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

Keeping your Brain Healthy: Advances in Aging and Alzheimer’s Research

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DISCLOSURES

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

My children have all my money, anyway
Before we go any further…

THANK YOU!

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. What we can take home from all these studies: What are the keyways to Maintain Brain Health
4. Our Michigan Alzheimer’s Disease Research Center
AAIC 2022: San Diego, CA

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

Background on AD
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

The elderly population is growing rapidly and living longer

U.S. POPULATION AGE 65+ (MILLIONS)

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
Pathological hallmarks of Alzheimer’s disease

Amyloid plaques

Tau tangles

Tau lesions and senile plaques in Alzheimer’s disease

Tau PET ([11C]PBB3)

Plaque PET ([11C]PIB)

Hippocampal formation (arrowheads)
New Understanding of the Disease Course

Asymptomatic Period

- Over 5 years, ~50% will transition to dementia.
- Less than 10% will improve.
- ~40% will remain stable
- Only 1/3 will ever convert to MCI

Mild Cognitive Impairment

- Amnestic
- Non-Amnestic

Dementia of Alzheimer’s Type

New Research Findings

AAIC 2022
Background and Lifestyle

- AAIC 2022

New Insights into Cognition & Covid-19 Pandemic

- Persistent loss of sense of smell may be better predictor of long-term cognitive 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.
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

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

Lifetime experiences of major discrimination and cognitive decline in diverse cohort of Asian, lack, 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 1 had > baseline semantic memory & executive ability compared to Group 2

Group 3 had worse semantic memory at baseline

Across groups, no differences in cognitive decline over time

Discrimination has indelible impact on cognitive health

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
Blood-Based Biomarkers (BBMs)

• AAIC 2022
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”

Most Studied Types of plasma BBMs

- Plasma amyloid-beta 42/amyloid-beta 40 (Aβ42/Aβ40)
- Phospho-tau (p-tau)
- Neurofilament light (NfL)
- Glial fibrillary acidic protein (GFAP)
- Potential combinations of markers
Combination of plasma biomarkers in NC

A combination of plasma Aβ42/40 and pTau can predict cerebral Aβ pathology

Individualized prediction of Aβ pathology

Clinical Trials
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.

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
  - Non-amyloid focused, 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).
Lots of issues with Aducanumab, however, they bring direction for what might need to be done for Biogen (Ban 2401), Eli Lilly (Trailblazer), Genetech (Gantenerumab), although Roche Holding AG just announced (June 16, 2022) Crenezumab did not slow Alzheimer’s symptoms in trials.

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.
What Is on the Horizon for AD Treatments?

• Taking Aim at Placques
  • Recruiting the immune system
    • Monoclonal antibodies may prevent AB from clumping into placques 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

• Prevent Destruction

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
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 of 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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**WW-FINGERS Network**

- Participating countries 2022: 45+

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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 South Korean study to Prevent cognitive impairment and protect BRAIN health through lifestyle intervention in at-risk elderly people

Eun Hye Lee, et al., 2022
Primary Aim
- Test whether random assignment to 2 years of Self-Guided (SG) versus Structured (STR) lifestyle intervention results in different cognitive trajectories

Site Infrastructure
- Academic Medical Centers
- Community Partners
- Alzheimer's Association

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)

LATam Fingers

Flexible lifestyle intervention
- Regular medical advisory
  - One meeting reviewing the recommendations of health care based in guidelines

Outcomes
- Primary:
  - LatAm NTB
- Secondary:
  - Changes in diet,
  - Physical activity,
  - Cognitive activity,
  - Sleep habits,
  - Mood and CV risk

Sistematic lifestyle intervention
- Physical Exercise
  - 4 educational meetings (1 month) + 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
The Original Finger Model So Far

- Cognitive benefits
- 20% lower risk cardiovascular events
- 30% lower risk for functional decline
- 60% lower risk of chronic diseases
- Better health related quality of life
- Health-economical benefits

Risk and Protective Factors – What Can We Do?

Non-modifiable
- Age
- APOE genotype
  - Other primary genetic markers
- Sex

Modifiable
- Education
- Hypertension
- Obesity
- Hearing Loss
- Diabetes
- Smoking
- Diet
- Head injuries/falls
- Physical Inactivity
- Depression
- Stress
- Social isolation

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

Participants

600 participants
competitive recruitment

→ Age 60-79
→ Increased risk of dementia based on risk factors and cognitive assessment
  → CAIDE score ≥ 5
  → Average or slightly lower cognitive performance (MoCA – CERAD Word list)
1. Brain Health Basics

- Watch (monitor and manage) these numbers for optimal brain health
  - Blood pressure
  - Cholesterol
  - Blood Sugar
- Damage to small blood vessels in vulnerable parts of the brain may have direct effects on thinking
  - Higher Bp in young adulthood linked to poorer brain health as early as middle age
  - Lower HDL ("good cholesterol") and higher triglycerides in persons as young as 35 associated with dementia decades later
  - High Blood glucose between ages 51-60 linked to higher risk of future cognitive problems

2. Brain Health Basics

- Have Your Meds Reviewed
  - Review all, regular meds, including over-the – counter
  - At least once a year
    - Drug interactions
    - Older antihistamines
    - Some older antidepressants and overactive bladder meds have been linked to higher dementia risk
  - Regular health screenings (at least yearly) are essential for healthy aging
    - Catch chronic disease early, reduce risk factors for disease
    - Find out the latest tests and advances available
3. Brain Health Basics

• Go for a Hearing Exam
  • Age-related hearing loss linked to an increased risk of cognitive decline
  • Even minor, uncorrected losses seem to contribute
  • Clear that wax
  • Don’t be afraid of hearing aides

• Get your vision checked
  • What goes in tempers what you understand and how you act
  • Poor hearing and vision are risks for isolation, as well

4. Brain Health Basics

• Get Good Sleep
  • Sleeping brains are actually busy brains
    • Solidifying memories and cleaning out toxins
  • 7 hours seems to be that sweet spot
    • Having ≤ six hours of sleep in your 50’s and 60’s leads to higher dementia risk
  • Regular afternoon naps of not more than 2 hours can be helpful, too
    • Associated with better memory and language skills in older adults
  • Oversleep—9 hours or more, could be a sign of a problem
  • Treat Sleep Apnea—CPAPs are not scary; alternative clinics
    Sleep and Depression, together, linked risk of dementia
  • To improve sleep: Have a routine; exercise, but not too close to bedtime; try mindfulness exercises
5. Brain Health Basics

- Take care of your mental health
  - Essential for your overall health and quality of life
  - Feeling anxious or depressed—Get treatment
    - Appears to increase dementia risk and hippocampal shrinkage
    - Mood issues can reduce desire to see friends and family leading to isolation
      - Older adults who are socially isolated or feel lonely are at higher risk for heart disease, chronic lung conditions, depression and cognitive decline
      - In a study of over 3,000 older adults – making new social contacts associated with improved self-reported physical and psychological well-being

Stress, a clear risk factor

- Watch out for stress arising from both positive and negative life events – constant stress is a clear risk factor for dementia
- Constant stress can change brain connections, rewiring the brain and affecting memory and increasing risk of dementia
- Cortisol, the stress hormone, increases steadily after middle-age, which may drive risk for stress-bound problems
- What can you do?
  - Meditation techniques
  - Physical activity
  - Doing things you enjoy
  - Getting some help
6. Brain Health Basics

- Get Moving: Exercise and physical activity
  - Cornerstone of healthy aging
  - Essential tool for maintaining a healthy weight
    - In those over 55, muscle mass better predictor of longevity than weight or BMI
  - 8,000 steps instead of 4,000 associated with a 51% lowering of risk of death in those aged 40 and over
  - Maintaining muscle mass and reducing frailty are critical

Exercise that Body

- Get Enough Physical Activity
- Give Yoga or Tai Chi a Try
- Take a Dance Lesson (or Two)
- Pump Some Iron
Understanding exercise

- We don’t need to be marathon runners, as regular walks in through the neighborhood and grocery store trips may still reduce risk of dementia a bit
  - Moderate and vigorous intensity physical activity is associated with reduced risk
  - Now, even light-intensity physical activity lowers risk (very large study from Harvard Medical school)
  - > exercise = lowered risk, even for those below high/moderate exercise expectations

7. Brain Health Basics

- Healthy eating: Making smart food choices
  - Mediterranean Diet-style eating patterns
    - Fresh produce, whole grains, healthy fats, less dairy and more fish
  - Dietary Approaches to Stop Hypertension (DASH Diet)
    - Limits sodium, saturated fats and added sugars
  - MIND Diet = Mediterranean + DASH
    - Directly tied to cognition
  - Even a small part such as more fish and more leafy greens can improve health outcomes and thereby lower risk
8. Brain Health Basics

- **Quit Smoking**
  - Even those 60 or over who have been smoking for decades get a health advantage
  - If you quit
    - Lowers your risk of cancer, heart attack, stroke, and lung disease
    - Improves your circulation
    - Improves your sense of taste and smell
    - Increases your ability to exercise
    - Sets a healthy example for others
  - Never too late: In one study of 200,000 persons
    - Older adults who quit smoking between 45 and 54 lived about six years longer than those continuing to smoke
    - Those who quit between 55 and 65 lived about four years longer

9. Brain Health Basics

- **Alcohol and other substance use**
  - Drinking among older individuals, especially women, is on the rise
  - Avoid or limit alcohol consumption
    - No more than 2 drinks for men and 1 drink for women per day
  - Other substances can be misused, as well
    - Care with opioids for pain and benzodiazepines for anxiety and sleep
10. Brain Health Basics

- Take up leisure activities and/or hobbies
  - People who take these up may be at lower risk for a host of health problems and dementia
  - Spending an hour reading or engaged in other hobbies significantly decreases risk of cognitive decline as compared to those who spend less than 30 minutes
  - Even pet ownership or spending time with pets has been associated with improved cognition and lower risk of dementia
  - Arts, music, and dance have all been noted to reduce dementia in research studies

Things that are Hard on our Brains

- Smoking
  - Current smokers 34% higher risk in later life for every 20 daily cigarettes
- Junk Food
  - Highly processed foods and those high in saturated fats
    - increase inflammation
- Too Much Alcohol
  - >14 drinks at a sitting linked to brain damage and higher dementia risk
  - Advice is no more than 2 drinks for men per day and one for women
- Air Pollution
  - > fine particle pollutants (auto emissions) linked to dementia risk and increased amyloid
  - Restrict activities if air quality index is over 100
  - Limit fireplace use and keep rooms ventilated
- Accidents
  - Leading cause of both fatal and nonfatal injuries for persons 65 years & up
  - Exercise, fake a fall prevention class or have your house evaluated, review medicines, have your vision checked, get enough sleep
## Keep Your Brain Engaged

<table>
<thead>
<tr>
<th>Make</th>
<th>Make Learning a Lifelong Pursuit</th>
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</thead>
<tbody>
<tr>
<td>Retire</td>
<td>Retire a Little Later (considering what you do)</td>
</tr>
<tr>
<td>Focus on</td>
<td>Focus on Simple acts</td>
</tr>
<tr>
<td>Hang Out</td>
<td>Hang Out with Friends</td>
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<tr>
<td>Practice</td>
<td>Practice Relaxation (Mindfulness)</td>
</tr>
<tr>
<td>Take</td>
<td>Take care of your Physical, Mental, and Cognitive Health</td>
</tr>
<tr>
<td>Keep on</td>
<td>Keep on Walking</td>
</tr>
<tr>
<td>Mix</td>
<td>Mix Things Up—Variety, Variety!</td>
</tr>
</tbody>
</table>

## Mental Activity and Risk of AD

Activities like reading, writing letters, playing cards or doing puzzles may prolong brain health even for those in their 80's

- Those who had the *highest* levels of mental activity developed dementia at 94
- Those with the *lowest* levels developed dementia at 89
- **But**, in 695 autopsies there was no association between mental activity and markers of AD/ADRD
- Keeping mentally active is not a pill to stop the underlying plaques and tangles, but it may be a prescription for cognitive longevity

Wilson et al., 2021
Michigan Alzheimer's Disease Research Center (MADRC)

Connecting across the region...

MICHIGAN ADCC UNIVERSITIES
1. University of Michigan
2. Wayne State University
3. Michigan State University
4. Eastern Michigan University

MICHIGAN ADCC OUTREACH
1. Michigan Great Lakes Chapter
2. Greater Michigan Chapter
3. Northwest Ohio Chapter

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REU Co-Leader

Wellness Initiative
Rinne LBD Initiative

Outreach and Recruitment Core
Scott Roberts, PhD
Core Leader

Michigan Alzheimer's Disease Research Center
McArdle Research Building
University of Michigan

NIH
National Institute on Aging
Alzheimer's Disease Research Center
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

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
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
- 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)

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

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!

https://www.makingitcount.voyage/blog

Now delivering stimulation around the state of Michigan!

https://hampstead.lab.medicine.umich.edu/home


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
But, we also do more than research!

- 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

M | RINNE LEWY BODY DEMENTIA INITIATIVE

Flyers available!
**MICHIGAN BRAIN BANK**

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

Brochure available!

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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

Flyers available!

Laura Rice-Oeschger, LMSW
Wellness Initiative Coordinator

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Contact Us

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