Update from the Wisconsin Registry for Alzheimer's Prevention (WRAP)

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Impact of Alzheimer's Dementia on Wisconsin Residents

NUMBER OF WI RESIDENTS AGED 65+ WITH ALZHEIMER'S:	
2019	110,000
2025	130,000

6th LEADING CAUSE OF DEATH IN WISCONSIN

MEDICARE

$20,083

Per capita Medicare spending on people with dementia (2018 dollars)

195,000

Number of caregivers of persons with dementia in WI

https://www.alz.org/media/Documents/wisconsin-alzheimers-facts-figures-2019.pdf
https://www.cdc.gov/nchs/pressroom/states/wisconsin/wisconsin.htm

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

Clinical spectrum of cognitively unimpaired–mild cognitive impairment–dementia with its multiple potential etiologies (Ron Petersen, Neurology, 2018 Aug 28; 91(9): 395–402.

Caption: The contribution of Alzheimer disease (AD) is expressed by β-amyloid (Aβ) and tau. However, the other protein abnormalities, including TDP-43 and α-synuclein, as well as vascular disease may also contribute to cognitive impairment. The ring of yellow symbols indicates the biomarkers that exist or are being developed for each pathologic entity. Ultimately, treatments will developed for each pathologic component based on its biomarker.

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

Jack, et al. *Alzheimers Dement.* 2018

UW 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 31 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: National Institutes of Health (NIH) UW-Madison SMPH State funds Philanthropy	Funded by: Federal, foundation, and education grants UW-Madison SMPH State funds Philanthropy

UW School of Medicine and Public Health

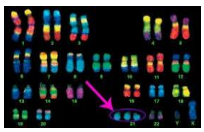
UW-Madison Alzheimer's Disease Program

Wisconsin Alzheimer's Disease Research Center (WADRC)	Wisconsin Alzheimer's Institute (WAI)
Wisconsin ADRC (1000 participants): • Alzheimer's dementia • Mild cognitive impairment • Cognitively unimpaired • Caregivers	**Wisconsin Registry for Alzheimer's Prevention (WRAP) (1500 participants):** • Cognitively unimpaired
• Data linked to other 30 NIH Centers • Detailed questionnaires • Cognitive testing • Clinical assessment • Blood and spinal fluid tests • Brain imaging • Resources for UW and outside investigators	• Partnering with other international studies • Detailed questionnaires • Cognitive testing • Clinical assessment • Blood and spinal fluid tests • Brain imaging • Resources for UW and outside investigators

Early Detection of Dementia Risk

WRAP, Wisconsin ADRC, and UW-Madison Waisman Center Down Syndrome Cohorts

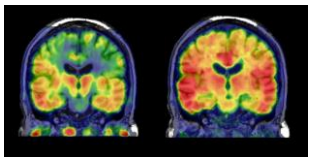
- Brain imaging
- Spinal fluid tests
- Blood tests
- Genetic tests




Sterling Johnson, PhD


Barbara Bendlin, PhD


Cindy Carlsson, MD, MS


PET scans can detect amyloid and tau deposits in the brain before cognitive changes


Spinal fluid tests detect the earliest brain changes before memory loss begins

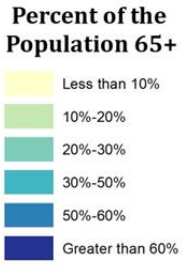

Ozioma Okonkwo, PhD


Kimberly Mueller, PhD, CCC-SLP


Brad Christian, PhD


Lindsay Clark, PhD

WRAP and the **Wisconsin ADRC** partner with ***over 2500 research participants*** to find ways to prevent Alzheimer's disease



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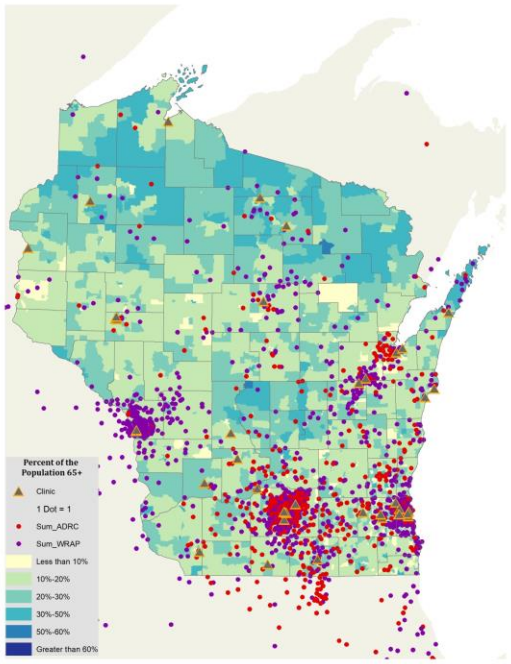
Wisconsin Alzheimer's Institute
Wisconsin Alzheimer's Disease Research Center



Maps courtesy of William Buckingham, PhD

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*

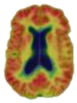
WRAP Goals

Identify AD in its **Preclinical** phase, before symptoms

Identify **biological, health, and lifestyle** factors that increase or decrease risk of 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% diabetic
- 41% APOE4+
- 50% high cholesterol

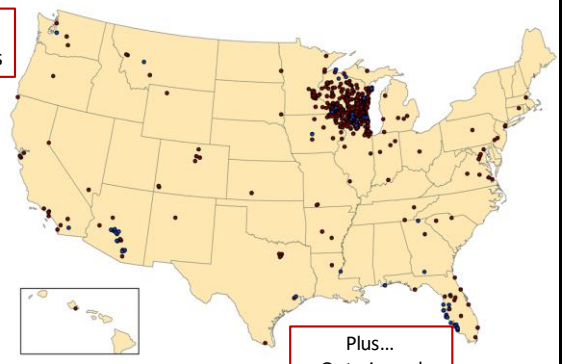


Current focus on biomarker research

25% have amyloid in their brains

WRAP Participants Come From…

32 States



Plus… Ontario and Alberta, Canada and Scotland

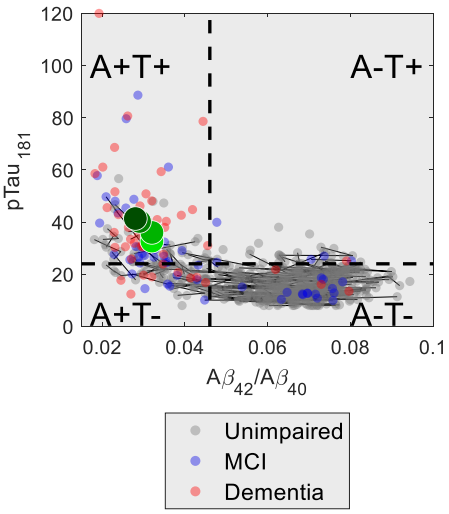
See Johnson et al 2018 *A&D DADM*
DOI: https://doi.org/10.1016/j.dadm.2017.11.007

For More Information, Contact WRAP: Madison: 1 (800) 417-4169 · Milwaukee: (414) 219-7911 · LaCrosse: (608) 392-7187

Consensus diagnosis of advanced MCI

Slide courtesy of Tobey Betthauser, PhD

NTK CSF Results



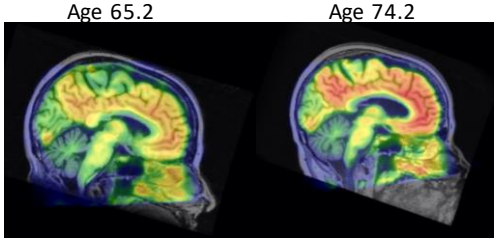
Age	PET	CSF
65.2	A+	A+T+
67.28	A+	A+T+
69.07	A+	A+T+
70.28	-	A+T+
72.04	A+T+	-
74.15	A+T+	-

Est PiB(+) Age = 50.6 years

N- for NFL, neurogranin, alpha syn

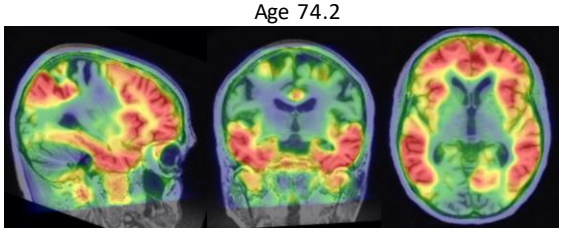
PIB

Age 65.2 Age 74.2



MK-6240

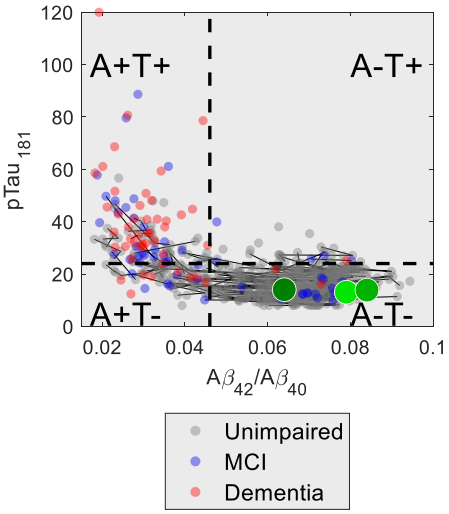
Age 74.2



Slide courtesy of Tobey Betthauser, PhD

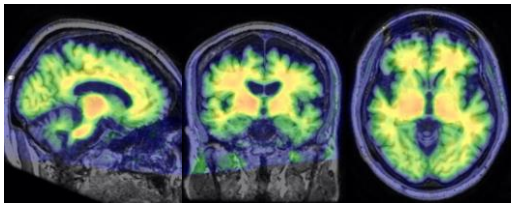
Consensus diagnosis of CU with decline

NTK CSF Results

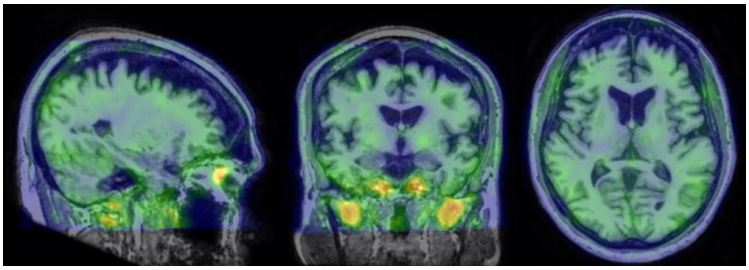


Age	PET	CSF
62.4	A-	A-T-N-
64.7	A-	A-T-N-
66.2	-	A-T-N-
68.9	A-T-	
70.7	**A-T-**	

PiB negative
Age 70.7

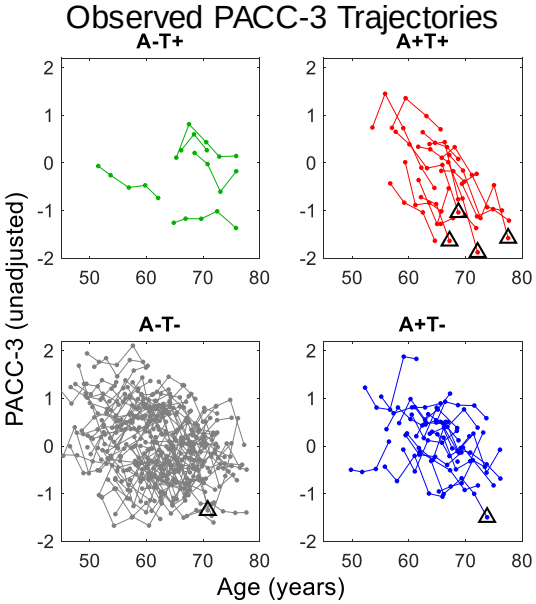


MK-6240 negative
Age 70.7

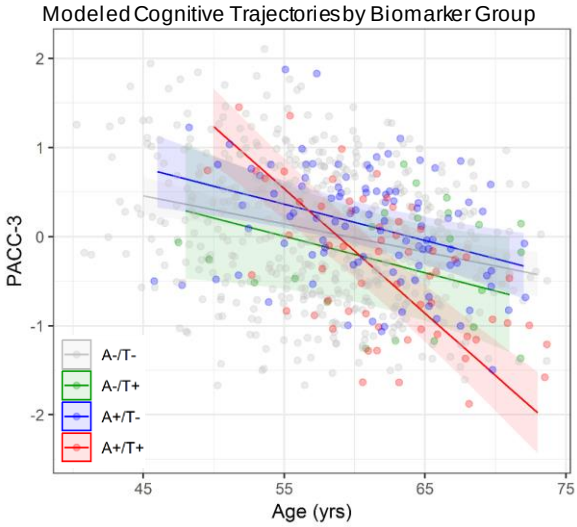


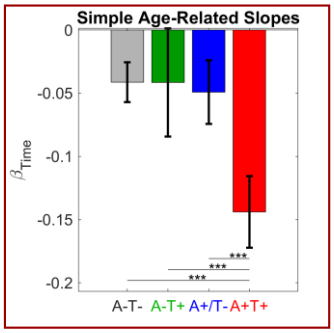
N- for NFL, neurogranin

Results: Retrospective PACC-3 and A/T Groups



Results: Retrospective Cognitive Decline by Biomarker Group

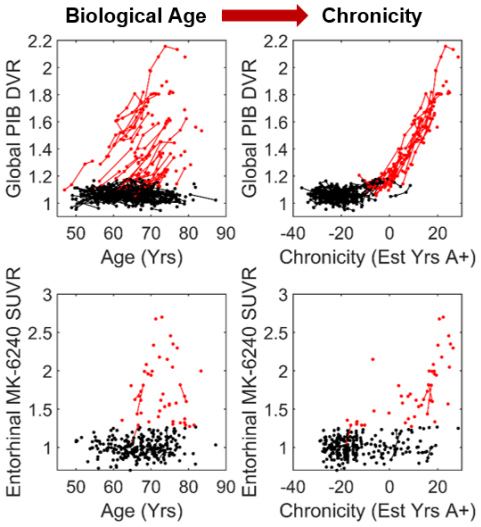


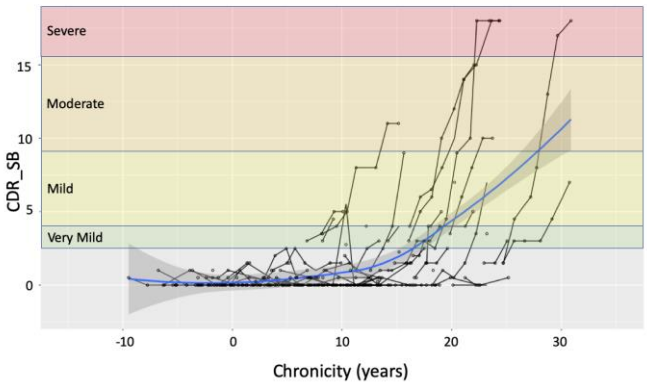


- Significant Group×Time Effect
- +/+ ~3x faster decline than -/-

Betthauser, et al. In press, *Brain*

Amyloid duration can be estimated-–related to cognitive decline (Koscik, Betthauser et al 2020 DADM)

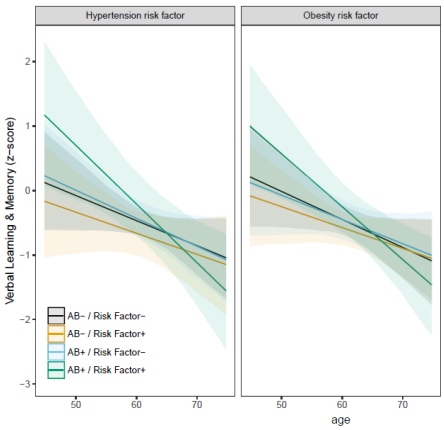




Birdsill et al in preparation; to be presented at AAIC

Some vascular findings

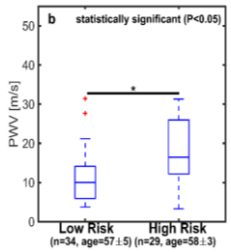
Lindsay Clark et al Neurology 2019

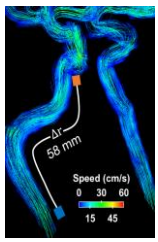


4D flow studies

Collaboration with Leo Rivera-Rivera and Kevin Johnson

JCBFM 2020





Faster pulse-wave velocity in AD-dementia and AD risk

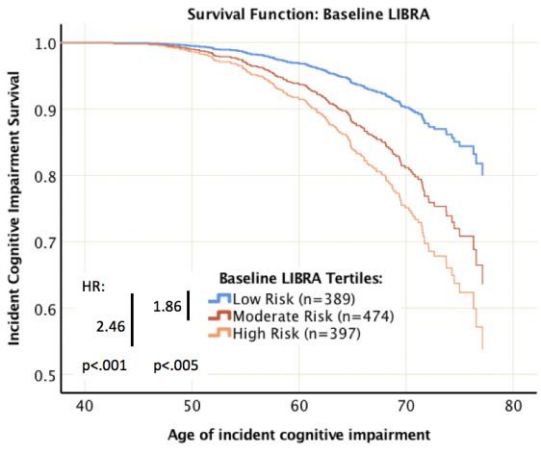
Higher pulsatility index in AD continuum-stiffer vessels

Poor quality perfusion and pressure—more tortuous arterioles—in AD continuum

Lifestyle and cognition

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^2[b]	+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		



Outcome measure	Risk index		HR (95% CI)	*p*-value[b]
Incident cognitive impairment[a] (n=1244)	Baseline LIBRA		1.18 (1.10, 1.27)	<0.001
	Baseline LIBRA Risk Tertiles: (reference)	Low	--	--
		Moderate	1.86 (1.20, 2.86)	0.005
		High	2.46 (1.60, 3.78)	<0.001

Note: HR, hazard ratio.
[a]Incident cognitive impairment was defined as 1.5 SD below mean performance on a covariate-adjusted PACC-3
[b]Tertiles, p-value for significant difference from low risk (reference) category

LIBRA results

Cody et al, in preparation

- Poorer lifestyle is related to cognitive decline over time
- *Not* related to amyloid PET rate of progression
- *Not* a factor related to onset age or duration of amyloid PET
- It is possible that modifiable factors may confer brain resilience to dementia in the presence of amyloid;
  - but they don't affect amyloid itself

Summary

- AD begins in midlife
- It is detectable with biomarkers
- Amyloid in the brain accrues slowly, is not benign
- The longer you have had it, the more likely you are to exhibit cog decline
- Lifestyle and health factors influence cognition, but not AD proteinopathy

Our UW-Madison Alzheimer's Disease Program Team