Welcome!

…and Welcome Back!

Alzheimer’s Disease in 2023

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!
Treatments that Target Amyloid

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

Lecanemab Impacts Amyloid

Results from Clarity AD research study

Lecanemab Impacts Cognition

Results from Clarity AD research study

Measuring AD in WRAP

Proteins
- Imaging
- Lumbar Puncture
- Blood

Clinical Stage
- Tests of Memory & Thinking
- Questionnaires & Interviews
- Medical Exams
Alzheimer’s Disease Progression

- Amyloid plaques
- Tangles
- Brain cell death
- Mild cognitive impairment
- Pre-Clinical ‘Window’
  ~10-30 years from detectable levels of amyloid to dementia

How did we get here?

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

Who is in the Wisconsin Registry for Alzheimer’s Prevention?

<table>
<thead>
<tr>
<th>67</th>
<th>70%</th>
<th>72%</th>
<th>18%</th>
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<tbody>
<tr>
<td>45%</td>
<td>39%</td>
<td>44%</td>
<td>12%</td>
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<tr>
<td>39%</td>
<td>26%</td>
<td>6%</td>
<td>0%</td>
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*Note: The asterisk indicates additional information or qualifications related to the risk for Alzheimer’s dementia.

Average years in the study: 6.7
Average Age: 67
Amyloid+: 39%
APOE4+: 72%
Family History: 6%
Clinically Impaired: 39%
Obesity: 18%
WRAP Information Sessions
2023 - Madison

Participant Contributions
- 725 Participants completed over 1900 MRI Scans
- 505 Participants completed over 1040 Amyloid PET Scans
- Nearly 600 Brain Donor Program Enrollees
- 466 Participants completed over 680 Tau PET Scans
- Banked over 6500 blood samples
- Banked over 750 spinal fluid samples
- SHARED data (anonymously) over 117 times
- Over 220 publications

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

From 2001 to 2023…and Beyond

NIH Awards
Wisconsin Registry for Alzheimer’s Prevention
5-Year Grant Renewal

Discoveries Made, Questions Remain
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

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?

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?

Impact of WRAP

*The value of PET imaging to define the “preclinical window” of Alzheimer’s Disease*
The clarity of PET imaging

Two WRAP subjects with mild memory loss

Amyloid scan

Participant 1

Participant 2

Amyloid positive

Amyloid negative

Tau scan (tangles)

Tau positive

Tau negative

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

Betthauser, 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 Koscik and others published in 2020, DADM

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)

Mayo Clinic: Study of Aging
**WRAP Finding Replicated Several Times**

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

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

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**WRAP Finding Replicated Several Times**

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

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**Alzheimer's Disease Neuroimaging Initiative (ADNI)**

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**People Develop Amyloid at Different Ages**

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**Wisconsin PiB Amyloid Series**

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**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?

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

Personalized Estimates of Cognitive Trend

Addressing Disparities in AD Research

Increasing Your Impact
WRAP Linked Studies

Gina Green-Harris
Director, WAI-Regional
Milwaukee Office

Asset-Based Community Model

- Bi-directional research and intentional community engagement
- Relationship building through trust and transparency
African Americans Fighting Alzheimer’s in Midlife

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

Progress 2017 - 2023

AA-FAiM Engagement Give-Back

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.
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.

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?

Stress and Resilience in Dementia (STRIDE)

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

Participants who report higher social support perform better on tests of mental flexibility

- This relationship is stronger at higher levels of plasma amyloid
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)?


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)

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

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?

Blood Biomarkers Strongly Agree with PET

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>AUC (95% CI)</th>
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<tr>
<td>Aβ1-42</td>
<td>0.95 (0.93 - 0.98)</td>
</tr>
<tr>
<td>pTau217 ratio</td>
<td>0.94 (0.91 - 0.97)</td>
</tr>
<tr>
<td>pTau818 ratio</td>
<td>0.92 (0.85 - 0.90)</td>
</tr>
<tr>
<td>Ab42/40</td>
<td>0.87 (0.83 - 0.92)</td>
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Blood biomarkers predict cognitive change

Cognition vs. Age

- Low
- Mid
- High
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

Recent blood biomarker papers from WRAP

Ptau217 best predicts cognitive change among other blood markers

Pttau217 agrees with amyloid PET

Findings replicated in other cohorts

The protocol is mostly the same

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

Adding

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

Encouraging
V is for Vascular Disease

Vascular disease is best detected with MRI

Faster cognitive decline

Cognition

Vascular disease is best detected with MRI

Figure by Lianlian Du, PhD

All WRAP Participants Invited for

Carotid Artery Ultrasound

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

Carotid Artery Ultrasound Visit

Carotid Artery Ultrasound

intima

media

plaque

adventitia
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.

Research results to empower you and your healthcare

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

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
Amyloid Disclosure: Future Directions

- 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

About Wisconsin Alzheimer's Institute (WAI)

- wai.wisc.edu
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

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