

**Michigan
ADRC**
Alzheimer's Disease Research Center

A statewide partnership between the University of Michigan, Michigan State University, and Wayne State University to support dementia research.

*Update on
Alzheimer's
Research
AAIC 2022*




Bruno Giordani, PhD
Associate Director,
Michigan Alzheimer's Disease
Research Center
Professor,
University of Michigan
Senior Director,
Mary A Rackham Institute

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DISCLOSURES

- Research Support: NIH, Alzheimer's Association
- Other related disclosures: None

My children have all my money, anyway



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Before we go any
further...

**THANK
YOU!**

alzheimer's
association

Michigan
ADRC

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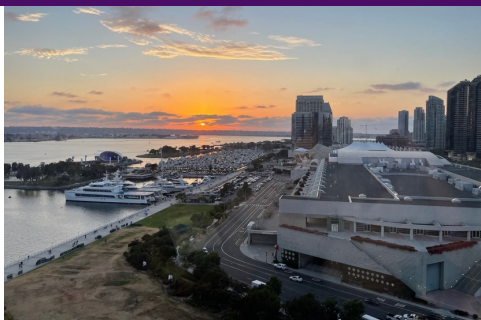
What We Hope To Cover Today

1. Brief review of dementia/AD to put us on the same page
2. New research findings from AAIC 2022
 - Plasma Biomarkers
 - Lifestyle and other factors affecting the brain
 - Clinical Trials news
3. Our Michigan Alzheimer's Disease Research Center

Michigan
ADRC

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AAIC 2022: San Diego, CA



- Close to 9,500 persons registered with a little over half attending
- Over 4,000 scientific presentations



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Background on AD



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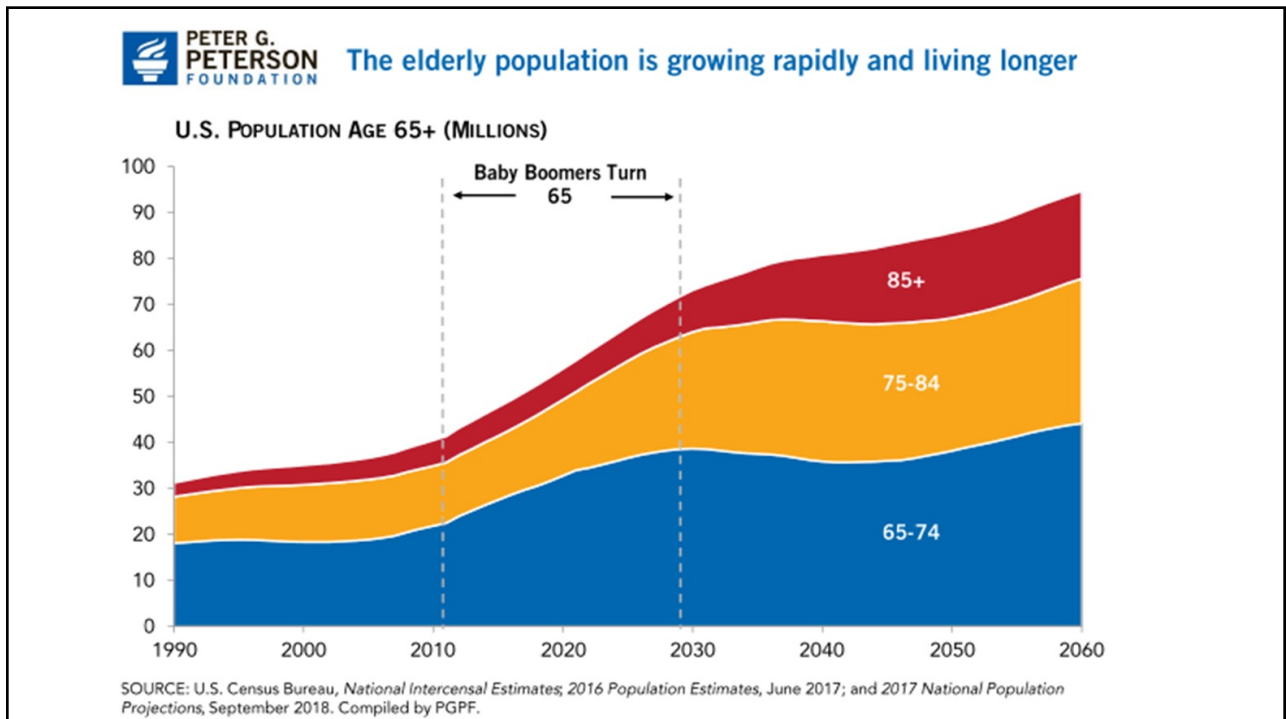
DEMENTIA IS A SYNDROME

- Dementia is a collection of symptoms related to cognitive decline
- Can include cognitive, behavioral and psychological symptoms
- Due to biological changes in the brain
- Alzheimer's is most common cause
- Mixed dementia is very prevalent
- Some causes of cognitive decline are reversible and not truly dementia

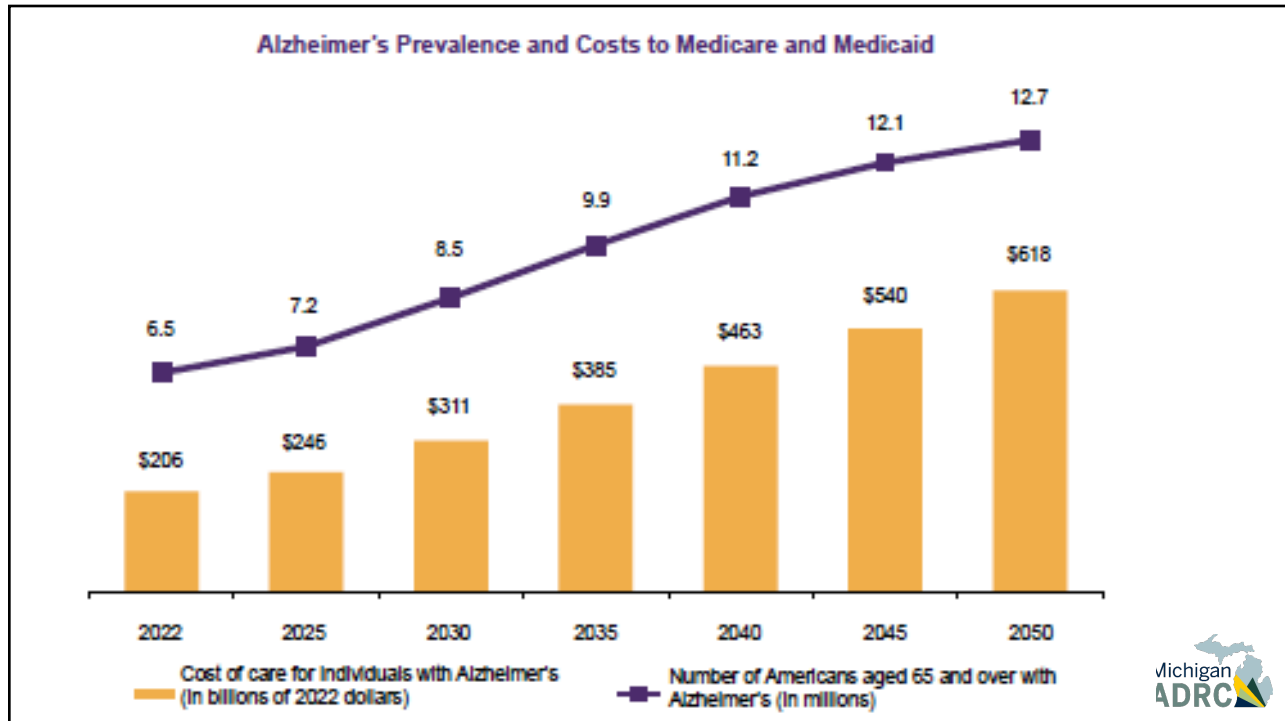
Dementia
An 'umbrella' term used to describe a range of symptoms associated with cognitive impairment

Category	Prevalence
Alzheimer's	60%-80%
Vascular	10%-40%
Lewy Bodies	10%-25%
Frontotemporal	~10%
Mixed Dementia (=> 1 Neuropathology)	Prevalence ~50%

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Alzheimer's Disease History

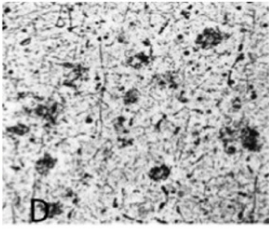
- Auguste D was 51 years of age when she met Dr. Alzheimer and 55 when she died in 1906
- In his writings he described common AD symptoms
- At autopsy, he described the now classic hallmarks of Alzheimer's disease
- In 1910, Kraepelin wrote the condition should be named after his student, Alzheimer










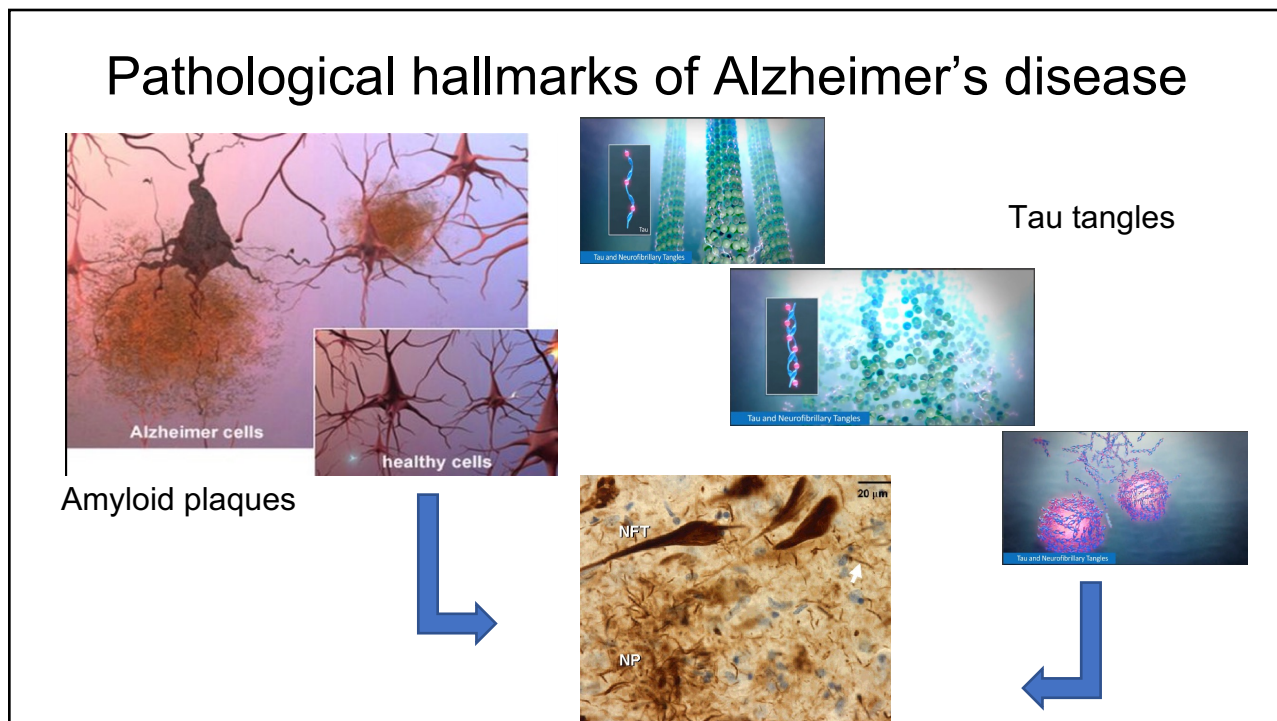
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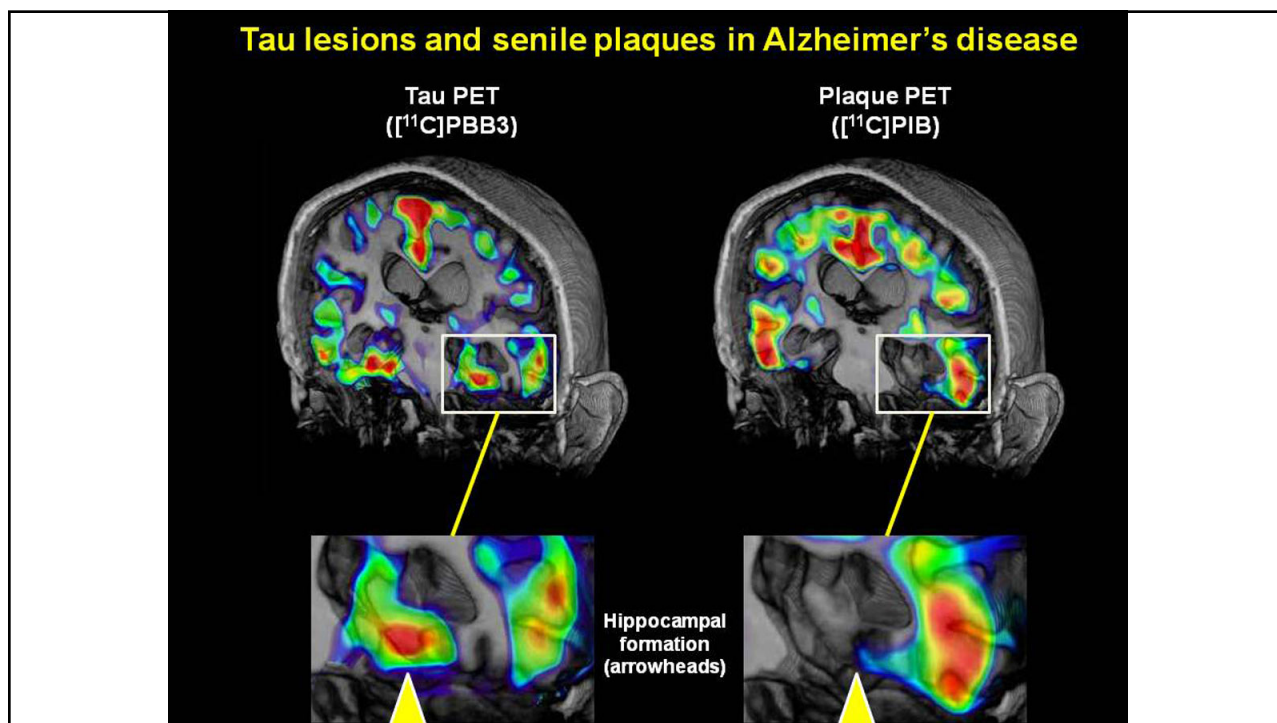
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New Research Findings

AAIC 2022



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Background and Lifestyle



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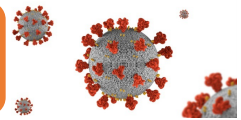
New Insights into Cognition & Covid-19 Pandemic

Persistent loss of sense of smell may be better predictor of long-term cognitive a functional impairment than severity of COVID-19 disease

Hospitalization in the intensive care units was associated with double the risk of dementia in older adults,

During the pandemic, female gender, not working, and lower socioeconomic status were associated with more cognitive symptoms

Positive life change during the pandemic (e.g., more quality time with friends/family or spending more time in nature) reduced the negative impact of the pandemic on memory and thinking skills



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ALZHEIMER'S ASSOCIATION **AAIC>22** ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®
JULY 31-AUG. 4 > SAN DIEGO, USA, AND ONLINE

AGING IN HOMELESS POPULATIONS

Margot Kushel MD
Professor of Medicine UCSF
@Mkushel



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Homelessness is common around the world



580,000 people on a single night in the United States

Over 700,000 people on a single night in Europe

25-35,000 people on a single night in Canada



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High and Rising Prevalence of ADRDs in Homeless Populations

- Due to:
- The aging of homelessness population
 - Shared risk factors between homelessness and ADRDs
 - ADRDs increase the risk of homelessness
 - The direct impact of homelessness on brain health

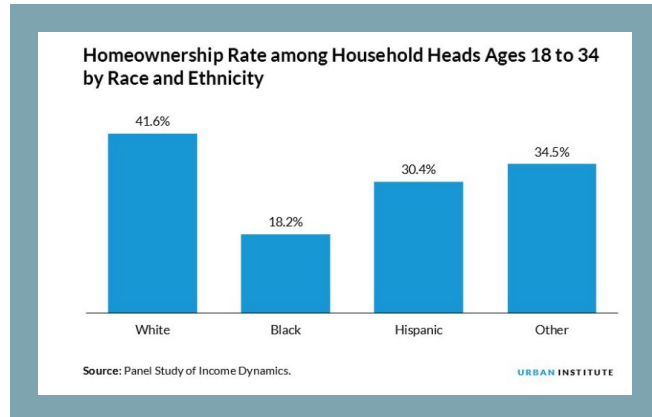


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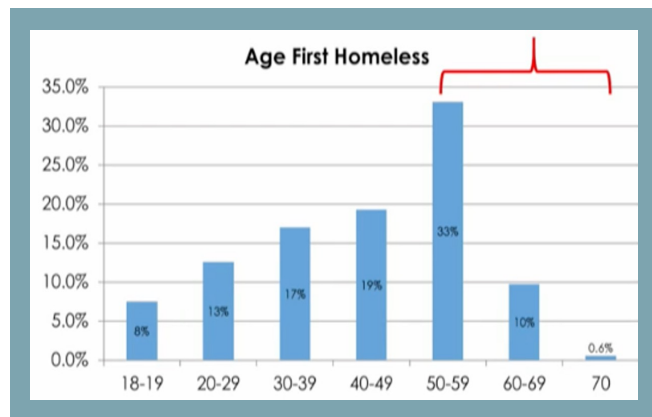
Homelessness is a racial (in)justice issue

Kushel, 2020

- Home ownership is the primary means of wealth building
- Factors contributing:
 - Racial Covenants
 - Redlining
 - Ongoing discrimination in rental markets
 - Predatory lending
 - Criminal justice
 - Employment and educational discrimination



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Brown RT, Goodman L, Guzman D, Tieu L, Ponath C, Kushel MB (2016) Pathways to Homelessness among Older Homeless Adults: Results from the HOPE HOME Study. PLoS ONE 11(5): e0155065. doi:10.1371/journal.pone.0155065

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- Many homeless services are not prepared to serve persons with ADRD
- People experiencing homelessness with ADRD have narrow social networks and often co-occurring psychiatric and substance use disorders
- Need for personal, experienced care; architecture changes; appropriate staffing
- Educate/empower homeless service providers on best practices for ADRD population

Solutions?





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Poorer Cognition among Oldest Old (Super Agers) Linked to Experiences of Discrimination

Lifetime experiences of major discrimination and cognitive decline in diverse cohort of Asian, Black, White, Latino, and multiracial participants

- Average age of enrollment was 93
- Three cognitive assessments over an average of 1.2 years



Three groups based on self-report of major lifetime discrimination

- Group 1: Workplace discrimination (mostly white men)
- Group 2: Little to no discrimination (White women, Asian, Black, and Latino older adults)
- Group 3: Discrimination across several domains (e.g., workspace, financial, housing) (all non-White)


Group 3 had worse semantic memory at baseline

Across groups, no differences in cognitive decline over time

Discrimination has indelible impact on cognitive health

Kristen George,
2002



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Lower SES in Childhood & Persistent Low Wages Linked to Risk for Dementia and Faster Memory Decline

Individuals who experience high socioeconomic stress are significantly more likely to develop dementia compared to individuals of better socioeconomic status, even considering high genetic risk

Lower-quality neighborhood resources and difficulty paying for basic needs associated with lower cognition among Black & Latino individuals

Higher parental socioeconomic status was associated with increased resilience to the negative effects of Alzheimer’s marker ptau-181, better baseline executive function and slower cognitive decline in older age

Compared with workers earning higher wages, sustained low-wage earners experienced significantly faster memory decline in older age

Matthias Klee, 2022; Anthony Longoria, 2022; Jennifer Manly, 2022; Katrina Kezios, 2022



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High blood pressure during pregnancy linked to increased risk of vascular dementia¹

Study of nearly 60,000 women who experienced pregnancy found gestational hypertension² is associated with 2.75x higher risk of vascular dementia

New research presented at the Alzheimer’s Association International Conference (AAIC) 2022

1. Karen Schlep, Ph.D., MSPH, et al. What subtypes are driving the association between hypertensive disorders of pregnancy and dementia? Findings from an 80-year retrospective cohort study (Funders: National Institute on Aging, National Center for Research Resources, National Cancer Institute)

2. Gestational hypertension – high blood pressure in pregnancy – is associated with vascular dementia, a condition characterized by changes in thinking skills that occur as a result of impaired blood flow to the brain.

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Blood-Based Biomarkers (BBMs)



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PROGRESS TOWARDS A BLOOD TEST

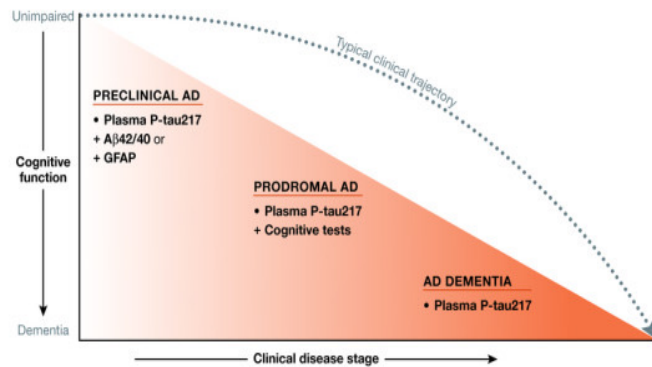
- Global race to uncover and develop blood based biomarkers for Alzheimer's and other dementia
- More research validating amyloid beta and tau in blood by comparing to imaging and cognitive testing
- New research on blood tests for alpha synuclein and neurofilament light and other markers
- But, a little bit like the "wild west"



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Most Studied Types of plasma BBMs

- Plasma amyloid-beta 42/amyloid-beta 40 (A β 42/A β 40)
- Phospho-tau (p-tau)
- Neurofilament light (NfL)
- Glial fibrillary acidic protein (GFAP)
- Potential combinations of markers



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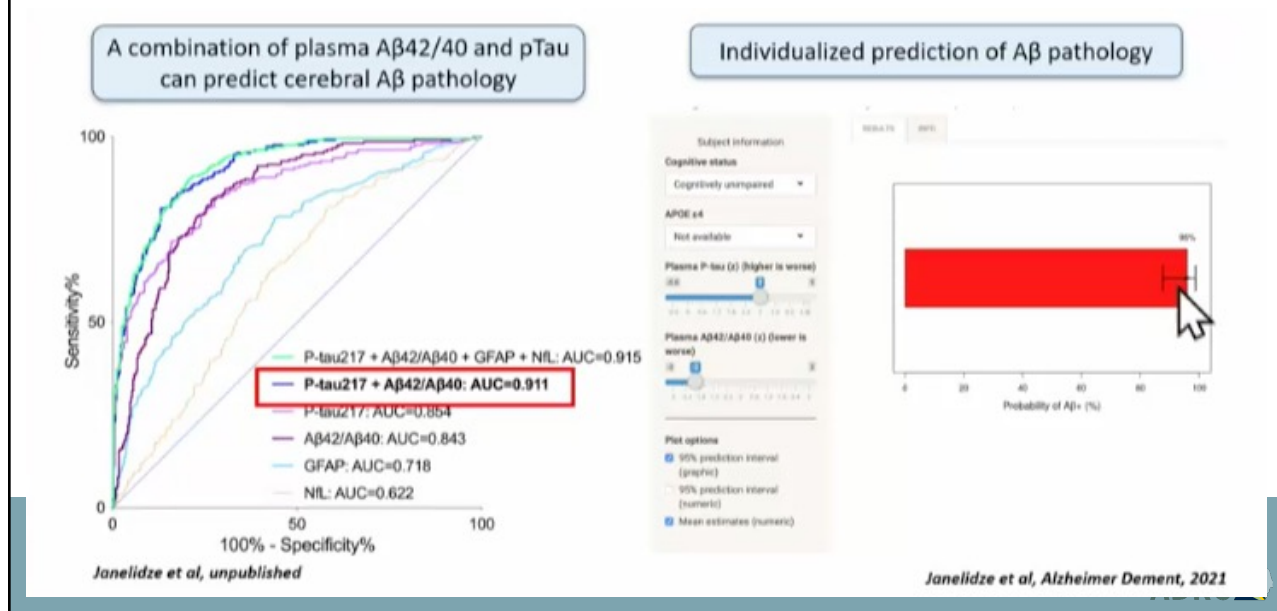
Alzheimer's Association Global Workgroup Recommendations

- Perform prospective studies in primary care settings, including representative and diverse populations with cognitive symptoms
- Evaluate the causes of false positives and negatives
- The reference standard must be of high quality and preferably include CSF or PET
- Study whether BBMs outperform what is already available today in primary care, and if they also improve diagnosis and management, including treatment decisions
- Gain better understanding of biological and disease-associated variability and potential impact of medical comorbidities and concomitant medications.
- Learn whether certain BBM-based algorithms can be used alone to support an Alzheimer's diagnosis, or should they only be used as a gatekeeper to CSF/PET.
- Eventually (a) perform head-to-head comparisons of different plasma biomarker assays, and (b) establish the most optimal combinations of easily accessible biomarkers, (c) assess test-retest variability



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Combination of plasma biomarkers in NC



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Clinical Trials



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EXERT Trial



It has been shown that exercise increases both anti-inflammatory activity and release of nerve growth factors

Phase 3 study of exercise in older adults with mild cognitive impairment (MCI).

Conducted during COVID-19 pandemic, but 80% completed full study

After 12 months, both aerobic intervention and stretching arm showed no cognitive decline

Comparison group of MCI From ADNI showed significant cognitive decline over 12 months

Regular physical activity, even modest or low exertion may protect brain cells



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Other Clinical Trials

- ADAD Columbia Prevention Study, Phase 3—Crenezumab (Roche) study was negative
 - Did show that family cohort of 6,000 people in Colombia with high incidence of younger onset, genetic version of AD was uniquely suited for prevention trials, because age of onset highly predictable in a under-studied and under-represented population
- Phase 2 trials of T3D-95 (T3D Therapeutics) positive interim results, with final results in 2023
 - Overcoming insulin resistance in brain to restore metabolic brain health
- Brexpiprazole for Agitation in AD in Phase III in 12-week study of anxiety, third trial to show success and will apply FDA for approval
- ALZ-NET announced by the Alz Association as a platform to collect long-term clinical and safety data from persons treated with FDA-approved AD therapies in real world settings (as more drugs are approved)



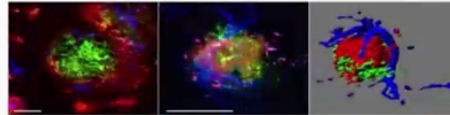
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Subcutaneous gantenerumab, a fully human anti-A β monoclonal antibody in development for Alzheimer's disease¹

Highest affinity for aggregated A β including oligomers, fibrils and plaques^{2,3}

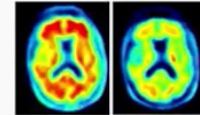
Clearance of aggregated A β

Microglia-mediated phagocytosis²



Triple labelling of microglia (blue) adjacent to gantenerumab (red) bound to A β deposits (green)

Amyloid plaque removal⁴



PET SUVR reduction following 1 year of gantenerumab treatment

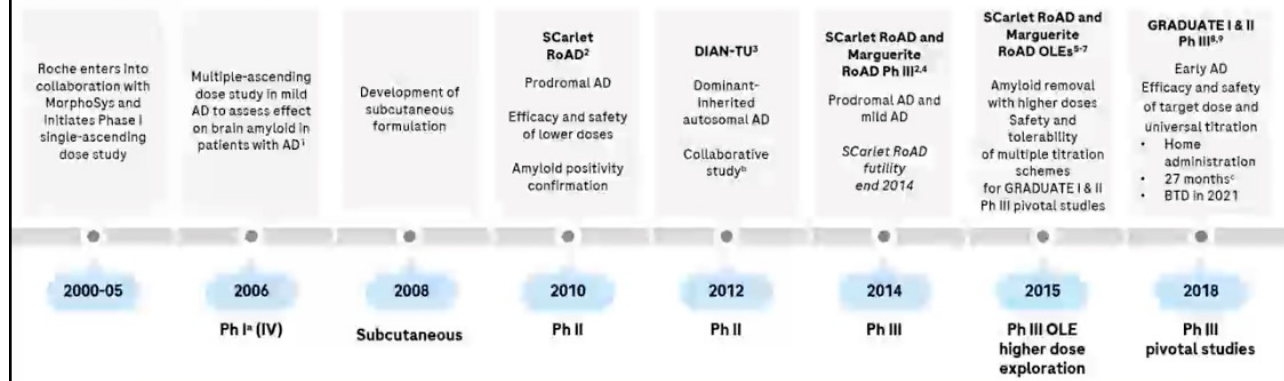
Gantenerumab has shown downstream effects on multiple biomarkers of AD pathology and neurodegeneration in clinical trials^{5,6}

A β , amyloid-beta; AD, Alzheimer's disease; IgG, immunoglobulin; PET, positron emission tomography; SUVR, standardised uptake value ratio.
 1. Doody R. J *Prev Alzheimers Dis* 2017;4:264-272; 2. Bohrmann B, et al. *J Alzheimers Dis* 2012;28:49-69; 3. Chen Y, et al. *ACS Chem Neurosci* 2020;11:3233-3244;

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Gantenerumab clinical development programme

Nearly two decades of continued learning and knowledge generation, combining science and patient focus



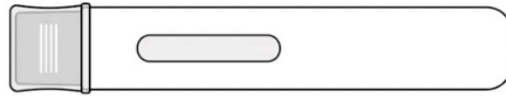
Results of the GRADUATE I and II studies are expected in Q4 2022

AD, Alzheimer's disease; BTD, breakthrough designation; DIAN-TU, The Knight Family Dominantly Inherited Alzheimer Network Trials Unit; IV, intravenous; OLE, open-label extension; Ph, Phase.
^aGantenerumab has been studied in single- and multiple-dose Phase I clinical trials. ²Sponsored by Washington University School of Medicine, co-funded by Eli Lilly and Company, F. Hoffmann-La Roche, Alzheimer's Association, National Institute on Aging, GHR Foundation, anonymous organisation, Avid Radiopharmaceuticals, and Accelerating Medicines Partnership. ³GRADUATE studies could be extended to 30 months in total, in the event that COVID-19-related interruptions in dosing and other study procedures worsen significantly. 1. Ostrowitzki S, et al. *Arch Neurol* 2012;69:198-207; 2. Ostrowitzki S, et al. *Alzheimers Res Ther* 2017;9(1):95; 3. Salloway S, et al. *Nat Med* 2021;27:1187-1196; 4. Voyle N, et al. Presented at AAIC 2018, Chicago, IL, USA; 5. Klein G, et al. Presented at AAIC 2018, Chicago, IL, USA; 6. Abi-Saab D, et al. Presented at AAIC 2018, Chicago, IL, USA; 7. Andjelkovic M, et al. Presented at AAIC 2018, Chicago, IL, USA; 8. Pross N, et al. Presented at AD/PD 2019, Lisbon, Portugal; 9. Data on file.

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Development of autoinjector conducted in parallel to GRADUATE I and II

Results of ongoing studies available in 2023



Quick and easy
to use
autoinjector

Enables non-HCP
care partner
administration in
different settings
from start
of treatment

Injection time
<15 sec

Injection volume
<2 mL

Increasing flexibility for patients and families

HCP, healthcare practitioner.

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What Is on the Horizon for AD Treatments?

• Taking Aim at Placques

• Recruiting the immune system

- Monoclonal antibodies may prevent AB from clumping into plaques or remove AB plaques, mimicking antibodies produced naturally by the immune system in response to foreign invaders or vaccines
- June 2021, FDA approved aducanumab
- Lecanemab and Donemab successful in Phase II and moving to Phase III trials
- Solanezumab did not demonstrate benefit with mild or moderate AD, but being evaluated in preclinical stage of disease

• Prevent Destruction

- Saracatinib (possible cancer treatment) in mice turned off protein to allow synapses to start working again and treatment trials underway in humans

• Production Blockers

- To reduce amount of AB formed in the brain from APP (precursor protein on the cells) by inhibiting beta- and gamma-secretase
- Beta-secretase inhibitors did not work in mild or moderate AD and significant side effects

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What Is on the Horizon for AD Treatments (2)?

Keep Tau from Tangling

- Tau aggregation inhibitors and tau vaccines being studied

Reduce Inflammation

- AD causes chronic, low-level brain cell inflammation
- Sargramostim (Leukine) may stimulate immune system to protect brain from harmful proteins

Insulin Resistance

- Insulin changes in the brain may be related to AD
- Insulin nasal spray wasn't effective, but other approaches being considered



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What Is on the Horizon for AD Treatments (3)?

Studying the Heart-Head Connection

- Risk for dementia increases as a result of many conditions that damage heart or arteries (e.g., high BP, heart disease, diabetes, high cholesterol)
- Do drugs (e.g., blood pressure medications) now used to treat vascular disease may also be beneficial AD or reduce the risk dementia
- New drugs under development that look for new targets at the molecular level
- Lifestyle choices with known heart benefits (e.g., special diets, exercise) are being studied

Hormones

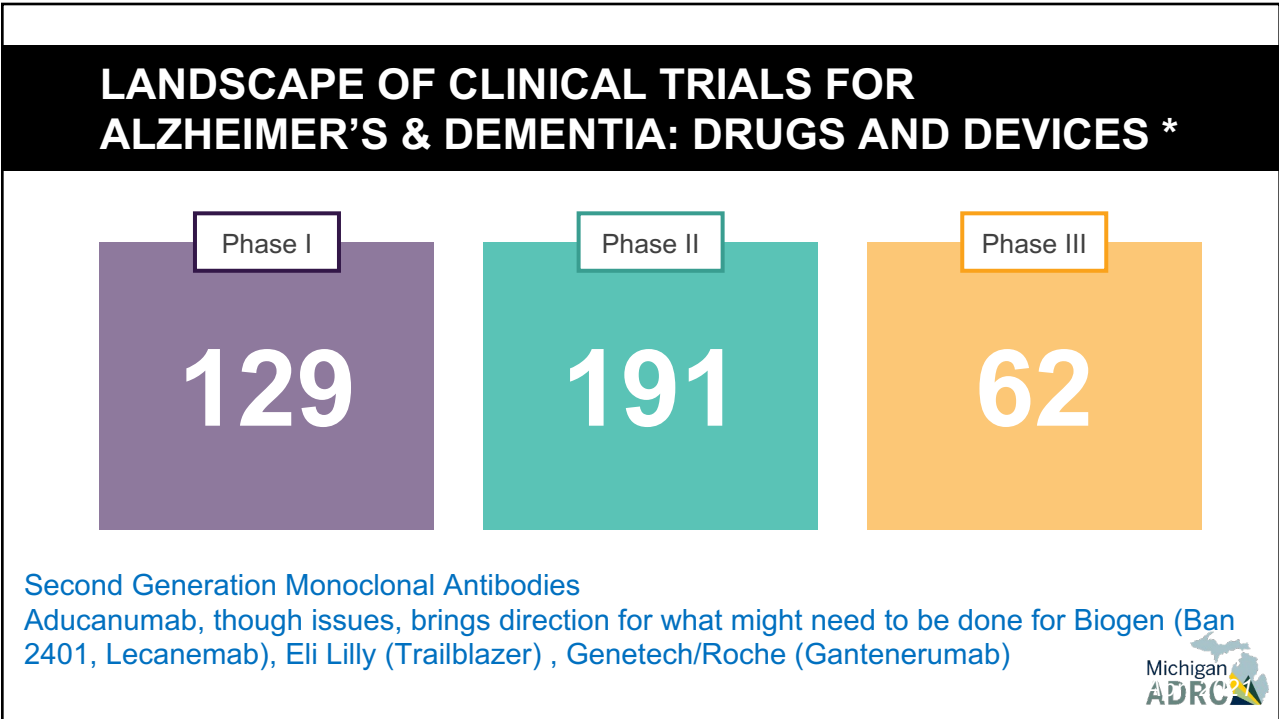
- Taking estrogen-based hormone therapy for at least a year during perimenopause or early menopause appeared to improve memory and thinking in women at high risk for AD, but further research has been conflicting

Speeding Treatment Development

- Coalition Against Major Diseases (CAMD), alliance of pharma, companies, nonprofits, and government forging partnership to share data
- CAMD collaborating with Clinical Data Interchange Standards Consortium (CDISC) to create data standards



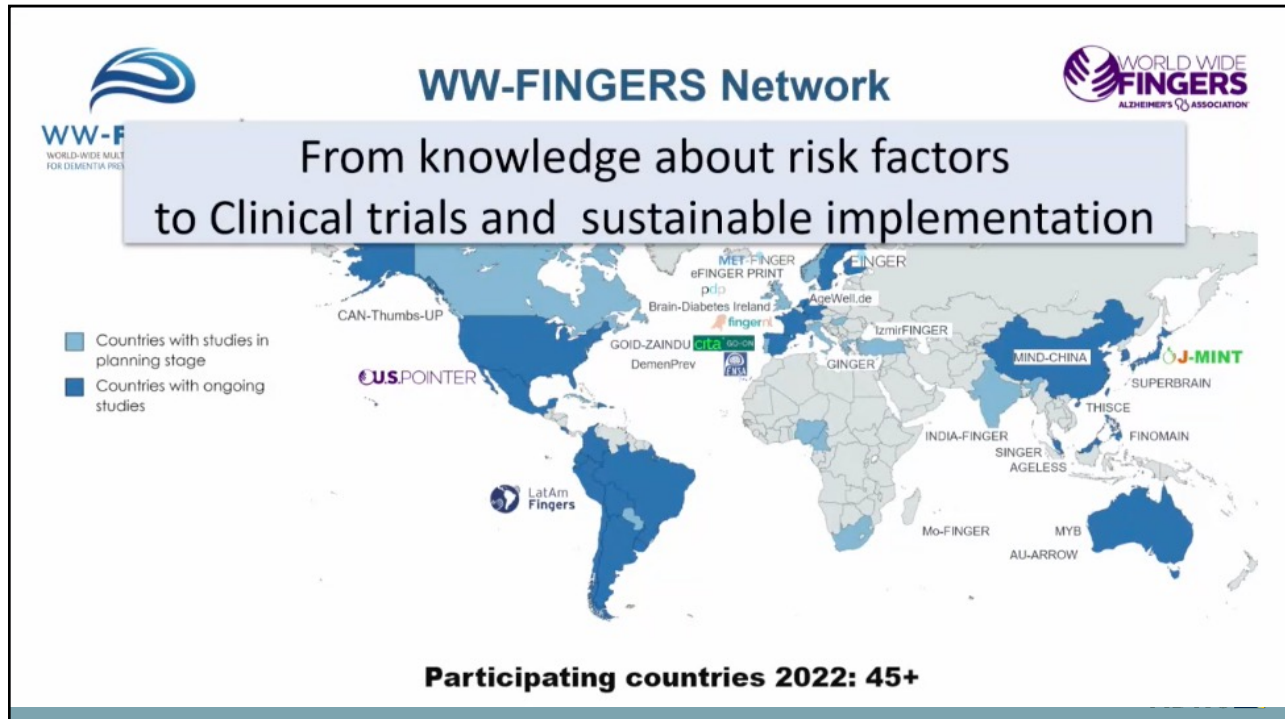
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South Korea – Super Brain Program

Effect of SUPERBRAIN With Nutritional Supplements in Amyloid PET positive Early Stage Cognitive Impairment Patients: Cognitive Outcome and Stool Microbiome

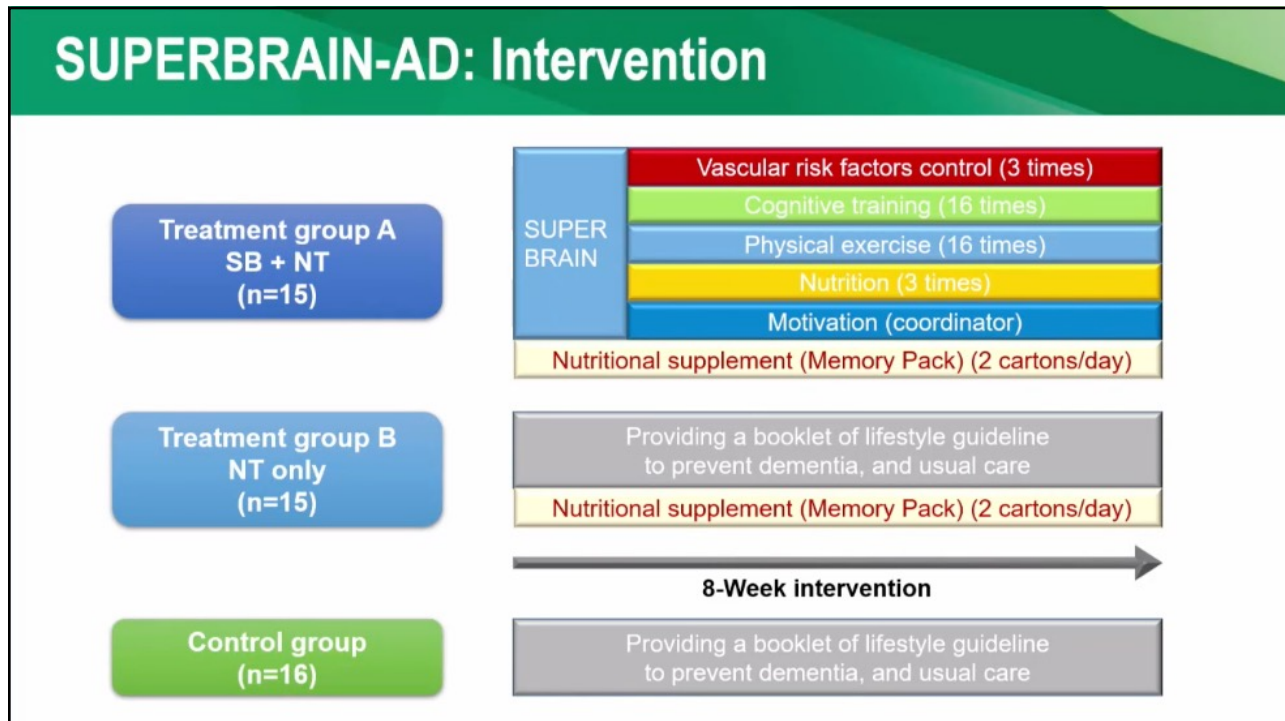
• **SUPERBRAIN:**

The **SoU**th Korean study to **PrE**vent cognitive impai**R**ment and protect **BRAIN** health through lifestyle intervention in at-risk elderly people

Eun Hye Lee, et al., 2022



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Results of SUPER BRAIN-AD Study

Cognition

Group A better than C and in most cases B for Total Ability, Mental Status, Visuospatial Ability, Attention

Physical Performance

Group A showed significant improvements in Sit-to-Stand Time & Short Physical Performance Battery (SPPB)

Gut Measures

Group A showed differences in Complete Gut measures and favoring more diverse gut and better bio flora

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Primary Aim

- Test whether random assignment to 2 years of Self-Guided (SG) versus Structured (STR) lifestyle intervention results in different cognitive trajectories

Design

- Phase 3, multi-center, randomized clinical trial
- 24-month multi-domain lifestyle intervention

Sample

- N=2000
- Cognitively healthy adults aged 60-79 years
- Increased risk for decline (sedentary, suboptimum diet, CVD risk)

Site Infrastructure

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LATam Fingers

OUTCOMES

Primary:
LatAm NTB

Secondary:
Changes in diet,
Physical activity,
Cognitive activity,
Sleep habits,
Mood and CV risk

Flexible lifestyle intervention

Regular medical advisory
One meeting reviewing the recommendations of health care based in guidelines

Months

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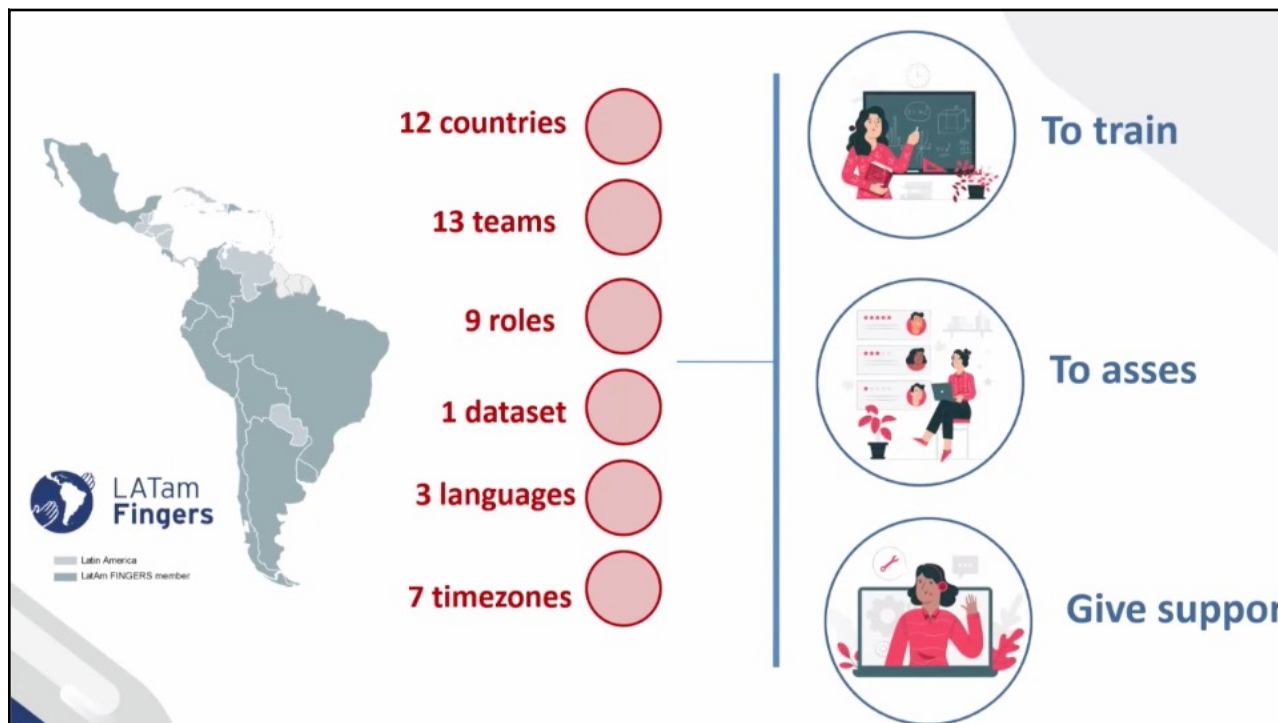
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Systematic lifestyle intervention

- *Physical Exercise:*
4 educational meetings (1 month) + Group exercises on regular basis
- *Nutrition:*
4 educational meetings (1 month) + diet with nutritionist follow up
- *Cognition:*
4 educational meetings (1 month) + computerized regular cognitive training
- *Medical monitoring:*
4 educational meetings (1 month) + individual medical appointments

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AAIC>22 ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE®
JULY 31-AUG. 4 > SAN DIEGO, USA, AND ONLINE

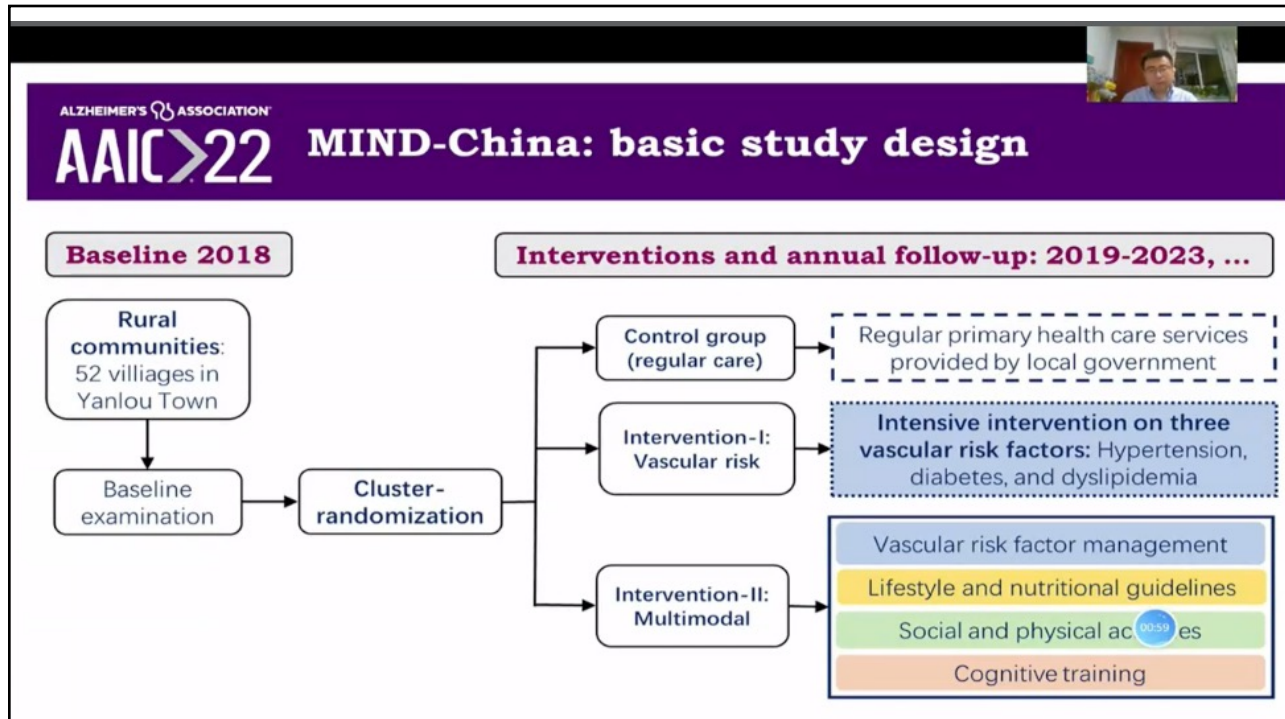
MIND-China: an Update 2018-2021

Yongxiang Wang, Chengxuan Qiu, Yifeng Du,

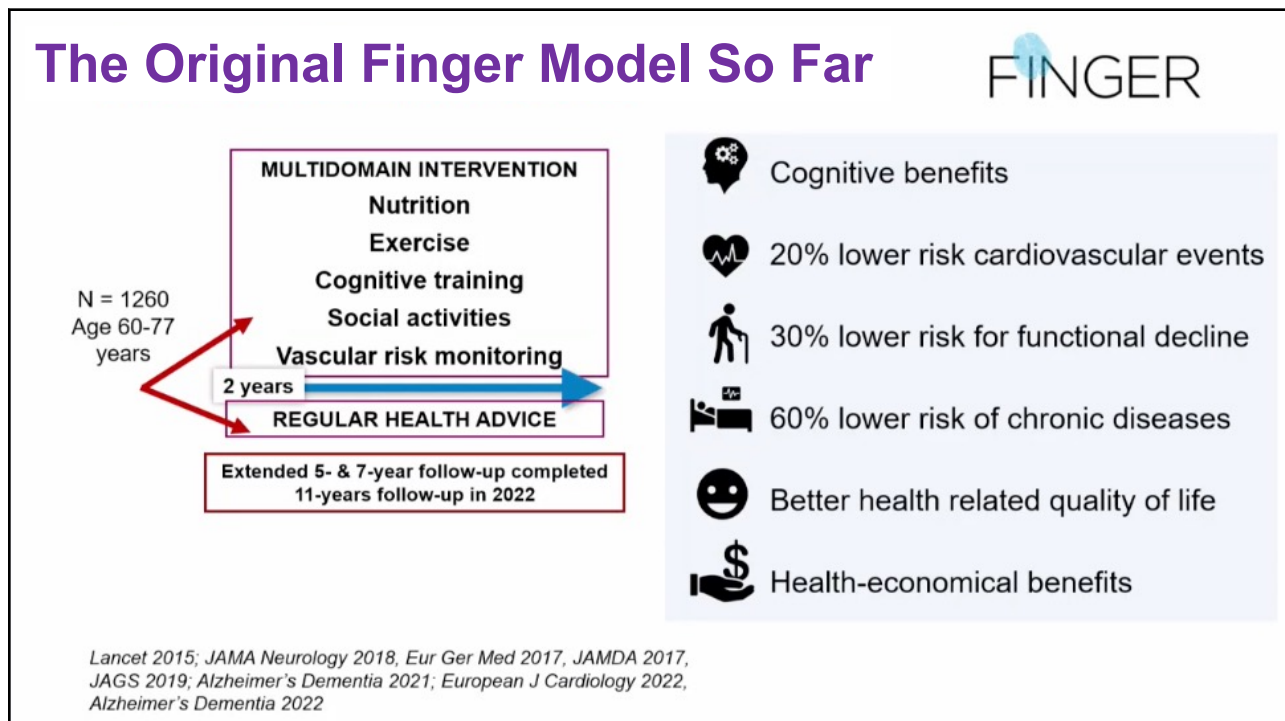
Shandong Provincial Hospital, China
Karolinska Institutet, Sweden

AAIC Annual meeting, Aug 1st, 2022

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Participants

600 participants competitive recruitment

~300 Imperial College London

~100 KAROLINSKA UNIVERSITY HOSPITAL

~200 Finnish institute for health and welfare

- Age 60-79
- Increased risk of dementia based on risk factors and cognitive assessment
 - CAIDE score ≥ 6
 - Average or slightly lower cognitive performance (MoCA – CERAD Word list)

Metformin/Placebo:




- Increased risk of diabetes based on Elevated adiposity OR Impaired fasting glucose
- No diabetes/metformin contraindications


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Take-Home Phrases Heard a Lot at AAIC 2022

Hope and Looking Forward

- Research to Implementation
- Social determinants of health
- Inclusive science—risk from all angles and for all individuals
- Treatment and Care Methods
- Early Detection Tools and Technologies
- Strategies for Risk Reduction
- Strategies for Treatment and Cures in the Future



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Michigan Alzheimer's Disease Research Center (MADRC)

Connecting across the region...

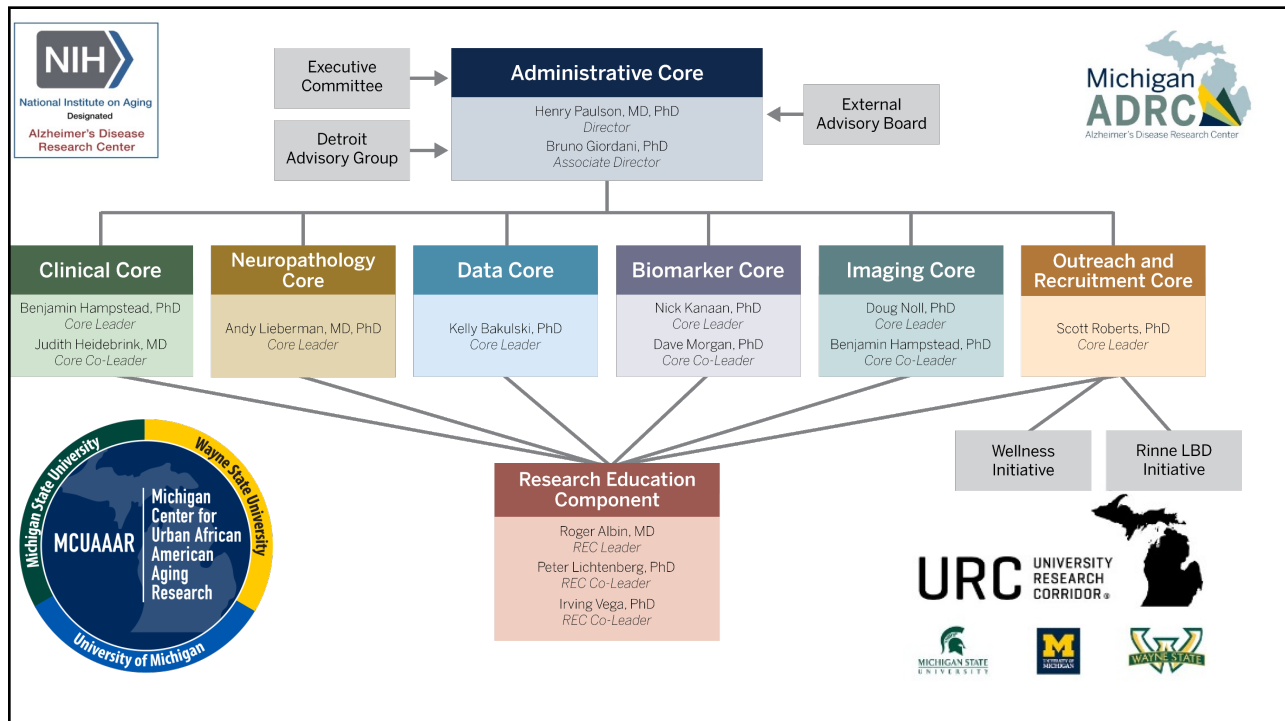
MICHIGAN ADCC UNIVERSITIES

- 1 University of Michigan: Ann Arbor, MI
- 2 Wayne State University: Detroit, MI
- 3 Michigan State University: East Lansing and Grand Rapids, MI

MICHIGAN ADCC OUTREACH

- 1 Michigan Great Lakes Chapter: Chelsea, MI
- 2 Greater Michigan Chapter: Southfield, MI
- 3 Northwest Ohio Chapter: Toledo, OH

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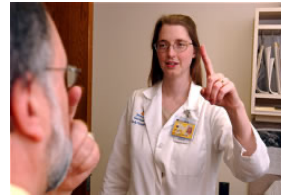
University of Michigan Memory & Aging Project (UM-MAP)

- The information gathered will help researchers develop new strategies to prevent neurological disorders
- The UM-MAP study helps researchers learn more about normal memory changes and about specific diseases that cause dementia



We need you!

- ✓ Over 55 years old
- ✓ Volunteers with and without memory concerns are important



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The SuperAging Research Initiative

What contributes to excellent memory in older age? We need your help to find out!

You may be eligible if:

- Age 80 or over
- Cognitively healthy and actively engaged in life
- Fluent in English

What is involved?

- Visiting our Center every 2 years
- Thinking and memory tests
- Surveys and questionnaires
- Blood collection
- MRI brain scan (if eligible)

If you would like to learn more or volunteer, please contact us at 734-936-5985 or superagingUM@med.umich.edu



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Diverse VCID

Using advanced brain imaging and blood-based techniques to better understand how vascular changes cause brain injury and cognitive decline, especially in racially diverse communities



You may be eligible if:

- Age 80 or over
- Cognitively healthy and actively engaged in life
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What is involved?

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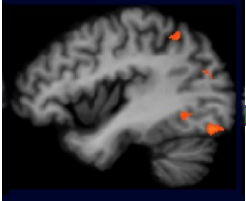
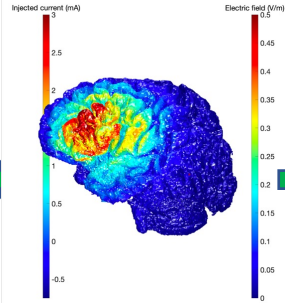


To learn more, visit michigan.myhealthybrain.org or contact us at 734-615-8378


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Overcoming Barriers: Brain Stimulation To Go!

- Use patient's MRI scan to determine target & create personalized headgear
 1. Acquire MRI
 2. Create individualized brain model
 3. Create individualized headgear & train informant to administer
 4. At home HD-tDCS!



→

→

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*patent submitted

<https://www.makingitcount.voyage/blog>

Now delivering stimulation around the state of Michigan!

<https://hamostead.lab.medicine.umich.edu/home>

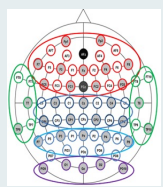


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Feature Selection for MCI vs. Control

Features	Frequency
regional PLI between RF and LC	1
One Card Learning	0.83
degree divergence	0.76
Dimensional Card Sorting	0.74
Picture Sequence Memory	0.55
regional PLI between RF and RP	0.21
regional average PLI for RF	0.19
leaf fraction	0.05
maximum vertex degree	0.02
Pattern Comparison	0.02
One Back-Working Memory	0.02



Požar R, Giordani B, Kavcic V: Effective differentiation of mild cognitive impairment by functional brain graph analysis and computerized testing. PLoS One 15(3): e0230099, 2020. PM32176709/PMC7075594

Kavcic V, Daugherty AM, Giordani B: Post-task modulation of resting state EEG differentiates MCI patients from controls. Alzheimers Dement (Amst) 13(Micr)12153, 2021. PM33665343/PMC7896632



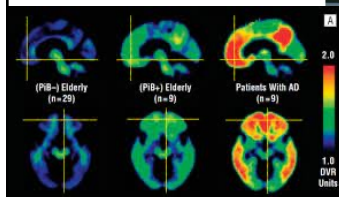
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Are you currently 65 or older, and drive at least twice per week?

If so, you may be eligible to participate in a research study looking at the relationship between driving and cognition over time.

Participants will be compensated up to \$1,050 over 2 years.

Please Contact Cameron at 734-232-0128



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But we also do more than research!



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M | RINNE LEWY BODY DEMENTIA INITIATIVE

- Statewide initiative to increase awareness of Lewy body dementia among healthcare professionals and the public
- 5 monthly support groups across the state
 - Ann Arbor, Lansing, Brighton, Harbor Springs, Boyne City
- Annual educational lectures
 - Upcoming lecture on October 29 in Ann Arbor by Melissa Armstrong, MD, MSc of the University of Florida: “Lewy Body Dementia Basics & What to know about Hospitalization in LBD”
- Awarded Lewy Body Dementia Research Center of Excellence from the Lewy Body Dementia Association



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M | MICHIGAN BRAIN BANK

- Brain donation program available to research participants and patients of the U-M clinic
- Researchers can learn more about disease mechanisms
- Participants receive the autopsy report which can help families understand their loved one's disease



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Caregiver Wellness Initiative

- Stress resilience and wellbeing programs for family caregivers
- Monthly programs, retreats, and courses
- Newly launched statewide THRIVE network
 - Bringing programs to all of Michigan, including online
 - thrivenetworkmi.org



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Wellness Initiative Coordinator



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Contact Us



To get involved in research:

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