

# Sex differences in AD biomarker progression: Sensitive measures of cognition

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# Why care about sex\* differences in cognition?

1) They impact  
who gets  
diagnosed early

2) They impact  
who gets into  
clinical trials, and  
the results

3) If addressed, we  
will understand  
Alzheimer's better  
for everyone

\*I will use "sex" as a very  
oversimplified, binary term  
which sometimes involves  
gender

# Considerations for how we measure cognition in AD

Lifelong sex differences in  
cognition

The verbal memory advantage

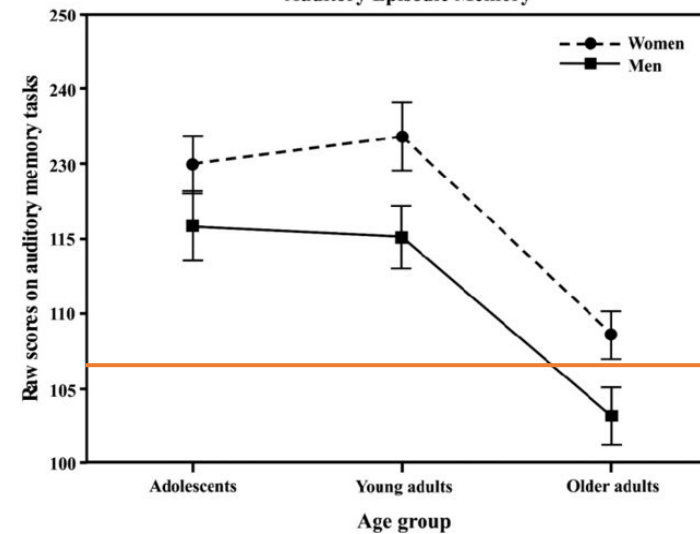
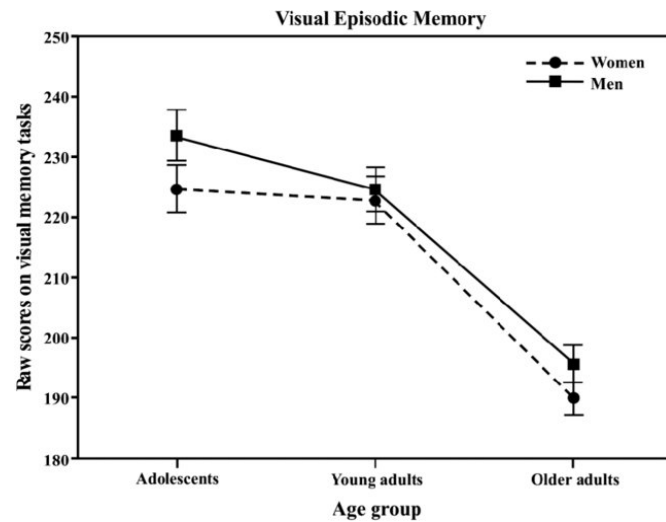
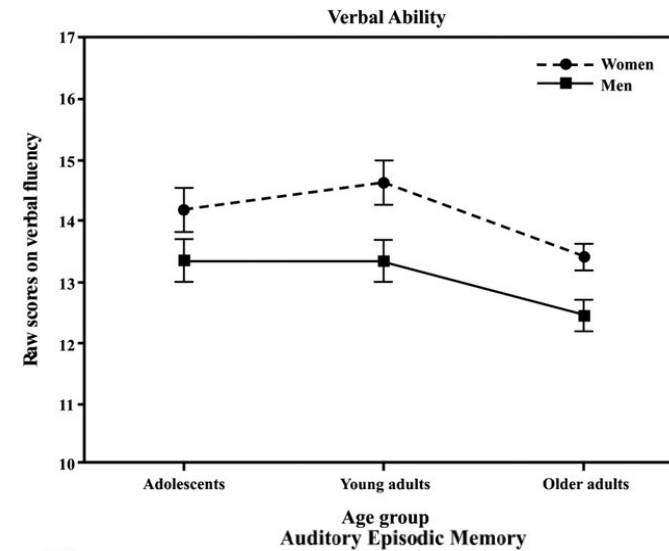
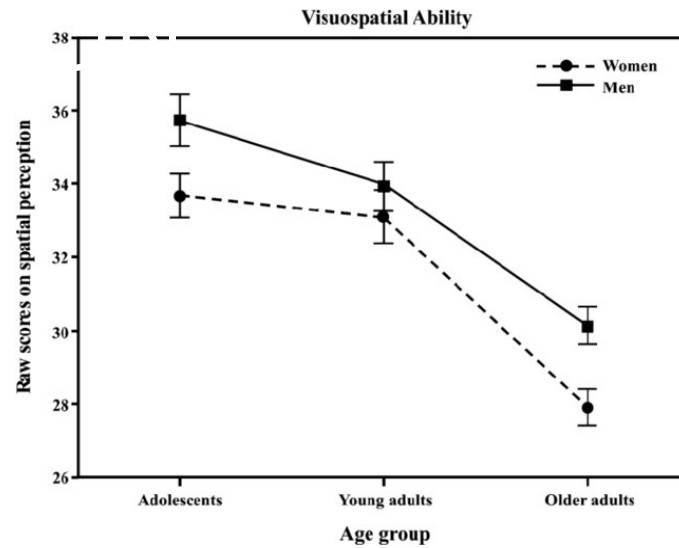
What about visual memory?

Subtle preclinical changes and  
sex differences

Relationships with biomarkers



Cognitive development is lifelong, and women and men show lifelong cognitive differences (on average)

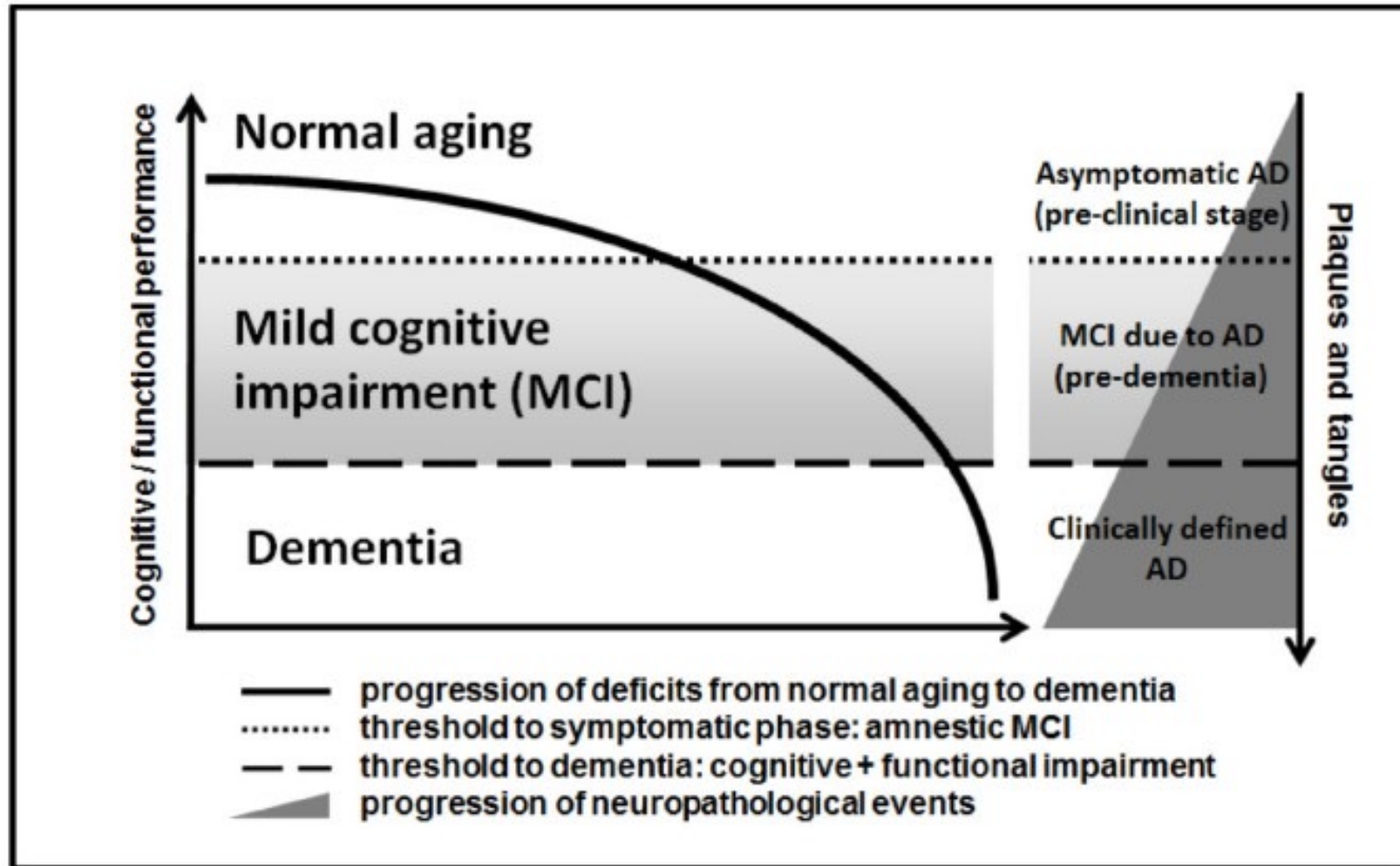


Cut off for trial inclusion

# What do we use to test memory in AD?

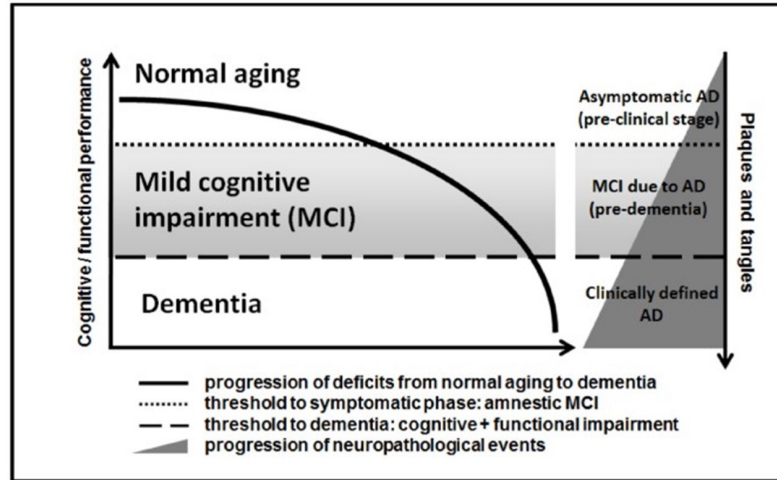
	<u>Trial 1</u> <u>Recall</u>	<u>Trial 2</u> <u>Recall</u>	<u>Trial 3</u> <u>Recall</u>	<u>Trial 4</u> <u>Recall</u>	<u>Trial 5</u> <u>Recall</u>
football					
notebook					
island					
billiards					
paper					
river					
tennis					
cake					
folder					
boxing					
mountain					
pie					
candy					
envelope					
valley					
ice cream					
	___/16	___/16	___/16	___/16	___/16
<b>Total Learning</b>	<b>___/80]</b>				

These tests are used to identify cognitive impairment which declines with progression of the disease





# VERBAL MEMORY, WOMEN'S ADVANTAGE?



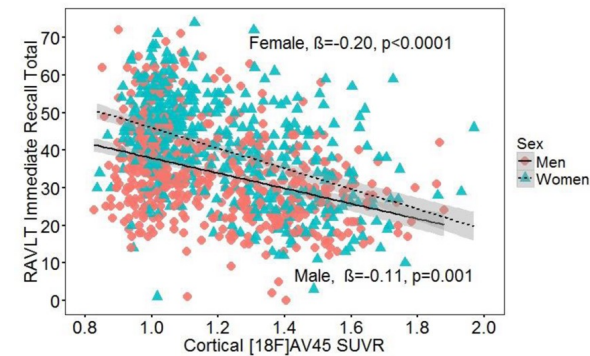
Published in final edited form as:

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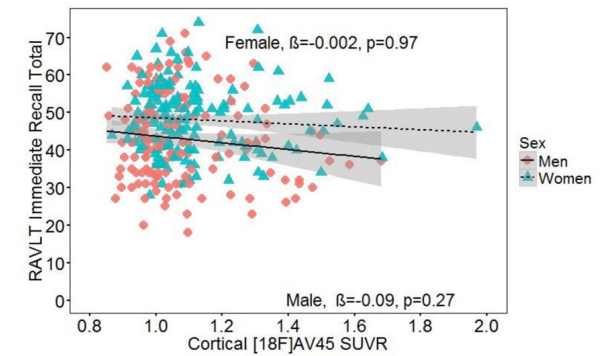
**Does the female advantage in verbal memory contribute to underestimating AD pathology in women versus men?**

Erin E. Sundermann, PhD<sup>a</sup>, Anat Biegon, PhD<sup>b</sup>, Leah H. Rubin, PhD, MPH<sup>c</sup>, Richard B. Lipton, MD<sup>a</sup>, Susan Landau, PhD<sup>d</sup>, Pauline M. Maki, PhD<sup>c</sup>, Alzheimer's Disease Neuroimaging Initiative<sup>¥</sup>

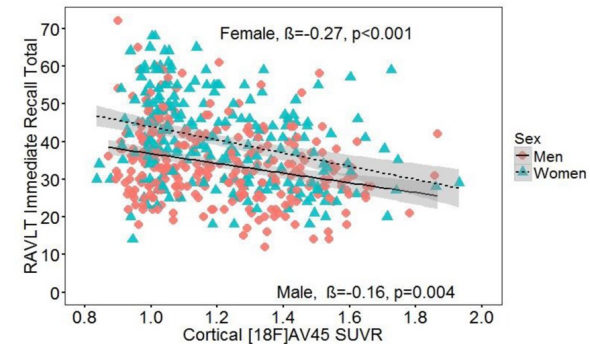
A. Overall sample (N=994)



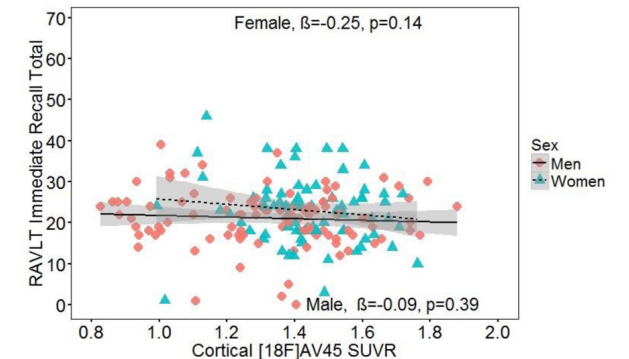
B. Normals (N=304)



C. aMCI (N=515)

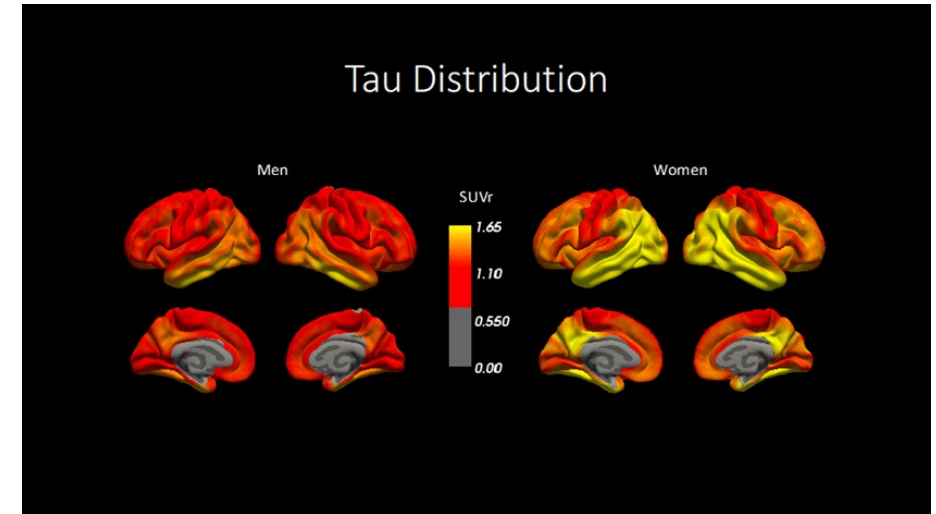


D. AD Dementia (N=175)





Women accumulate more tau pathology, especially during MCI phase



Sex differences in Alzheimer's disease: do differences in tau explain the verbal memory gap?

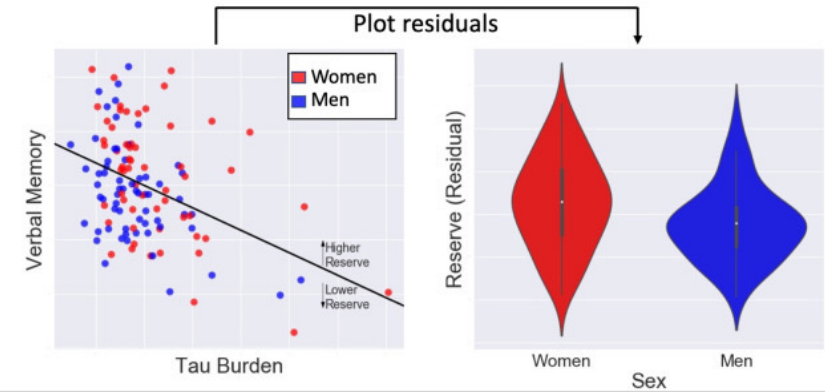
Sarah J. Banks<sup>a,b,\*</sup>, Murray J. Andrews<sup>a</sup>, Leonardino Digma<sup>a</sup>, John Madsen<sup>a</sup>, Emilie T. Reas<sup>a</sup>, Jessica Z.K. Caldwell<sup>b</sup>, Linda K. McEvoy<sup>a</sup>, Chun Chieh Fan<sup>c</sup>, Anders M. Dale<sup>a,d,e,f</sup>, James B. Brewer<sup>a,d</sup>, for the Alzheimer's Disease Neuroimaging Initiative<sup>#</sup>

# BRAIN COMMUNICATIONS

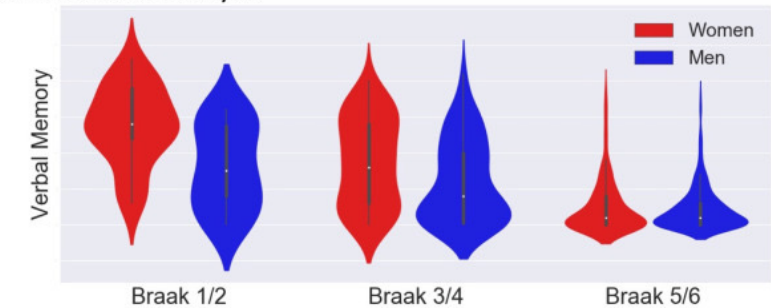
## Women can bear a bigger burden: ante- and post-mortem evidence for reserve in the face of tau

Leonardino A. Digma,<sup>1</sup> John R. Madsen,<sup>1</sup> Robert A. Rissman,<sup>1,2</sup> Diane M. Jacobs,<sup>1</sup> James B. Brewer<sup>1,3</sup> and Sarah J. Banks<sup>1,4</sup>, for the Alzheimer's Disease Neuroimaging Initiative\*

### Study 1: In Vivo PET Analysis

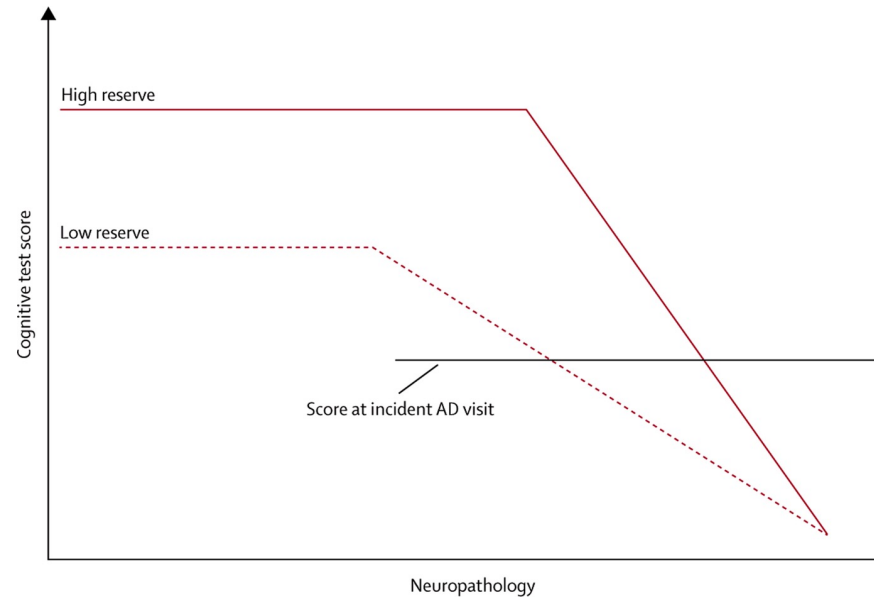


### Study 2: Post Mortem Path Analysis



# Why is the verbal memory advantage a problem?

- Sex differences influence who gets diagnosed when
- Late diagnosis may lead to lack of intervention

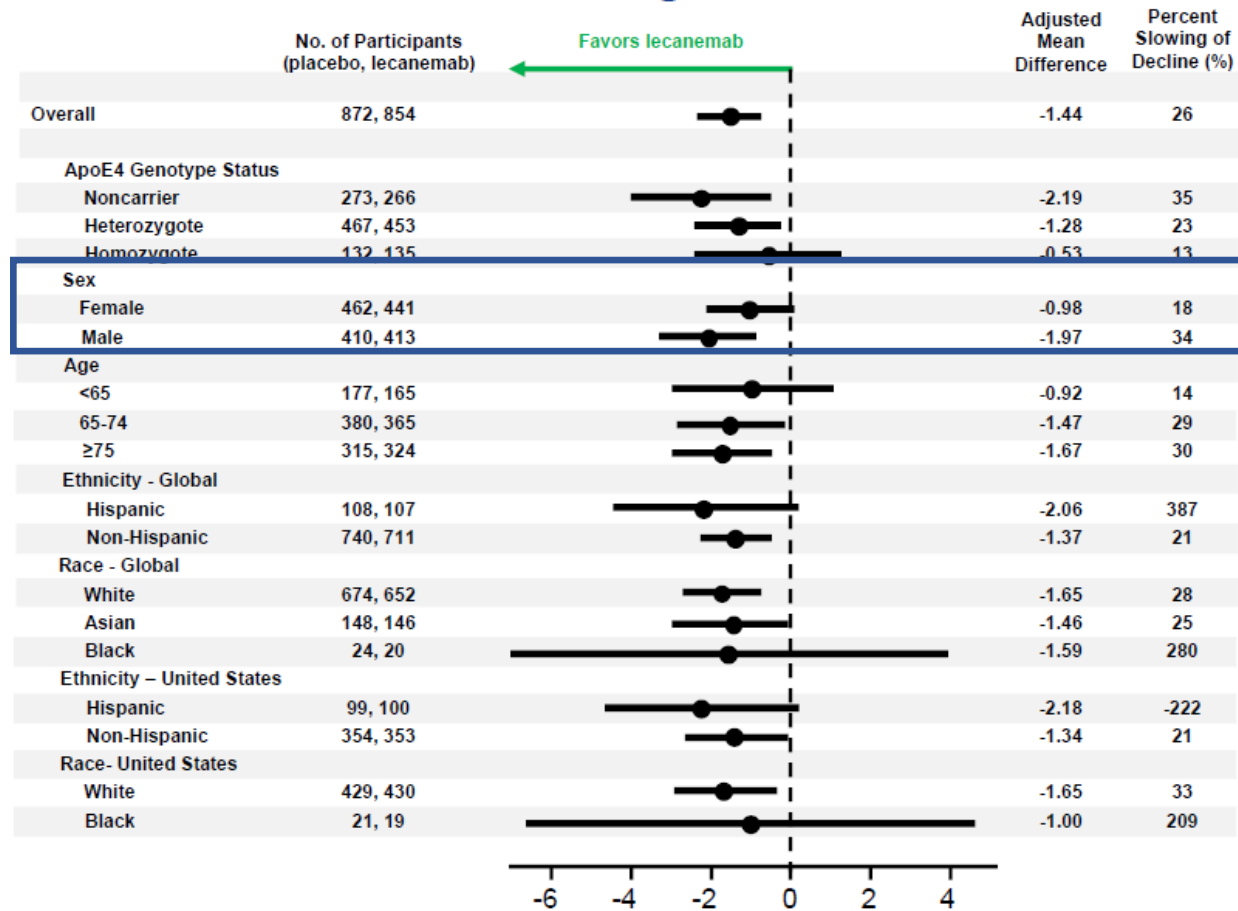


Stern, 2012

- And who participates in clinical trials:
- E.g. for lecanemab which used a cut off on Logical Memory (as verbal memory task) for inclusion:
  - Women may have been further along
  - And did not show same benefits when analyzed separately
- And how their outcomes are measured

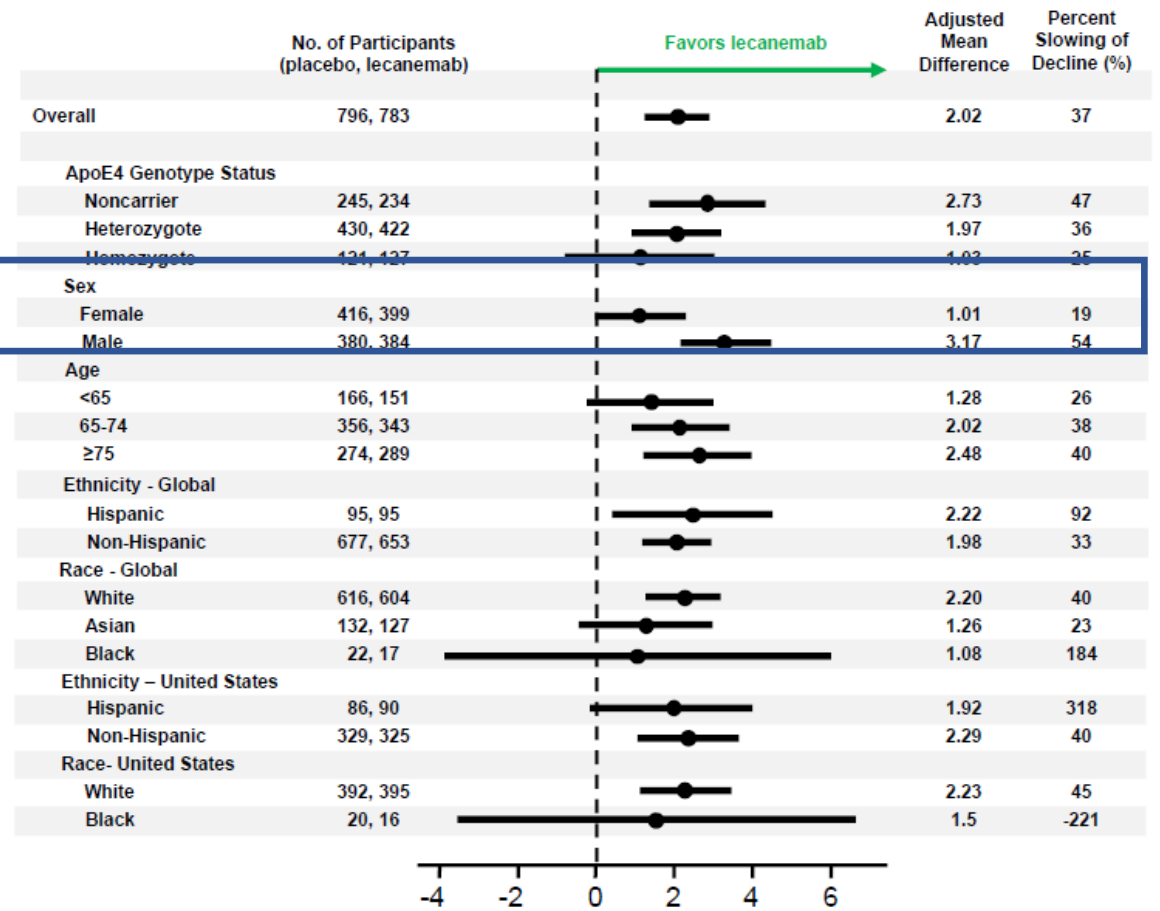
# Why is the verbal memory advantage a problem?

## ADAS-Cog14



Adjusted Mean Difference in ADAS-Cog14 versus Placebo (95% CI)

## ADCS MCI-ADL

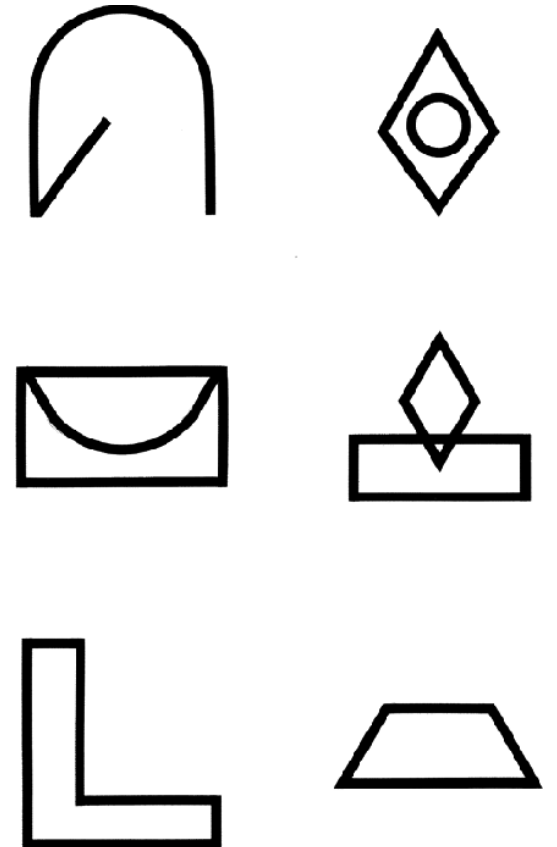


Adjusted Mean Difference in ADCS MCI-ADL versus Placebo (95% CI)

# What about visual memory in women?

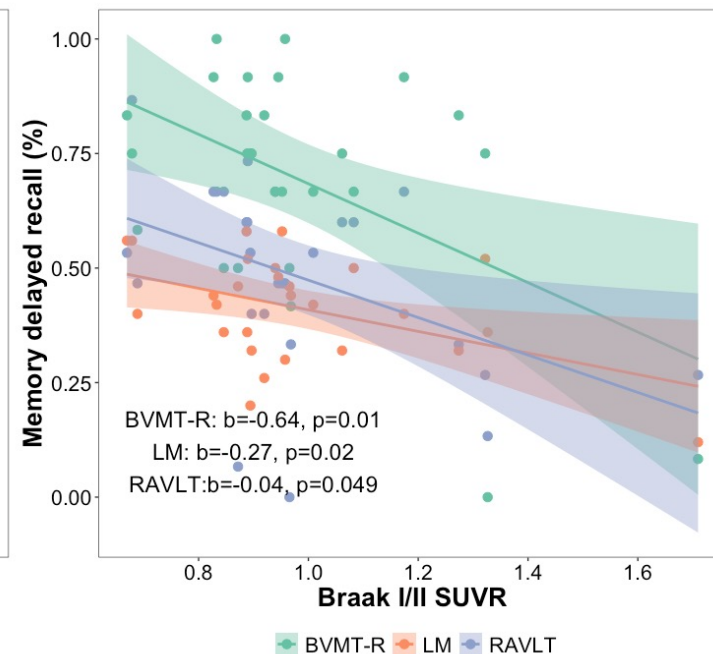
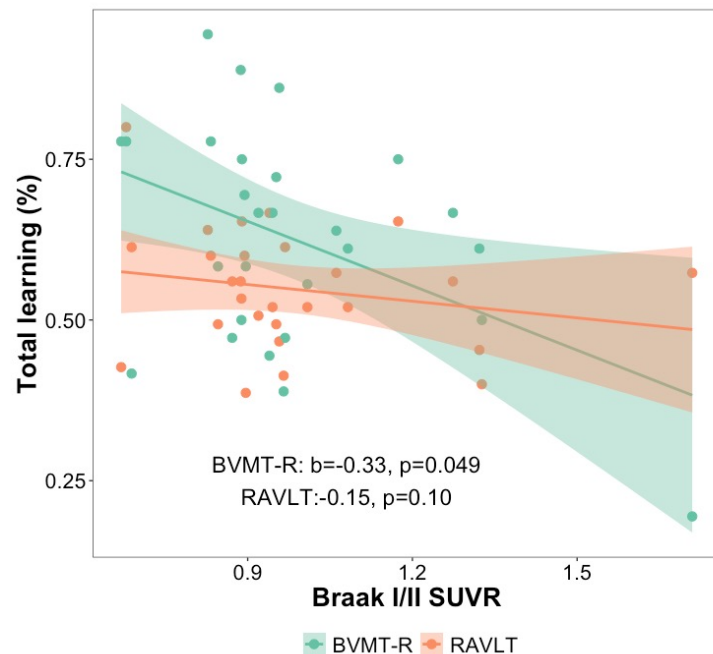


- Recruiting women with MCI and elevated genetic risk
- Battery designed to compare with ADNI
- Also focus on nonverbal memory
- Brief-Visuospatial Memory Test-R
- Does not show sex differences like verbal memory



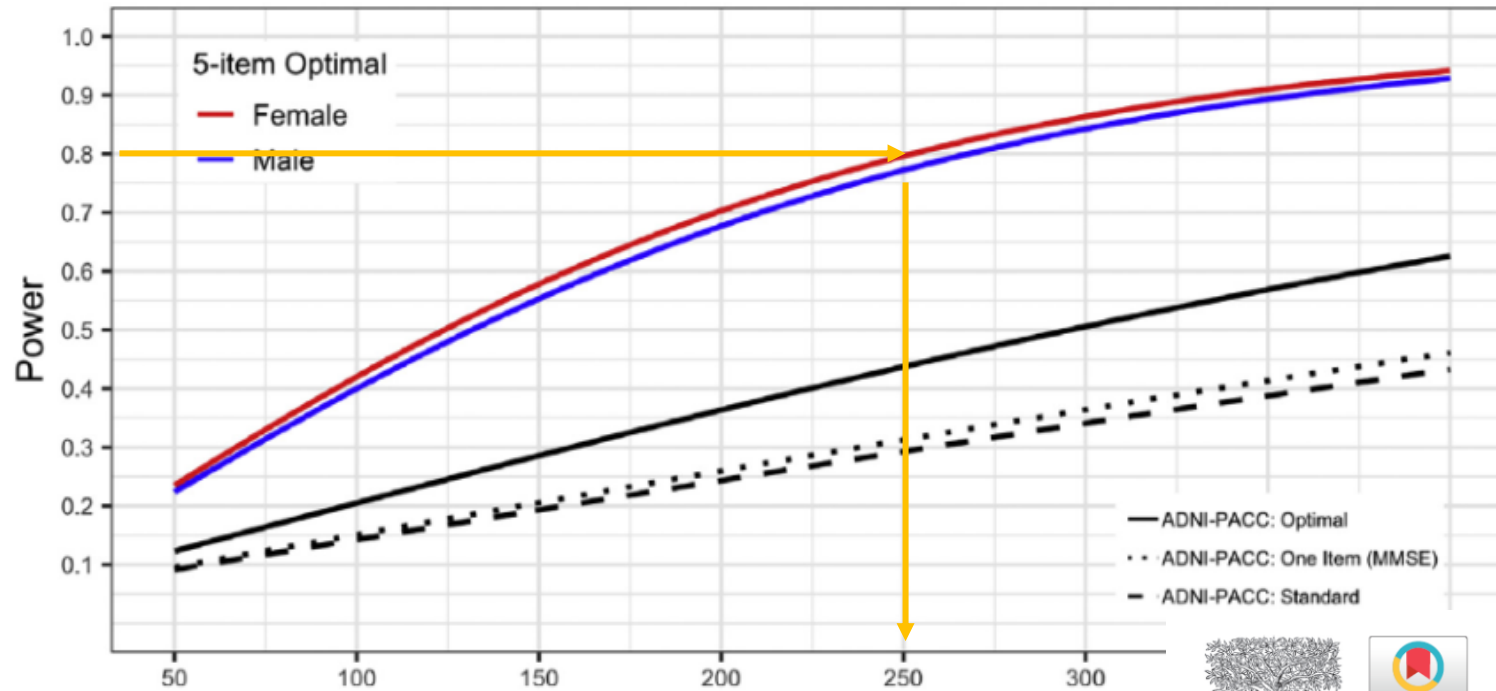
# Visual memory and tau

- WITS data shows stronger associations with tau for visual than verbal memory
- Perhaps using visual memory measures would be more accurate?





# SEX DIFFERENCE IN COGNITION CAN IMPACT TRIAL DESIGN: Composite outcomes



Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019) 508-514

Alzheimer's  
&  
Dementia

Featured Article

Sex-specific composite scales for longitudinal studies of incipient Alzheimer's disease

LIFELONG SEX DIFFS

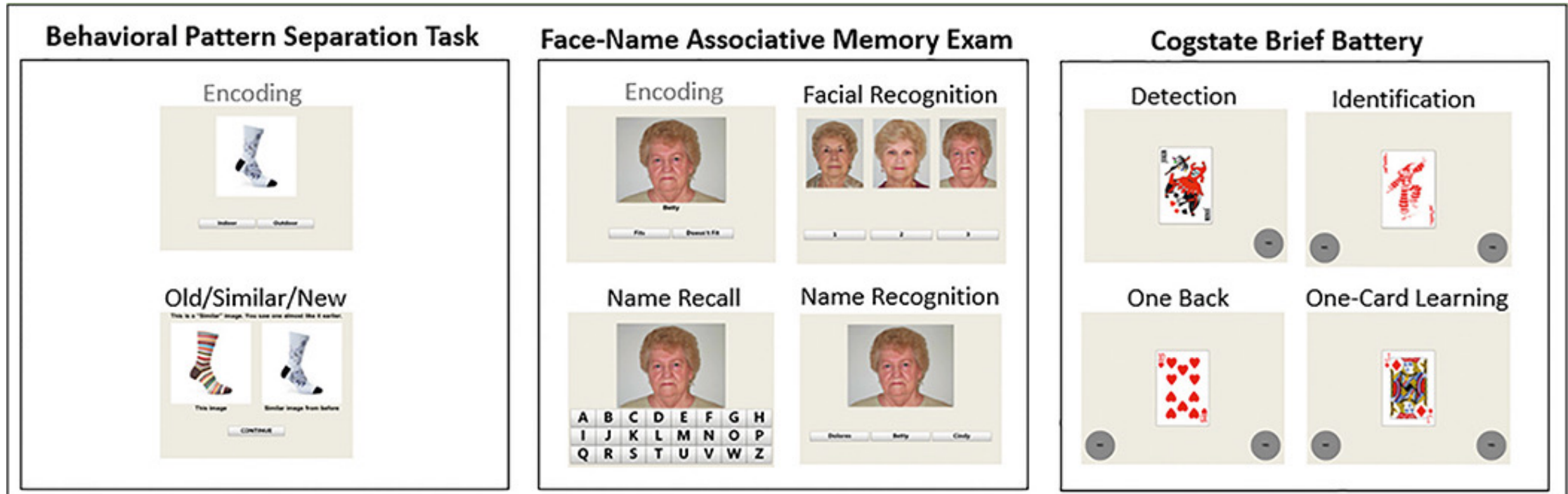
VERBAL MEM ADV

VISUAL MEM

Banks<sup>a,\*</sup>, Benjamin Shifflett<sup>b</sup>, Jody-Lynn Berg<sup>a</sup>, Erin Sundermann<sup>c</sup>, Guerry Peavy<sup>a</sup>, Bondi<sup>c,d</sup>, Steven D. Edland<sup>b</sup>, for the Alzheimer's Disease Neuroimaging Initiative<sup>1</sup>

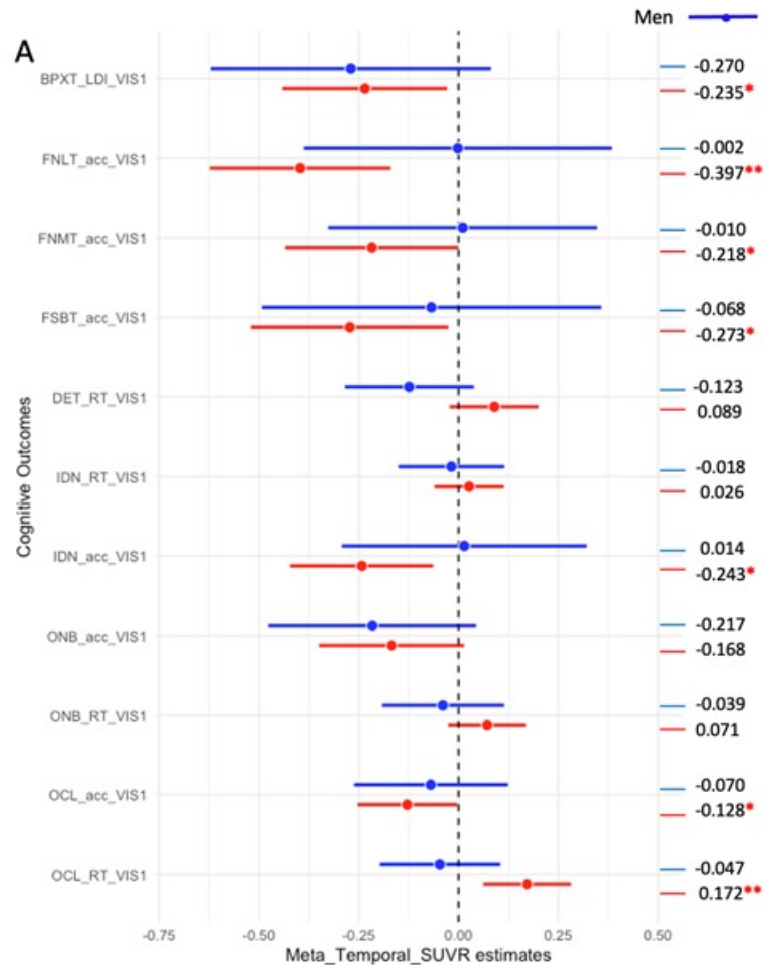
<sup>a</sup>Department of Neurosciences, University of California, San Diego, La Jolla, CA, USA

A4 study, uses various tasks to detect subtle changes in cognition in preclinical AD.



Papp et al., 2021

# SEX Differences in COGNITION IN preclinical phase



Study on A4 by Xin Wang  
Cognitive test results in preclinical AD  
show sex diffs in relation to tau PET



LIFELONG SEX DIFFS

VERBAL MEM ADV

VISUAL MEM

SUBTLE COG CHANGE

& BIOMARKERS

# Understanding AD risk in Black Women

- Black Women: Inflammation and Tau Study leverages progress in blood based biomarkers and community based participatory research to learn more about risk factors in Black women, who are at a particularly high risk of AD yet rarely studied
- Same cognitive test battery as WITS but all biomarkers accessed from blood, and all data collection completed in the community
- Watch this space!



# Sex differences in cognition are important for AD research

1) They impact who gets diagnosed early

2) They impact who gets into clinical trials, and the results

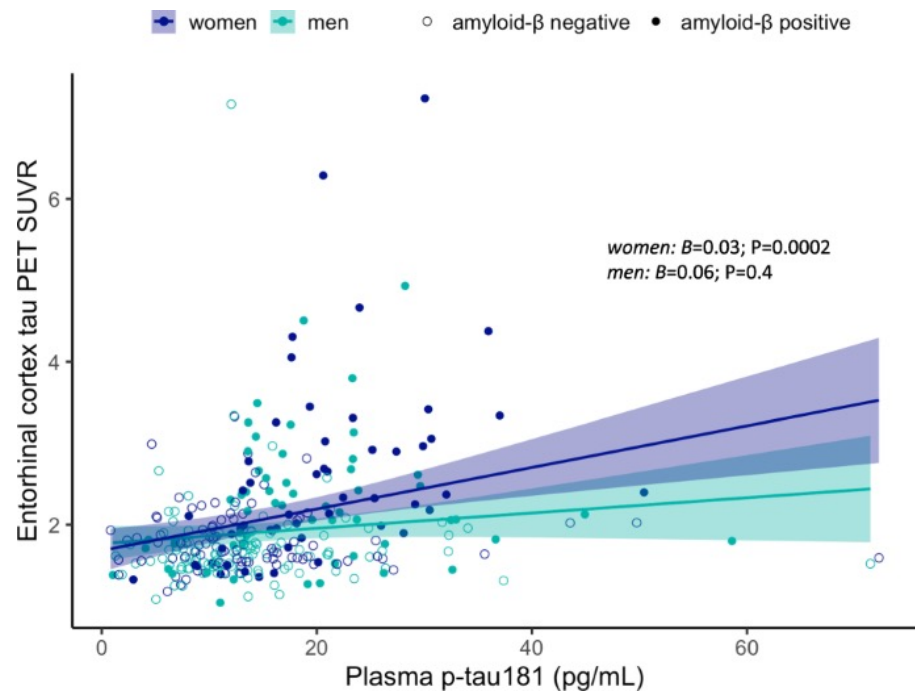
3) If addressed, we will understand Alzheimer's better for everyone

# Thank you

- Participants
- WITS and BWITS teams
  - Erin Sundermann
  - Marc Norman
  - April Thames
  - Nadine Heyworth
  - Alyx Shepherd
  - Melanie Dratva
- Human Memory Lab
  - Emilie Reas
  - Charlotte Rivera
  - Xin Wang
  - Qian Shen
- ADNI and A4 Study Teams
- Funders
  - NIA
  - CDPH
  - Alzheimer's Association
  - Women's Alzheimer's Movement



# SEX DIFFERENCES IN PTAU 181 in PLASMA



www.nature.com/mp

ARTICLE OPEN

Sex differences in plasma p-tau181 associations with Alzheimer's disease biomarkers, cognitive decline, and clinical progression

Amaryllis A. Tsiknia<sup>1</sup>, Steven D. Edland<sup>1,2</sup>, Erin E. Sundermann<sup>3,4</sup>, Emilie T. Reas<sup>1</sup>, James B. Brewer<sup>1</sup>, Douglas Galasko<sup>1</sup>, Sarah J. Banks<sup>1,3,5,6</sup> and for the Alzheimer's Disease Neuroimaging Initiative\*

Molecular

