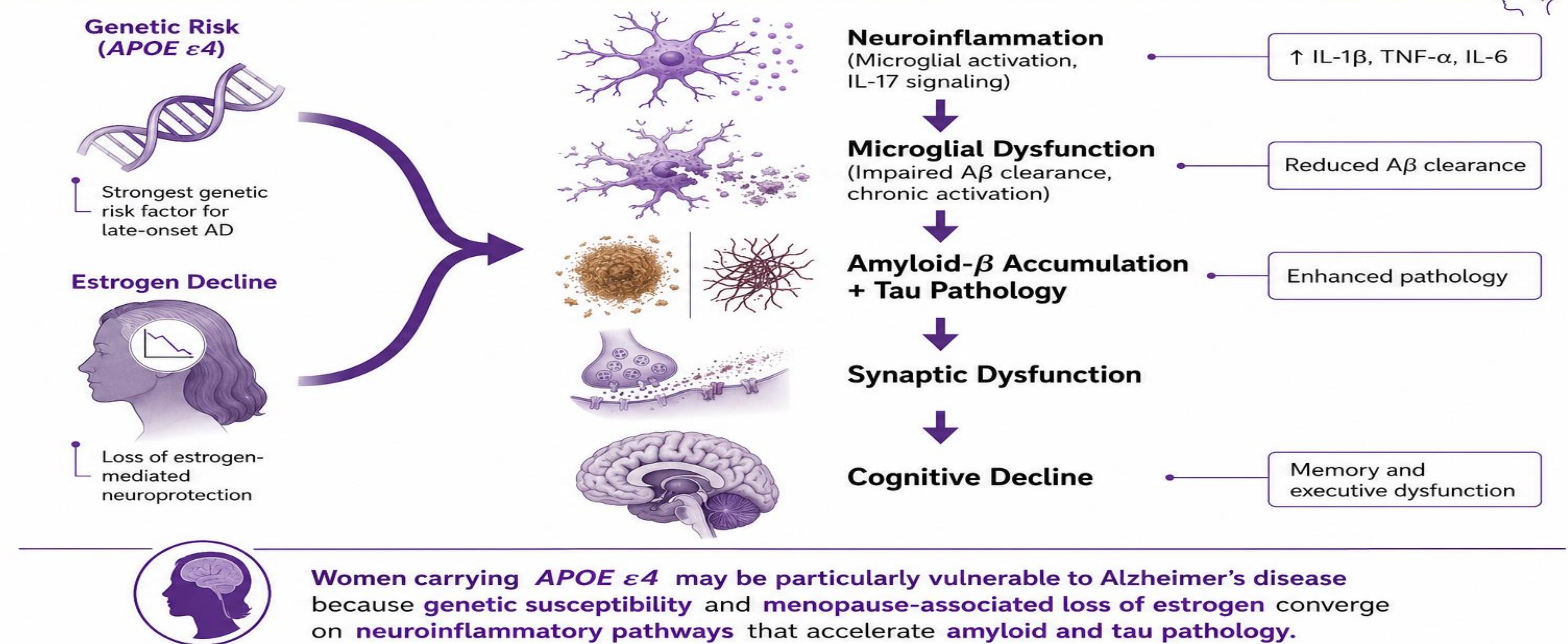
Sex-specific Vulnerability to Alzheimer's Disease



Take-Home Message

"Sex is not merely a demographic variable in Alzheimer's disease; it is a fundamental biological determinant influencing disease risk, pathology, progression, and therapeutic response."

Sex-Specific Mechanisms Underlying Alzheimer's Disease Vulnerability



KEY FINDINGS

APOE ϵ 4 and Sex-Specific Risk

- Strongest genetic risk factor for late-onset AD
- Female carriers exhibit greater vulnerability to tau pathology and cognitive decline
- Menopause may amplify APOE ϵ 4-mediated risk

Hormonal Contributions

Women

- Estrogen supports synaptic plasticity
- Maintains mitochondrial function
- Suppresses neuroinflammation

Men

- Testosterone contributes to neuroprotection
- Age-related decline may increase vulnerability

Neuroinflammation

- Sex-dependent microglial activation
- Enhanced inflammatory signaling in susceptible individuals
- APOE ϵ 4-microglia-neutrophil interactions contribute to disease progression

Mitochondrial Function

- Sex differences in oxidative stress resilience
- Hormonal regulation of cellular energetics
- Aging-associated metabolic dysfunction contributes to neurodegeneration

CONCLUSIONS

- Alzheimer's disease exhibits significant sexual dimorphism.
- Genetic, hormonal, immune, and metabolic pathways interact to shape disease susceptibility.
- APOE ϵ 4 remains the strongest genetic determinant of increased female vulnerability.
- Sex should be incorporated as a biological variable in AD research and therapeutic development.

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