The Role of Sex/Gender & Lifestyle on Alzheimer's Disease Risk

Sarah Banks, PhD and Erin Sundermann, PhD
Associate Professors of Neuroscience and Psychiatry
University of California, San Diego

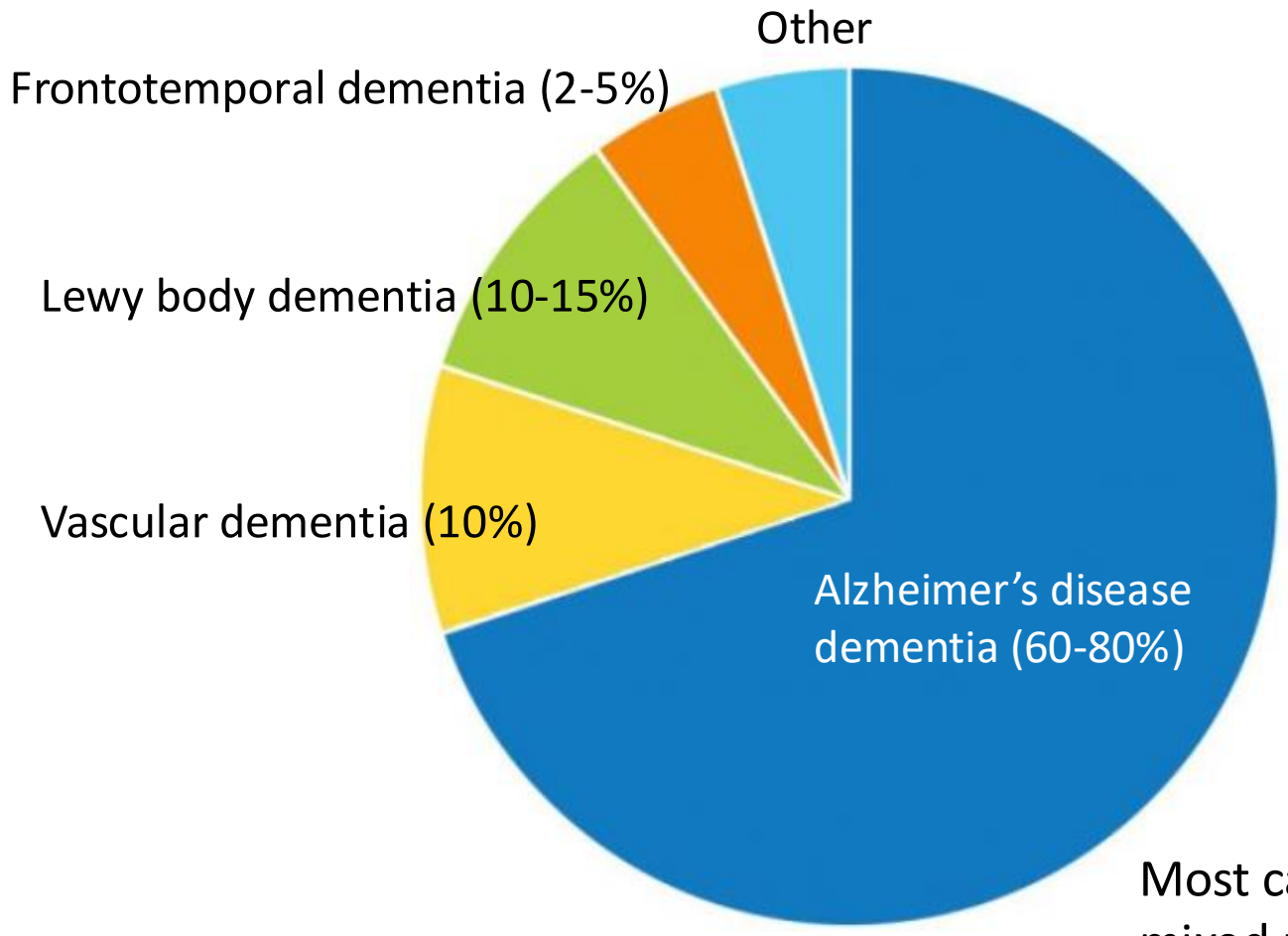
Ella Lifset, BS
Project Coordinator,
Women: Inflammation and Tau Study
University of California, San Diego

First, some terminology…

- Sex – Biological distinction of males versus females that primarily results from gonadal hormones and sex chromosome (XX vs. XY)
- Gender – a social construct referring to how one identifies themselves that can be influenced by environmental, social, and cultural factors

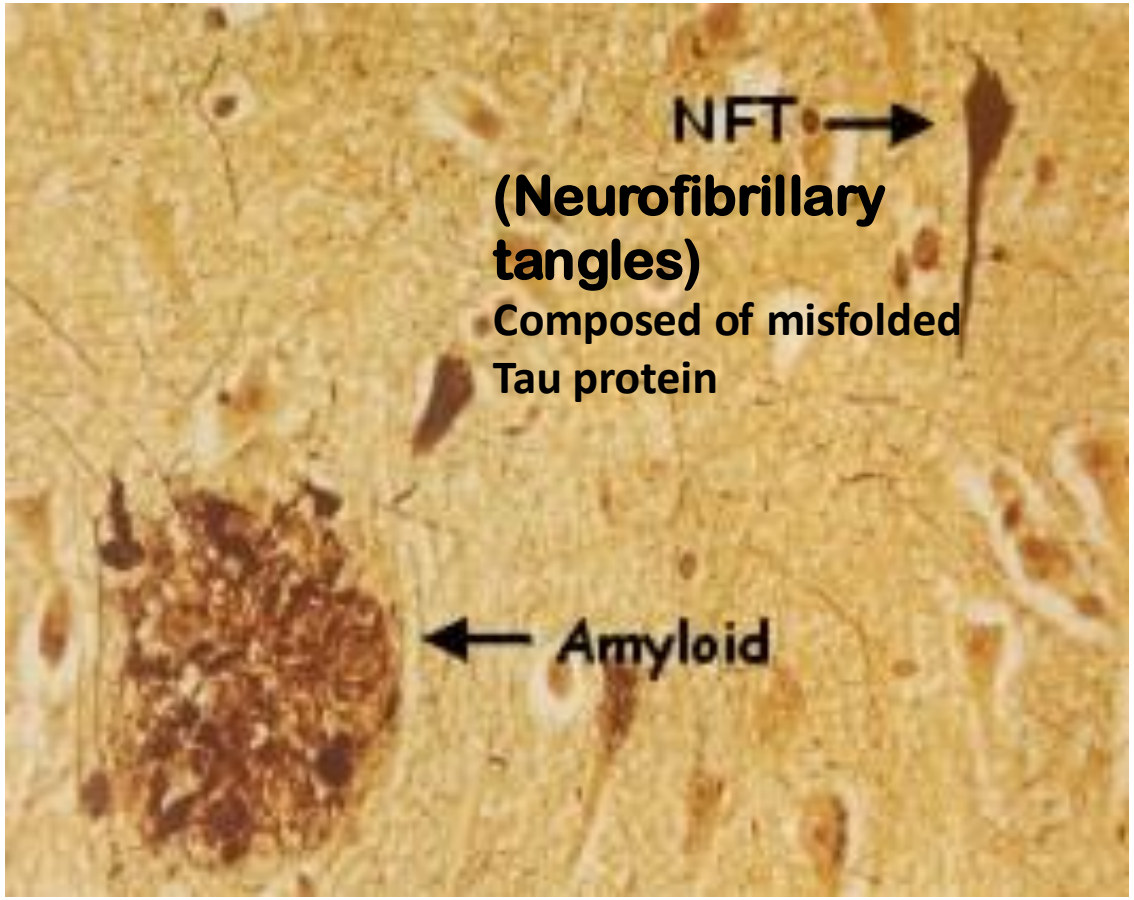
Dementia vs Alzheimer's

Dementia is a general term for any neurodegenerative disease that causes progressive loss of our cognitive abilities that is severe enough to interfere with daily life.



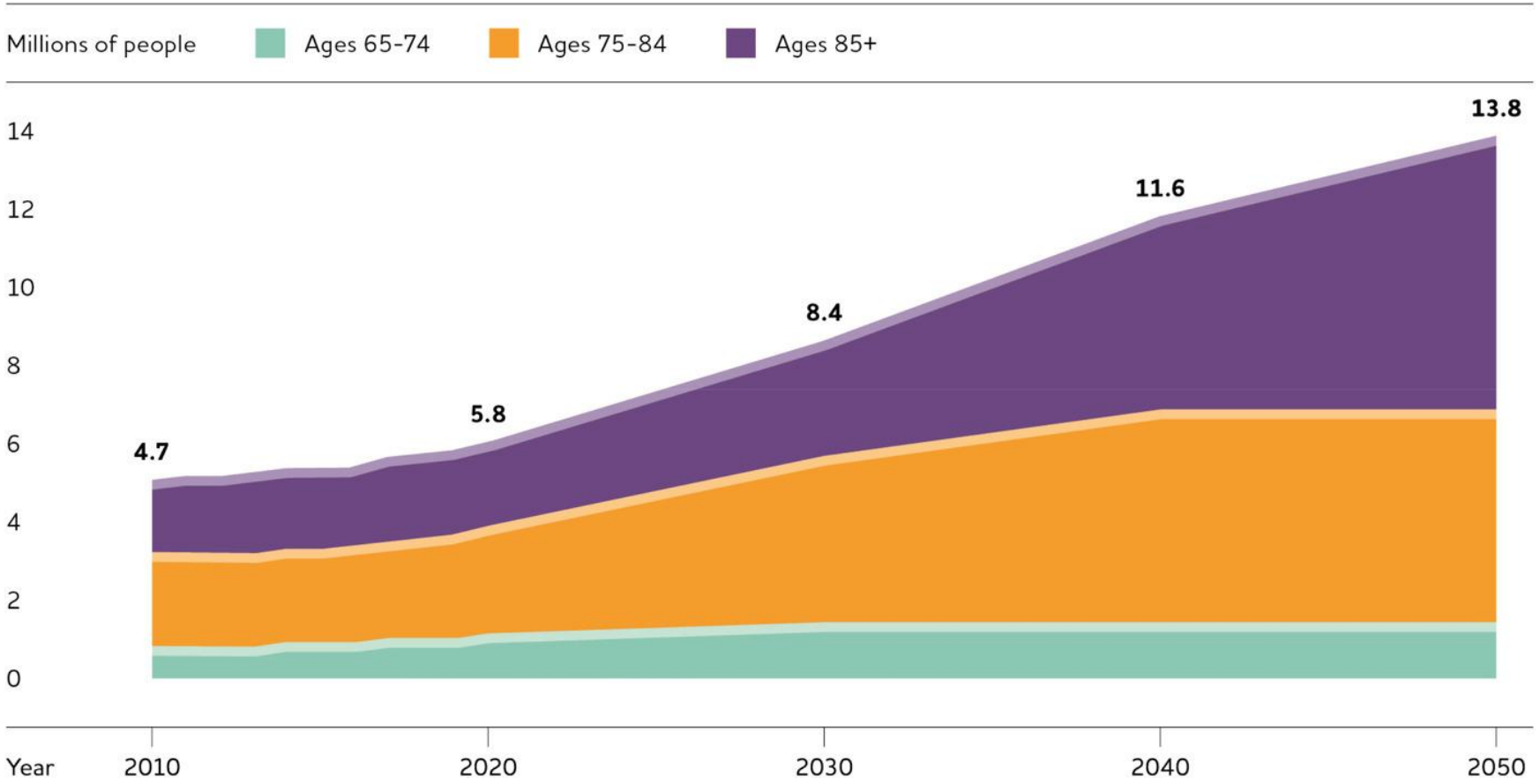
Most cases have mixed pathology

What is Alzheimer's?



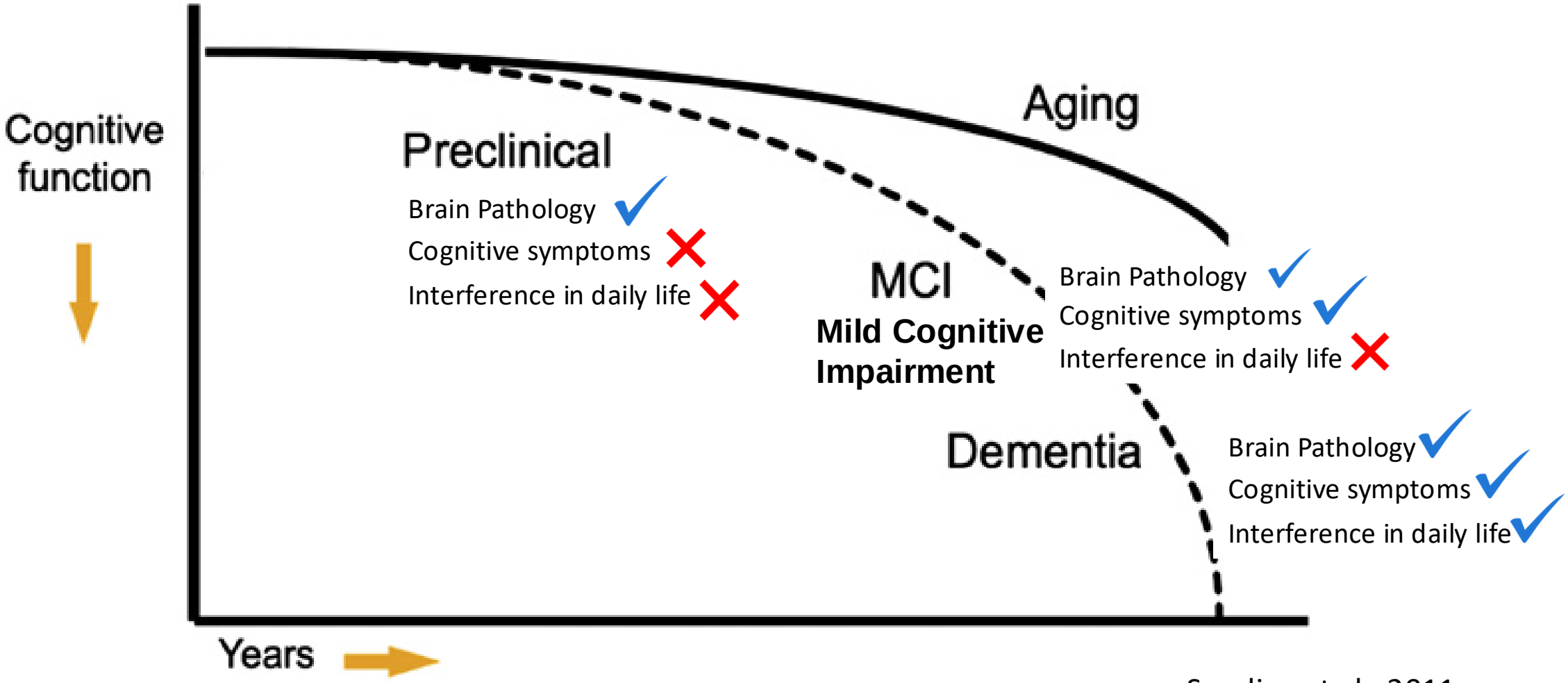
- Accumulation of *amyloid plaques* and *neurofibrillary tangles (Tau)* in the brain
- Other brain changes include neuroinflammation, loss of connections between brain cells, brain volume loss
- Most prominent symptom is memory impairment
- Cognitive decline starts gradually and continues to deteriorate until death, affecting all cognitive abilities.

Number of Americans with dementia is expected to rise dramatically in coming years



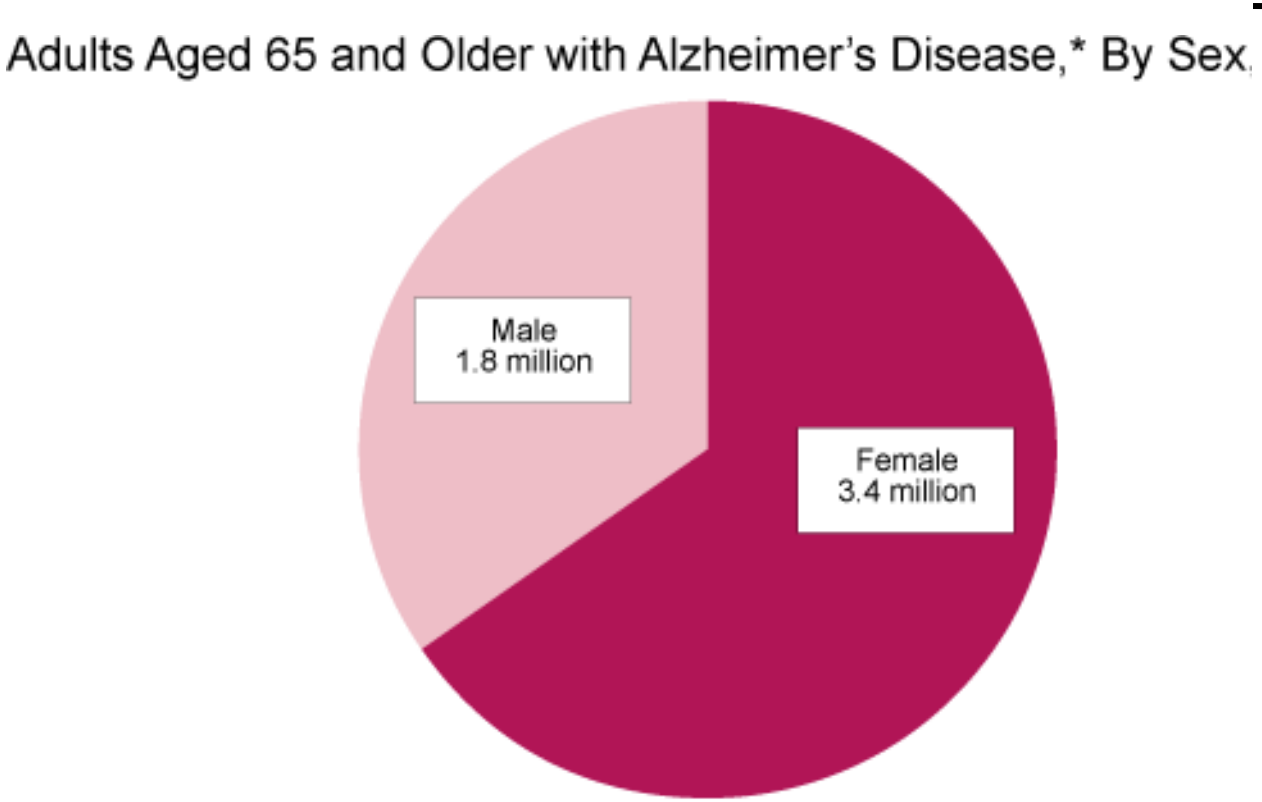
2020 Alzheimer's disease facts and figures
https://doi.org/10.1002/alz.12068

Trajectory of Dementia



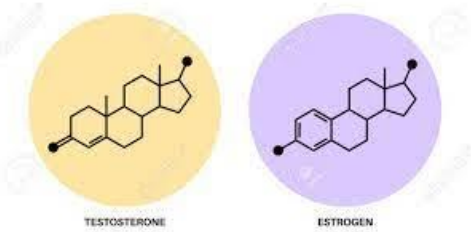
Sperling et al., 2011

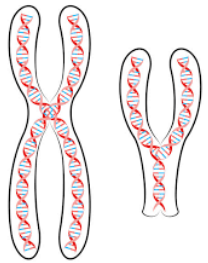
Women are 2/3 of Alzheimer's cases

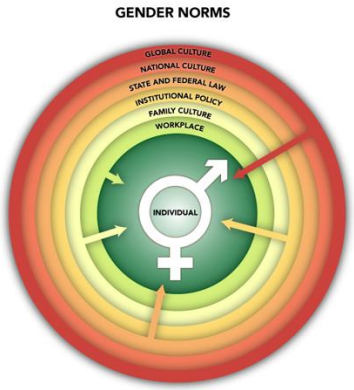


But why?

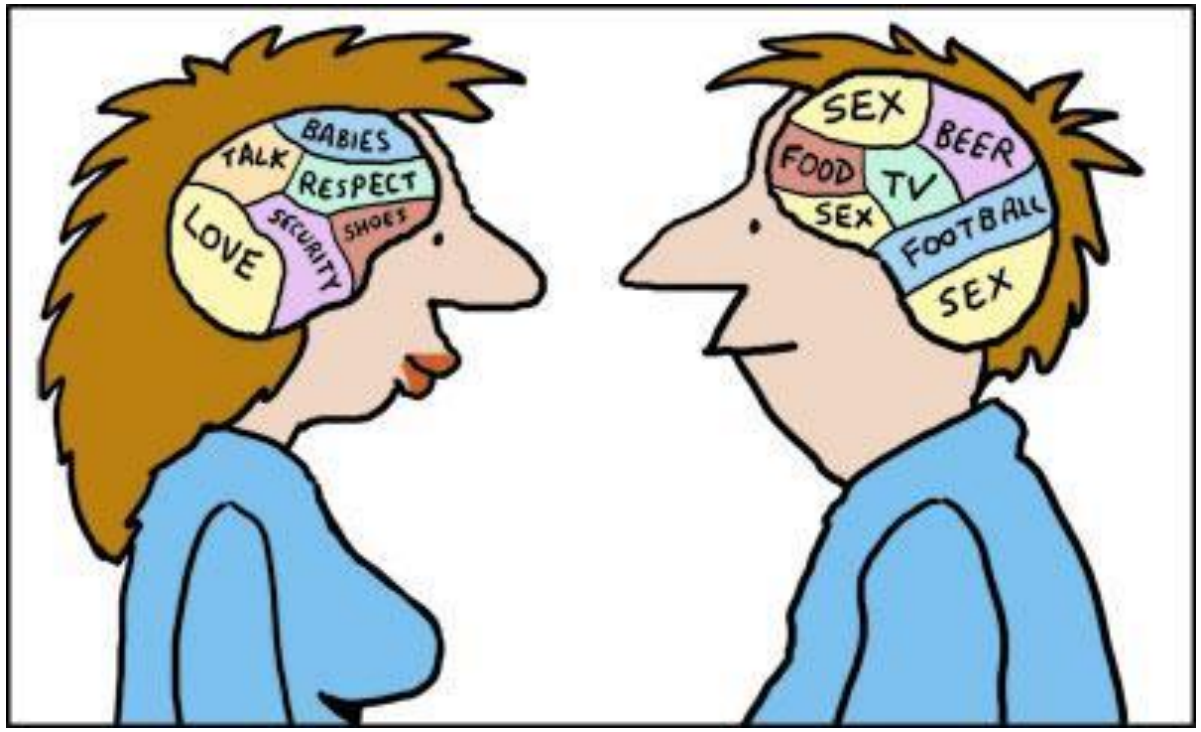
Sex/gender-related factors can provide clues







The female and male brains are unique



By Ellid Nadler of Toonpool.com

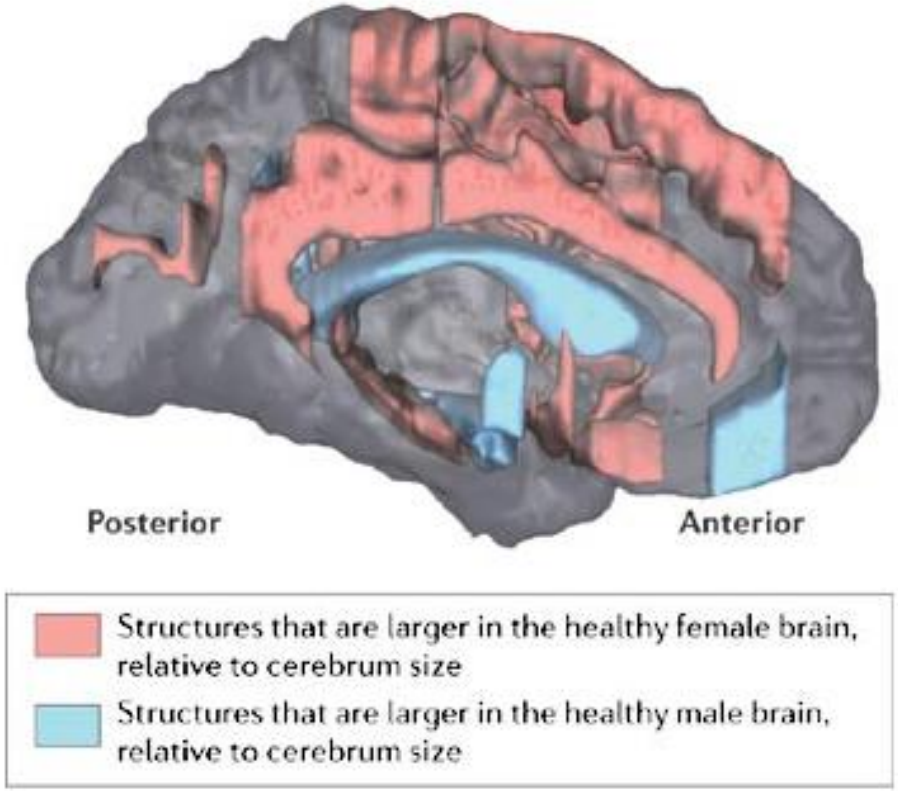


Image from Brainfacts.Org, May 2014

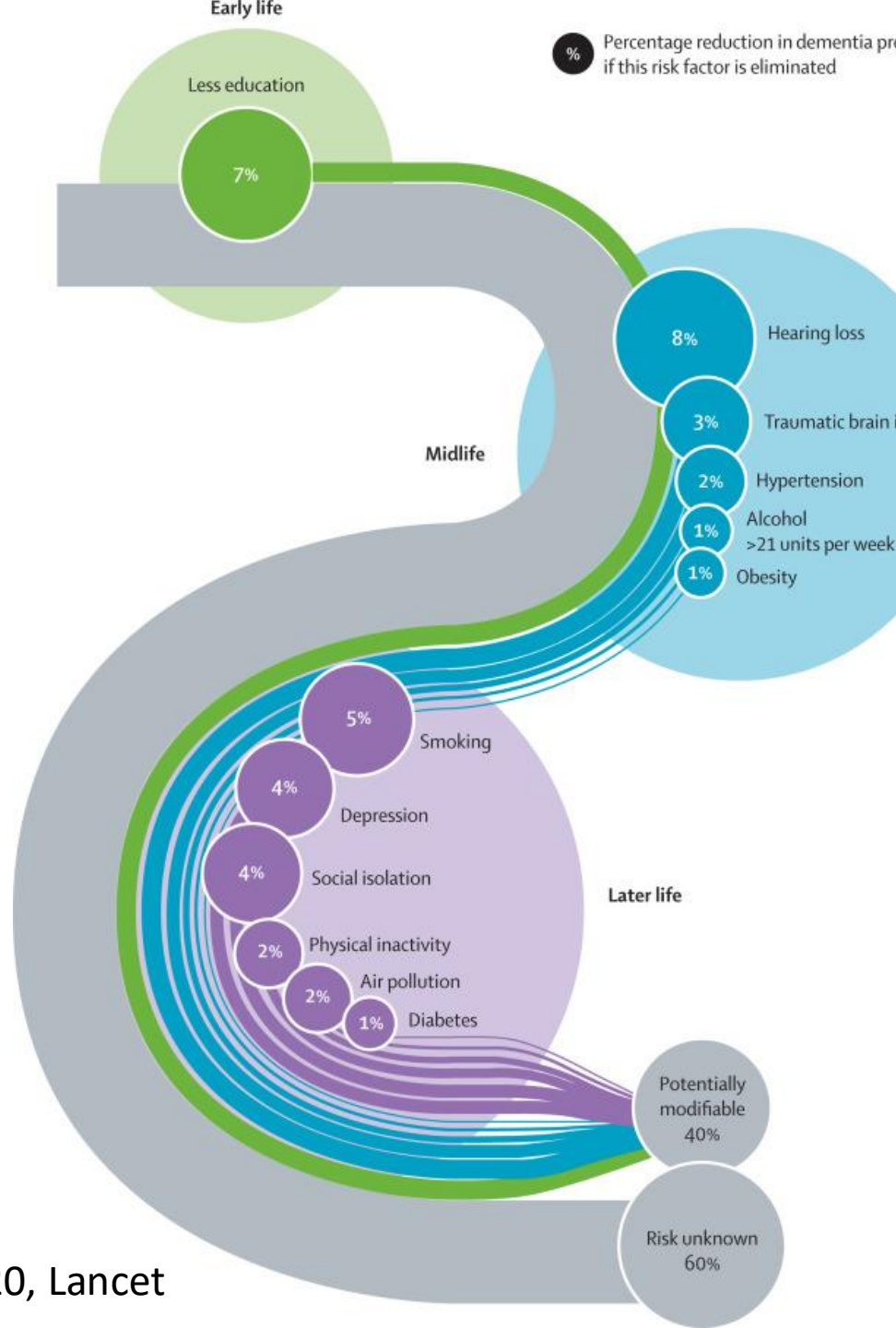
Now for some good news!

40%

of dementia cases could be prevented by addressing lifestyle factors

What are modifiable risk factors?

- 12 modifiable risk factors for dementia with strong scientific evidence
  - Some early (like education)
  - Some midlife
  - Some late life
  - Probably not a complete list



Livingston et al., 2020, Lancet

Six Pillars *of* **Brain Health**

AARP's Global Council on Brain Health

Physical Activity

Exercise causes physical changes in brain that promotes healthy cognitive function and safeguards against dementia!

- What's good for the heart is good for the brain!
- Enhances blood flow, pumping more oxygen and nutrients to the brain
- Stimulates increases levels of crucial brain compounds (e.g., brain derived neurotrophic factor)
- Helps build new brain cells
- Relieves anxiety & depression
- Decreases inflammation

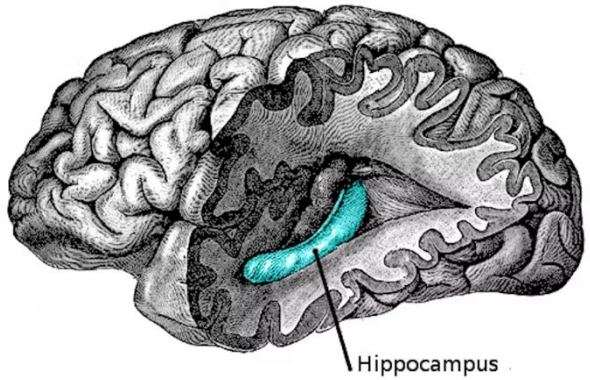
But, what type of exercise and how much?

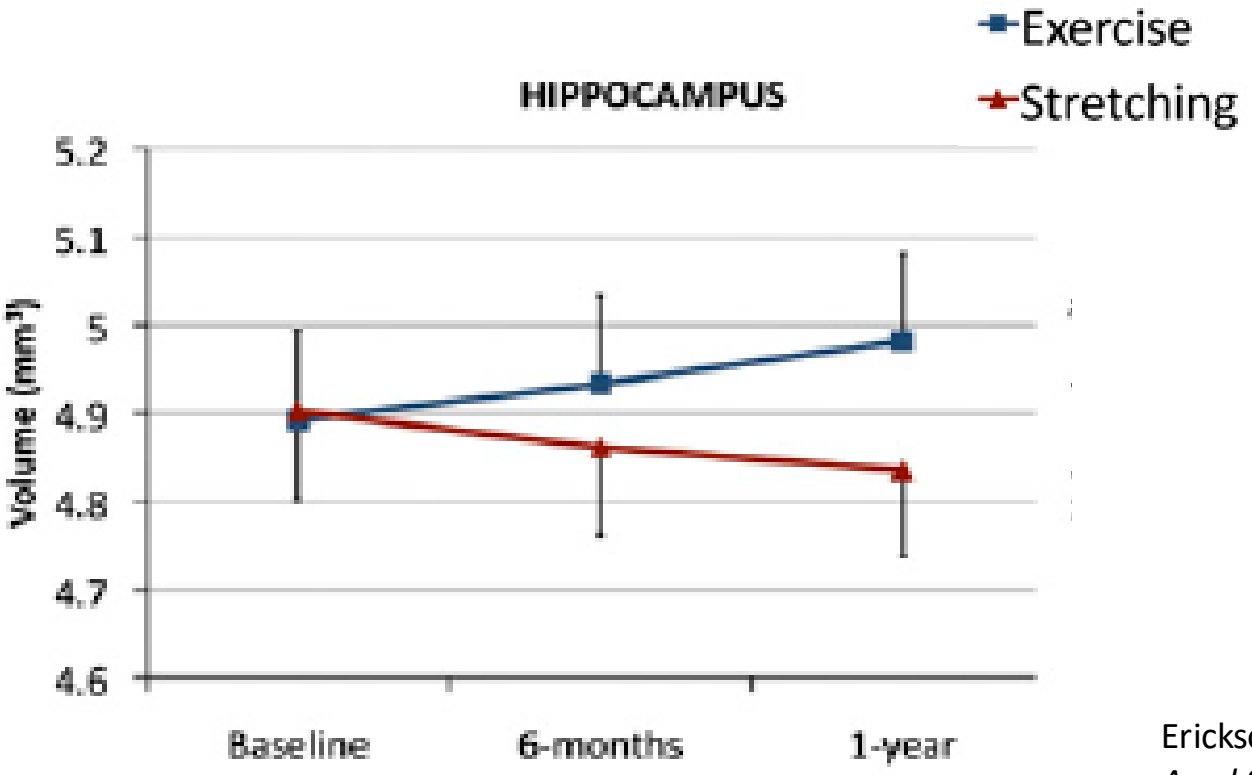
Physical activity recommendations

- Aerobic exercise is particularly brain healthy
  - Examples are brisk walking, biking, swimming, jogging, tennis
- Strength building & balance exercises should supplement aerobic exercise
  - Resistance training, tai chi, yoga, pilates
- Exercise regimens are not one-size-fits-all

Aerobic exercise reversed brain volume loss in older adults

120 sedentary older adults randomized to: (1) a brisk walking regimen or (2) a stretching regimen





Erickson et al, 2011, *Proc Natl Acad Sci*

Sex/gender considerations in physical activity

- Some evidence that exercise seems to lower risk of cognitive decline and AD in women more so than in men

- Physiological differences between the sexes that cause different responses to exercise
  - Higher % of Type I muscle fibers in women - suited for long, sustained activity
  - Higher % of Type II muscle fibers in men - suited for shorter, intense bursts

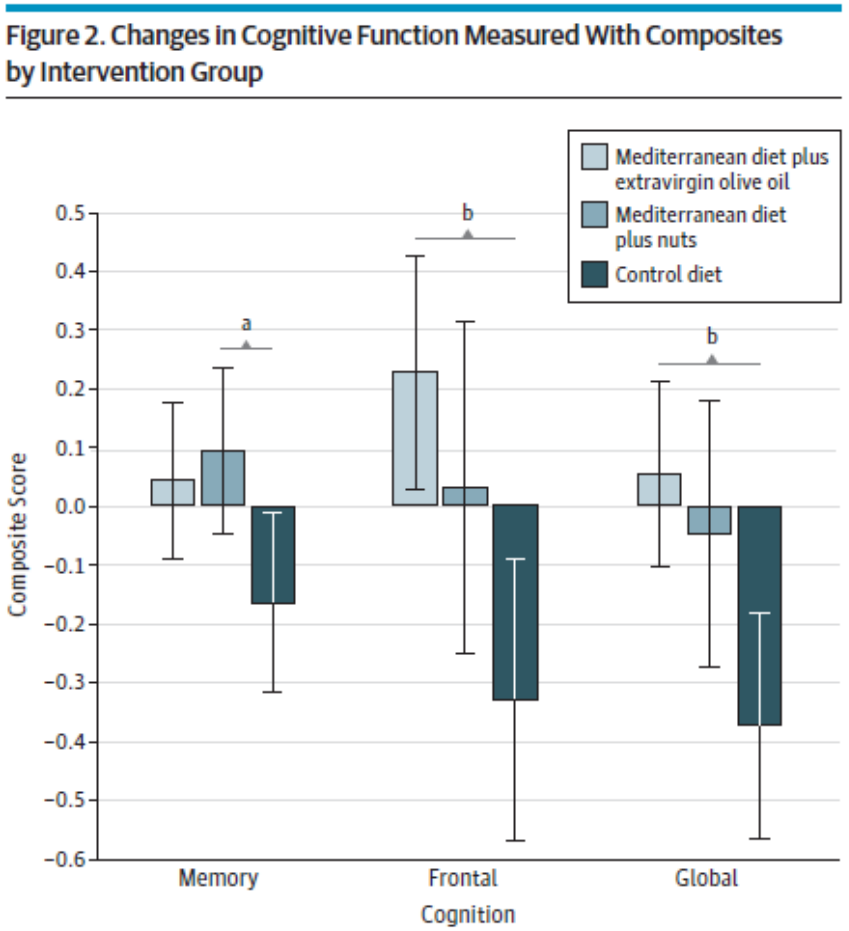
- <u>Women - be the tortoise & men – be the hare!</u>

Nutrition

- Brain is most energy demanding organ
- Strongest evidence for Mediterranean diet in supporting brain health
- Foods with antioxidant effects particularly helpful to the brain
- Eat the rainbow!

Mediterranean diet led to improved cognitive function

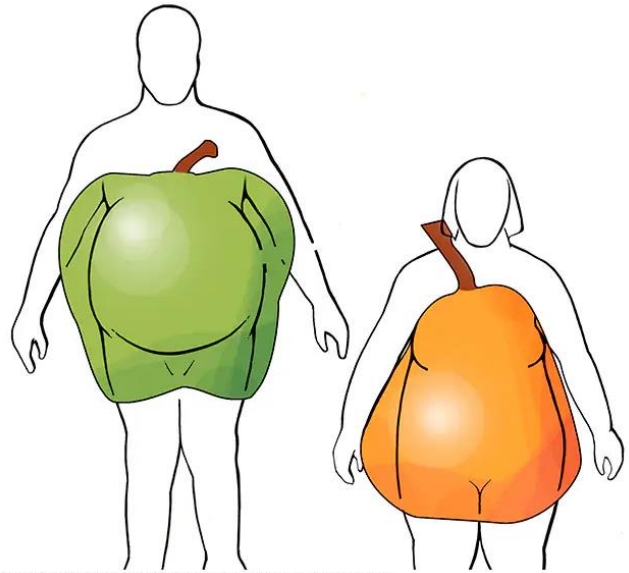
- 447 older, Spanish adults who were cognitively healthy but high cardiovascular risk were randomly assigned to:
  - Mediterranean diet + extra virgin olive oil
  - Mediterranean diet + mixed nuts
  - Western diet (advised to reduce dietary fat)
- Assessed cognitive function after about 4 years



Valls-Pedret et al., 2011, JAMA Internal Medicine

Diets don’t deliver same results for women and men

- Men & women have different metabolic requirements
- Sex hormones influences body fat, muscle distribution, and blood sugar levels
  - Greater fat storage and carb-burning in women favors a diet of good carbs over bad fats
  - Greater lean muscle mass in men favors a diet with more caloric intake, healthy fats & protein



Why is sleep so important for the brain?

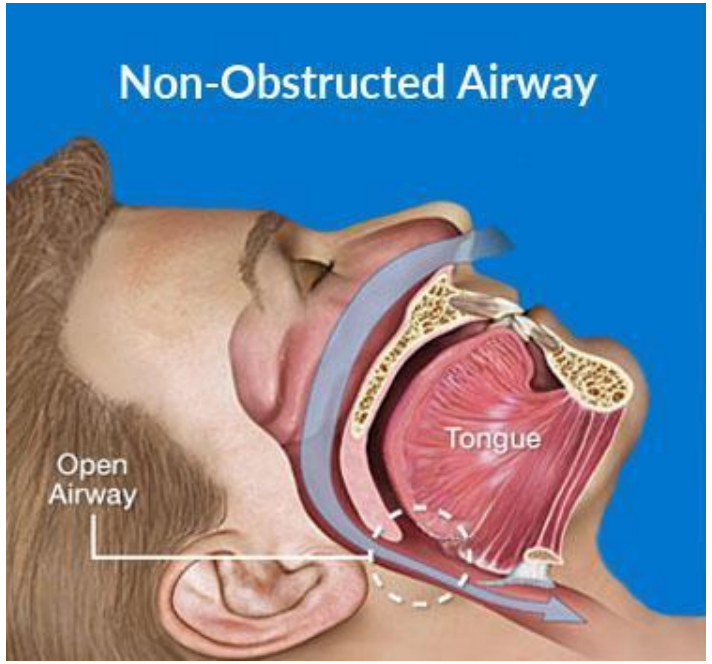
- Important for learning and memory; memories are consolidated during sleep
- Brain “housekeeping” occurs during sleep; waste proteins (including beta-amyloid) are cleared by glymphatic system
- Poor sleep linked with the AD risk factors of depression, obesity, hypertension and diabetes.
- Individuals with sleep problems had a 55% higher risk of AD (Bubu et al., 2017)

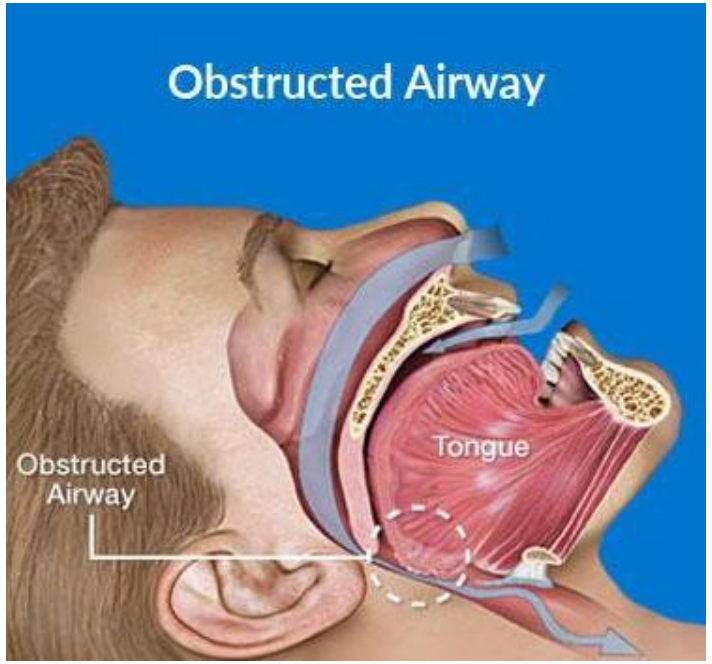
Sleep Recommendations:

- **6-8 hours per night is ideal but depends on the person**
- **Try lifestyle changes to improve sleep before sleeping pills**
- **A kind of therapy (CBTi) that teaches tricks to avoid insomnia is gold standard**

Sleep Apnea

- Sleep apnea is common and gets more so in old age (60% of adults age 65+ have symptoms)
- Typically considered a “male” issue; however, equally common in women after menopause
- Associated with higher risk of dementia (e.g. Yaffe et al 2011)
- CPAP use appears to delay cognitive decline (e.g. Osorio et al, 2015)

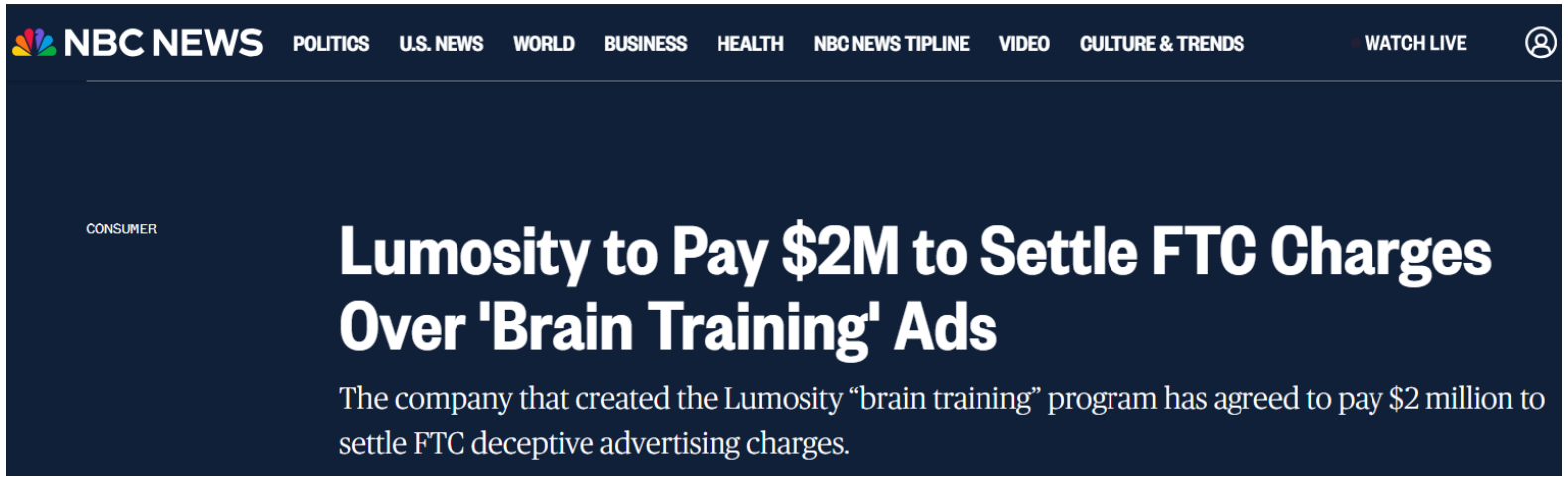




What doesn’t work?

- Supplements
  - Unless you have a deficiency
  - Be careful! – can have unwanted side effects and interactions with other medicines

- Brain games or other repetitive sedentary activities



What you can do now?

- Never too late to make lifestyle changes that can reduce dementia risk
- Get involved in Alzheimer's research and play a part in making an Alzheimer's free world!

HELPFUL RESOURCES

Mind Over Matter: Quarterly publication by the Women's Brain Health Institute

Habit tracker apps such as BrainFit

Move Your Way Campaign Resources from the U.S. Office of Disease Prevention and Health Promotion

MOVE YOUR WAY®

Women: Inflammation and Tau Study (WITS)

Neuroinflammation

Tau Pathology

Cognitive Function

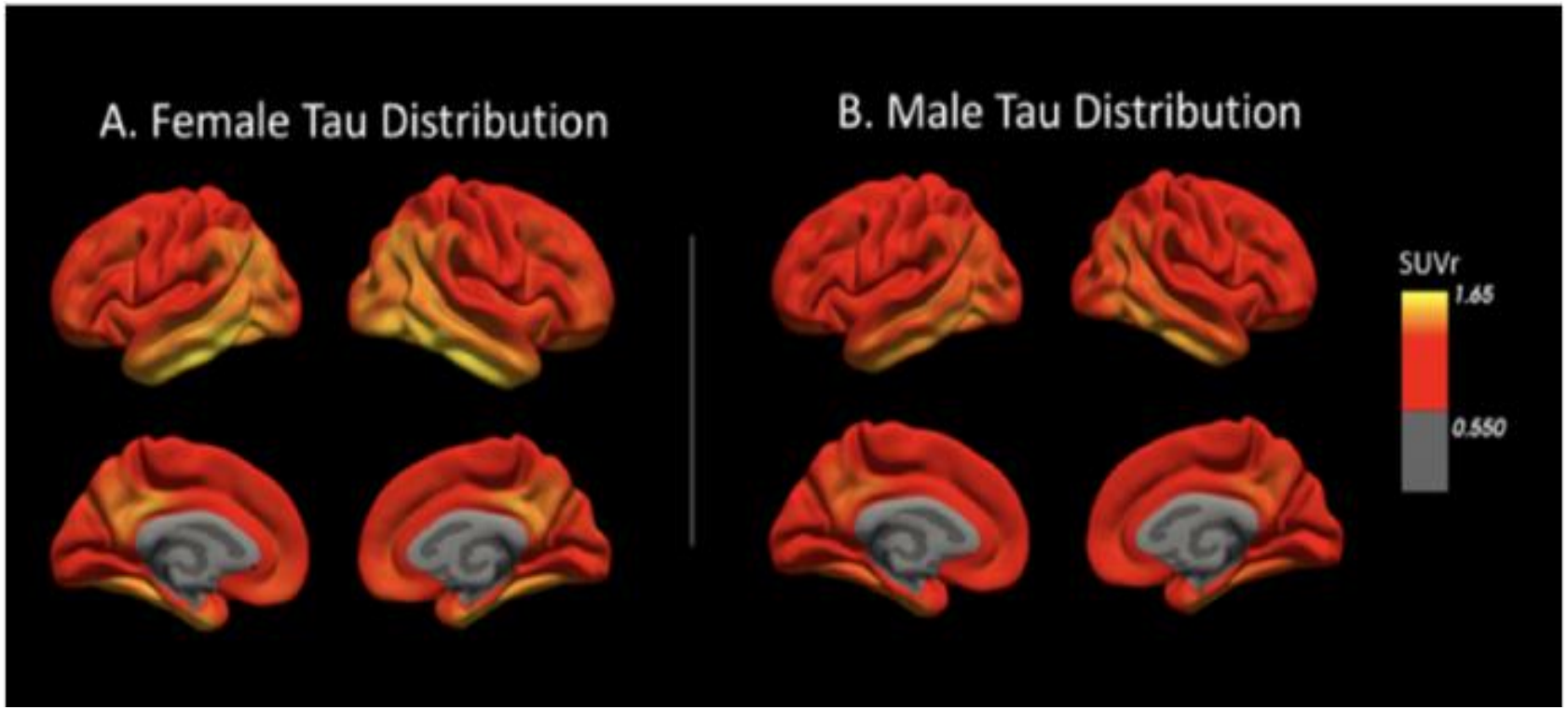
UC San Diego

WITS

Women: Inflammation and Tau Study

Greater Tau burden (tangles) in women versus men in the preclinical & MCI stages

Tau, but not amyloid, pathology relates to cognitive function



Banks et al. (2021), *Neurobio of Aging*

WHY?...

Could inflammation be a culprit?

Inflammation is central to AD pathology

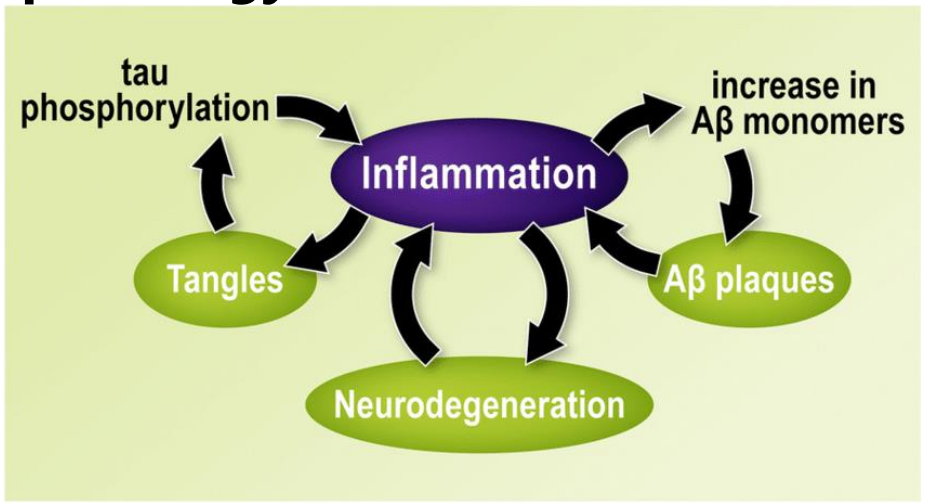
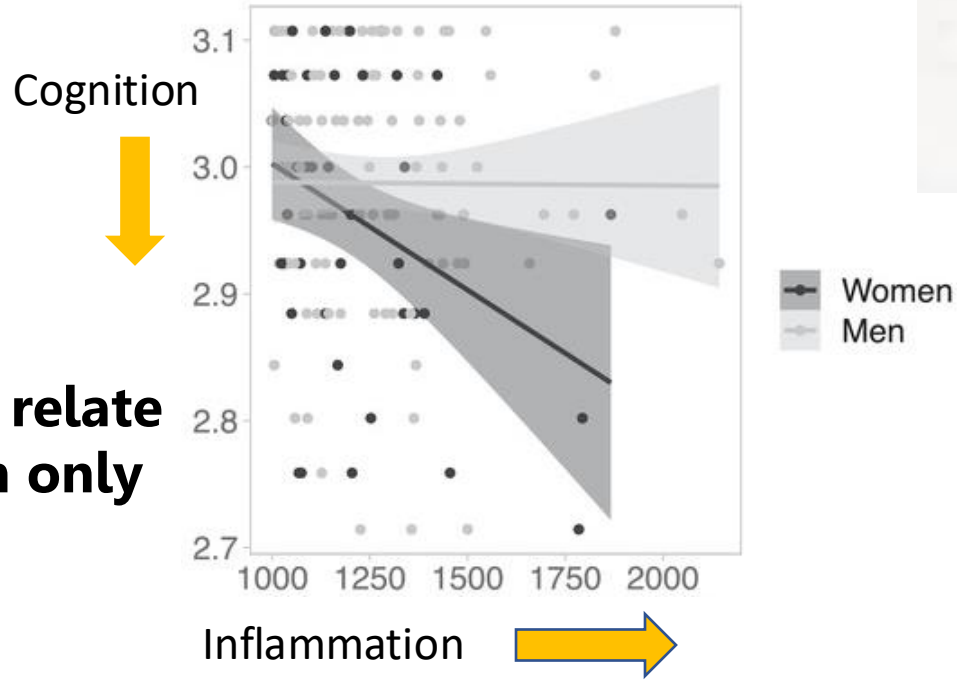


Image from Newcombe et al., 2018, Journal of Neuroinflammation

Predominance of autoimmune disorders in women

Inflammation markers relate to cognition in women only



The Women: Inflammation & Tau Study (WITS)

- Could inflammation be the key to the greater tau in women, and could understanding that help us learn how to restrict or slow spread of tau?
- How do lifestyle factors that impact inflammation (physical activity, sleep, diet, vascular risk) contribute to the spread of Tau?

UC San Diego

Led by Drs. Sarah Banks &
Erin Sundermann