# 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-β 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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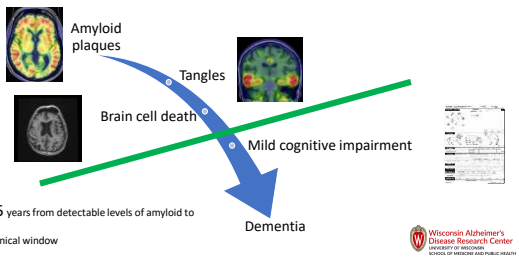
## Alzheimer's disease progression heuristic




~10-25 years from detectable levels of amyloid to dementia
The preclinical window

Wisconsin Alzheimer's Disease Research Center
UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE AND PUBLIC HEALTH

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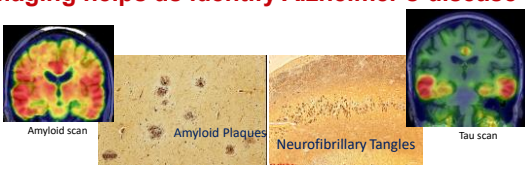
## Imaging helps us identify Alzheimer's disease




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

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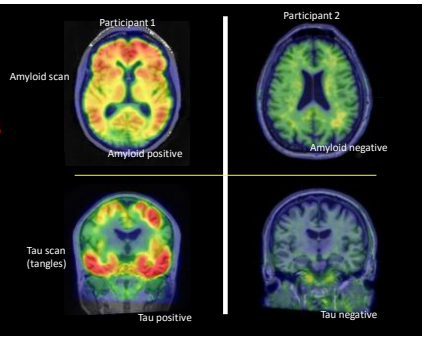
## Two patients with mild cognitive impairment

*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 $A\beta_{42}$; $A\beta_{42/40}$ $ptau_{181}$/ $A\beta_{42}$ ratios

Amyloid scan [C-11]PiB

**T tau**
- [F18]flortaucipir (FDA approved)
- [F18]PI2620
- [F18]MK-6240
- [F18]RO948
- $Ptau_{181}$; $Ptau_{217}$ ; $Ptau_{231}$

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-$tau_{181}$ to work for N (r=.99)

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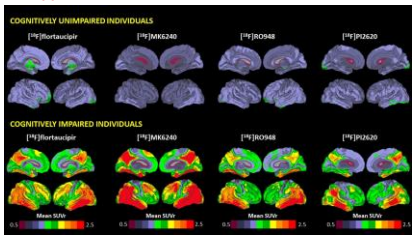
## Tau PET ligands:

***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) (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 |
| Funded by:<br>National Institutes of Health (NIH)<br>UW-Madison SMPH<br>State funds<br>Philanthropy | Funded by:<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)** |
| **WADRC clinical core (1000 participants; 650 active):**<br>• Alzheimer's dementia<br>• Mild cognitive impairment<br>• Cognitively unimpaired | **WRAP (1725 participants; 1250 active):**<br>• Cognitively unimpaired at baseline |
| • Data linked to other NIH Centers<br>• Detailed questionnaires<br>• Cognitive testing<br>• Clinical assessment<br>• Blood and spinal fluid tests<br>• Brain imaging<br>• Resources for UW and outside investigators | • Partnering with other international studies<br>• Detailed questionnaires<br>• Cognitive testing<br>• Clinical assessment<br>• Blood and spinal fluid tests<br>• Brain imaging<br>• Resources for UW and outside investigators |

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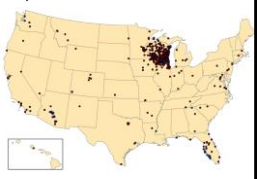
**WRAP:** One of the world's largest and longest running studies of individuals at risk for Alzheimer's dementia
*Risk from parental family history of dementia presumed due to AD*

Average WRAP Participant

67 years old · 70% female · 73% family history of AD · 40% obese · 11 years in study · 40% high blood pressure · 10% diabetes · 41% APOE4+ · 50% high cholesterol

**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

**01** 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 $A^+$ and T+ status relate to cognitive decline?

Betthauser et al., 2020, *Brain*

20 YEARS
WRAP
2001 – 2021
Wisconsin Registry for Alzheimer's Prevention

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## Betthauser 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- (n=124) | A-T+ (n=5) | A+T- (n=23) | A+T+ (n=15) | Group P-Val | Total (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 [103,115] | 104 [99, 115] | 111 [106, 115] | 109 [105, 113] | 0.73† | 110 [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

Betthauser et al 2020, *Brain*

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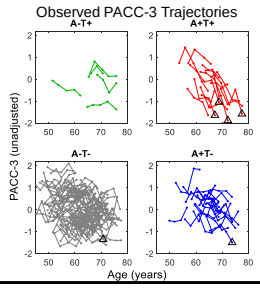
## Results: Retrospective PACC-3 and A/T Groups

Betthauser et al 2020, *Brain*

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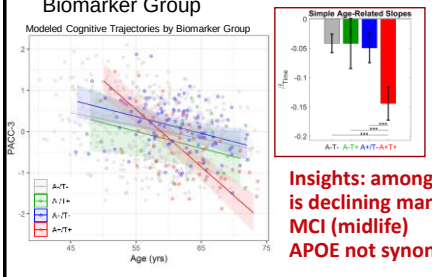
## Results: Retrospective Cognitive Decline by Biomarker Group




- Significant Group×Time Effect
- +/+ ~3x faster decline than -/-

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

Betthauser, 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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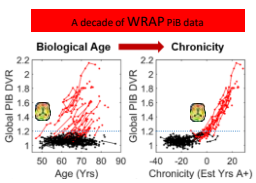
## Background: Amyloid PET trajectories are predictable




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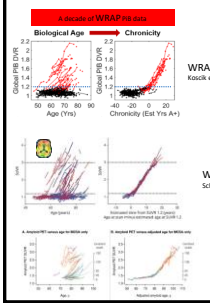
## Insight: Once A+, it continues to rise; predictable rate of change; Temporal estimates of onset age and duration of A+



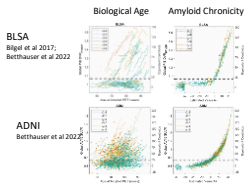

WRAP
Koscik et al 2020 DADM



Wash U ACS
Schindler Neurology 2021



Mayo Clinic
MCSA

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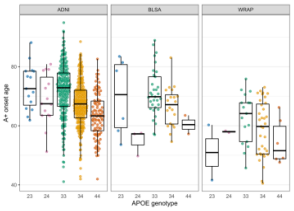
## Results: *APOE* Genotype and A+ onset Age (AOA)




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

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

- **APOE4** carriers have a **significant**ly 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+

*Betthauser, et al. 2022 Brain*

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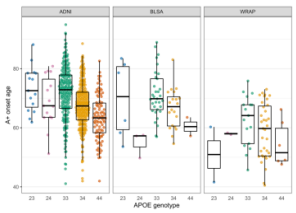
## Insight: Age of amyloid onset can be anytime in midlife or beyond. Its not enough to binarize A+ status

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

Betthauser et al Brain 2022

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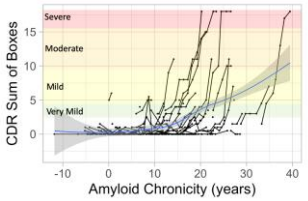
## Insight: Although the avg time to dementia is 24 yrs from A+ onset, there is heterogeneity




Heterogeneity in CDR vs A+ chronicity?

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

Birdsill et al (2022) DADM

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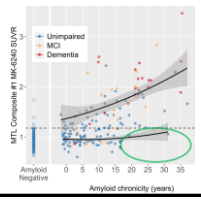
## Insights on the relationship between amyloid and tau

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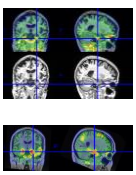
## Insight: When tau spreads outside the mesial temporal lobe (MTL & neocortical), its meaningful

- 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.

| 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 bs 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** |
| e65 age | -0.0012 | -0.0108 – 0.0083 | 0.799 |
| e65 age^2 | -0.0001 | -0.0008 – 0.0006 | 0.805 |
| AVR group f [A+/T-] * e65 age | 0.0002 | -0.0239 – 0.0243 | 0.986 |
| AVR group f [A+/T+ MTL only] * e65 age | 0.0077 | -0.0472 – 0.0625 | 0.784 |
| AVR group f [A+/T+ MTL and Neo] * e65 age | -0.1049 | -0.1316 – -0.0782 | **<0.001** |
| AVR group f [A+/T-] * e65 age^2 | -0.0011 | -0.0034 – 0.0011 | 0.334 |
| AVR group f [A+/T+ MTL only] * e65 age^2 | -0.0001 | -0.0043 – 0.0040 | 0.944 |
| AVR group f [A+/T+ MTL and Neo] * e65 age^2 | -0.0046 | -0.0070 – -0.0021 | **<0.001** |

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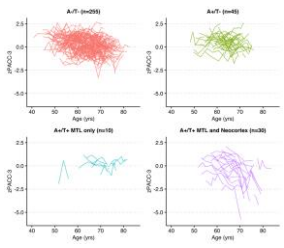
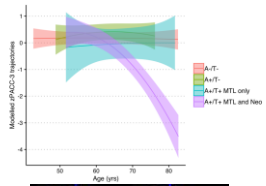
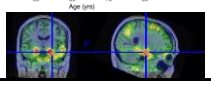



**Insight: When tau spreads outside MTL its clinically meaningful**




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 |
|---|---|---|
| *Modifiable factors* | | |
| 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[a] | +1.1 |
| Renal dysfunction | Kidney disease diagnosis or estimated glomerular filtration rate < 60 ml/min/1.73m[2a] | +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 |
| *Non-modifiable factors* | | |
| Age | | |
| Sex | | |

Cody et al 2022 DADM

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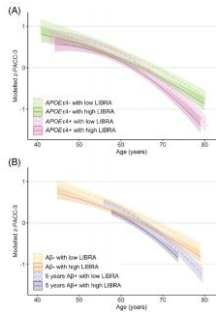
## LIBRA results

Cody et al, 2022 DADM




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

Diagnosis, Assessment & Disease Monitoring

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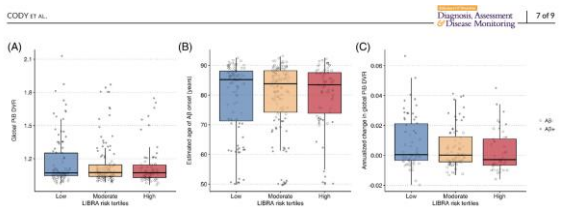
## LIBRA results




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

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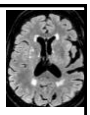
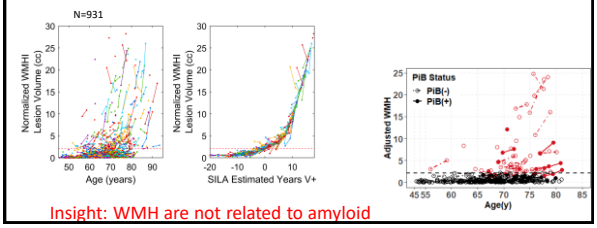
## What about WMH? (new data)
## Ischemic lesions grow in a predictable way such that time models can be applied






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)

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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%) |

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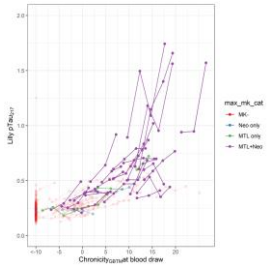
Ptau$_{217}$ is higher in people who have had amyloid longer and higher still in people who are T+ extending out of the MTL




Amyloid chronicity of >=0 are A+
Chronicity is expressed in years

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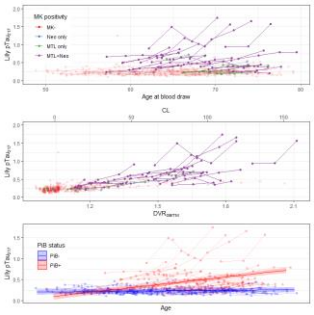
- Plotted against raw age, pTau$_{217}$ shows relationship with MK (top) and PiB (bottom; fitted line = mixed effects regression)
- Plotted against model-estimated PiB DVR, clustering with MK becomes clearer (middle)

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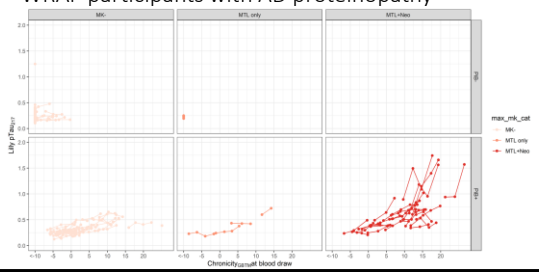
Change over time in ptau217 is pronounced in WRAP participants with AD proteinopathy

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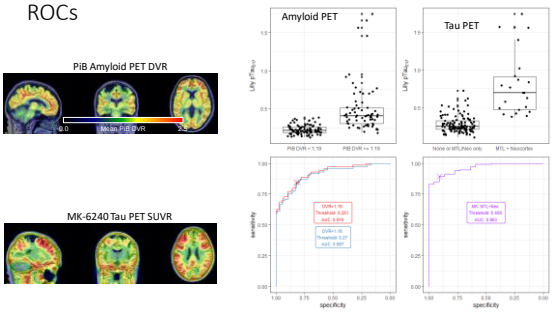
ROCs

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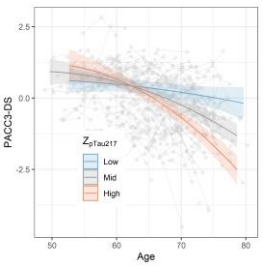
**Cognitive** decline on a cognitive composite is faster in people with higher levels of plasma MSD ptau217 at first visit

cognitively unimpaired at time of first blood draw




Low=10$^{th}$ percentile; Mid=median; High=90$^{th}$ percentile

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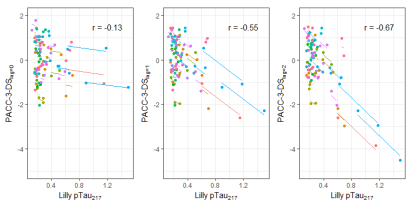
Lagged relationship with cognition




**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$_{217}$-cognition relationship)

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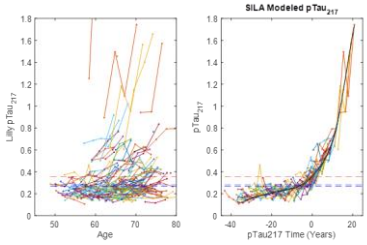
## Ptau217 appears to be able to confer temporal information

Tobey Betthauser's SILA model
Per Brain 2022 paper

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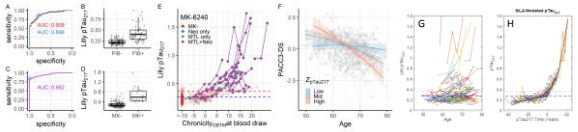
## Summary of blood data

- Plasma ptau217




Accurate for A+ and T+ | surrogate for aPET | predicts decline | chronicity and onset age

N=160

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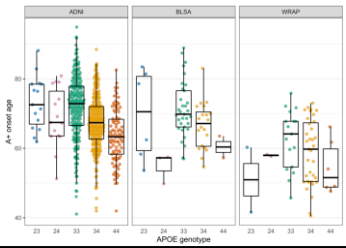
## Context: The disease can start anytime in midlife or beyond!




- 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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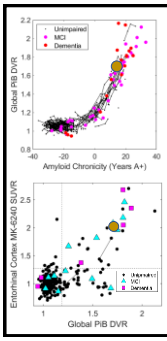
## Case example

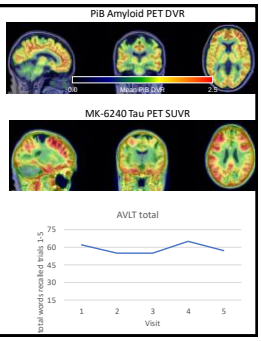



<u>Demographics</u>
Female, APOE-e3e3
Baseline Age 54, last WRAP assessment Age 64
- 5 visits and 10 years of follow-up

Paternal and maternal history of dementia
Baseline IQ - 120
12 yrs ed

<u>MK-6240 and PiB PET at Age 64</u>
- Entorhinal SUVR = 2.08
- Global DVR = 1.73
- Est Duration A+ = **~18 years**
- **Est Age A+ = 47**

**<u>Cognitively normal and stable for 10 years!! When will decline be evident?</u>**

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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

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