



## Updates from the Wisconsin Registry for Alzheimer's Prevention






2023 WRAP INFO SESSIONS



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## Welcome!

...and Welcome Back!




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## Alzheimer's Disease in 2023




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## What do we know now?

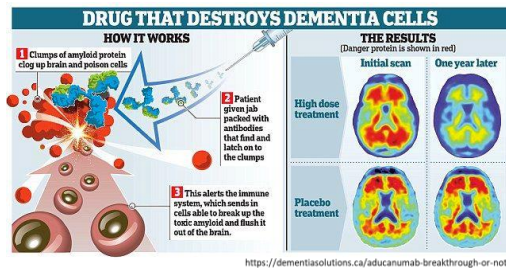
- Alzheimer's Disease and related disorders affect ~6.5 million in the U.S.
- AD is defined by **two proteins**: amyloid- $\beta$  and tau
  - Clinical stage of AD is defined separately
- There is a long **pre-symptomatic stage** that WRAP is defining
- Imaging and CSF **protein measurements** are current gold standard
  - Blood biomarkers are here
- **Other diseases may mimic or co-occur** with AD, increasing symptoms
- Two **new treatment drugs** approved; more are likely!



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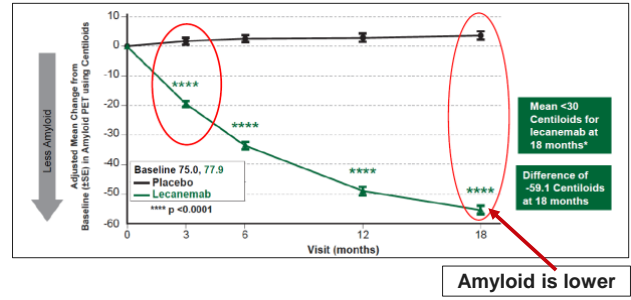
### Treatments that Target Amyloid

- Aducanumab & Lecanemab
- Monoclonal antibody
- Infusion therapy removes aspects of amyloid-beta



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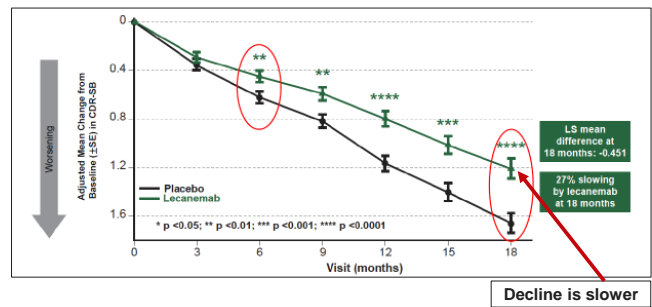
### Lecanemab Impacts Amyloid



Results from Clarity AD research study

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### Lecanemab Impacts Cognition

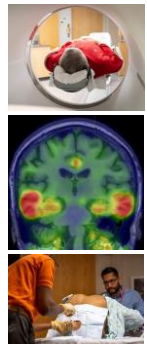


Results from Clarity AD research study

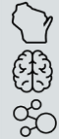
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### Measuring AD in WRAP

- Proteins
- Imaging
- Lumbar Puncture
- Blood

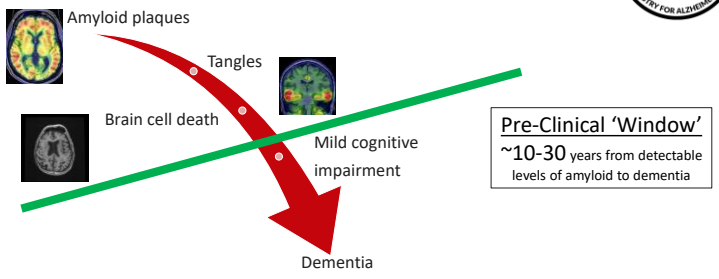


- Clinical Stage
- Tests of Memory & Thinking
- Questionnaires & Interviews
- Medical Exams



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### Alzheimer's Disease Progression



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### How did we get here?



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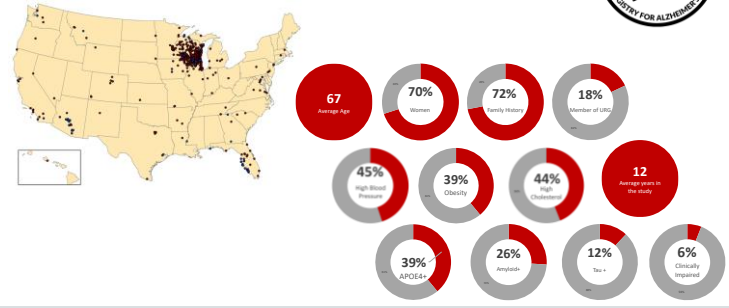
### What is the Wisconsin Registry for Alzheimer's Prevention?

One of the world's largest and longest running studies of individuals at risk\* for Alzheimer's dementia



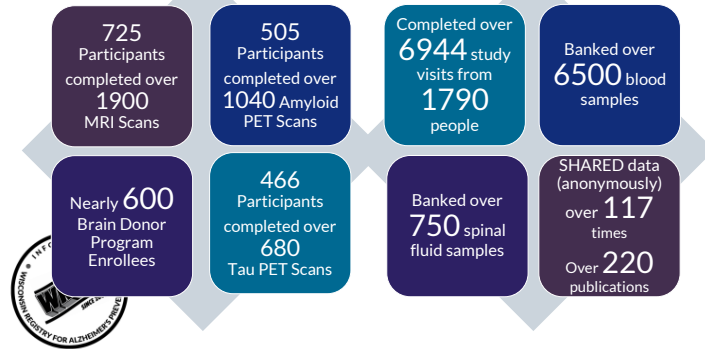
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### Who is in the Wisconsin Registry for Alzheimer's Prevention?



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## Participant Contributions



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## Mission Driven Research

### Mission and Purpose:

Discover and share knowledge on early identification and prevention of AD&RD

### Vision:

Empower individuals from all communities to prevent AD&RD

### Why us?

- We serve the largest cohort of risk-enriched people starting at the time that is most valuable-midlife
- We have world-leading biomarker technology and teams

### Core values:

- Scientific discoveries—that are generalizable to all communities
- Safe and respectful engagement — informed by our participants and the ways they want to be respected and valued
- High quality research data — that is easy to access and share
- Improved brain health — for our participants and their communities

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## From 2001 to 2023...and Beyond



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Discoveries Made,  
Questions Remain

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## WRAP Impact on Scientific Discovery



Discovered new ways to identify subtle cognitive decline



Discovered a way to identify when the disease starts



Helped discover new genes and molecules tied to AD



Discovered methods for studying resilience to cognitive decline



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## Current Research Questions



Are these discoveries generalizable to all communities?



How do lifestyle and social determinants of health affect AD?



What diseases may co-occur with AD to affect cognition?



How can we enable personalized precision healthcare?



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## Current Research Questions



What shapes the preclinical window prior to symptoms?



Does our data validate new blood biomarkers of AD?



How can we expand the time between Amyloid onset and impact on memory and thinking?



How and when do Tau proteins become a problem?



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## Impact of WRAP

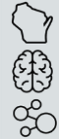
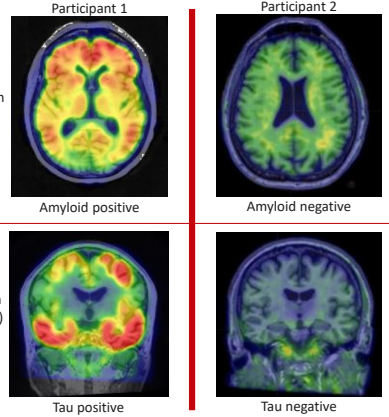
*The value of PET imaging to define the "preclinical window" of Alzheimer's Disease*



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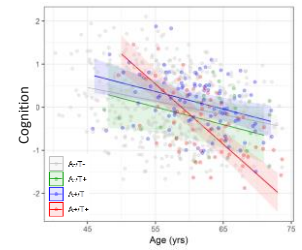
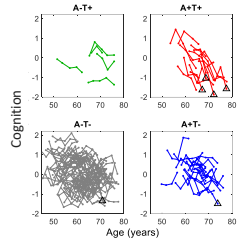
The clarity of PET imaging

Two WRAP subjects with mild memory loss



Effect of Amyloid and Tau on Cognition

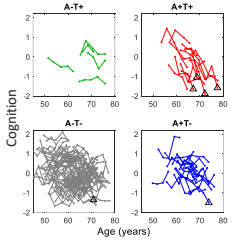
Observed cognitive Trajectories



Beththausen, et al. 2020, Brain

Effect of Amyloid and Tau on Cognition

Observed cognitive Trajectories



Cognition begins to decline many years prior to a clinical diagnosis in people who have amyloid and tau in their brain



Beththausen, et al. 2020, Brain

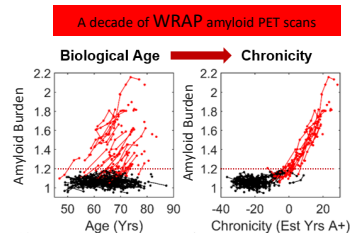
Can we determine when amyloid starts?

505 WRAP participants (and counting!) have had repeat amyloid scans

This resulted in a major finding...



### Amyloid PET Trajectories are Predictable

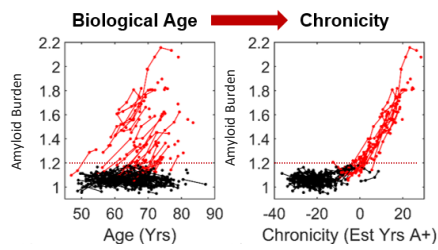


- Because we know amyloid accumulates at a consistent rate, we can estimate age of amyloid onset from a **single scan**
- There is a relationship among the length of time amyloid is in the brain, development of tau (based on PET), and cognitive decline

Rebecca Langhough Kosciak and others published in 2020, DADM

### WRAP Finding Replicated Several Times

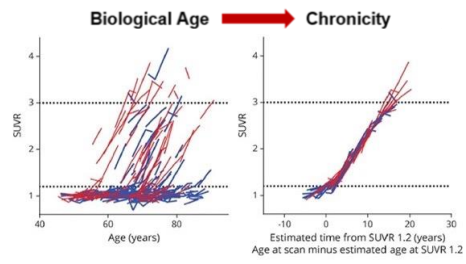
If amyloid is present, it will continue to rise and is predictable



Wisconsin Registry for Alzheimer's Prevention (WRAP)

### WRAP Finding Replicated Several Times

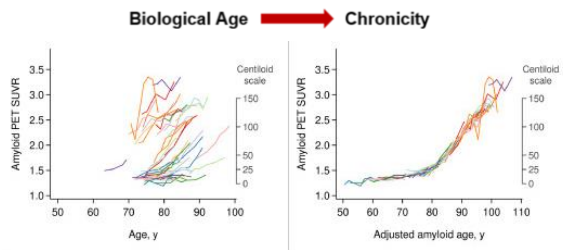
If amyloid is present, it will continue to rise and is predictable



Washington University: Adult Children Study (ACS)

### WRAP Finding Replicated Several Times

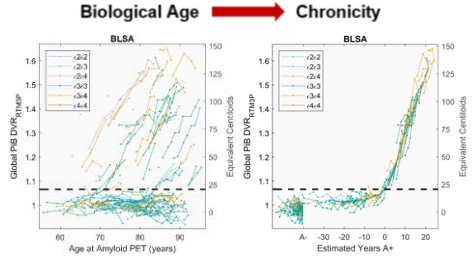
If amyloid is present, it will continue to rise and is predictable



Mayo Clinic: Study of Aging

### WRAP Finding Replicated Several Times

If amyloid is present, it will continue to rise and is predictable

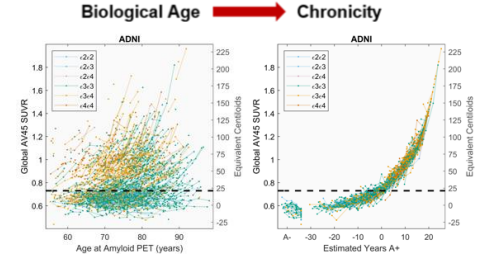


John's Hopkins: Baltimore Longitudinal Study on Aging (BLSA)



### WRAP Finding Replicated Several Times

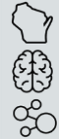
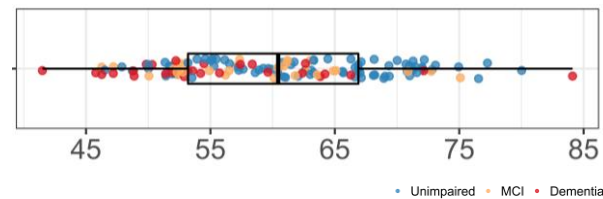
If amyloid is present, it will continue to rise and is predictable



Alzheimer's Disease Neuroimaging Initiative (ADNI)



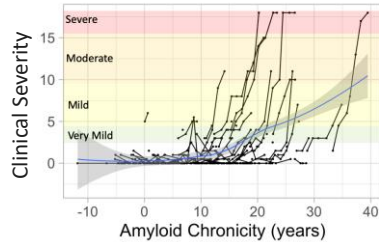
### People Develop Amyloid at Different Ages



Wisconsin PiB Amyloid Series



### 24 Years: Average Time A+ Onset to Dementia



**Risk:** older age and vascular disease, genetics

**Resilience:** can we slow down eventual symptoms through healthy living and other modifiable factors?

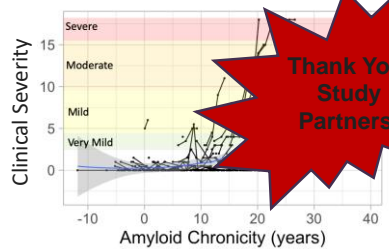


Alex Birdsil, et al (2022) *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*





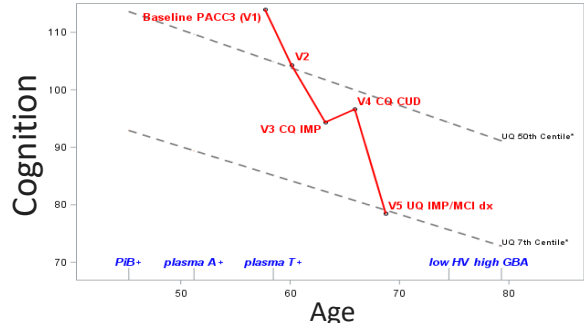
24 Years: Average Time A+ Onset to Dementia



Under age and vascular disease, genetics  
**Resilience:** can we slow down eventual symptoms through healthy living and other modifiable factors?

Alex Birdsil, et al (2022) *Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring*

Personalized Estimates of Cognitive Trend



WRAP Case Study, Erin Jonaitis & Rebecca Langhough Kosick

20 Years

WRAP

2023-2025

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Increasing Your Impact

WRAP Linked Studies

Addressing Disparities in AD Research

Asset-Based Community Model

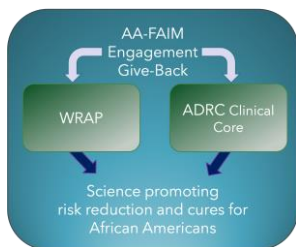


Gina Green-Harris  
Director, WAI-Regional  
Milwaukee Office



- **Bi-directional research** and intentional community engagement
- **Relationship building** through trust and transparency

## African Americans Fighting Alzheimer's in Midlife



Dr. Carey Gleason, PhD, MS

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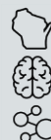
## Progress 2017 - 2023

Where we started (2017):

AA - ADRC Clinical Core	Madison WRAP	Milwaukee WRAP
~100	~2	~115

Where we are now (April 2023):

Baseline cognitive assessments	446
MRI Scan	181
Amyloid PET	70
Tau PET	65
CSF collection	84
Baseline plasma samples with Abeta measurements	318
Participants providing longitudinal data	235



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## AA-FAiM Participant Contributions

**HHS Public Access**  
Author manuscript  
*J Alzheimer's Dis*. Author manuscript; available in PMC 2020 March 19.  
Published in final edited form as:  
*J Alzheimer's Dis*. 2019; 72(3): 919-929. doi:10.3233/JAD-190645.

**Association of Cardiovascular and Alzheimer's Disease Risk Factors with Intracranial Arterial Blood Flow in Whites and African Americans**

Lindsay R. Clark<sup>1,2,3</sup>, Derek Norton<sup>1</sup>, Sara E. Berman<sup>1</sup>, Sterling C. Johnson<sup>1,2,3</sup>, Barbara B. Bendlin<sup>1,3</sup>, Oliver Wieben<sup>1,2</sup>, Patrick Turski<sup>1,2</sup>, Cynthia Carlsson<sup>1,2,3</sup>, Sanjay Athanas<sup>1,2</sup>, Carey E. Gleason<sup>1,2,3</sup>, Heather M. Johnson<sup>1,2</sup>

**81**  
(20.7%)  
participants who have participated in at least one ancillary study



Dr. Carey Gleason, PhD, MS

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## Fitness and Vascular Function

Cerebral blood flow and vessel stiffness (pulsatility) are important preclinical biomarkers of AD

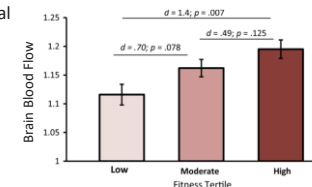
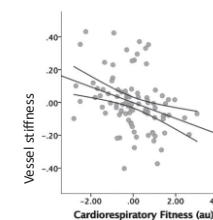
Aerobic fitness may provide protection against cerebrovascular changes related to the progression of clinical AD symptoms

Higher CRF associates with lower pulsatility and greater cerebral blood flow in several large cerebral arteries



Dr. Ozioma Okonkwo, LIFE Study

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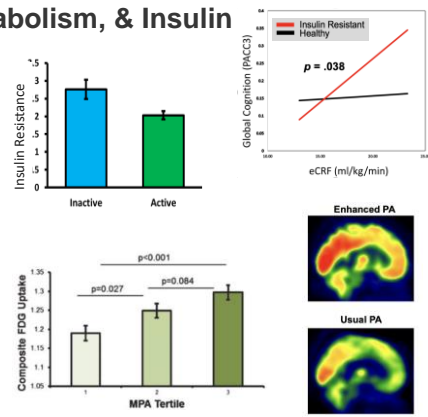
### Fitness, Glucose, Metabolism, & Insulin Dysregulation

Insulin resistance is linked with reduced cerebral glucose metabolism and may contribute to the cause and development of AD

Aerobic fitness/ physical activity are associated with improved insulin sensitivity and enhanced brain glucose metabolism

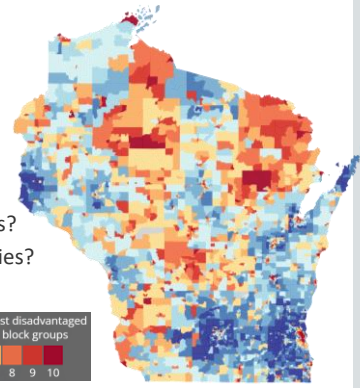
**Conclusions:** Physical activity and cardiorespiratory fitness levels show positive associations on vascular and glucoregulatory function.

Dr. Ozioma Okonkwo, LIFE Study



### Area Disadvantage Index & Neighborhood Atlas

- Does area deprivation impact risk for dementia?
- What is the effect on brain health?
- What is the effect on Alzheimer proteins?
- What about memory and thinking abilities?

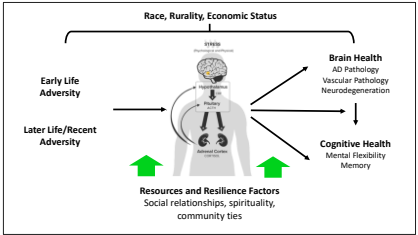


least disadvantaged block groups — most disadvantaged block groups  
1 2 3 4 5 6 7 8 9 10

Dr. Amy Kind, MD, PhD and Dr. Barbara Bendlin PhD



### Stress and Resilience in Dementia (STRIDE)



Dr. Megan Zuelsdorff, PhD



How does stress get “under the skin” to impact brain health, and what are the personal and social resources that protect us?

- Stress is a *modifiable* risk factor for all-cause dementia
- Communities face unique challenges and rely on unique assets and strengths to cope
- Key goal: Include perspectives of Wisconsin’s rural, Black, and tribal communities



### New Findings from STRIDE

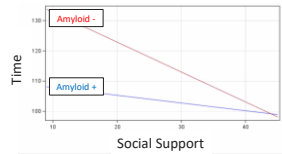
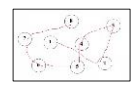


Associations of social support and cognitive test performance, by amyloid status, in African American participants

Social support might buffer cognitive decline – even in the presence of amyloid (*resilience*)

Participants who report higher social support perform better on tests of memory, regardless of level of amyloid accumulation

Trails B (lower times are better!)



Participants who report higher social support perform better on tests of memory and thinking abilities

- This relationship is stronger at higher levels of plasma amyloid

Dr. Megan Zuelsdorff, PhD - STRIDE

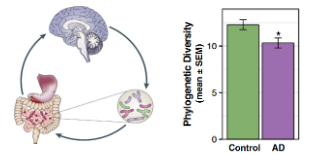


### Gut microbiome update!

Microbiome Alzheimer's Risk study (MARS)



- 492 people provided stool samples.
- People with Alzheimer's dementia have lower gut microbiome diversity
- Gut bacteria are associated with amyloid, even before people show symptoms of dementia.



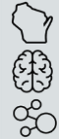
But how is the brain influencing the gut (or vice versa)?

Vogt et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep. 2017



### Big Picture

- Gut and brain are linked, we are starting to figure out how the gut may impact the brain.
- Thank you for donating your stool! 429 people have donated at least one sample! 200 people have provided two or more samples!
- We have started collecting stool annually so we can understand when the gut starts to change.
- We are conducting animal studies to better understand the mechanisms by which the gut impacts the brain.

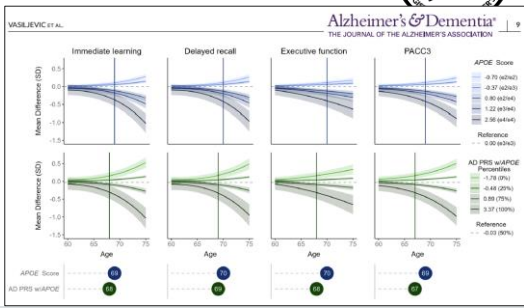


### Genetics and Alzheimer's Disease

- Cognitive decline in all 4 cognitive composite scores starts to differ by **APOE genotype (score)** around age 65, resulting in a half standard deviation difference by age 69-70
- Adding in additional genetic variants with smaller effects (AD polygenic score [PGS]) results in a half standard deviation difference about a year earlier (ages 67-69)



Eva Vasiljevic, PhD, Post-doctoral Fellow, CDC, Dr. Corinne Engleman's Lab  
Vasiljevic et al. Alzheimer's & Dementia 2023



Will there be a Blood Test for AD?



## Yes!

Many studies have shown AD proteins are detectable in blood – and there are many unanswered questions

### A blood test will:

- ✓ Improve accurate diagnosis
- ✓ Accelerate scientific discovery
- ✓ Increase access to information for doctors to advise and treat their patients

### You are helping by:

- ✓ Scheduling in-person visits
- ✓ Taking tests of memory and thinking
- ✓ Giving a blood sample and consenting to share
- ✓ Volunteering for PET scans or Lumbar Punctures



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## Yes! And...



How much Amyloid and Tau protein in blood is normal?



What do we mean by abnormal? What is the threshold?



Will the result be the same as PET scans or CSF?



Will a blood test predict cognitive decline?



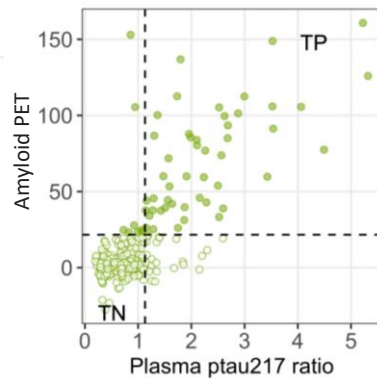
Will the results be generalizable to all communities?



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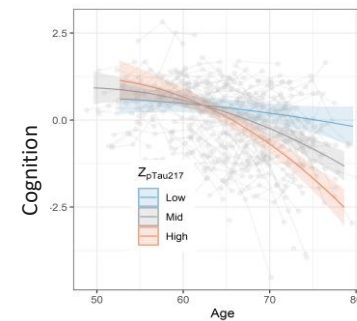
## Blood Biomarkers Strongly Agree with PET

Biomarkers	AUC (95% CI)
APS-2	0.95 (0.93 - 0.98)
pTau217 ratio	0.94 (0.91 - 0.97)
pTau181 ratio	0.72 (0.65 - 0.80)
Ab42/40	0.87 (0.83 - 0.92)



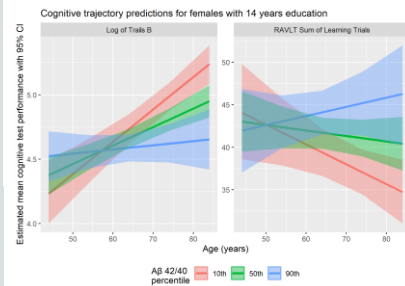
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## Blood biomarkers predict cognitive change

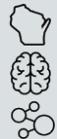


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## Cognitive change in Black participants predicted with blood biomarkers

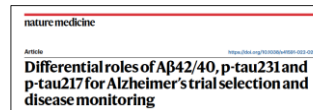


- 179 African American participants from our program
- Cognitively normal at the start
- Amyloid levels in blood associated with cognitive change



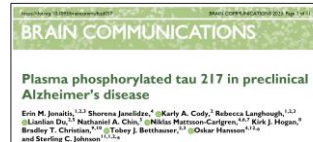
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## Recent blood biomarker papers from WRAP



*Ptau217 best predicts cognitive change among other blood markers*

*Ptau217 agrees with amyloid PET*



*Findings replicated in other cohorts*



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## What is next for you and WRAP?



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## The protocol is mostly the same



### Adding

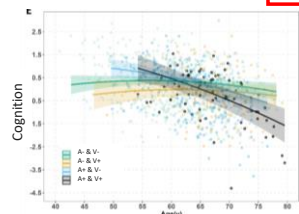
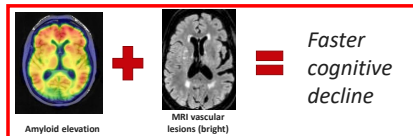
- 200 new African American participants
- MRI in Milwaukee, exploring option in La Crosse
- Ultrasound of blood vessels supplying the brain

### Encouraging

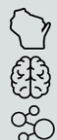
- WRAP visits in-person every two years including Blood Draw and Medical Exam
- Lumbar Puncture and PET biomarkers

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## V is for Vascular Disease



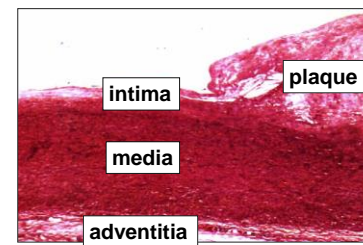
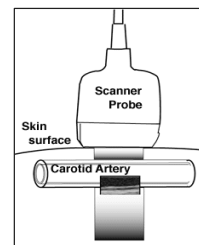
Vascular disease is best detected with MRI



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## All WRAP Participants Invited for

### Carotid Artery Ultrasound



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## Carotid Artery Ultrasound



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## Carotid Artery Ultrasound Visit



Safe – no radiation, no harmful exposures, no known biological effects

Identifies range of disease – changes in the composition of the arterial wall, increased wall thickness, non-occlusive plaque, stenosis

Predicts future heart attacks, strokes, and death from cardiovascular disease

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## Lewy Body Disease

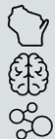
Lewy-Body disease second most common neurodegenerative disease

Can co-exist with AD and accelerate cognitive decline

Neurological exam can help detect early subtle movement changes

Questionnaire responses may help identify early symptoms

Currently considering adding an optional smell test to visits



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Research results to empower you and your healthcare



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## You asked for personalized results



1

Your **Amyloid PET** result can be disclosed to you, if you wish

2

We will contact you with **abnormal cognitive testing, MRI, and Ultrasound** results

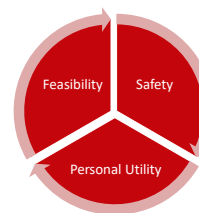
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Standard **Blood lab** results with clinician feedback are sent after blood draws

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## Amyloid Disclosure Study Goals



Evaluate feasibility, safety, and personal utility of amyloid PET results disclosure with cognitively unimpaired adults

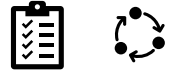
Dr. Lindsay Clark, Amyloid Disclosure Study

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### Amyloid Disclosure: Future Directions



Continue gathering participant feedback to improve process



Expand post-disclosure participant support and resources



- Study how participants use this information
- Share more in-depth results
- Expand to include other biomarkers, including tau PET
- Referrals to treatment studies and clinical care



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Name:  MRI Date:  Survey Date:

Health and lifestyle factors relevant to brain health (based on your WRAP survey responses)			
Modifiable Factor	Recommendation	Your Response or Measured Value	Key
Alcohol use	1 drink/day or less	Missing data	
Sleep	7-9 hours/day	9 hours/day	
Physical activity	Strike for 150+ minutes of moderate activity each week	Moderate activity (avg minutes/week): 75	
Tobacco use / exposure	Be a non-smoker and avoid tobacco products	Non-smoker	
Weight	Body mass index 18.5-30	22.3 BMI	
Cholesterol	Less than 200 mg/dL	187 mg/dL	
Blood pressure	Less than 120/80 mmHg	95/73 mmHg	
Blood sugar management	Fasting blood sugar 70-99 mg/dL	Fasting blood sugar 87 mg/dL	

Key: ■ Doing great ■ Could be improved ■ Needs attention ■ No data available

**Making healthy lifestyle choices may reduce your risk of dementia.**

We don't yet know for certain what, if anything, can prevent dementia, but there may be steps you can take to help reduce your risk.

Learn more about brain health and dementia prevention from The National Institute on Aging [www.alzheimers.gov/can-i-prevent-dementia](http://www.alzheimers.gov/can-i-prevent-dementia)

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*[name of participant and date of scan]*

This is a Magnetic Resonance Image (MRI) of your brain.  
The image above is a 3D-rendering of the right side of your brain  
*Research image not for diagnostic use.*

V3.10/14/2022

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### Wisconsin Alzheimer's Institute

Shaping a future free from Alzheimer's disease

WAI is advancing health equity through research, education, clinical care and community engagement for all people impacted by Alzheimer's disease and related disorders.

#### Program Areas

- Health Equity
- Research
- Education
- Community Engagement
- Clinical Care

Offices in Madison and Milwaukee 
 [wal.wisc.edu](http://wal.wisc.edu)
[wai@medicine.wisc.edu](mailto:wai@medicine.wisc.edu)

About Wisconsin Alzheimer's Institute (WAI) – [wal.wisc.edu](http://wal.wisc.edu)

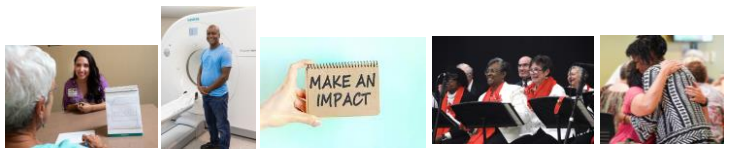


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### Become a Memorable Friend



- Support Alzheimer's disease research, education, health equity and patient care at UW-Madison
- Receive regular communications and updates
- Connect with others at educational and fundraising events
- Help build public awareness
- **More details in your folder and online**



Initiative to End Alzheimer's (IEA) – [www.iea.wisc.edu](http://www.iea.wisc.edu)

### THANK YOU!



WRAP Participants, Friends, and Family

WRAP Research Staff, Faculty, and Partners

Wisconsin Alzheimer's Institute

Wisconsin Alzheimer's Disease Research Center

National Institutes of Health



### Question & Answer Session



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