Sex and gender influences on healthy brain aging and dementia

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Objectives

Define sex and gender.

Describe sex- and gender-influences on the aging brain and dementia risks.

Explore impact of sex and gender on brain health interventions.

Review ways that psychology can inform intervention for women.

List take-aways for busy clinical practice

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Defining brain health, sex, and gender

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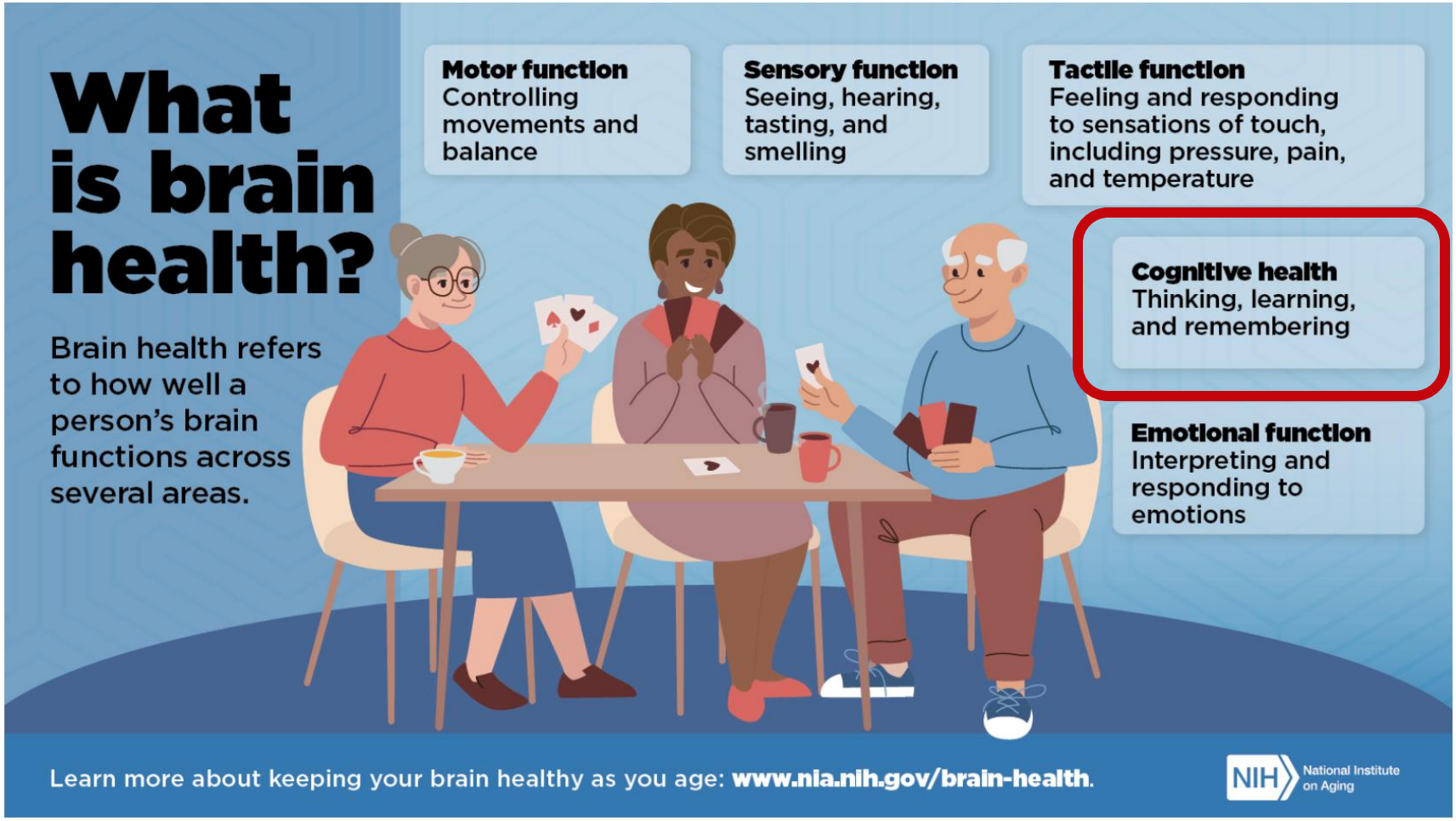
Brain health can have different meanings



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Sex is a biological variable defined by characteristics encoded in DNA.

Gender refers to a social construct.

Most studies measure **sex/gender**

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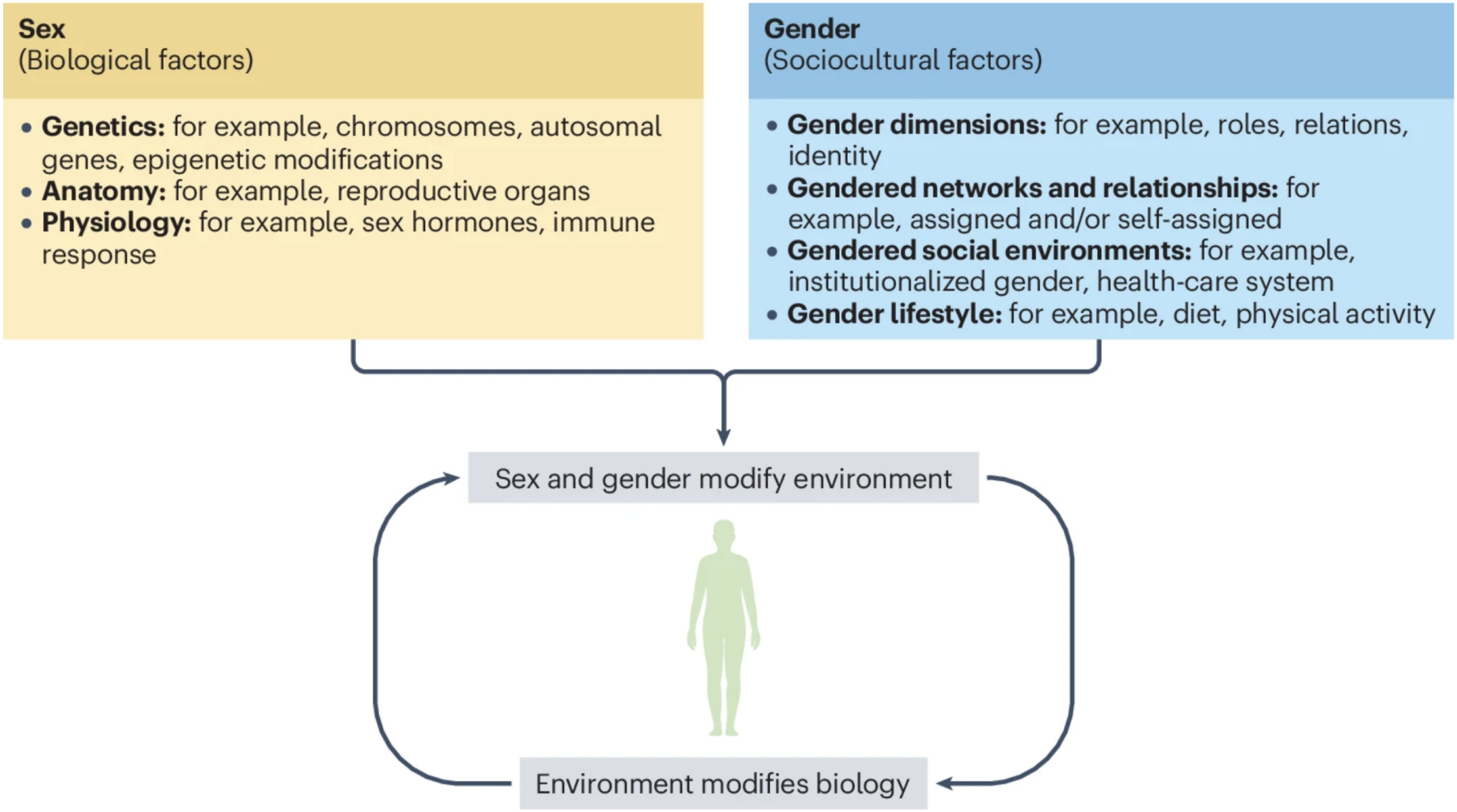
https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf; **e.g., Stites, et al., 2022, J Gerontol B Psychol Sci Social Sci**

Sex and gender are multidimensional



Lee, et al., 2025, Nat. Reviews Endocrinology

What is the role of sex and gender in brain health and dementia?

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Healthy brain aging may favor women

- Women live longer than men
- Recent meta-analysis
  - >12,000 MRIs from nearly 5000 individuals
  - All cognitively normal
  - Age 17-95
  - Men have greater cortical thickness declines overall

Ravndal, et al., 2025, PNAS

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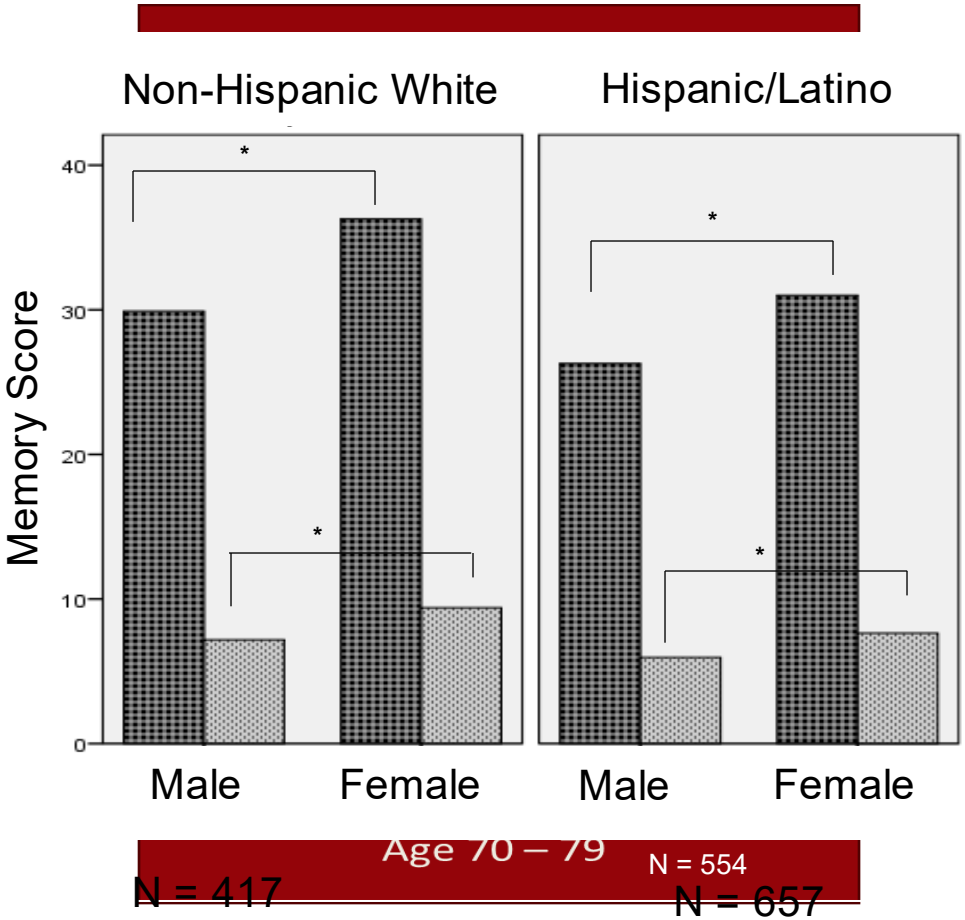
Memory in aging may favor women



*p<0.0001

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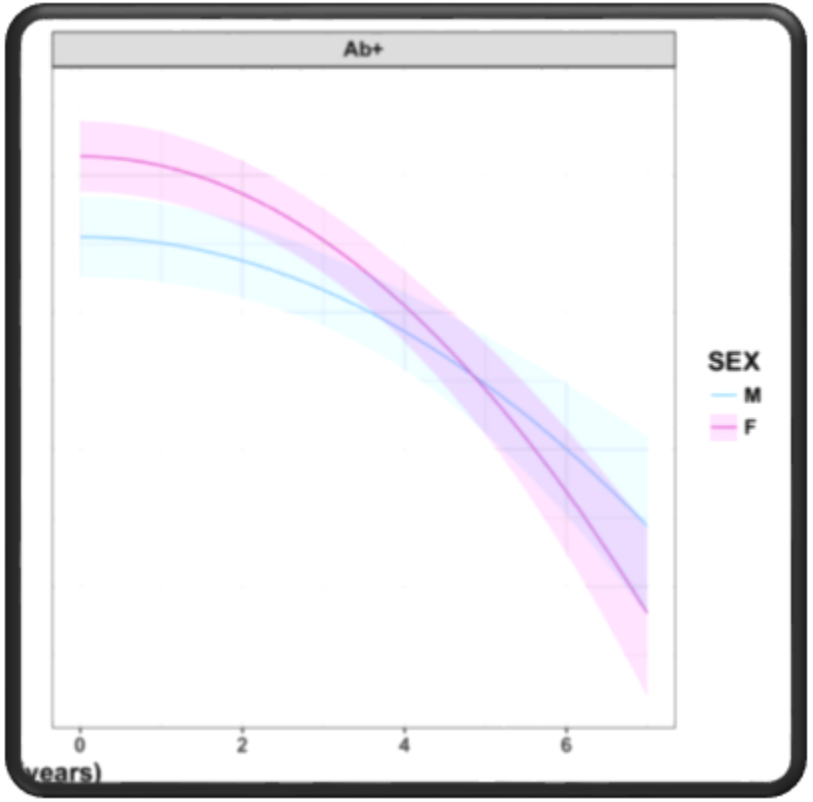
Alzheimer's Association, 2023; Modified from Buckley, et al., Alz. & Dementia, 2018; Brunet et al., Aging, Neuropsych & Cognition, 2019

Women have disproportionate AD impact

Caregiving

Diagnosis

Prognosis



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Alzheimer's Association, 2023; Modified from Buckley, et al., Alz. & Dementia, 2018; Brunet et al., Aging, Neuropsych & Cognition, 2019; Caldwell, et al., 2023, in preparation

Risks can be impacted by sex, gender, or both

Maria Orlova, 2020 – Pexels, Mikhail Nilov, 2021 -Pexels, Jane Doan, 2017 – Pexels, Jane Doan, 2018 - Pexels, RODNAE Productions, 2021 - Pexels

Antsey, et al., Scientific Reports, 2021; Dong, et al., Bio of Sex Differences, 2022; Guo, et al., Molecular Neurodegeneration, 2023; Lee, et al., 2025 Nat. Reviews Endocrinology; Livingston, et al., Lancet Neurology, 2020 & 2024; Moran, et al., BMJ Open Diab Res Care, 2021; Neu, et al., JAMA Neurology, 2017; Sindi, et al., Alz. & Dementia, 2021; Thomas, et al., Front. Aging Neurosci, 2022.

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Sex and gender-influenced factors increase AD risk

Genetics

4x

- APOE ε4
- Gene expression, regulation of expression

Comorbidities

1.5x

- Diabetes
- Cardiovascular disease

Lifestyle

Men: 1.7x

Women: 2.6x

- Physical activity
- Cognitive activity

Antsey, et al., Scientific Reports, 2021; Dong, et al., Bio of Sex Differences, 2022; Guo, et al., Molecular Neurodegeneration, 2023; Livingston, et al., Lancet Neurology, 2020 & 2024; Moran, et al., BMJ Open Diab Res Care, 2021; Neu, et al., JAMA Neurology, 2017; Ponjoan, et al., Alz. Research & Therapy, 2024; Sindi, et al., Alz. & Dementia, 2021; Thomas, et al., Front. Aging Neurosci, 2022.

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Endocrine transitions may confer sex-specific risk

EARLY LIFE RISKS: **MIDLIFE RISKS:** **LATER LIFE RISKS:**

Puberty **Pregnancy** **Menopause**

Pre-menopause **Peri-menopause** **Post-menopause**

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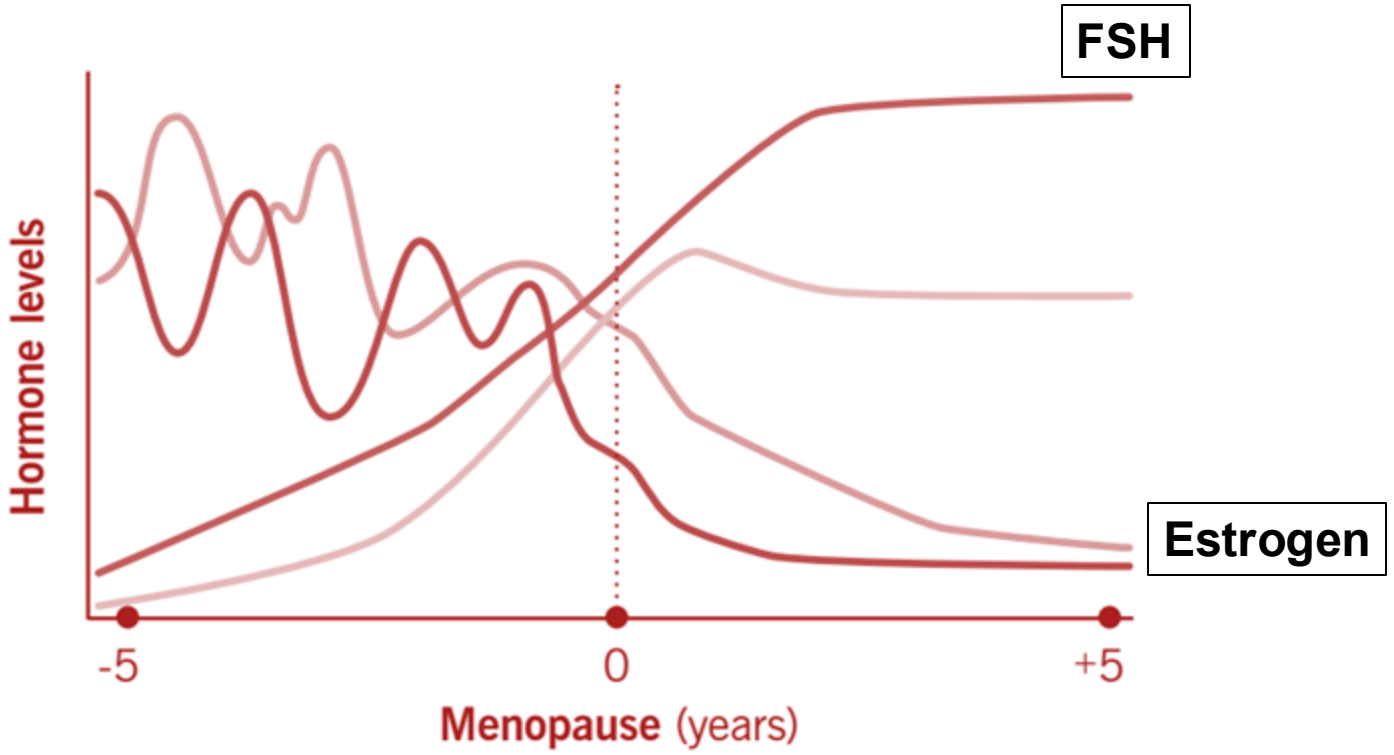
Sex hormones undergo change at menopause



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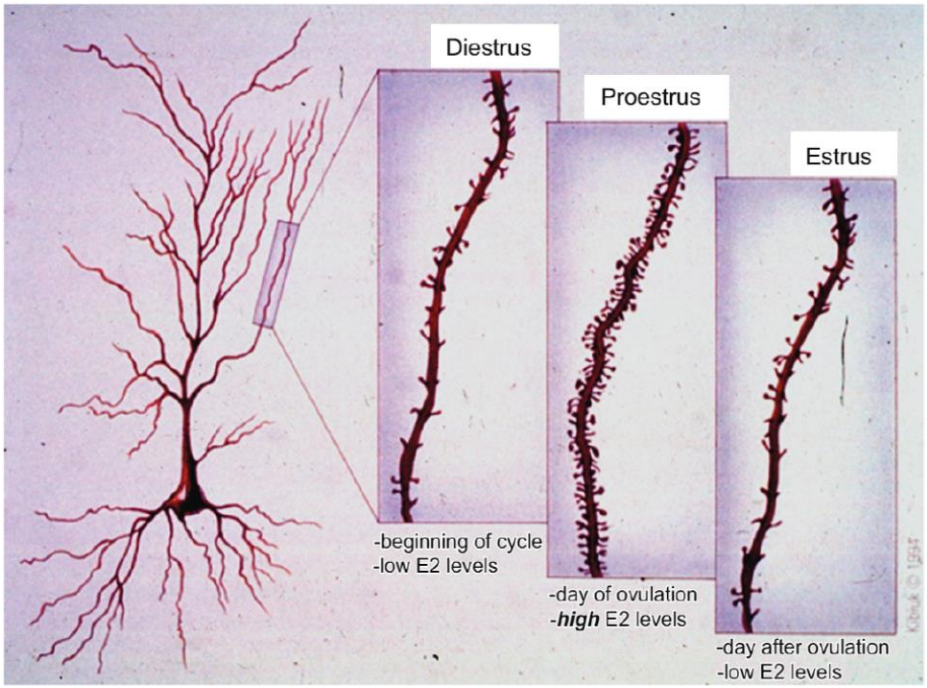
Estrogen supports plasticity



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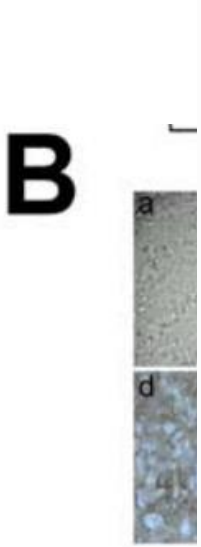
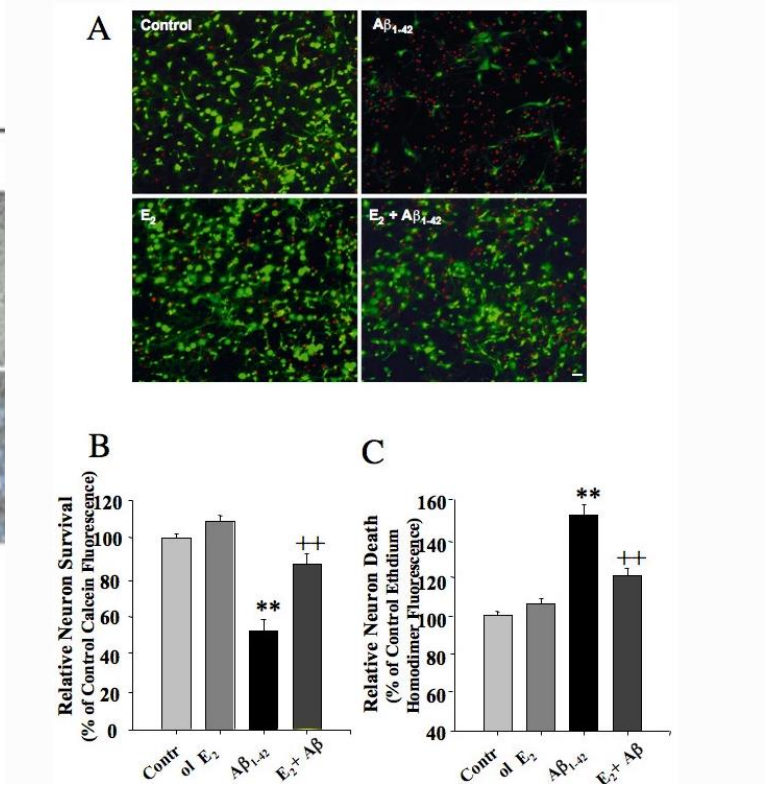
Hara, et al., *Physiology Reviews* 2015.

Estrogen counters Alzheimer's pathology

- Amyloid
- Tau
- Neurodegeneration





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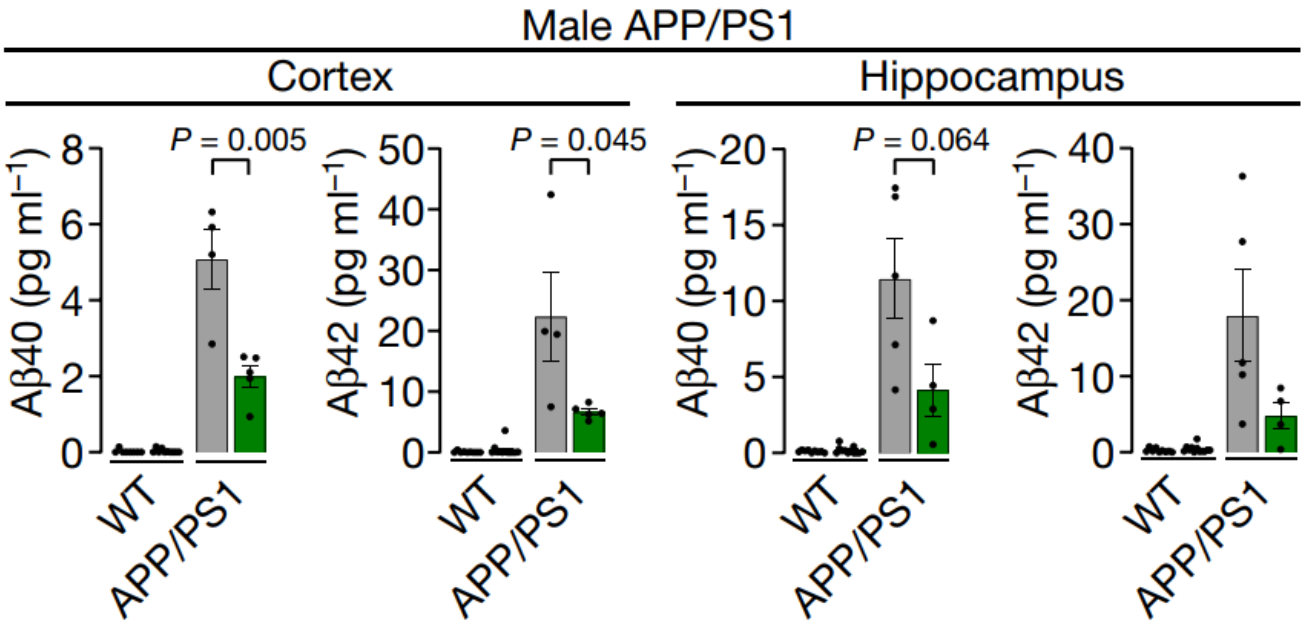
Nilsen, et al., *BMC Neuroscience* 2006*; Xu, et al., Nature Medicine 1998;* Zhang, et al., *J. Neuroscience* 2008

Estrogen may not be the key



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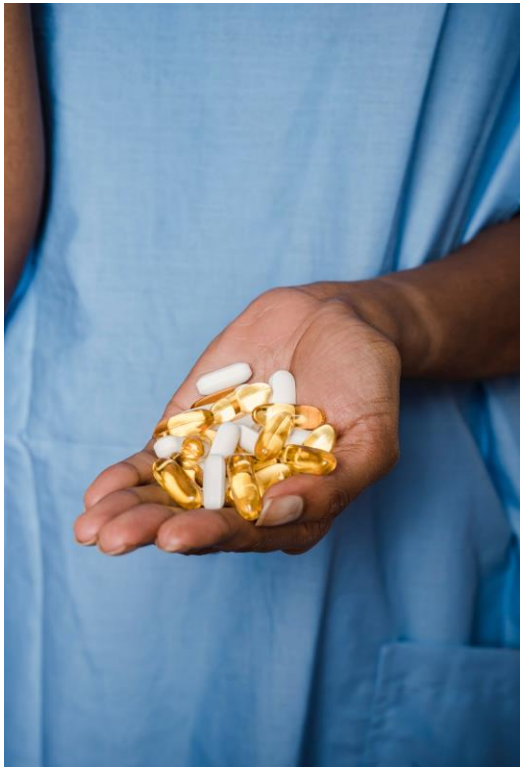
Xiong J et al. *Nature*. 2022.

Hormone therapy is not an easy fix

- WHI study results
  - >30,000 post-menopausal women
  - Increased mortality
  - Breast cancer, stroke, dementia
  - Most findings in older women



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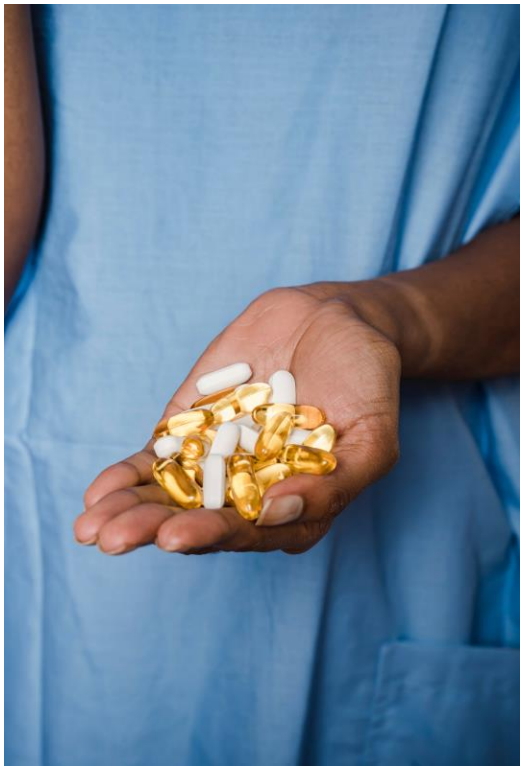
Hormone therapy is not an easy fix

- Pro-, anti-, and neutral results for brain heatlh
- Recent meta-analyses
  - Replacement of estrogen within 5 years reduced AD risk, including in APOE-4 carriers
  - Midlife estrogen replacement, longer replacement reduced AD risk, but only in APOE-4 non-carriers
- Impact likely depends on timing, type, genetics, and other person-related factors



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Schumacher, et al., JAMA, 2003;

What is the role of sex and gender in AD intervention?

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Some greater risks in women are modifiable

EARLY LIFE RISKS:	MIDLIFE RISKS:		LATER LIFE RISKS:
Low education	High LDL cholesterol	Depression	Vision loss
	High blood pressure	Smoking	Social isolation
	Diabetes	>7 drinks/week	Air pollution
	Obesity	Head injury	
	Physical inactivity	Hearing loss	

Levine, et al., in preparation; Livingston, et al., Lancet, 2024

Risks can be unique, more likely, and more impactful for women.

What does this mean for intervention outcomes?

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https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf; For more, see Stites, Flatt

Non-pharmacological intervention outcomes may differ in men and women

- 2023 meta-analysis:
  - Impact on memory only in women
- Personalized medicine:
  - Greater risk score improvement in women

Isaacson, et al., Alz. & Dementia, 2019; Saif, et al., Alz. Research & Therapy, 2022; Wittmann, et al., JPAD, 2024; Zulke, et al., Scientific Reports, 2023; Zunzunegui, et al., 2003, The Journals of Gerontology: Series B; Sindi, et al., 2021; Alz. & Dementia

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Pharmacological intervention outcomes may differ in men and women

- Supplementary analyses of lecanemab and donanemab trials
  - **Women 6* more likely to have no effect than an effect of lecanemab**
    - No difference for donanemab
  - Women had better effect with donanemab>lecanemab
    - Men no difference

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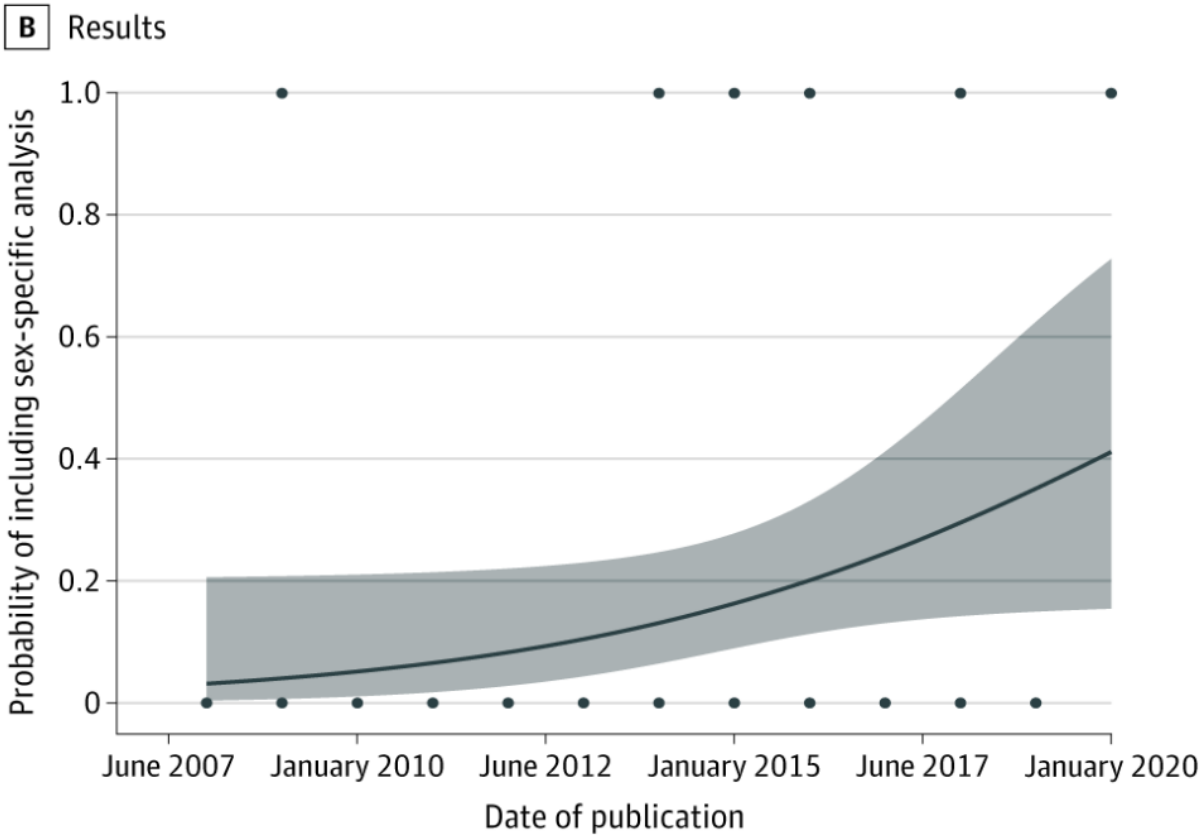
Tiepel, Tang, & Katchaturian, 2025, Alz & Dem: TRCI

Intervention outcomes *may* differ



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Martinkova, et al, JAMA Neurology, 2021.

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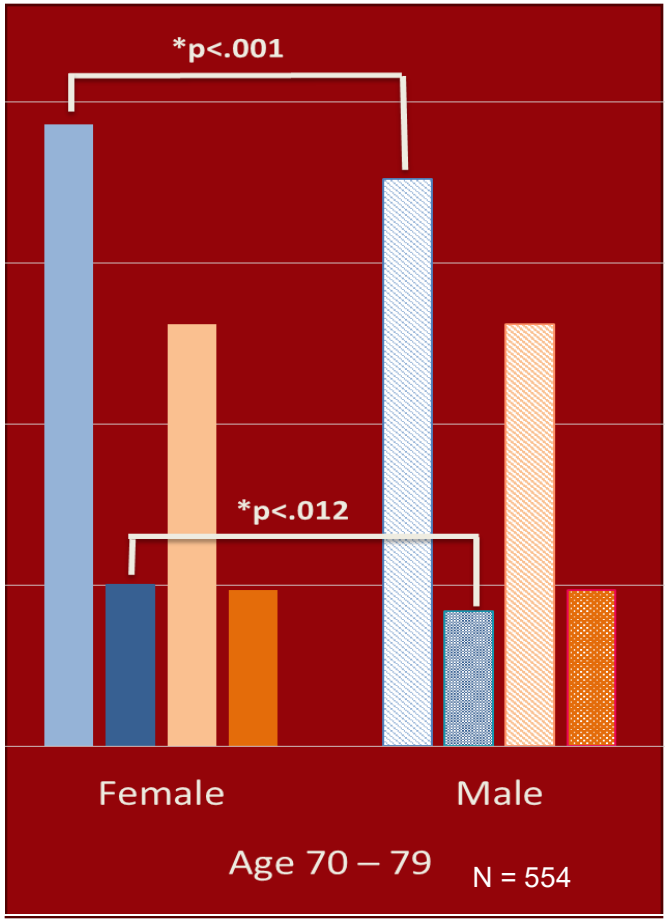
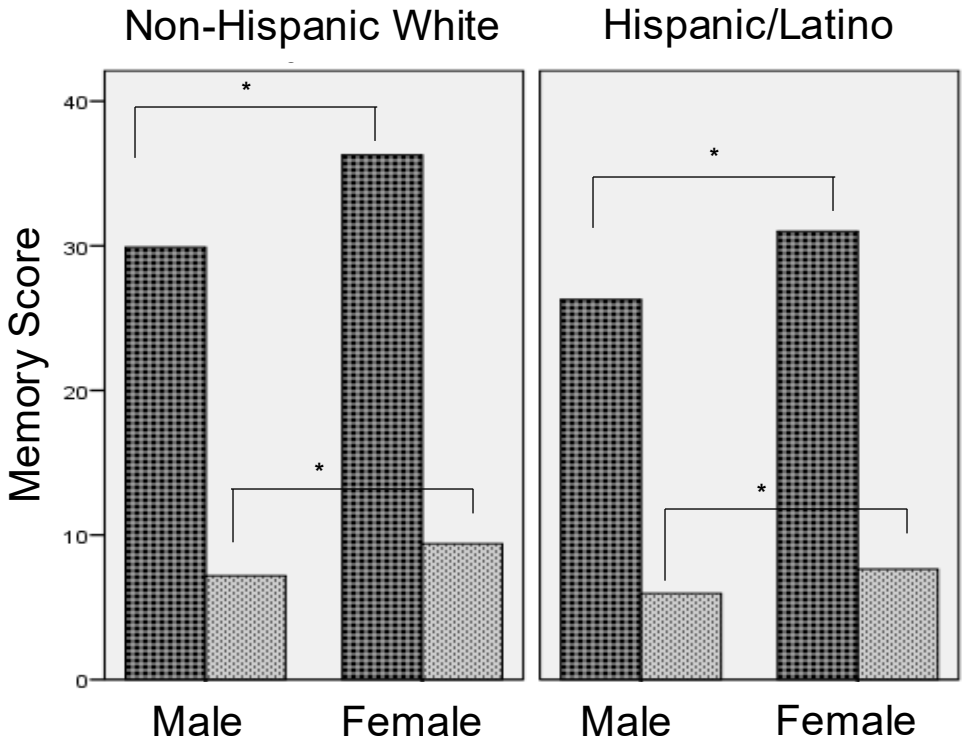
Intervention outcomes *may* differ





N = 417

N = 657

*p<0.0001

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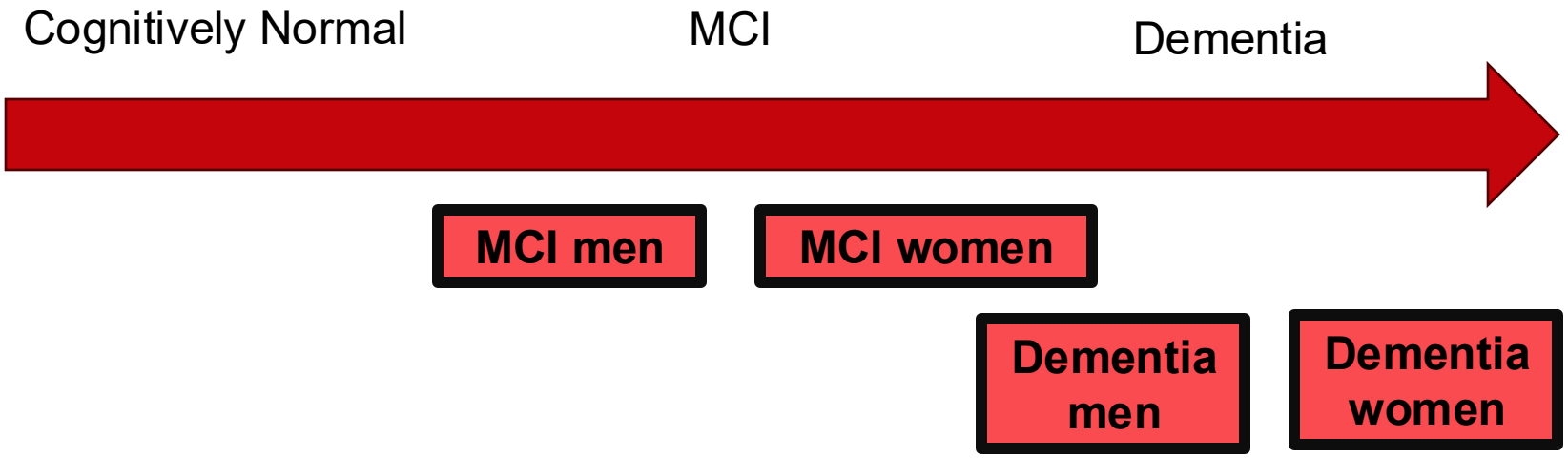
Ermani & Sundermann, 2025; Brunet, et al., 2019; Levine, et al., 2025

Intervention outcomes *may* differ

Diagnosis,
(defined in part by memory scores)



Pathology,
(defined by biomarker measurement)

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Risks can be unique, more likely, and more impactful for women.

What does this mean for intervention design and approach in clinic?

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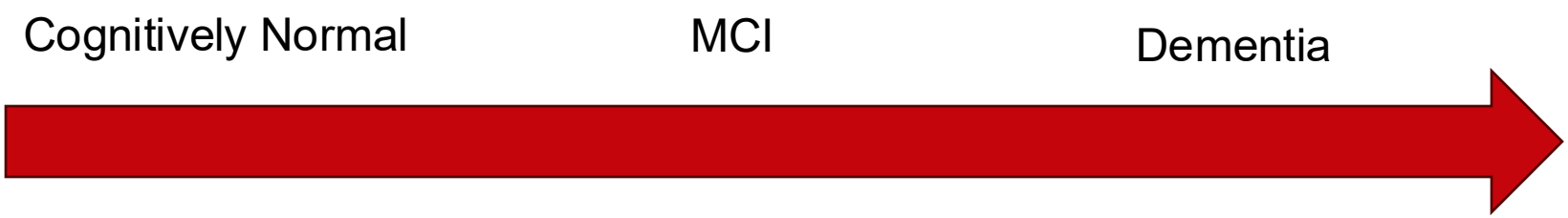
https://orwh.od.nih.gov/sites/orwh/files/docs/NOT-OD-15-102_Guidance.pdf; For more, see Stites, Flatt

Intervention must assess women equally well

Diagnosis,
(defined in part by memory scores)



Pathology,
(defined by biomarker measurement)

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Intervention must reach those at highest risk

- Cleveland Clinic survey showed 57% of women are concerned
  - 24% knew women are at greater risk

- Transgender individuals have higher dementia risk scores and subjective cognitive decline
  - Older transgender women have reduced episodic memory scores
  - Transgender women with subjective cognitive decline less likely to receive help

Brady, et al., 2023, Alz & Dementia; Cleveland Clinic, 2024; Cicero, et al., 2023, Alz. & Dementia, Lambreau, et al., 2020, Alz & Dementia; van Heesewijk, et al., 2023, International Journal of Transgender Health

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Intervention must reach those at highest risk

- Black/African American women have greater risk
  - Represented 1% of AD trial participants
- Hispanic/Latino women have greater risk
  - Large cross-sectional study, 1/4 Hispanic/Latino
    - 30% of respondents knew about ethnicity risk
    - Hispanic individuals most interested in prevention

Canevelli, et al., 2019, Neurosci. Biobehavioral Rveiws; Chen, et al., 2024; GSA; Hsieh, et al., 2024; The Journals of Genrontology: Series B; Talkad, et al., 2024; The Journal of Aging Research & Lifestyle; Son, et al., 2025, JPAD; Trani, et al.,2025, Alz&Demn; Wang, et al., 2024, eClinicalMedicine;

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Intervention should reflect women's risks

- Lancet risks
  - Education
  - Diabetes
  - Physical Activity
  - Depression

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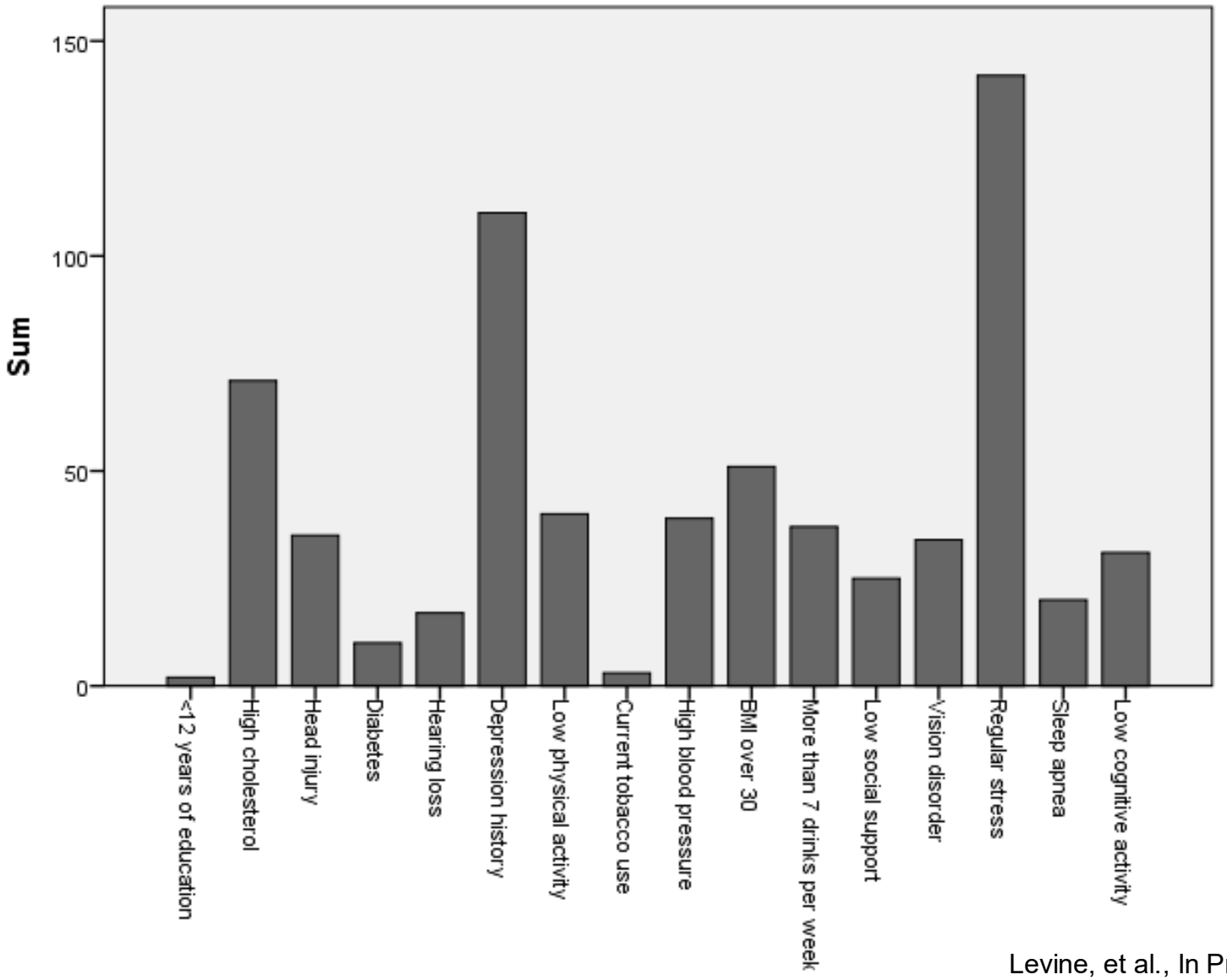
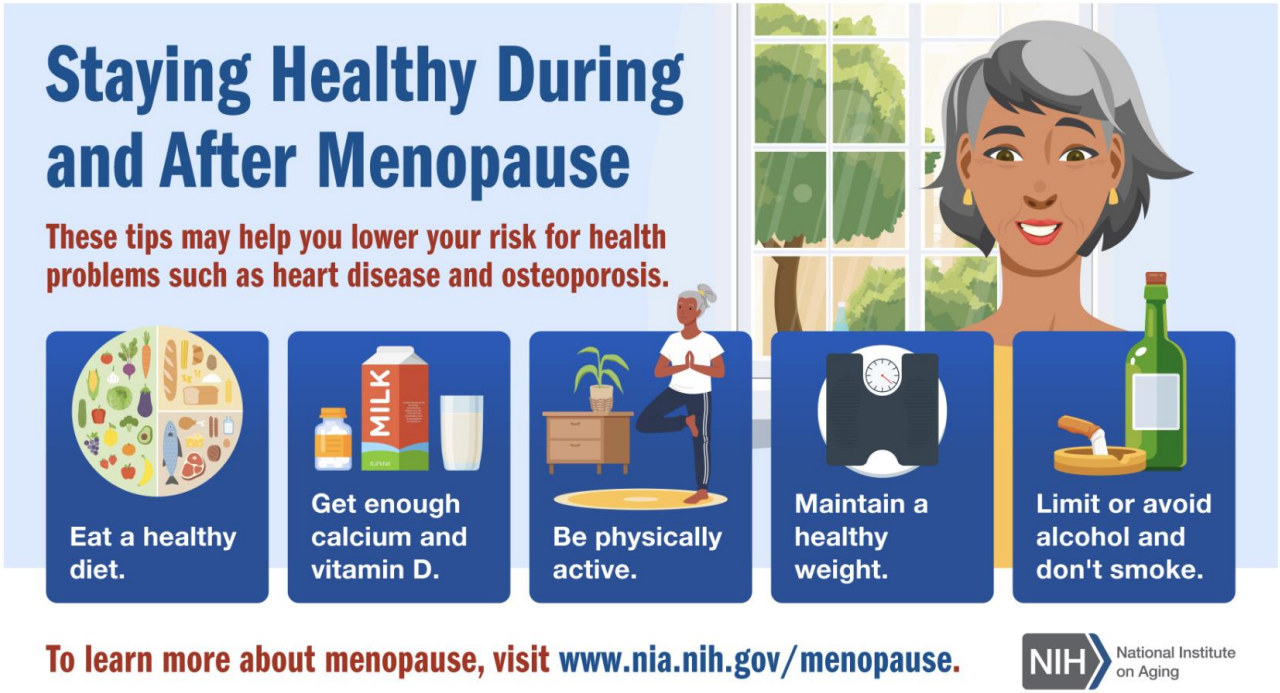
Intervention should reflect reported risks



Levine, et al., In Preparation

Intervention for women should reflect context



- **Social roles and expectations**
  - Caregiving, mental load
  - Low priority for self care
  - Work and “having it all”
- **Stigma of treatment**
  - CPAP
  - Hearing aids
  - Psychotherapy

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Intervention for women should reflect reality

Temporal inequity

Lifestyle stigma

- Focus on weight without reasoning or support
- Focus on “gold standard” exercise only
- Focus only on foods that may be financially inaccessible or ignoring cultural culinary context

Rohr, et al., 2025, Lancet Healthy Longevity; Wilson & Antsey, 2024, The Gerontologist

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Psychology-informed approaches may add

Women's Alzheimer's Movement Prevention and Research Center at Cleveland Clinic

Risk + Resilience Profile

Physical Activity
- Weekly minutes
- Types
- Intensity

Nutrition
- Mediterranean comparison
- Processed foods

Alcohol
- Weekly drinks
- Concern about alcohol use

Stress
- Regular stress
- Caregiving stress
- Discrimination
- Stress management

Information Gathering

Questions
- Typical pattern?
- Barriers (e.g., time, money, dislike)?
- How might this fit?

Questions
- Detailed review of recent intake
- Barriers (e.g., allergies, intolerances, time)?
- What is a reasonable start?

Questions
- Accuracy?
- What are current concerns?
- What role does alcohol play for you?

Questions
- Describe major current stressors
- Frequency of stress management techniques
- Is stress disruptive (e.g., to sleep, mood, energy)?

Goals + Recommendations

Goals
- Increase weekly minutes to 300
- Add 2x weekly strength training
- 2 week pedometer inventory

Goals
- 2-week food diary
- Discontinue soda
- Meet MIND diet targets

Goals
- Reduce to <7 drinks/week
- Discontinue alcohol
- Drink tracking for 2 weeks; assess where reduction would be easiest

Goals
- Prioritize daily exercise
- Add daily mindfulness meditation
- Consider psychotherapy

Levine, et al., in Preparation

Psychology informed approaches impact risk

- N=280 (96 Y1), 30-85 yo
- Cognitively normal
- Family history of AD, variable additional risk
- One year, 5 visits of personalized psychosocial and medical risk evaluation and recommendations

Significantly reduced total dementia risks

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Levine, et al., in Preparation

Promoting resilient aging in clinic

- Ask about stress
- Have community resources ready
- Exercise
- Meditation

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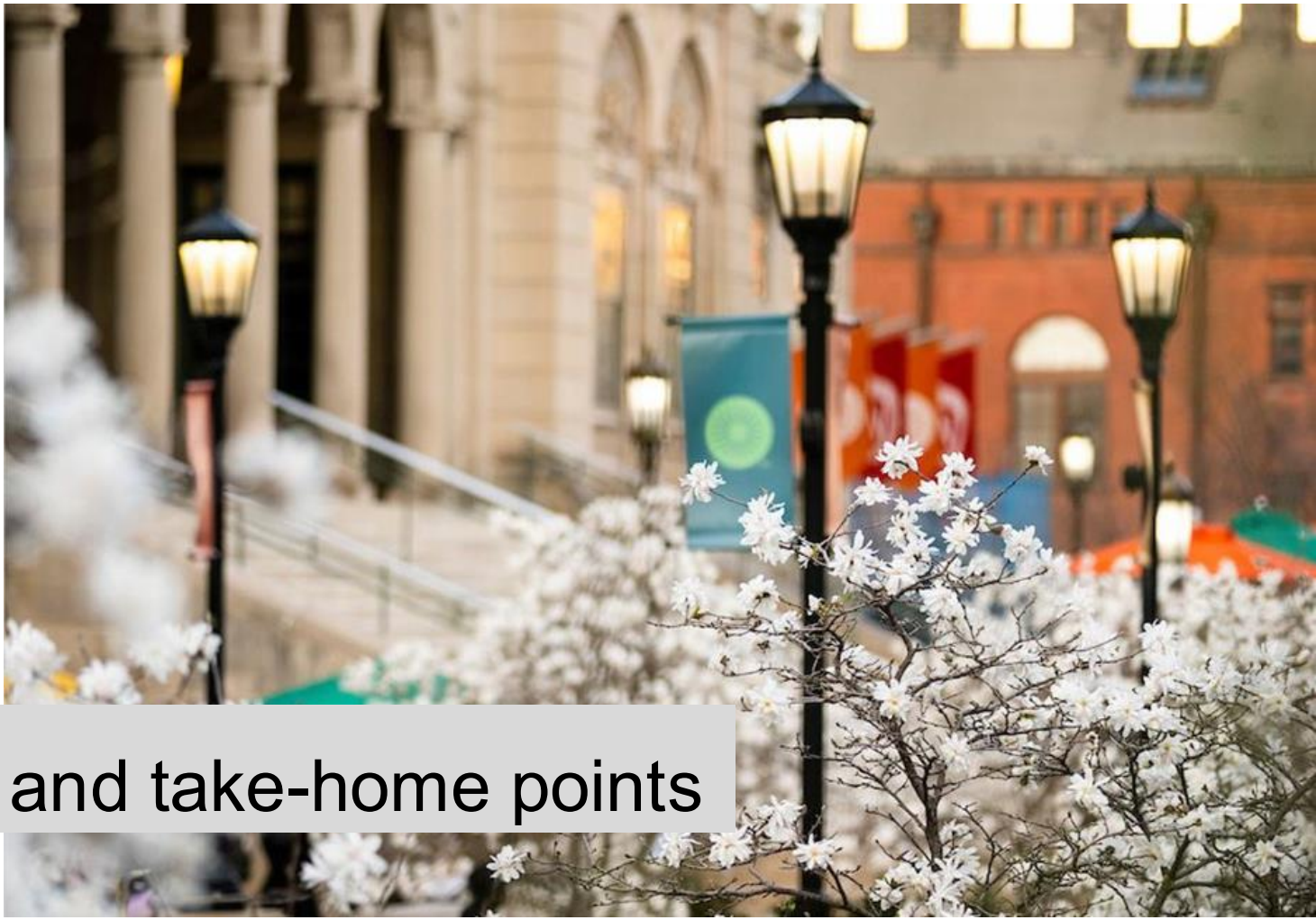

Summary and take-home points

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Summary

- Sex and gender have unique impacts on brain health
- Sex and gender factors impact risk for and resilience to dementia
- Sex and gender also impact need for intervention, content of intervention, and outcomes intervention
- Stress and estrogen may play key roles in women's risk and and offer new opportunities for supporting resilience
- Using the lens of psychology to view brain health intervention can help with implementing practical changes

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Feixiong Cheng
Mark Brown
Chad Cross

Philanthropic Partners:
The Women's Alzheimer's Movement at Cleveland Clinic
Maria Shriver
Sandy Gleysteen
Erin Stein

Wisconsin Registry for Alzheimer's Prevention

Thank you

National Institute on Aging:
https://www.nia.nih.gov/menopause

The Menopause Society: www.menopause.org

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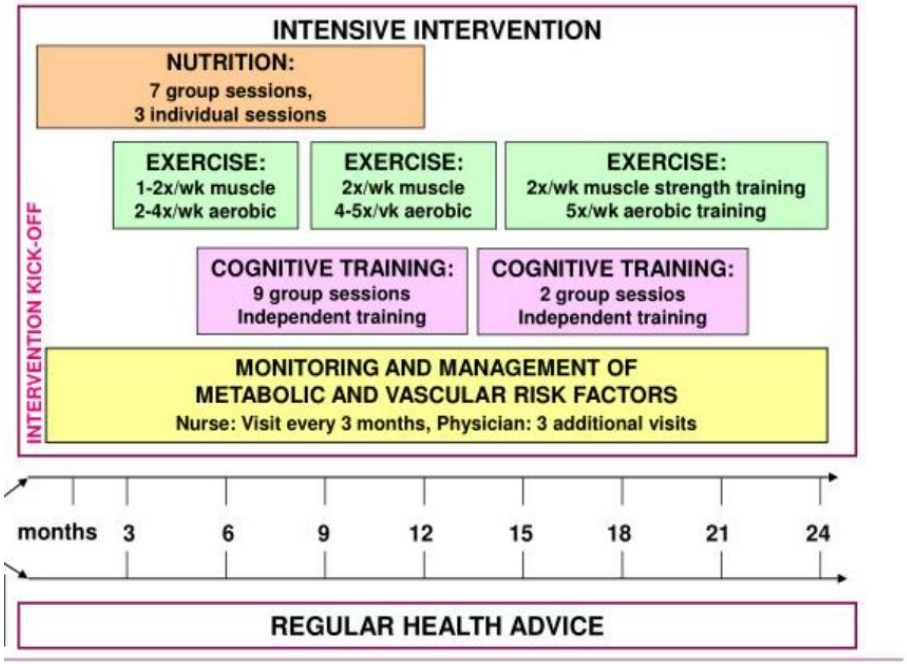
Lifestyle prevention interventions benefit those at risk



FINGER trial:

- N=1200, 60-77yo
- CAIDE >6
- Mean or slightly lower cognitive performance
- 2-year intervention

Improved or maintained cognition

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Kiivipelto, et al., Alz. & Dementia, 2013; Ngandu, et al., Lancet, 2015;
Yaffe et al., JAMA Int. Med, 2024

Personalized interventions benefit those at risk

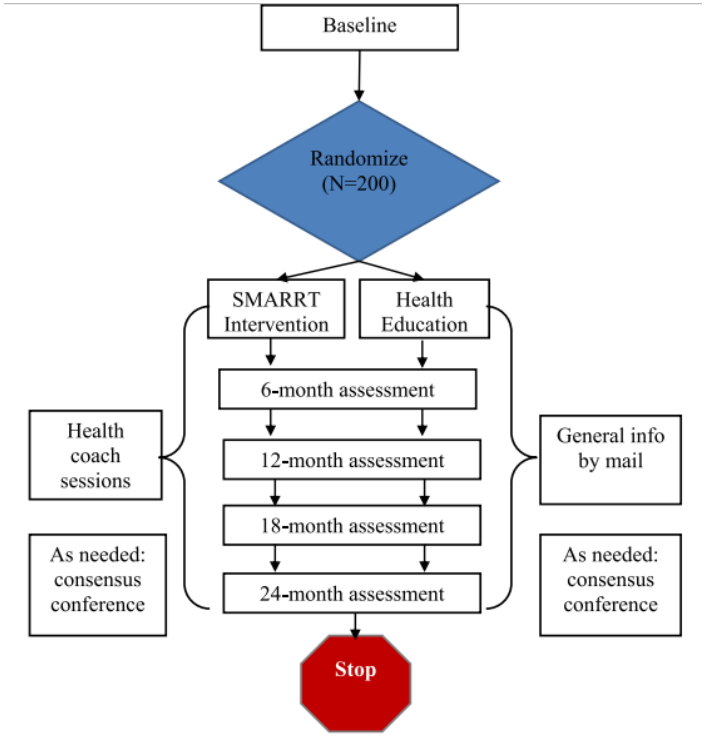

Fig. 1. Systematic Multi-domain Alzheimer's Risk Reduction Trial (SMARRT) Study Flow.

SMAART Trial:

- N=172, 70-89yo
- > 2 dementia risks
- 2-year intervention
- Personalized intervention (medical, lifestyle) with health coaching

Improved cognition and total dementia risks

Kiivipelto, et al., Alz. & Dementia, 2013; Ngandu, et al., Lancet, 2015; Yaffe et al., JAMA Int. Med, 2024

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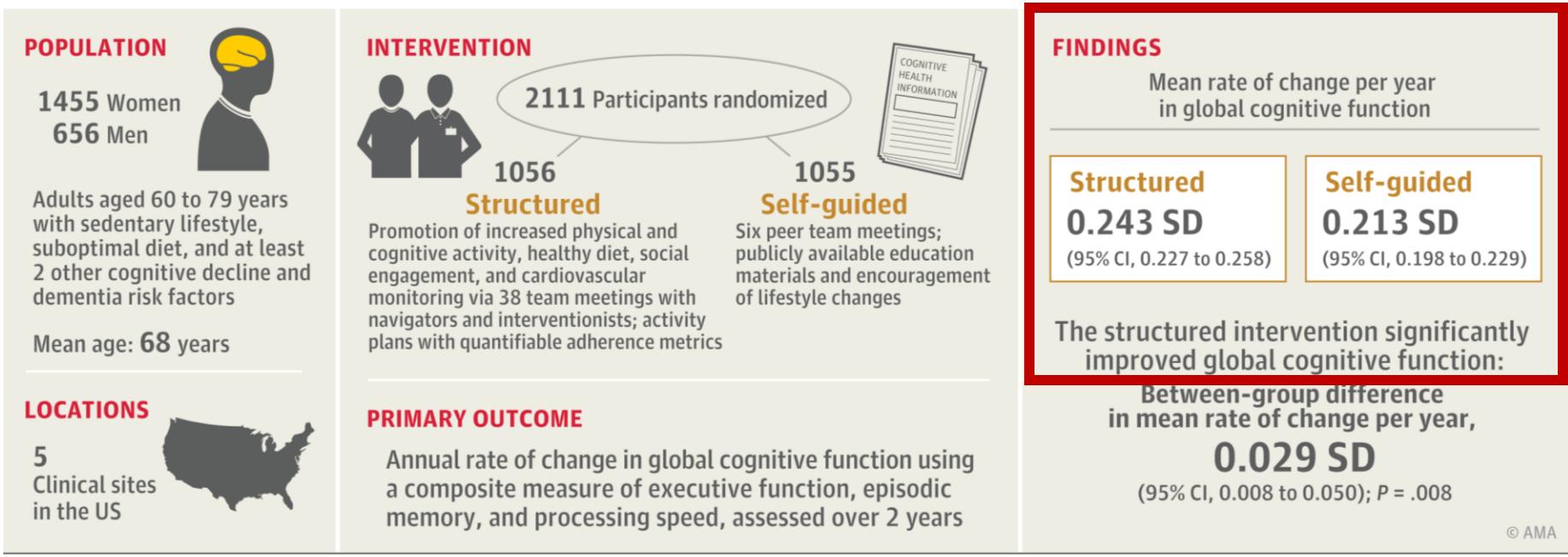
Structured interventions show more benefit than self-guided

POINTER Trial:



Baker LD, Espeland MA, Whitmer RA, et al. Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA*. Published online July 28, 2025. doi:10.1001/jama.2025.12923

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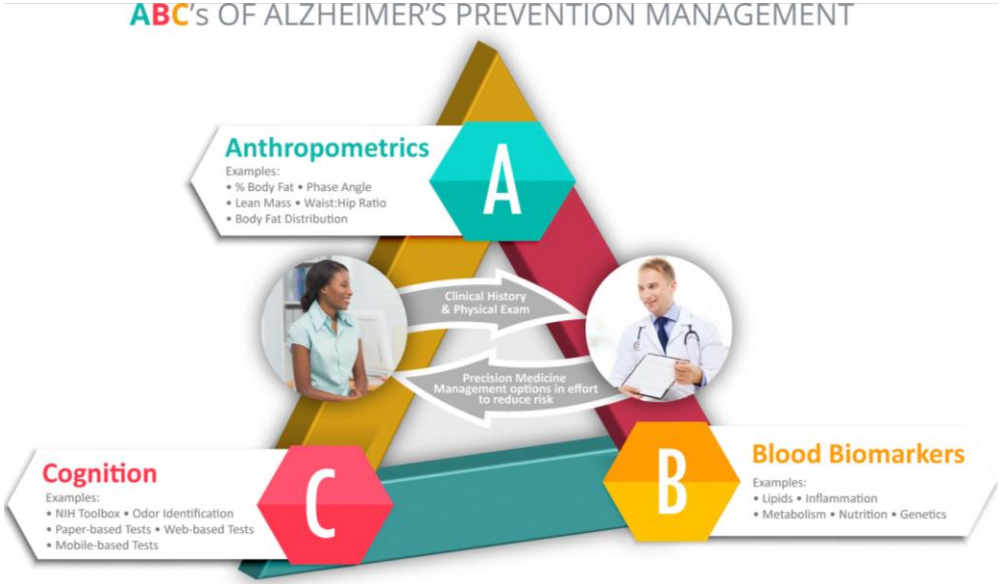
Clinical prevention interventions impact early disease

- **Isaacson personalized medical management:**
  - N=174, 25-86yo
  - Cognitively normal/MCI
  - 18 months
  - Personalized lifestyle, pharmacological, educational



Improved cognition

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Isaacson, et al., Alz. & Dementia, 2018, 2019

Stress relates to dementia risk

- High stress (experienced and perceived):
  - Increases AD risk
  - Causes synaptic loss and neuroinflammation
  - Promotes tau and Aβ
  - Leads to sequentially higher dementia risk if reported several times longitudinally

Franks, et al., Journal of Alzhiemer's Disease, 2021; Johansson, et al., Brain, 2010; Justice, Neurobiology of Stress, 2018; Lyons & Bartolomucci, Neuroscience & Biobehavioral Reviews, 2020; Wallensten, et a., Alz. Research & Therapy, 2023

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Gender impacts stressor exposure

- Women:
  - Greater lifetime exposure to interpersonal and assault-related stressors
  - More frequently caregivers

Alzheimer's Association, 2024; Munro, et al., Int. J. Geriatr. Psychiatry, 2019; Slavich & Shields, Psychosom. Med. 2018; Stewart, et al., JAHA, 2020

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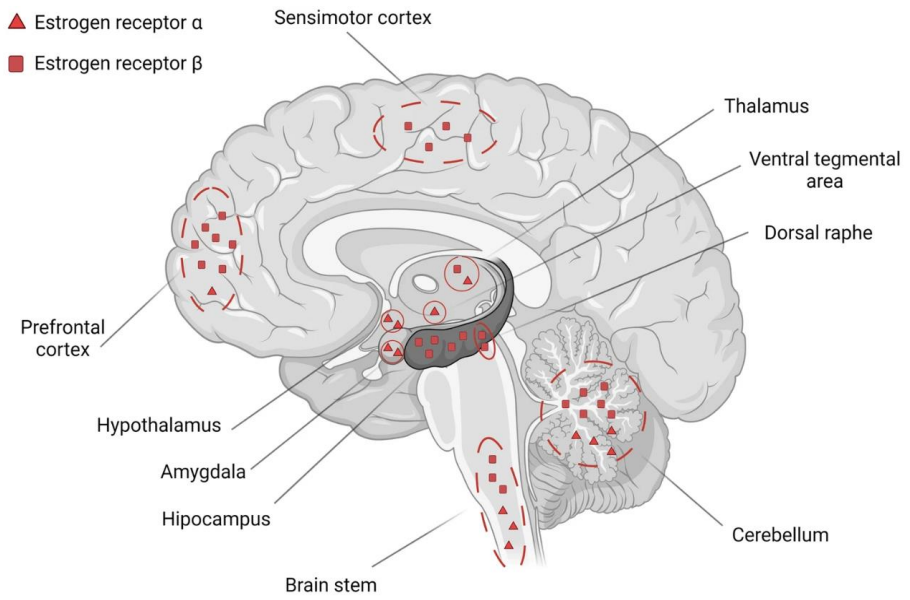
Sex impacts stress response



- **Estrogen**
  - Impacts inflammation
  - Active in memory and emotion circuitry
  - Regulates stress neurocircuitry across menstrual cycle

Image modified from Turek& Gasior, Pharmacological Reports, 2023; Jacobs, et al., Neuropsychopharmacology, 2015; Kirschbaum, et al., Psychosom. Med., 1999; McEwen&Alves, 1999; Stroud, et al., Biol. Psychiatry, 2002)

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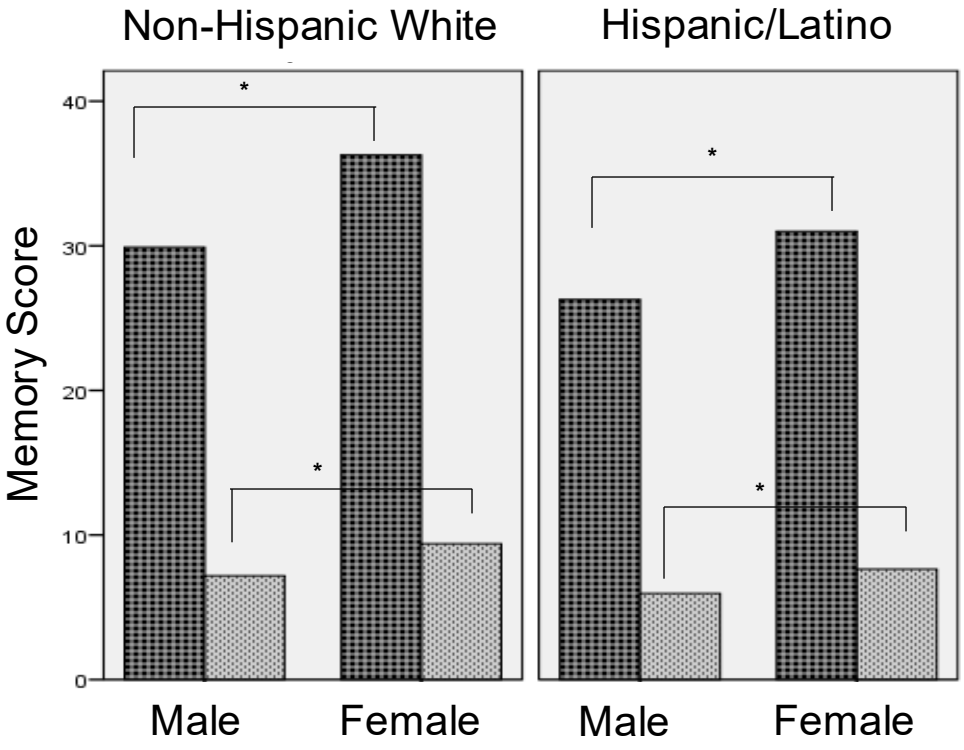
Stress may create memory vulnerability



N = 417

N = 657

*p<0.0001

Hispanic/Latino women with high neighborhood disadvantage do not have memory advantage over men

Caldwell, unpublished

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