SEX DIFFERENCES IN DEMENTIA

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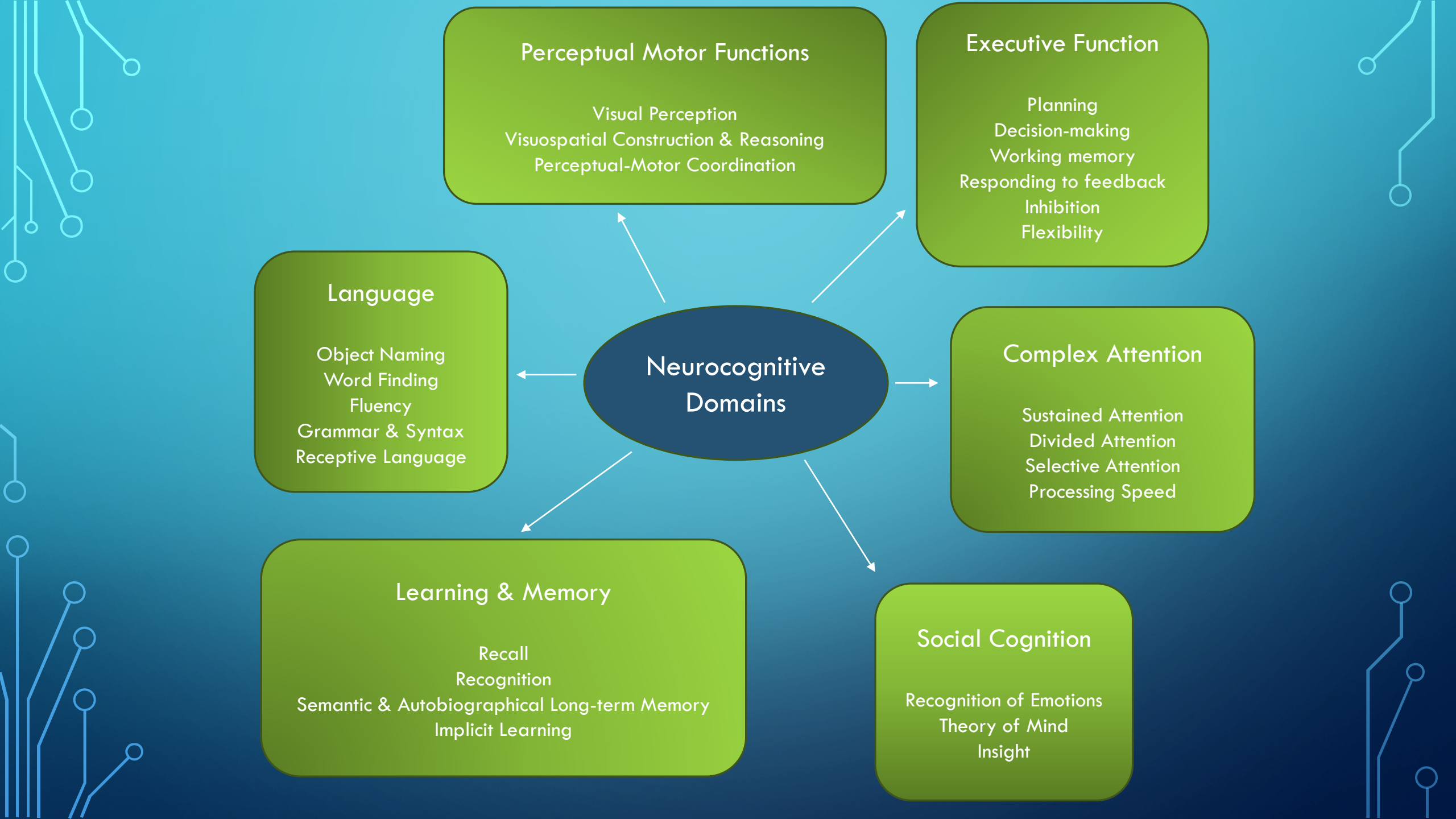
SECTION HEAD, NEUROPSYCHOLOGY

OCHSNER HEALTH – DEPARTMENT OF NEUROLOGY

- No Financial Disclosures

OUTLINE

- Introduction to Neuropsychology
- Ochsner Menopause Clinic
- Sex/Gender differences in dementia risk
- Cognitive Reserve
- Menopause
- Future Directions


Perceptual Motor Functions
Visual Perception
Visuospatial Construction & Reasoning
Perceptual-Motor Coordination
Executive Function
Planning
Decision-making
Working memory
Responding to feedback
Inhibition
Flexibility
Language
Object Naming
Word Finding
Fluency
Grammar & Syntax
Receptive Language
Neurocognitive Domains
Complex Attention
Sustained Attention
Divided Attention
Selective Attention
Processing Speed
Learning & Memory
Recall
Recognition
Semantic & Autobiographical Long-term Memory
Implicit Learning
Social Cognition
Recognition of Emotions
Theory of Mind
Insight

OCHSNER MENOPAUSE CLINIC

- Started by GYN Dr. Elizabeth Lapeyre in 2023
- Dr. Lapeyre reached out to Neurology last year to partner for certain patients:
  - Treatment resistant cognitive complaints
  - Migraine
  - History of stroke

SEX/GENDER AND ALZHEIMER'S DISEASE

- Higher prevalence rate in females
  - Estimated 7.2 million Americans 65+ with AD (2025 Alzheimer's Disease Facts and Figures)
  - 4.4 million are women (about 66%)
- Strongest risk factor for AD after age
- Due to longer average lifespan in women vs men?

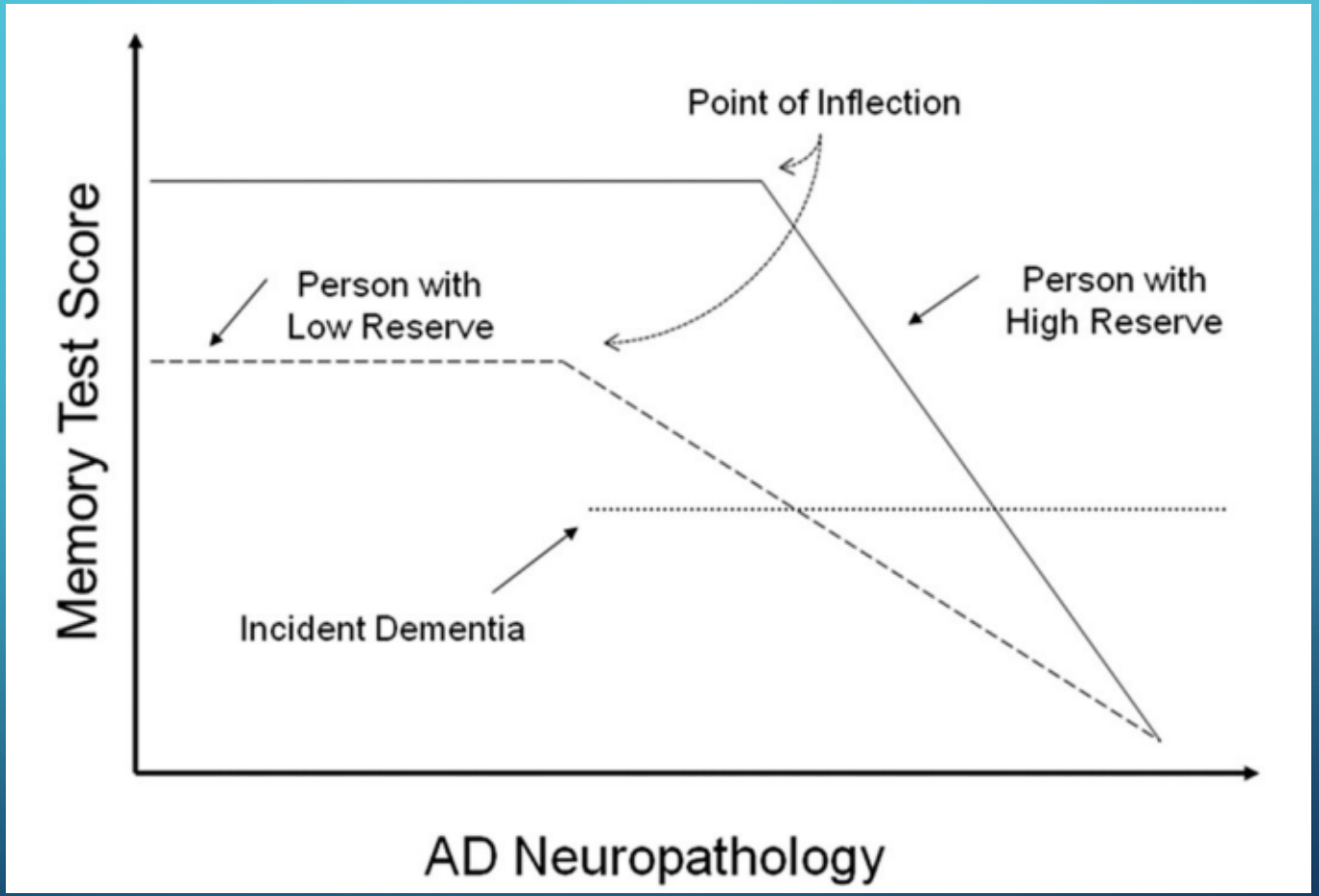
Emrani S, Sundermann EE. Sex/gender differences in the clinical trajectory of Alzheimer's disease: Insights into diagnosis and cognitive reserve. Front Neuroendocrinol. 2025 Apr;77:101184. doi: 10.1016/j.yfrne.2025.101184. Epub 2025 Feb 13. PMID: 39951912.

SEX/GENDER AND ALZHEIMER'S DISEASE

- Impact of genetics/biology
- Pattern of neuropathology
- Course/development of symptomatic disease

Emrani S, Sundermann EE. Sex/gender differences in the clinical trajectory of Alzheimer's disease: Insights into diagnosis and cognitive reserve. Front Neuroendocrinol. 2025 Apr;77:101184. doi: 10.1016/j.yfrne.2025.101184. Epub 2025 Feb 13. PMID: 39951912.

COGNITIVE RESERVE



Stern, 2009

CLINICAL COURSE

- Despite protective/risk factors being less advantageous for women (educational/occupational opportunities, APOE4), women still seem to have a cognitive advantage early in the disease course
  - Verbal learning/memory
  - Visual memory?
  - Relevant for early detection

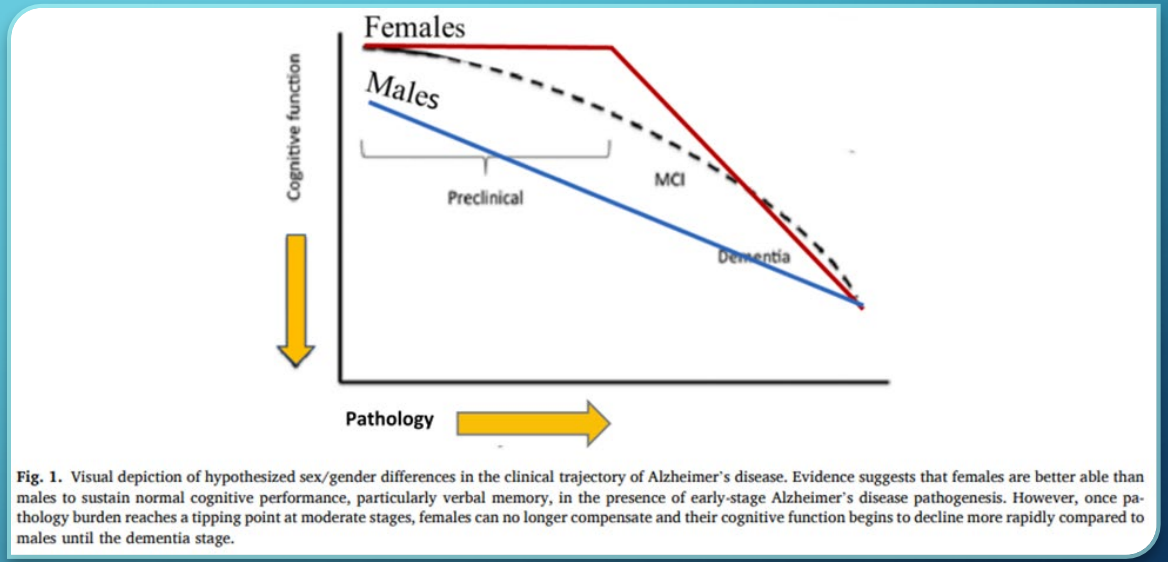


Fig. 1. Visual depiction of hypothesized sex/gender differences in the clinical trajectory of Alzheimer's disease. Evidence suggests that females are better able than males to sustain normal cognitive performance, particularly verbal memory, in the presence of early-stage Alzheimer's disease pathogenesis. However, once pathology burden reaches a tipping point at moderate stages, females can no longer compensate and their cognitive function begins to decline more rapidly compared to males until the dementia stage.

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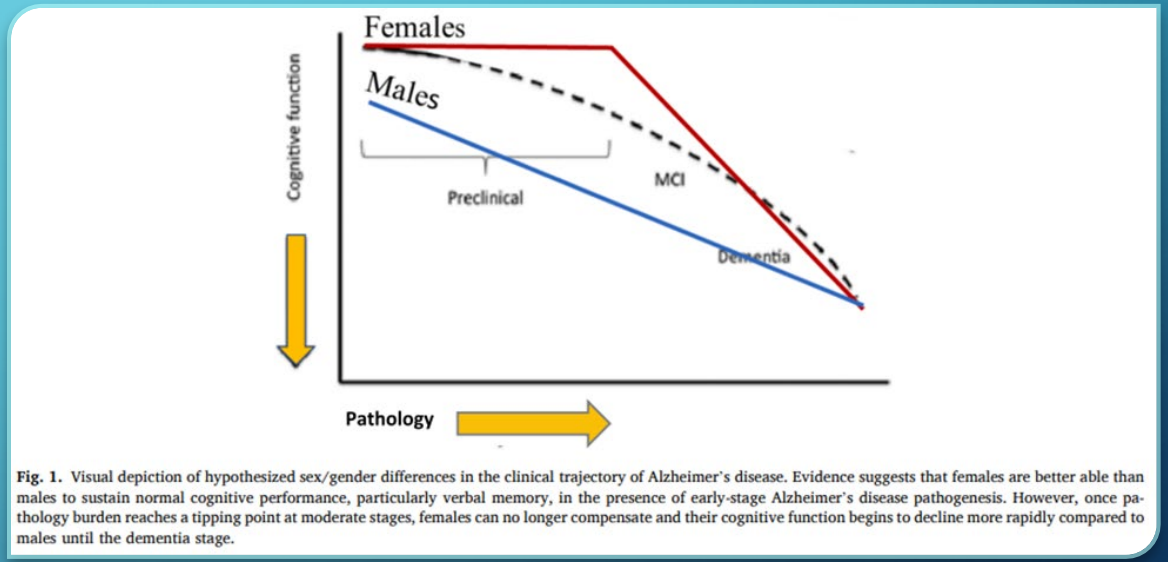
CLINICAL COURSE

- Higher resilience to AD pathology in early stages, but steeper decline and pathological burden at later stages
  - Tipping point of pathology
  - Tau more closely tied to cognitive change



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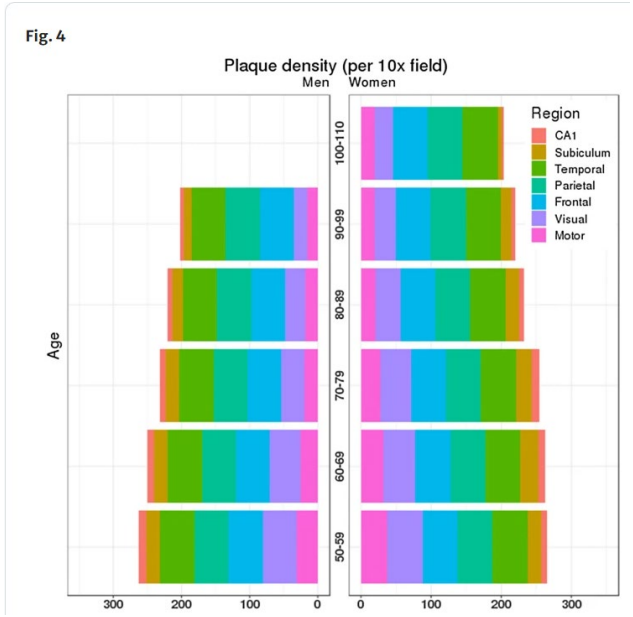
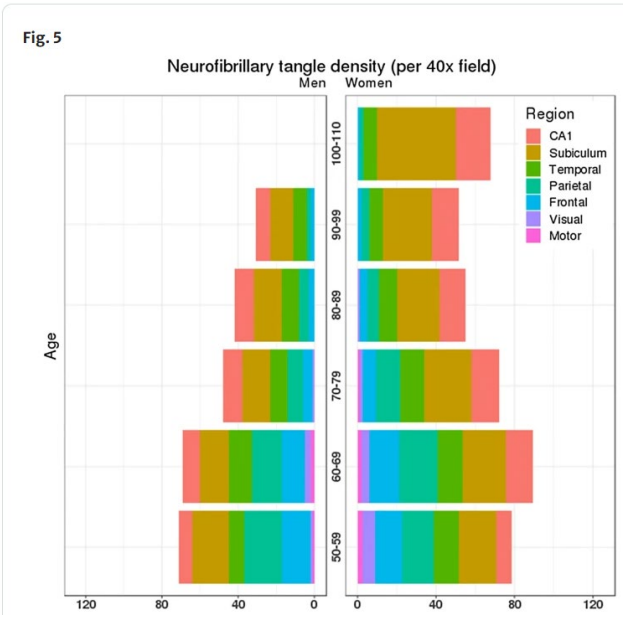
NEUROPATHOLOGY



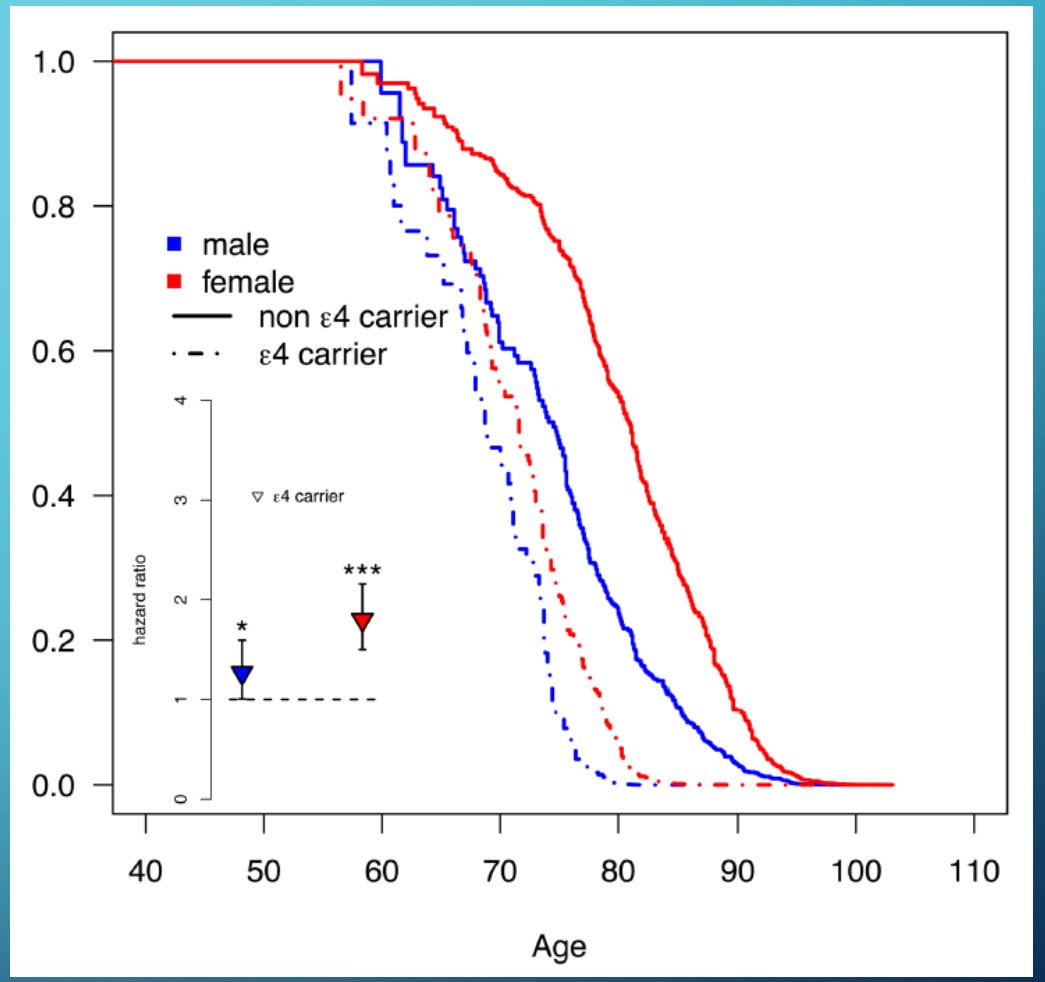


- Men and women have a similar Amyloid plaque density
- Women have a greater density of neurofibrillary tangles
- Women had greater hippocampal neurofibrillary tangles
  - Which may contribute to a more classic amnestic presentation in women vs more dysexecutive/behavioral variants in men

Liesinger AM, Graff-Radford NR, Duara R, Carter RE, Hanna Al-Shaikh FS, Koga S, Hinkle KM, DiLello SK, Johnson MF, Aziz A, Ertekin-Taner N, Ross OA, Dickson DW, Murray ME. Sex and age interact to determine clinicopathologic differences in Alzheimer's disease. Acta Neuropathol. 2018 Dec;136(6):873-885. doi: 10.1007/s00401-018-1908-x. Epub 2018 Sep 15. PMID: 30219939; PMCID: PMC6280837.

APOE4

- Non-carrier women lowest risk of conversion to MCI/dementia (80.9)
- Non-carrier men at intermediate risk (74.5)
- APOE 4 men with the highest risk (68.7)
- Marginal risk increase in non-carrier vs carrier men (1.3)
- Significant 1.8 fold increase in non-carrier vs carrier women (71.6)



Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. Ann Neurol. 2014 Apr;75(4):563-73. doi: 10.1002/ana.24135. Epub 2014 Apr 14. PMID: 24623176; PMCID: PMC4117990.

EARLY SURGICAL MENOPAUSE LINKED TO AD PATHOLOGY IN LATE LIFE

- Oopherectomy before age 46 increases risk of AD / cognitive impairment by 70%

Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women

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ABSTRACT

Objective: To determine the association between age at surgical menopause and both cognitive decline and Alzheimer disease (AD) pathology in 2 longitudinal cohorts.

Methods: Female subjects from 2 longitudinal studies of cognitive decline (Religious Orders Study and Rush Memory and Aging Project) were included (total n = 1,884). The primary analysis examined the association between age at surgical menopause and decline in a global cognition score. Secondary analyses examined additional outcomes: 1) decline in 5 cognitive subdomains and 2) a global measure of the burden of AD pathology. In exploratory analyses, we examined the effect of hormone replacement therapy (HRT). We adjusted all models for age, education, smoking, and cohort and stratified by surgical vs natural menopause.

Results: For the 32% of subjects with surgical menopause, earlier age at menopause was associated with faster decline in global cognition ($p = 0.0007$), specifically episodic memory ($p = 0.0003$) and semantic memory ($p = 0.002$). Earlier age at menopause was also associated with increased AD neuropathology ($p = 0.038$), in particular neuritic plaques ($p = 0.013$). HRT use for at least 10 years, when administered within a 5-year perimenopausal window, was associated with decreased decline in global cognition. No associations were seen in women who had natural menopause.

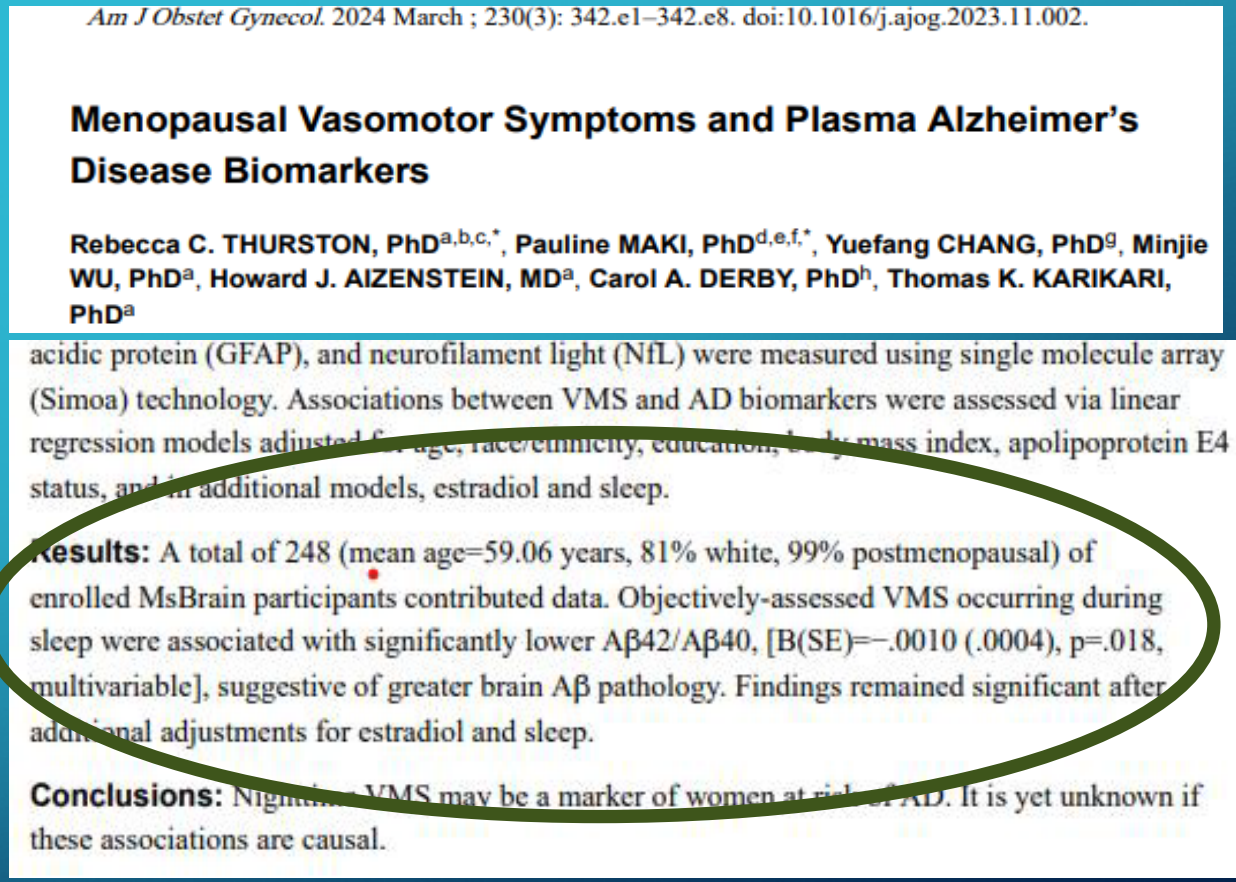
Conclusions: Early age at surgical menopause was associated with cognitive decline and AD neuropathology. Ongoing studies should clarify the potential effect of HRT on this relationship.

Neurology® 2014;82:222-229

Bove et. Al., Neurology, 2014

HOT FLASHES RELATED TO ADVERSE BRAIN OUTCOMES

- More hot flashes related to lower plasma amyloid beta ratio levels



Am J Obstet Gynecol. 2024 March ; 230(3): 342.e1–342.e8. doi:10.1016/j.ajog.2023.11.002.

Menopausal Vasomotor Symptoms and Plasma Alzheimer's Disease Biomarkers

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acidic protein (GFAP), and neurofilament light (NfL) were measured using single molecule array (Simoa) technology. Associations between VMS and AD biomarkers were assessed via linear regression models adjusted for age, race/ethnicity, education, body mass index, apolipoprotein E4 status, and in additional models, estradiol and sleep.

Results: A total of 248 (mean age=59.06 years, 81% white, 99% postmenopausal) of enrolled MsBrain participants contributed data. Objectively-assessed VMS occurring during sleep were associated with significantly lower Aβ42/Aβ40, [B(SE)=−.0010 (.0004), p=.018, multivariable], suggestive of greater brain Aβ pathology. Findings remained significant after additional adjustments for estradiol and sleep.

Conclusions: Nighttime VMS may be a marker of women at risk of AD. It is yet unknown if these associations are causal.

Thurston RC, Am J Obstet Gynecol. 2024 Mar;

KEEPS – LONG TERM DATA

GLEASON ET AL, PLOS 2024

RESEARCH ARTICLE

Long-term cognitive effects of menopausal hormone therapy: Findings from the KEEPS Continuation Study

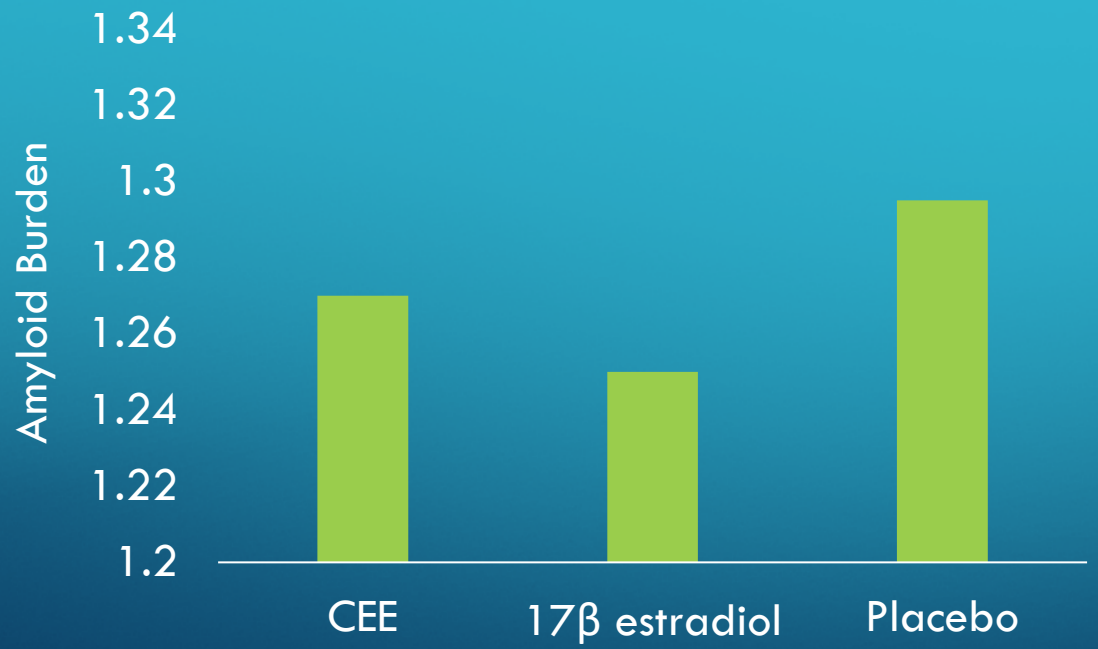
Carey E. Gleason[1,2]*, N. Maritza Dowling[3], Firat Kara[4], Taryn T. James[1], Hector Salazar[5], Carola A. Ferrer Simo[1], Sherman M. Harman[6], JoAnn E. Manson[7], Dustin B. Hammers[8], Frederick N. Naftolin[9], Lubna Pal[10], Virginia M. Miller[11], Marcelle I. Cedars[12], Rogerio A. Lobo[13], Michael Malek-Ahmadi[14], Kejal Kantarci[4]

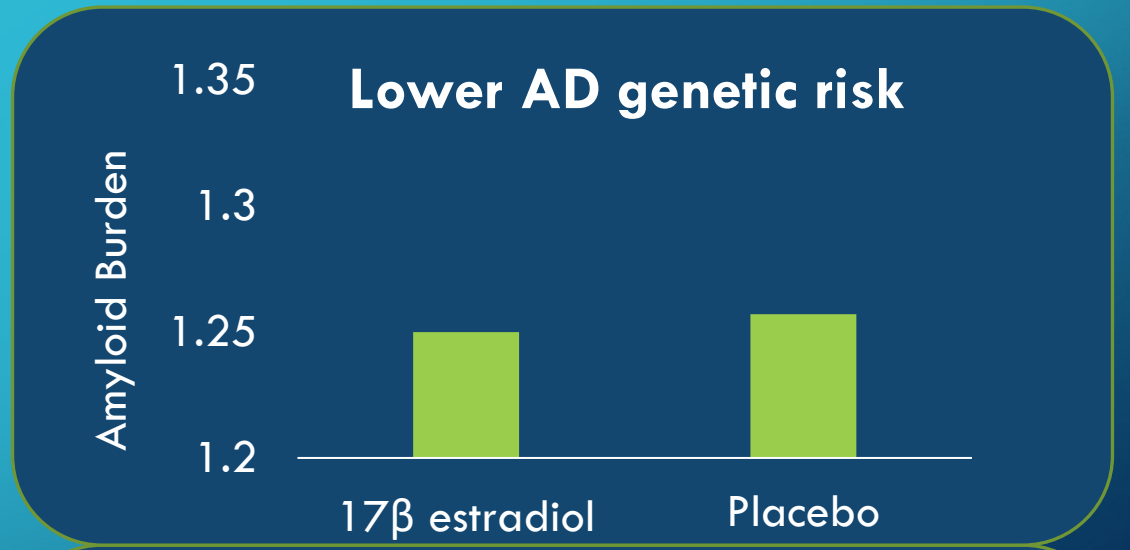
Conclusions

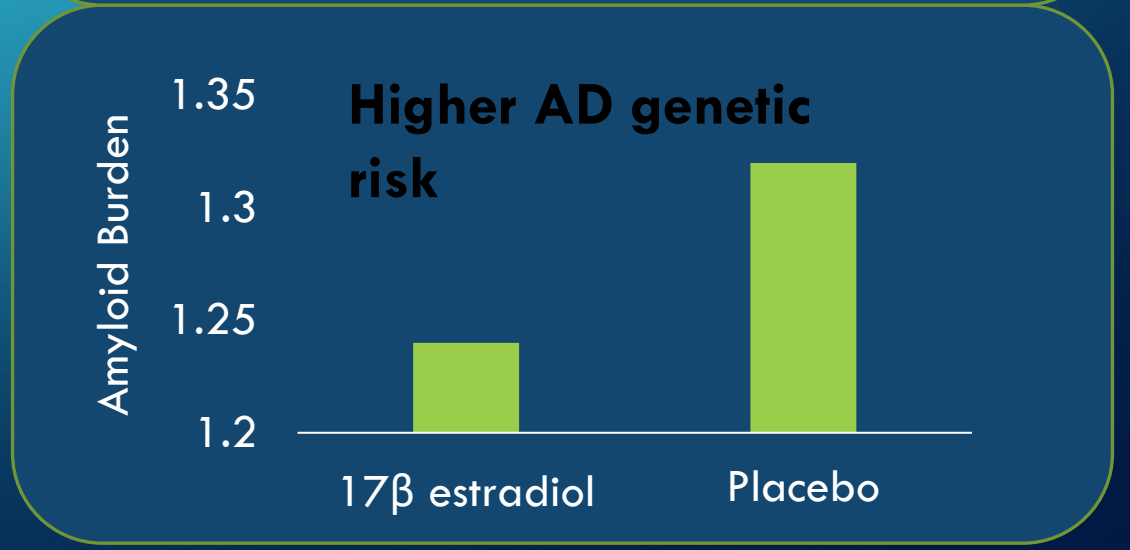
In these KEEPS Continuation analyses, there were no long-term cognitive effects of short-term exposure to mHT started in early menopause versus placebo. These data provide reassurance about the long-term neurocognitive safety of mHT for symptom management in healthy, recently postmenopausal women, while also suggesting that mHT does not improve or preserve cognitive function in this population.

IN KEEPS TRIAL, TRANSDERMAL ESTRADIOL ASSOCIATED WITH LESS AMYLOID IN WOMEN AT HIGHER AD GENETIC RISK

N=68 women, 7 years post randomization







Kantarci et al. 2016 Journal of Alzheimer's Disease

FUTURE DIRECTIONS?

EMERGING HYPOTHESES ON COGNITIVE EFFECTS OF MHT

- Critical window of time hypothesis? Neuroprotective action of MHT only occurs when initiated around menopause onset (5-10 yrs), but harmful if started much later
- Healthy cell bias hypothesis? Estrogen exerts beneficial effects on healthy neural tissue but may worsen established pathology

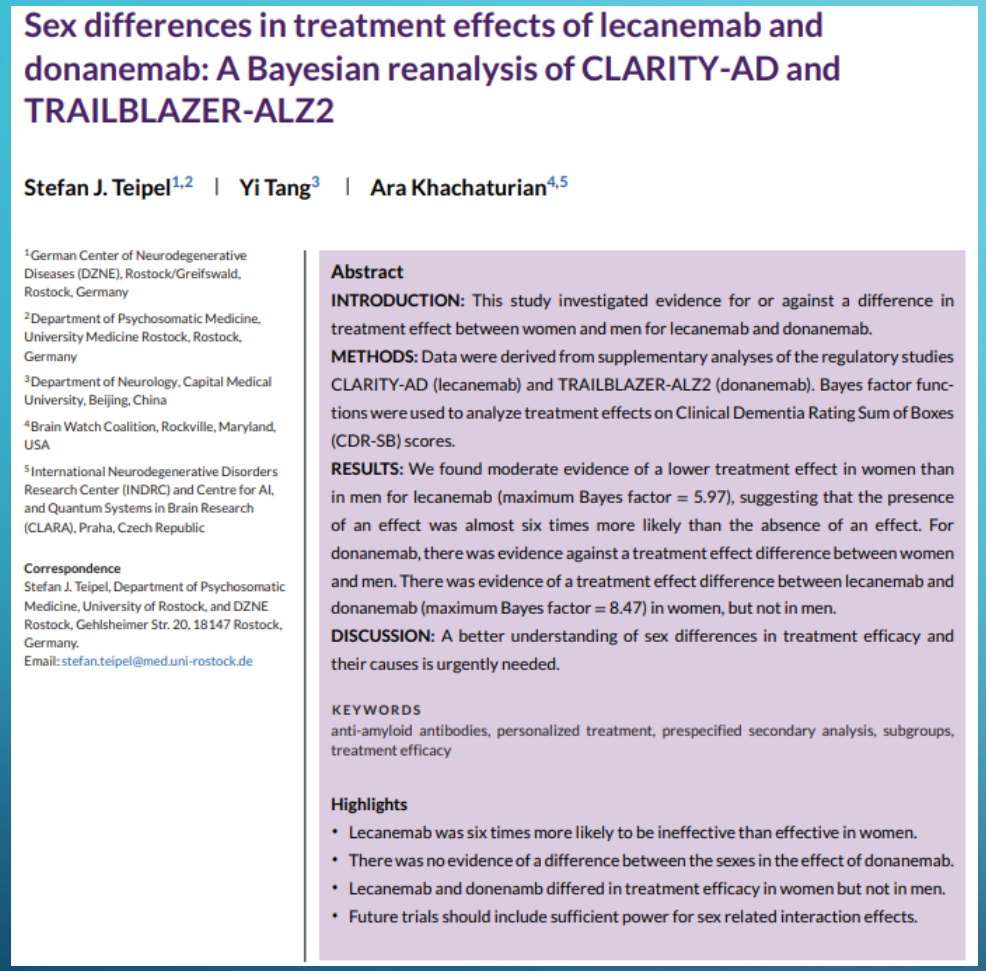
Highlights from the NAMS 2022 Hormone Therapy Position Statement

- Estrogen therapy may have cognitive benefits when taken immediately after surgical menopause
- For women more than 10 years from menopause onset or older than 60, the benefit-risk ratio is less favorable due to greater risks of coronary heart disease, stroke, and dementia
- For women younger than 60 or within 10 years of menopause onset with no contraindications, HT is favorable for treatment of VMS and bone loss but is not currently recommended for dementia prevention

NEUROPSYCHOLOGY

- Sex specific normative data?
- Visual memory as part of standard battery?

TREATMENT RESPONSE



Sex differences in treatment effects of lecanemab and donanemab: A Bayesian reanalysis of CLARITY-AD and TRAILBLAZER-ALZ2

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[2]Department of Psychosomatic Medicine, University Medicine Rostock, Rostock, Germany

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[5]International Neurodegenerative Disorders Research Center (INDRC) and Centre for AI, and Quantum Systems in Brain Research (CLARA), Praha, Czech Republic

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Abstract

INTRODUCTION: This study investigated evidence for or against a difference in treatment effect between women and men for lecanemab and donanemab.

METHODS: Data were derived from supplementary analyses of the regulatory studies CLARITY-AD (lecanemab) and TRAILBLAZER-ALZ2 (donanemab). Bayes factor functions were used to analyze treatment effects on Clinical Dementia Rating Sum of Boxes (CDR-SB) scores.

RESULTS: We found moderate evidence of a lower treatment effect in women than in men for lecanemab (maximum Bayes factor = 5.97), suggesting that the presence of an effect was almost six times more likely than the absence of an effect. For donanemab, there was evidence against a treatment effect difference between women and men. There was evidence of a treatment effect difference between lecanemab and donanemab (maximum Bayes factor = 8.47) in women, but not in men.

DISCUSSION: A better understanding of sex differences in treatment efficacy and their causes is urgently needed.

KEYWORDS
anti-amyloid antibodies, personalized treatment, prespecified secondary analysis, subgroups, treatment efficacy

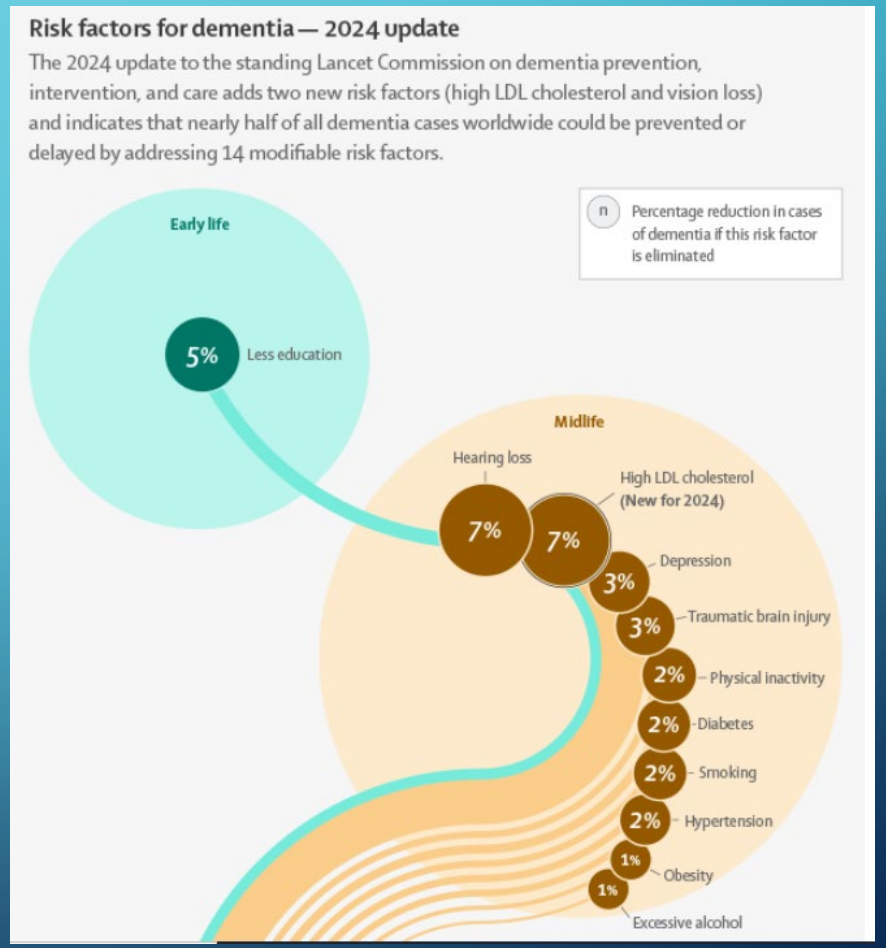
Highlights

- Lecanemab was six times more likely to be ineffective than effective in women.
- There was no evidence of a difference between the sexes in the effect of donanemab.
- Lecanemab and donenamb differed in treatment efficacy in women but not in men.
- Future trials should include sufficient power for sex related interaction effects.

- Sex differences in neuropathology
- Women could have more pathology with similar cognition to men
- Donanemab study controlled for tau, which could explain why this effect was more pronounced in lecanemab

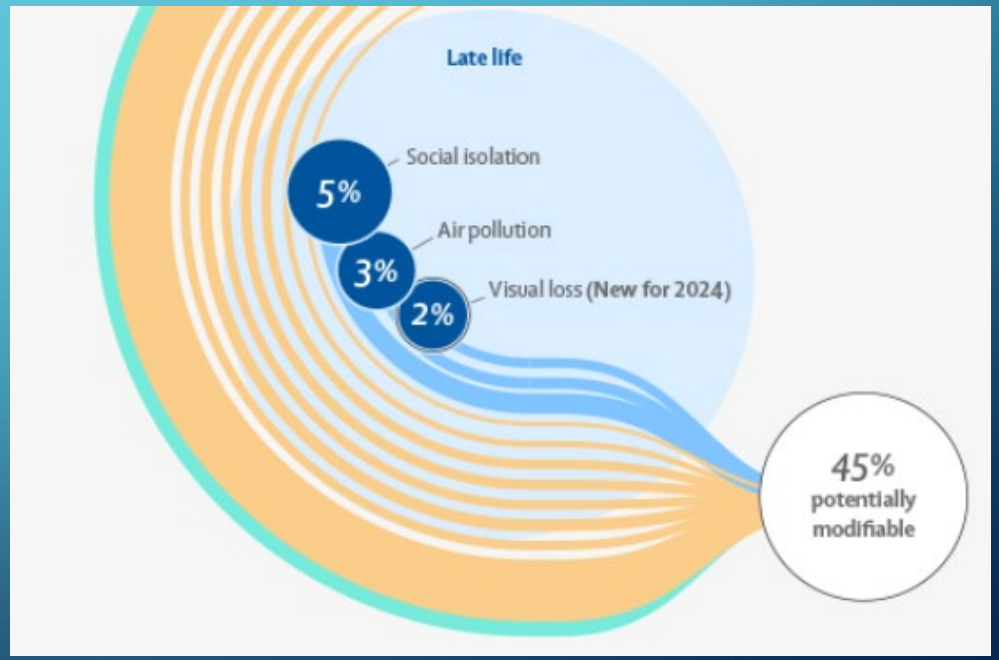
BRAIN HEALTH

- Highlighted many risk factors that can't be changed
  - Age
  - Genetics
  - Menopause
- Modifiable
  - Midlife untreated hearing loss
  - Midlife high cholesterol



BRAIN HEALTH

- Modifiable
  - Late life social isolation
  - Late life untreated vision loss



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