

# Changes in brain and cognition during the preclinical phase of Alzheimer's Disease: Findings from the Wisconsin Registry for Alzheimer's Prevention (WRAP)

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## Disclosures

Over the past two years:

- Consultant to Roche Diagnostics
- Consultant to Prothena
- Consultant to Merck
- Consultant to Eisai

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## Alzheimer's Disease in 2022

- AD is defined by its dual proteinopathy: amyloid- $\beta$  and tau
  - Clinical stage defined on a separate scale
- AD has a prolonged presymptomatic stage that may or may not progress to symptoms
  - This stage is being intensely studied by the field
- We have PET and CSF biomarkers appropriate for AD
  - Blood markers are coming
- Other diseases may mimic or co-occur with AD symptom expression
  - We have some MRI markers of cerebrovascular disease;
  - but no biomarkers for other neurodegenerative diseases
- AD affects ~5.8m in the U.S.
  - rough estimate-not informed by biomarkers

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## NIA-AA Research Framework

### Biomarker Profiles

| AT(N) profiles | Biomarker category                                                      |                       |
|----------------|-------------------------------------------------------------------------|-----------------------|
| A-T-(N)-       | Normal AD biomarkers                                                    |                       |
| A+T-(N)-       | Alzheimer's pathologic change                                           | Alzheimer's continuum |
| A+T+(N>        | Alzheimer's disease                                                     |                       |
| A+T+(N)+       | Alzheimer's disease                                                     |                       |
| A+T-(N)+       | Alzheimer's and concomitant suspected non Alzheimer's pathologic change |                       |
| A-T+(N)-       | Non-AD pathologic change                                                |                       |
| A-T-(N)+       | Non-AD pathologic change                                                |                       |
| A-T+(N)+       | Non-AD pathologic change                                                |                       |

### Syndromal Staging of Cognitive Continuum

**Cognitively unimpaired**

**Mild cognitive impairment**

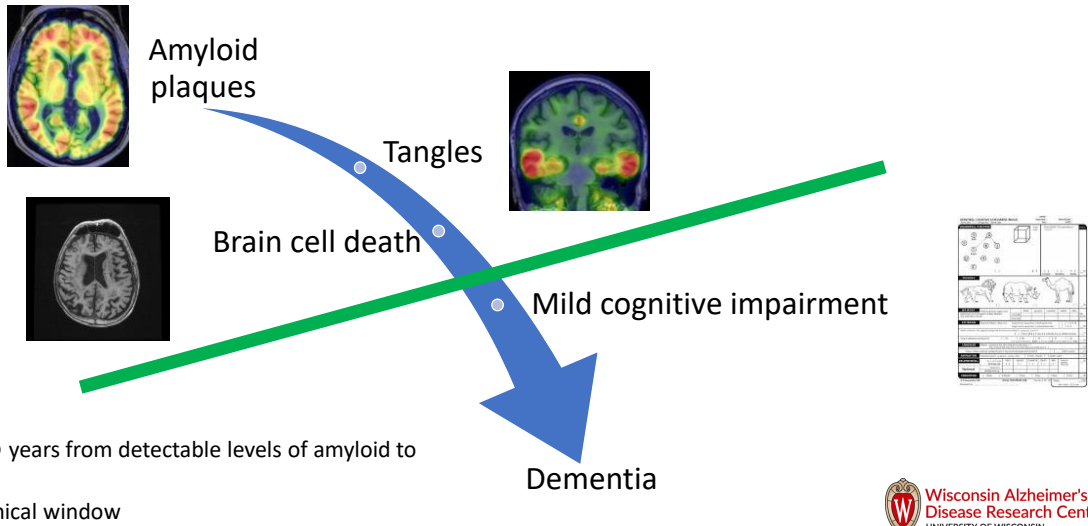
**Dementia**

"The AT(N) framework"

Jack, et al. *Alzheimers Dement.* 2018

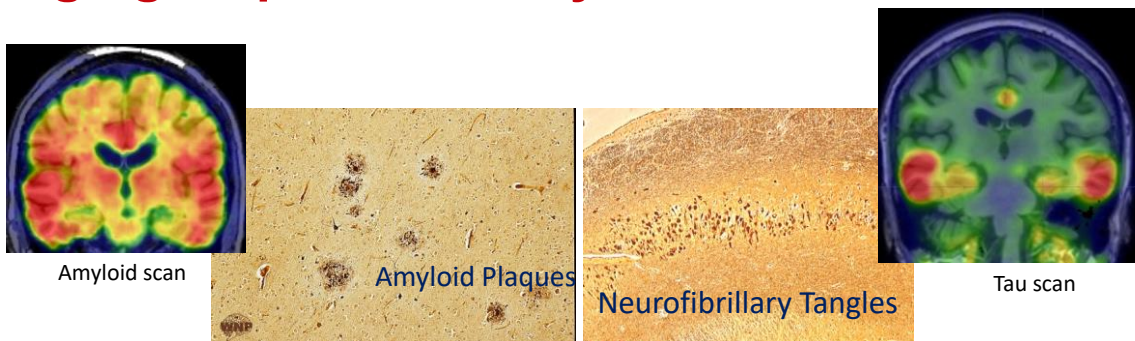
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# Alzheimer's disease progression heuristic



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## Imaging helps us identify Alzheimer's disease

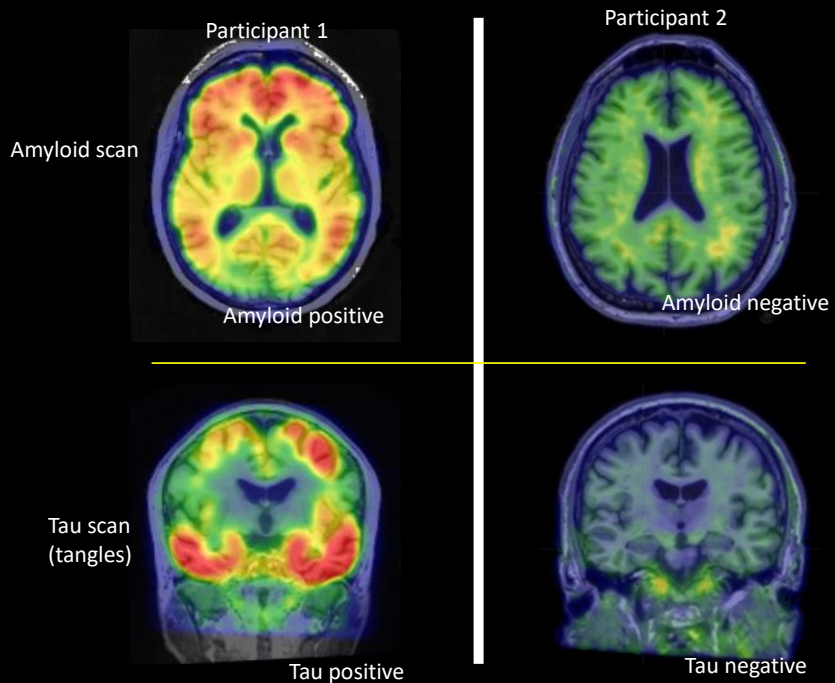


*No longer do we need to wait until death to learn if its Alzheimer's Disease!*

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## Two patients with mild cognitive impairment

*red is bad*



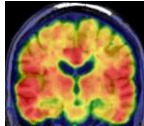
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## AD Biomarkers

### A amyloid

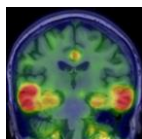
- [F18]florbetapir PET (FDA approved)
- [F18]florbetaben PET (FDA approved)
- [F18]flutemetamol PET (FDA approved)
- [F18]NAV4694 PET
- [C11]Pittsburgh compound B PIB PET
- CSF  $A\beta_{42}$ ;  $A\beta_{42/40}$  ptau<sub>181</sub>/  $A\beta_{42}$  ratios

Amyloid scan  
[C-11]PIB



### T tau

- [F18]flortaucipir (FDA approved)
- [F18]PI2620
- [F18]MK-6240
- [F18]RO948
- Ptau<sub>181</sub>; Ptau<sub>217</sub>; Ptau<sub>231</sub>



Tau scan  
[F-18]MK-6240

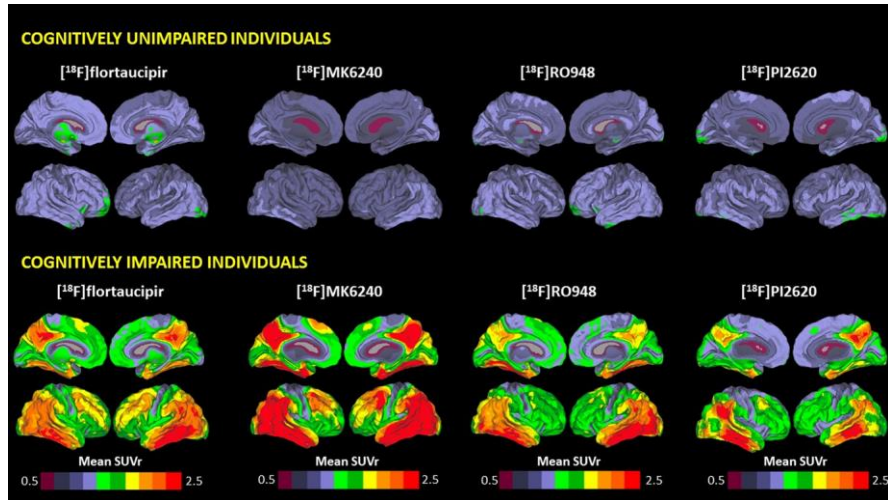
### Candidate (N)

- MRI (structure, diffusion, metabolism)
- FDG PET (metabolism)
- UCB-J SV2A PET
- CSF or plasma NFL (axons)
- CSF Neurogranin (post-synaptic)
- Plasma GFAP
- \*\*CSF total tau is too correlated with p-tau<sub>181</sub> to work for N (r=.99)

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# Tau PET ligands:

*Rik Ossenkoppele and Oskar Hansson, 2021*



ADNI; Wisconsin; BioFinder, and Stanford Cohorts  
PI2620 images provided by Beth Mormino, PhD

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20 YEARS

WRAP

2001 – 2021

Wisconsin Registry for  
Alzheimer's Prevention

- When is cognitive decline more than normal aging?
- What health, lifestyle and genetic factors increase or decrease risk for cognitive decline and AD proteinopathy?
- Longitudinal study starting at midlife
- Imaging and fluid biomarkers

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## UW-Madison School of Medicine and Public Health

### UW-Madison Alzheimer's Disease Program

| Wisconsin Alzheimer's Disease Research Center (WADRC)                                                      | Wisconsin Alzheimer's Institute (WAI)<br>(Madison and Regional Milwaukee Offices)                                |
|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| One of 33 national NIH-funded Alzheimer's Disease Centers                                                  | Closely tied to state public health and training initiatives                                                     |
| Emphasis on basic and clinical research, research engagement, and research training                        | Emphasis on research, clinical education, public health, and outreach                                            |
| Employs over 80 faculty and staff in Madison                                                               | Employs over 30 faculty and staff in Madison, Milwaukee, and LaCrosse                                            |
| <u>Funded by:</u><br>National Institutes of Health (NIH)<br>UW-Madison SMPH<br>State funds<br>Philanthropy | <u>Funded by:</u><br>Federal, foundation, and education grants<br>UW-Madison SMPH<br>State funds<br>Philanthropy |

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## UW School of Medicine and Public Health-Alzheimer's focused cohorts

### UW-Madison Alzheimer's Disease Program

| Wisconsin Alzheimer's Disease Research Center (WADRC)                                                                                                                                                                                                                                                      | Wisconsin Alzheimer's Institute (WAI)                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>WADRC clinical core (1000 participants; 650 active):</b> <ul style="list-style-type: none"> <li>• Alzheimer's dementia</li> <li>• Mild cognitive impairment</li> <li>• Cognitively unimpaired</li> </ul>                                                                                                | <b>WRAP (1725 participants; 1250 active):</b> <ul style="list-style-type: none"> <li>• Cognitively unimpaired at baseline</li> </ul>                                                                                                                                                                                  |
| <ul style="list-style-type: none"> <li>• Data linked to other NIH Centers</li> <li>• Detailed questionnaires</li> <li>• Cognitive testing</li> <li>• Clinical assessment</li> <li>• Blood and spinal fluid tests</li> <li>• Brain imaging</li> <li>• Resources for UW and outside investigators</li> </ul> | <ul style="list-style-type: none"> <li>• Partnering with other international studies</li> <li>• Detailed questionnaires</li> <li>• Cognitive testing</li> <li>• Clinical assessment</li> <li>• Blood and spinal fluid tests</li> <li>• Brain imaging</li> <li>• Resources for UW and outside investigators</li> </ul> |

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# WRAP is

## A longitudinal observational AD risk cohort from midlife

- (n=1725; ~1250 active; mean bsln age 54; mean followup 11 years)
- parental family history (73%)
- APOE4 (41%)

## A registry

- for ~18+ linked studies

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## The Wisconsin Registry for Alzheimer's Prevention: Research Goals

Identify  
Alzheimer's  
**before** symptoms

Identify **genetic**,  
**health**, and  
**lifestyle** factors that  
prevent Alzheimer's

*Wrap.wisc.edu*

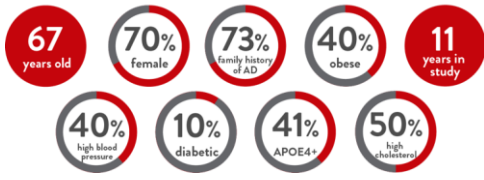
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**Wisconsin Registry  
for Alzheimer's Prevention**  
UNIVERSITY OF WISCONSIN  
SCHOOL OF MEDICINE AND PUBLIC HEALTH

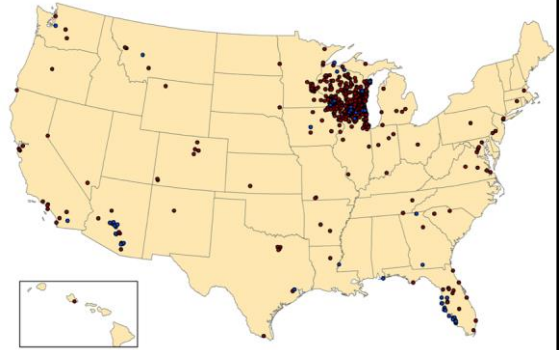
**WRAP:** One of the world's largest and longest running studies of individuals at risk for Alzheimer's dementia  
*Risk from parental family history of dementia presumed due to AD*

**Average WRAP Participant**



**Current focus on biomarker research**  
**25% have amyloid in their brains**

**WRAP Participants Come From...**



See Johnson et al 2018 A&D DADM  
DOI: <https://doi.org/10.1016/j.dadm.2017.11.007>



**For More Information, Contact WRAP:** Madison: (800) 417-4169 · Milwaukee: (414) 219-7911 · LaCrosse: (608) 392-7187

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## Discoveries in prevention science from WRAP

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Determine the age that Alzheimer's starts from brain scans

02

Identify subtle cognitive decline and its onset

03

Better health and lifestyle slow cognitive decline but not amyloid

### Our frontier

- How can we expand the interval between amyloid onset age and the cognitive decline onset age?
- Do health and lifestyle behaviors help?
- Make discoveries in the context of diversity
- AD rarely occurs by itself

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## Applications of amyloid and tau PET to preclinical AD

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## How does A<sup>+</sup> and T<sup>+</sup> status relate to cognitive decline?

Betthausen et al., 2020, *Brain*



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## Betthausen et al, Brain 2020

- A subset of n=167 healthy and cognitively normal adults from WRAP who also had PET imaging
- Do A/T groups differ in their cognitive trajectories?



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## Results: Demographics at PET

|                                               | A-T-<br>(n=124) | A-T+<br>(n=5) | A+T-<br>(n=23) | A+T+<br>(n=15) | Group<br>P-Val | Total<br>(N=167) |      |
|-----------------------------------------------|-----------------|---------------|----------------|----------------|----------------|------------------|------|
| Demographics                                  |                 |               |                |                |                |                  |      |
| Age at Most Recent Cognitive Assessment (yrs) | 65.7 ± 6.4      | 72.0 ± 6.0    | 69.3 ± 4.9*    | 69.9 ± 4.5     | 0.001 §        | 66.7 ± 6.3       |      |
| % Female                                      | 67.7            | 100           | 60.9           | 80.0           | 0.27‡          | 68.9             |      |
| % Non-Caucasian                               | 8.1             | 0.0           | 4.3            | 0.0            | 0.57‡          | 6.8              |      |
| % Family History of Dementia                  | 70.2            | 100.0         | 69.6           | 93.3           | 0.13‡          | 73.1             |      |
| WRAT-III Reading Score                        | 109             | 104           | 111            | 109            | 0.73†          | 110              |      |
|                                               | [103, 115]      | [99, 115]     | [106, 115]     | [105, 113]     |                | [103, 114]       |      |
| APOE-ε4                                       | % Carriers      | 33.3**        | 20.0*          | 65.2           | 86.7           | <0.001‡          | 42.5 |
|                                               | % Non-Carriers  | 66.7**        | 80.0*          | 36.4           | 13.3           |                  | 58.2 |
|                                               | % Heterozygous  | 31.7**        | 20.0*          | 54.5           | 66.7           | <0.001‡          | 37.6 |
|                                               | % Homozygous    | 1.6**         | 0.0*           | 9.1            | 20.0           |                  | 4.2  |

† Kruskal-Wallis    ‡  $\chi^2$

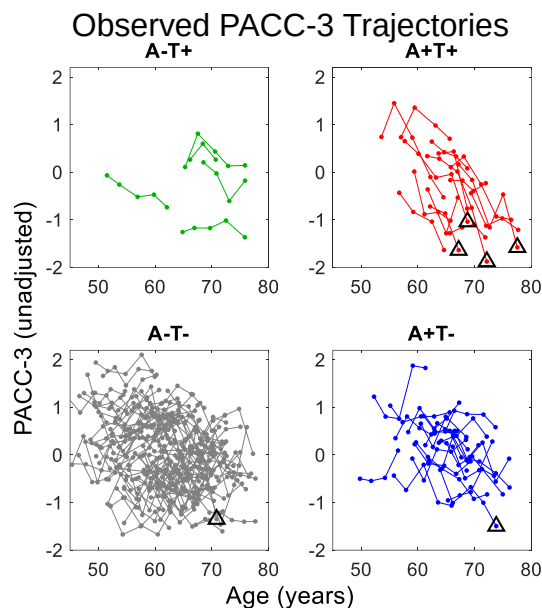
- Age Difference (A-T- and A+T-)
- No difference in WRAT-III, sex, race, or family history
- Significant difference in APOE-ε4 status

Betthausen et al 2020, *Brain*

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# Results: Retrospective PACC-3 and A/T Groups

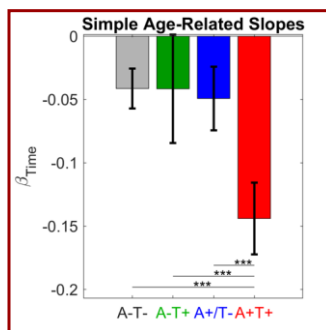
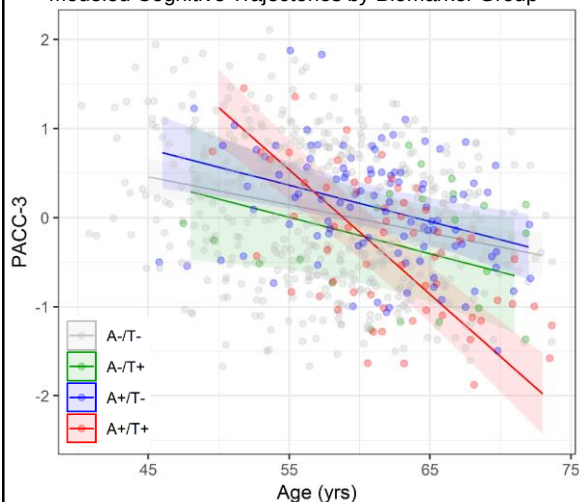
Betthausen et al 2020, *Brain*



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## Results: Retrospective Cognitive Decline by Biomarker Group

Modeled Cognitive Trajectories by Biomarker Group



- Significant Group $\times$ Time Effect
- +/+ ~3x faster decline than -/-

**Insights: among A+T+ cognition is declining many years prior to MCI (midlife)**  
**APOE not synonymous with A+**

Betthausen, et al. 2020, *Brain*

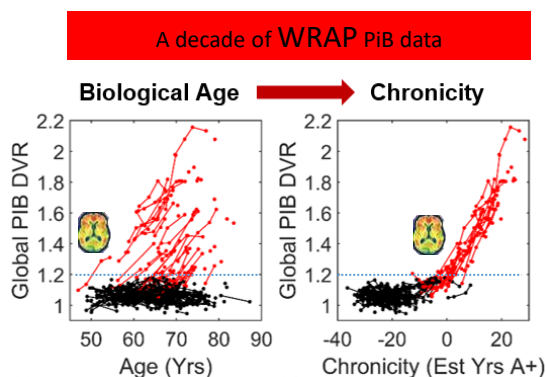
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## Other results and remaining questions

- Neurodegeneration
  - Marginally more MRI hippocampal volume loss in A+T+ group
- Health and vascular features
  - No meaningful differences at WRAP baseline or at time of later PET
    - BMI, WHR, cholesterol, blood pressure, blood glucose, Vit B12
- Can we derive more information if we go beyond A+ status?
- is there meaningful temporal information in the rate of change?

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## Background: Amyloid PET trajectories are predictable



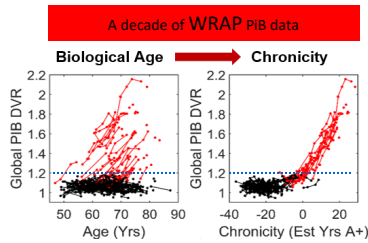
Koscik et al, DADM 2020 observed:

- Amyloid trajectories are predictable!
- Feasible to transpose amyloid to the time domain
- Can estimate A+ onset age from a single scan
- Longer A+ Chronicity (duration) was associated with tau PET and cognitive decline

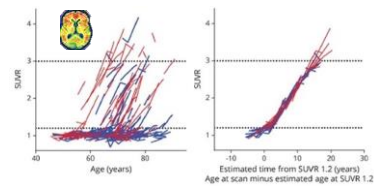
WRAP = Wisconsin Registry for Alzheimer's Prevention (Johnson et al 2018, DADM)

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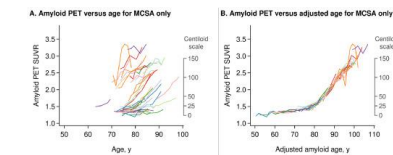
**Insight: Once A+, it continues to rise;  
predictable rate of change; Temporal  
estimates of onset age and duration of A+**



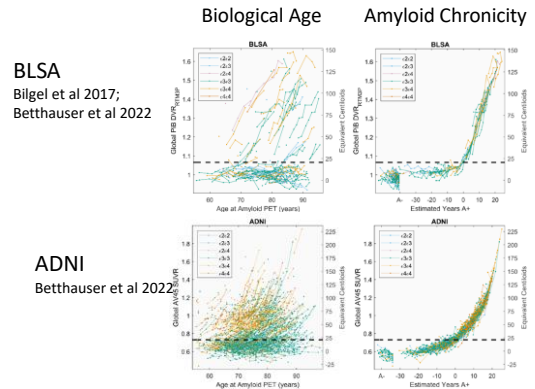
WRAP  
Koscik et al 2020 DADM



Wash U ACS  
Schindler Neurology 2021



Mayo Clinic  
MCSA

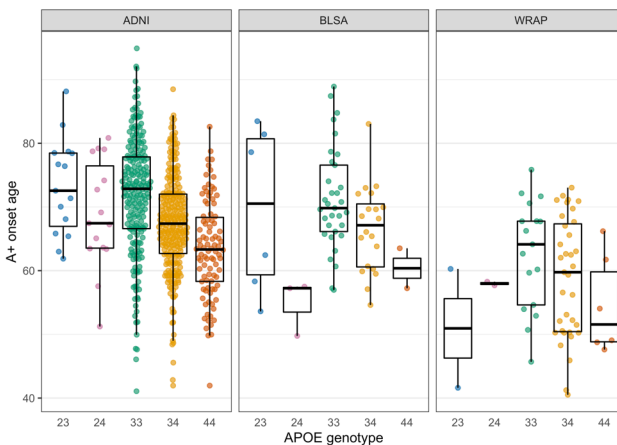


BLSA  
Bilgel et al 2017;  
Betthausen et al 2022

ADNI  
Betthausen et al 2022

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## Results: APOE Genotype and A+ onset Age (AOA)



|               | Accelerated Failure Time Models |                           |                            |
|---------------|---------------------------------|---------------------------|----------------------------|
| APOE genotype | ADNI<br>(n=1213)                | BLSA<br>(n=203)           | WRAP<br>(n=270)            |
| e2e3          | 0.12<br>(0.06, 0.17)***         | 0.01<br>(-0.13, 0.15)     | 0.08<br>(-0.09, 0.24)      |
| e2e4          | -0.11<br>(-0.18, -0.04)**       | -0.21<br>(-0.41, -0.01)*  | -0.10<br>(-0.32, 0.12)     |
| e3e3          | 0 (reference)                   | 0 (reference)             | 0 (reference)              |
| e3e4          | -0.14<br>(-0.16, -0.12)***      | -0.13<br>(-0.23, -0.04)** | -0.23<br>(-0.33, -0.14)*** |
| e4e4          | -0.24<br>(-0.28, -0.21)***      | -0.28<br>(-0.57, 0.01)    | -0.35<br>(-0.53, -0.17)*** |

\*p<0.05, \*\* p<0.01, \*\*\* p < 0.001; Models adjusted for sex

- **APOE4** carriers have a **significantly** earlier AOA: e4/4 ~10 yrs earlier than e3/3 consistently
- **Sex** and interaction of sex and APOE were **not significant** predictors of time to A+ onset
- AOA range varies widely from 40 to 90+

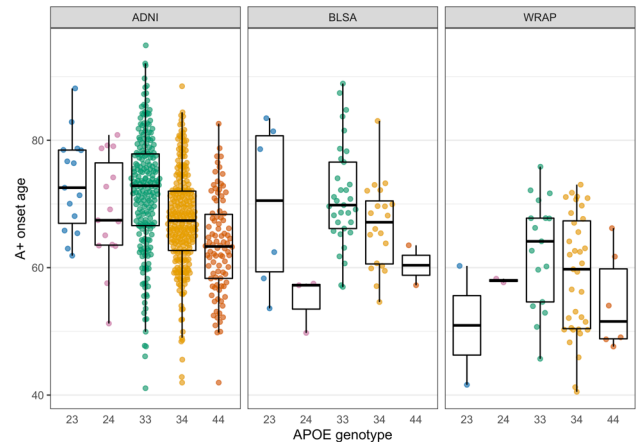
Betthausen, et al. 2022 Brain

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## Insight: Age of amyloid onset can be anytime in midlife or beyond. Its not enough to binarize A+ status

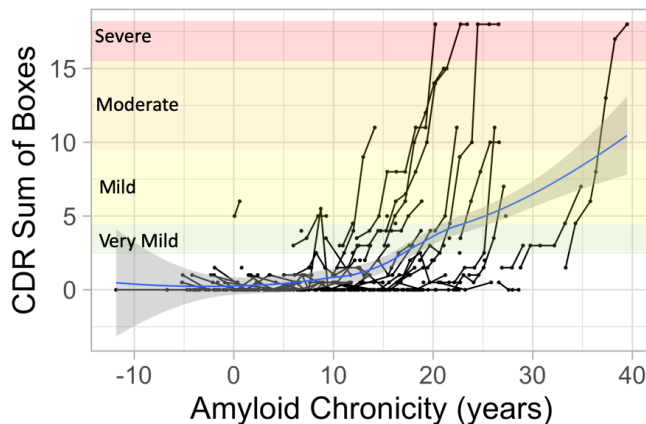
- What influences A+ onset age?
  - APOE4 only
  - 8-10 years sooner

Betthausen et al Brain 2022



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## Insight: Although the avg time to dementia is 24 yrs from A+ onset, there is heterogeneity



Birdsill et al (2022) DADM

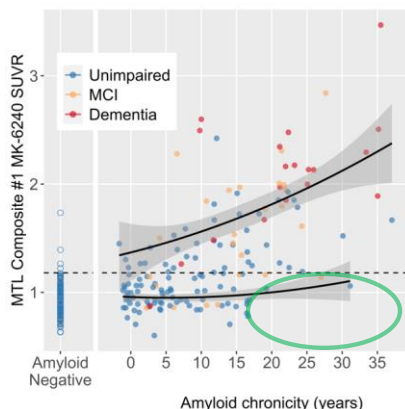
### Heterogeneity in CDR vs A+ chronicity?

age and vascular burden each predict the interval between amyloid onset and symptoms

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## Insights on the relationship between amyloid and tau

- The longer you have had amyloid the more likely to be T+
- T+ can occur anytime along the A+ continuum—why?
- T+ is rare when A-



Recent cross-sectional PET data from N=505 WRAP and ADRC subjects

Dx breakdown\*\*

- CU: N=451
- MCI: N=33
- Dem: N=21

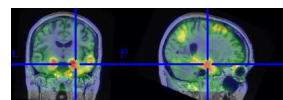
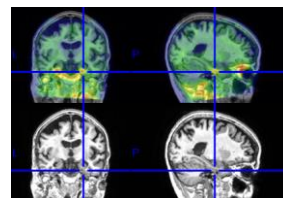
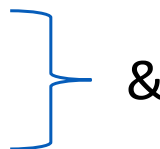
MK positivity—shown as dotted line

- Based on 1.18 threshold (GMM (k=2))

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## Insight: When tau spreads outside the mesial temporal lobe (MTL & neocortical), its meaningful

- simple visual rating Y|N (by SCJ) of MTL and cortical tau
- MTL: Ento, amygdala, hippocampus
- Cortical
  - 3—fusiform or
  - 4—ITG, MTG, cingulum, insula or
  - 5—lateral frontal or any parietal-occipital cortex or
  - 6—primary visual cortex or transverse temporal gyrus
- Stats: mixed effects longitudinal model of cognitive change



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## Question: Does MTL or MTL& relate to cognitive decline in initially CU?

- N=340 participants from WRAP or ADRC and CU at first cognitive visit
- Outcomes:
  - Cross sectional mean cognitive scores at exam most proximal to last PET, and annual rate of change in cognition
  - Mixed effects model of cognition over time (retrospective)

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## MTL& LME of retrospective cognitive decline

**Sample: N=340**

WRAP and WADRC subjects unimpaired at baseline PACC-3 (V2 for most) with complete covariates and last PACC-3 within 3 years of last tau PET

**Primary outcome:**

- Z-scored, cross-walked 3-test Preclinical Alzheimer's Cognitive Composite (PACC-3)
  - Trails B version
  - Years of cognitive follow-up → Median (IQR): 8.0 (6.1-9.8)

**Primary predictors:**

- Amyloid and VR Tau group:
  - A-T-, N=255
  - A+/T-, N=45
  - A+/T+ MTL only, N=10
  - A+/T+ MTL&Neo, N=30
    - Amyloid positivity (Global PiB DVR>1.16)
    - T+ based on Visual Rating of NFT stage (MTL only and MTL&)

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Model 1: MTL and neocortical tau is associated with faster decline

Model statistics

Parameter estimates, 95% confidence intervals (CI) and P-values are shown for the main model covariates and predictors of interest.

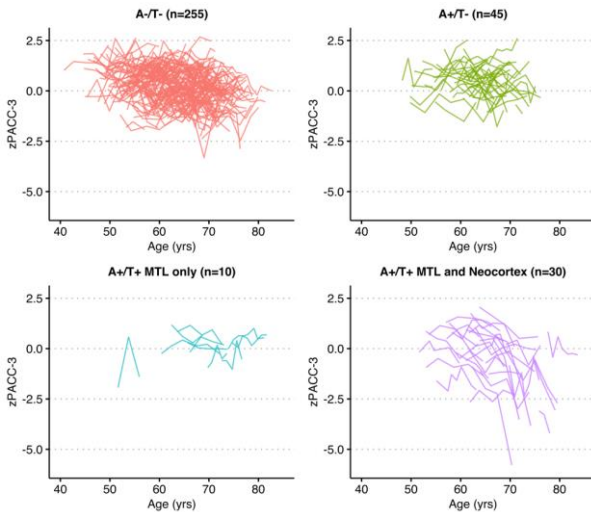
Interpretation:

Results of the LME indicated significant linear and quadratic amyloid duration by age interactions. These results suggest that the A+ group with MTL and neocortical tau had faster rates of retrospective cognitive decline during the ~8 years of cognitive follow-up.

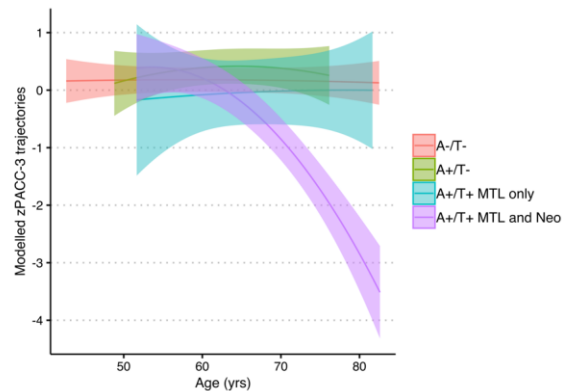
| Random Effects                                       |               |
|------------------------------------------------------|---------------|
| $\sigma^2$                                           | 0.22          |
| $\tau_{00}$ reggieid                                 | 0.53          |
| $\tau_{11}$ reggieid.c65_age                         | 0.00          |
| $\tau_{01}$ reggieid                                 | 0.33          |
| ICC                                                  | 0.73          |
| N reggieid                                           | 340           |
| Observations                                         | 1548          |
| Marginal R <sup>2</sup> / Conditional R <sup>2</sup> | 0.230 / 0.790 |

| pacc3.trib.xw.z                             |           |                   |        |
|---------------------------------------------|-----------|-------------------|--------|
| Predictors                                  | Estimates | CI                | p      |
| (Intercept)                                 | -0.0983   | -0.4088 – 0.2121  | 0.534  |
| gender f [Male]                             | -0.5169   | -0.6916 – -0.3421 | <0.001 |
| edu ba f [1]                                | 0.4887    | 0.3087 – 0.6687   | <0.001 |
| Data Source f [WRAP]                        | -0.0754   | -0.2606 – 0.1099  | 0.425  |
| practice                                    | 0.0591    | 0.0025 – 0.1156   | 0.041  |
| t lastpaccandlastmk                         | -0.0393   | -0.1160 – 0.0375  | 0.316  |
| AVR group f [A+/T-]                         | 0.2390    | -0.0192 – 0.4972  | 0.070  |
| AVR group f [A+/T+ MTL only]                | -0.2192   | -0.7613 – 0.3229  | 0.428  |
| AVR group f [A+/T+ MTL and Neo]             | -0.3823   | -0.6914 – -0.0732 | 0.015  |
| c65 age                                     | -0.0012   | -0.0108 – 0.0083  | 0.799  |
| c65 age^2                                   | -0.0001   | -0.0008 – 0.0006  | 0.805  |
| AVR group f [A+/T-] * c65 age               | 0.0002    | -0.0239 – 0.0243  | 0.986  |
| AVR group f [A+/T+ MTL only] * c65 age      | 0.0077    | -0.0472 – 0.0625  | 0.784  |
| AVR group f [A+/T+ MTL and Neo] * c65 age   | -0.1049   | -0.1316 – -0.0782 | <0.001 |
| AVR group f [A+/T-] * c65 age^2             | -0.0011   | -0.0034 – 0.0011  | 0.334  |
| AVR group f [A+/T+ MTL only] * c65 age^2    | -0.0001   | -0.0043 – 0.0040  | 0.944  |
| AVR group f [A+/T+ MTL and Neo] * c65 age^2 | -0.0046   | -0.0070 – -0.0021 | <0.001 |

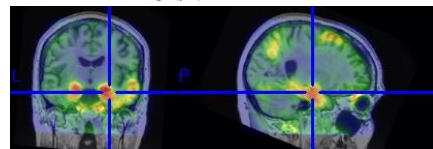
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Insight: When tau spreads outside MTL its clinically meaningful



WRAP and ADRC subjects n=340 Cognitively unimpaired at baseline



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## What increases or decreases risk for AD and its cognitive syndrome of dementia?

Does

- ☐ Hypertension
- ☐ Sleep
- ☐ Physical Activity
- ☐ Stress / Mood
- ☐ Neighborhood
- ☐ Diet
- ☐ Inflammation
- ☐ Cognitive Activity
- ☐ Social Support
- ☐ Genetics

prevent or slow amyloid onset or cognitive symptoms ?

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## The Lifestyle for Brain Health (LIBRA) index

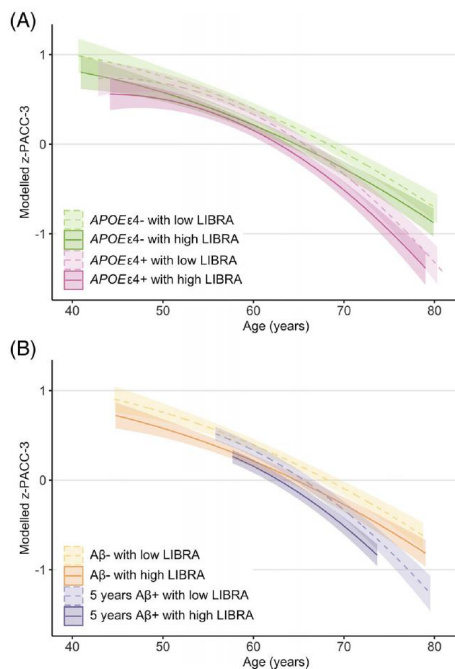
Deckers et al 2020

**Table:** Factor scores and definitions used to calculate the LIBRA index

|                               | Definition                                                                                       | Score |
|-------------------------------|--------------------------------------------------------------------------------------------------|-------|
| <i>Modifiable factors</i>     |                                                                                                  |       |
| Low/moderate alcohol use      | Self report, drink < 2 units/day (including non-drinkers)                                        | -1.0  |
| Cardiovascular disease        | Self report, history of heart attack, recurrent chest pain with exercise, or coronary bypass     | +1.0  |
| Physical inactivity           | Self report, < 30 minutes of moderate exercise 5 days/week or < 7.5 MET hours/week <sup>a</sup>  | +1.1  |
| Renal dysfunction             | Kidney disease diagnosis or estimated glomerular filtration rate < 60 ml/min/1.73m <sup>2b</sup> | +1.1  |
| Diabetes                      | Diabetes diagnosis or fasting glucose ≥ 126 mg/dL                                                | +1.3  |
| High cholesterol              | Hypercholesterolemia diagnosis or total serum cholesterol ≥ 240 mg/dL                            | +1.4  |
| Smoking                       | Self report of smoking in the past month                                                         | +1.5  |
| Obesity                       | Body mass index ≥ 30                                                                             | +1.6  |
| Hypertension                  | Hypertension diagnosis or SBP ≥ 130mmHg / DBP ≥ 80mmHg                                           | +1.6  |
| Depression                    | Sum score ≥ 16 on the Center for Epidemiologic Studies-Depression Scale                          | +2.1  |
| High cognitive activity       | Games score ≥ 4, on the Cognitive Activity Scale                                                 | -3.2  |
| <i>Non-modifiable factors</i> |                                                                                                  |       |
| Age                           |                                                                                                  |       |
| Sex                           |                                                                                                  |       |

Cody et al 2022 DADM

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## LIBRA results

Cody et al, 2022 DADM

- Main effect on cognition
  - *Higher LIBRA risk score—lower cognition*
  - *LIBRA not affecting rate of decline*

Alzheimer's & Dementia  
Diagnosis, Assessment  
& Disease Monitoring

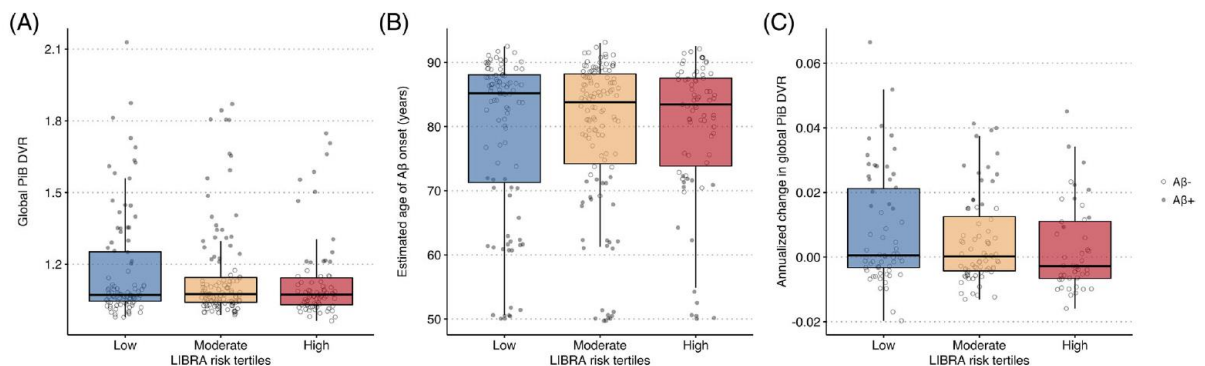
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## LIBRA results

CODY ET AL.

Alzheimer's & Dementia  
Diagnosis, Assessment  
& Disease Monitoring

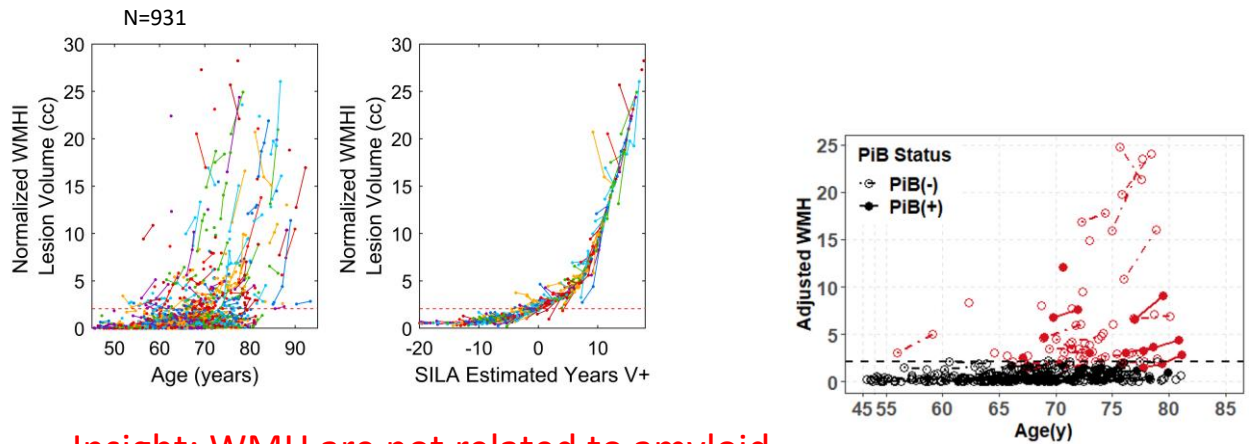
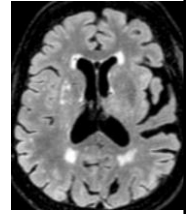
7 of 9



- *Not related to amyloid PET rate of progression*
- *Not related to onset age or duration of amyloid PET*

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What about WMH? (new data)  
Ischemic lesions grow in a predictable way  
such that time models can be applied



Insight: WMH are not related to amyloid

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## Blood Biomarkers in WRAP

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# Can we glean meaningful information from blood??

## Design for plasma ptau217 pilot study

- Collaboration with Oskar Hansson: His lab ran Lilly MSD ptau217 on 530 samples from 173 people; Lab was blind to participant status; serial samples ran on same plate; location on plate and amyloid status were randomized
  - N=173 WRAP participants: selected on the basis of PIB A+ status and availability of plasma and cognition
  - Mostly cognitively normal at first plasma sample (N=166 CU, 3 MCI, 2 Dementia, 1 Other, 1 missing)
  - All had at least one PIB PET and most (N=150) had at least one MK6240 PET
  - 44% (n=76) A+ based on PIB PET; 56% were PIB A-
  - Age at first plasma: M=63 SD 6.2
  - Age at last plasma: M= 68 SD 6.1
  - Median of 3 plasma samples (range 1-5)
  - Questions:
    - Ptau217 change over time by PIB status
    - Concordance with PIB and concordance with MK6240 status
    - Cognitive change over time
  - Plots and tables by Erin Jonaitis (except where otherwise noted)
- Jonaitis et al medrxiv and in review.

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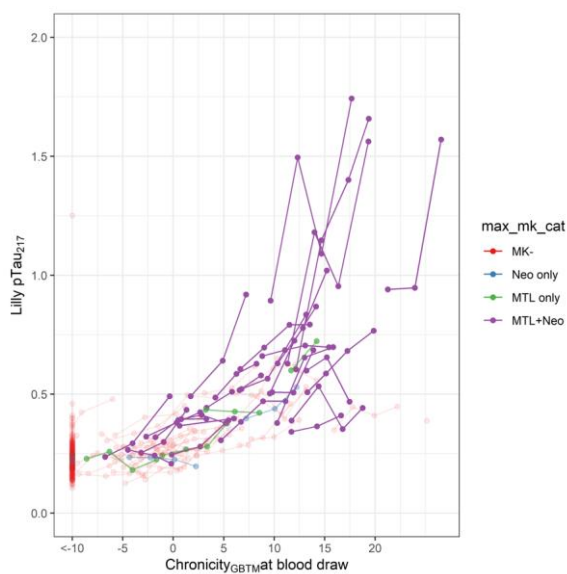
Table 1

| Variable                                                | Value        |
|---------------------------------------------------------|--------------|
| Number of participants                                  | 173          |
| Number of observations per participant, median (range)  | 3 (1-5)      |
| Age at first plasma, mean (SD)                          | 63.15 (6.21) |
| Age at last plasma, mean (SD)                           | 68.29 (6.13) |
| Years of plasma follow-up, mean (SD)                    | 5.14 (1.78)  |
| Female, N (%)                                           | 112 (65%)    |
| Male, N (%)                                             | 61 (35%)     |
| White, N (%)                                            | 165 (95%)    |
| Black, N (%)                                            | 5 (3%)       |
| Native American, N (%)                                  | 3 (2%)       |
| Cognitively unimpaired-stable at first plasma, N (%)    | 131 (76%)    |
| Cognitively unimpaired-declining at first plasma, N (%) | 35 (20%)     |
| MCI at first plasma, N (%)                              | 3 (2%)       |
| Dementia at first plasma, N (%)                         | 2 (1%)       |
| Non-MCI impairment at first plasma, N (%)               | 1 (1%)       |
| Cognitively unimpaired-stable at last plasma, N (%)     | 136 (79%)    |
| Cognitively unimpaired-declining at last plasma, N (%)  | 24 (14%)     |
| MCI at last plasma, N (%)                               | 9 (5%)       |
| Dementia at last plasma, N (%)                          | 3 (2%)       |
| Abeta42/40 - at last plasma, N (%)                      | 65 (38%)     |
| Abeta42/40+ at last plasma, N (%)                       | 44 (25%)     |
| PiB - at last plasma, N (%)                             | 99 (57%)     |
| PiB+ at last plasma, N (%)                              | 74 (43%)     |
| MK - at last plasma, N (%)                              | 115 (66%)    |
| MK+ / MTL only at last plasma, N (%)                    | 6 (3%)       |
| MK+ / MTL+Neo at last plasma, N (%)                     | 27 (16%)     |

Jonaitis et al medrxiv and in review.

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Ptau<sub>217</sub> is higher in people who have had amyloid longer and higher still in people who are T+ extending out of the MTL

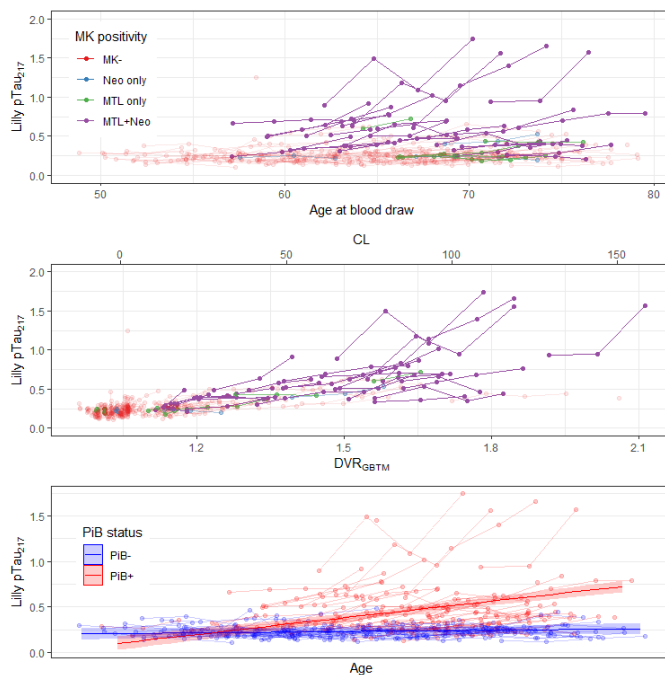


Amyloid chronicity of  $\geq 0$  are A+  
Chronicity is expressed in years

Jonaitis et al medrxiv and in review.

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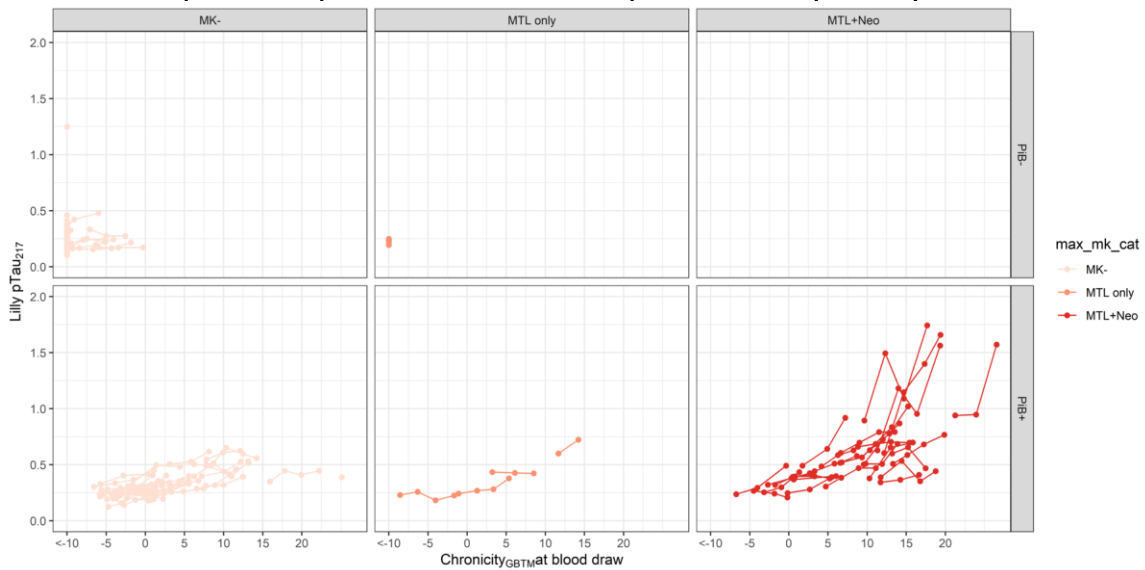
- Plotted against raw age, pTau<sub>217</sub> shows relationship with MK (top) and PiB (bottom; fitted line = mixed effects regression)
- Plotted against model-estimated PiB DVR, clustering with MK becomes clearer (middle)



Jonaitis et al medrxiv and in review.

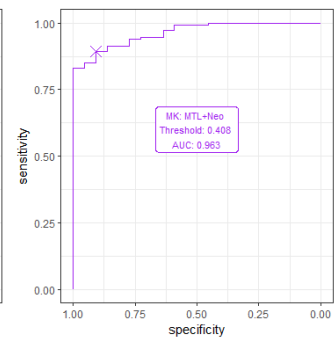
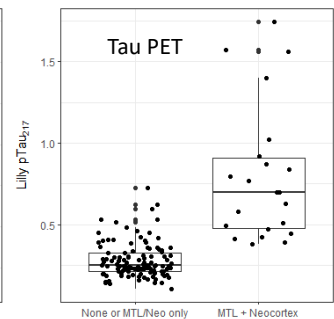
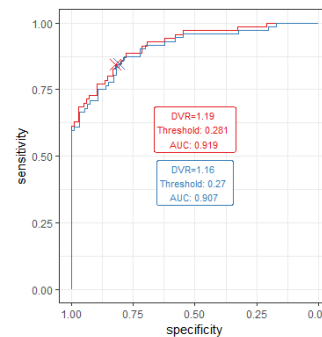
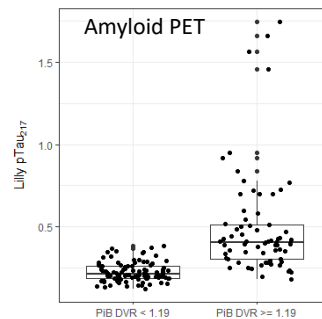
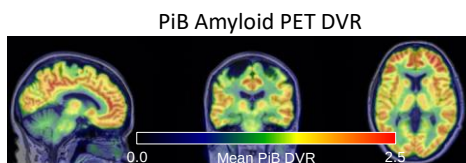
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## Change over time in ptau217 is pronounced in WRAP participants with AD proteinopathy



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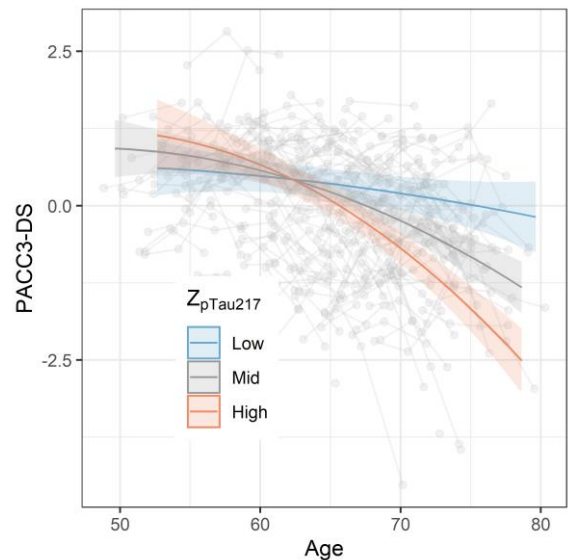
## ROCs



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**Cognitive** decline on a cognitive composite is faster in people with higher levels of plasma MSD ptau217 at first visit

cognitively unimpaired at time of first blood draw

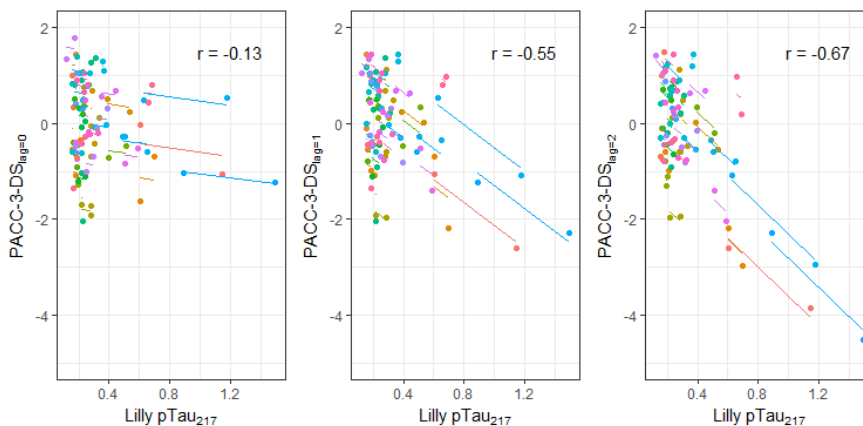


Low=10<sup>th</sup> percentile; Mid=median; High=90<sup>th</sup> percentile

Jonaitis et al medrxiv and in review.

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## Lagged relationship with cognition



**Lagged by visit:**  
Concurrent: lag=0

1 visit later: lag=1 (~2yrs)

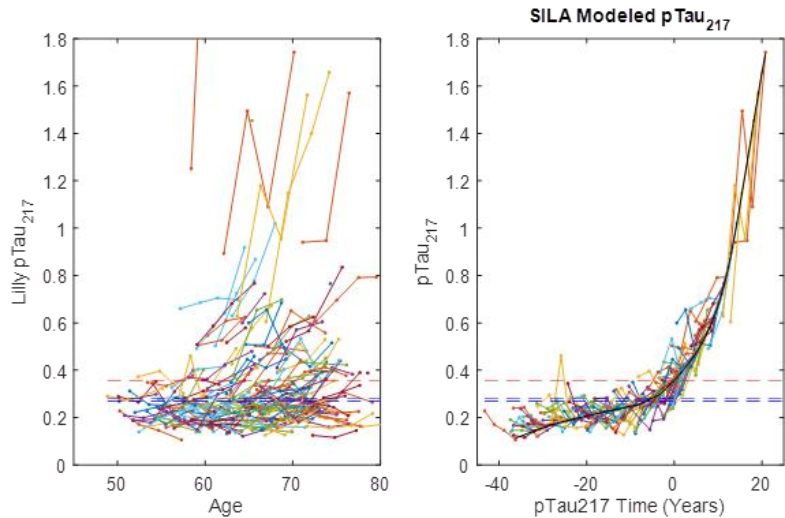
Two visits later  
Lag=2 (~4 yrs)

$r$ =repeated measures correlation  
(captures only **within-subjects** aspect of the pTau<sub>217</sub>-cognition relationship)

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# Ptau217 appears to be able to confer temporal information

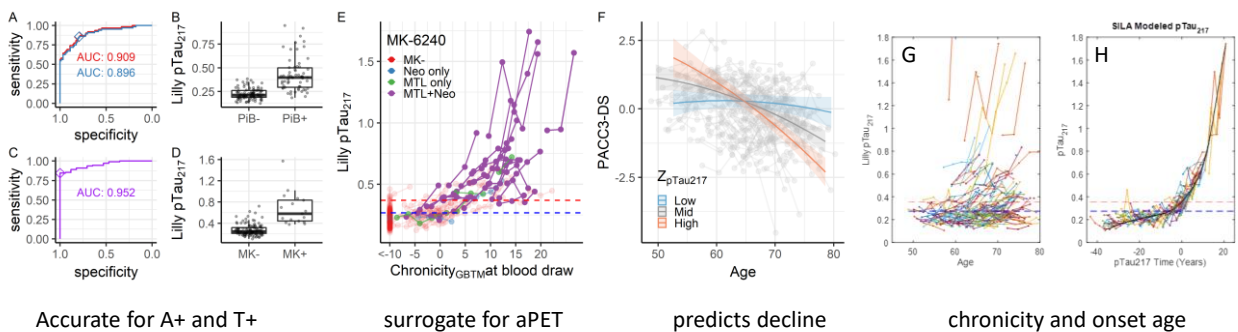
Tobey Betthausen's SILA model  
Per Brain 2022 paper



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## Summary of blood data

- Plasma ptau217



Accurate for A+ and T+

surrogate for aPET

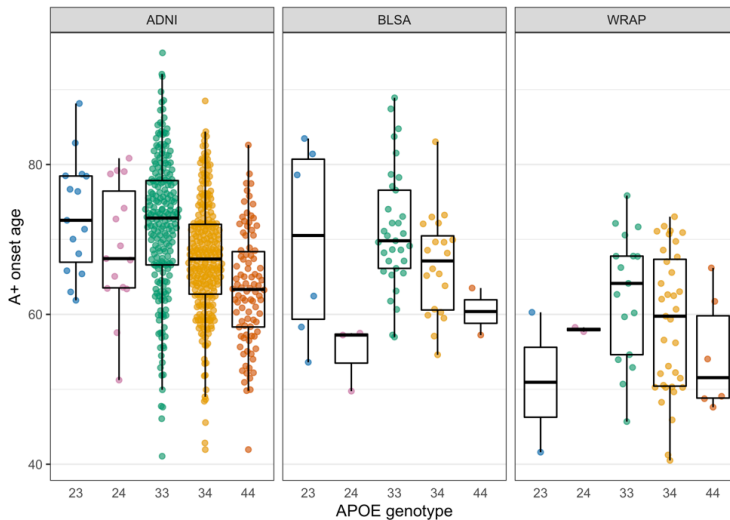
predicts decline

chronicity and onset age

N=160

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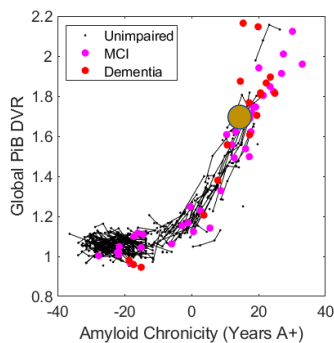
Context: The disease can start anytime in midlife or beyond!



- Amyloid proteinopathy onset anytime in midlife or beyond
- To screen for this disease we need a blood test that will be feasible to deploy

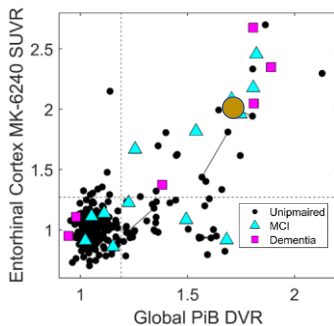
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## Case example



### Demographics

Female, APOE-ε3ε3  
 Baseline Age 54, last WRAP assessment Age 64  
 • 5 visits and 10 years of follow-up  
 Paternal and maternal history of dementia  
 Baseline IQ - 120  
 12 yrs ed

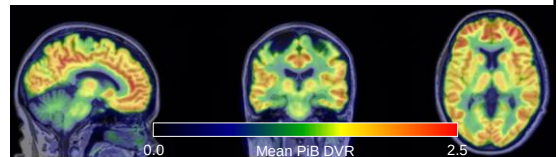


### MK-6240 and PiB PET at Age 64

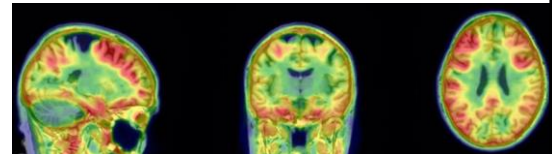
- Entorhinal SUVR = 2.08
- Global DVR = 1.73
- Est Duration A+ = ~18 years
- Est Age A+ = 47

**Cognitively normal and stable for 10 years!! When will decline be evident?**

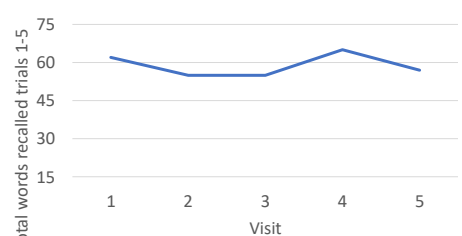
PiB Amyloid PET DVR



MK-6240 Tau PET SUVR



AVLT total



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## Summary

- AD is detectable years prior to symptoms with biomarkers;
- A+T+ groups have been declining from midlife
- The AT(N) framework (at least the A and T parts) works
  - But binarizing overlooks important temporal information
- AD amyloid onset age varies widely, but is estimable
  - Influenced by APOE4
- Temporal info can be derived from a single scan
- Amyloid in the brain accrues slowly and predictably; it is not benign
- The longer you have had it (chronicity), the more likely you are to exhibit cognitive decline—this appears to be through tau.
- Lifestyle and health factors influence cognition, but not amyloid proteinopathy (what about tau?)
- WMH not related to amyloid
- Blood markers are feasible and coming!

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## Thank you

### Acknowledgements

- R01 AG027161 (WRAP study)
- R01 AG021155 (PREDICT)
- P30 AG06715 (Wisconsin ADRC)
- Johnson lab staff
- WRAP Staff
- ADRC Staff
- Dedicated participants!

### Special thanks to:

- Karly Cody
- Tobey Betthausen, PhD
- Brad Christian, PhD
- Rebecca Kosciak, PhD
- Erin Jonaitis, PhD
- Lianlian Du, MA
- Howard Rowley, MD
- Laura Eisenmenger, MD



**Wisconsin Registry  
for Alzheimer's Prevention**  
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**Wisconsin Alzheimer's  
Disease Research Center**  
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