

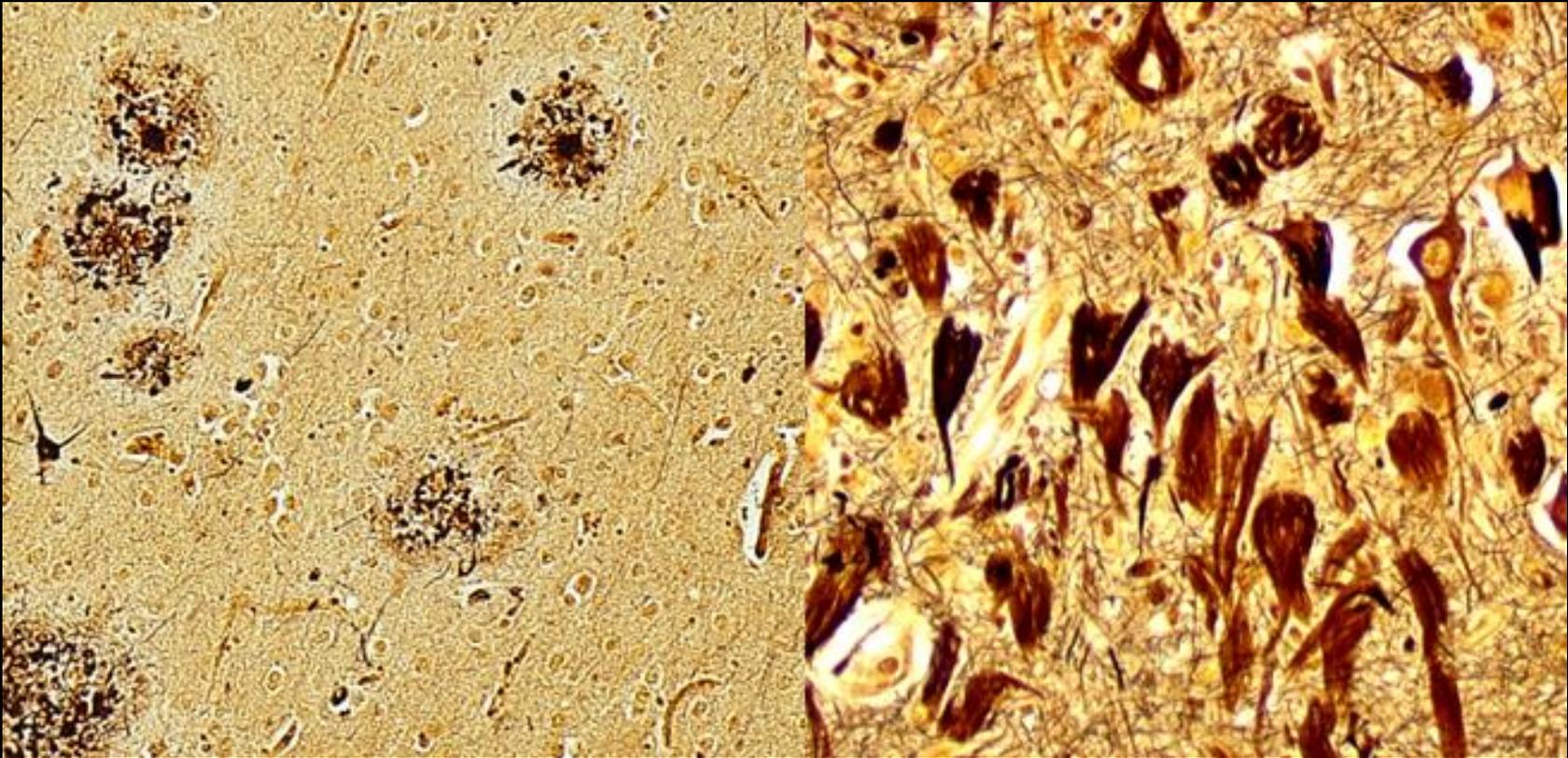
Factors that impact risk for dementia

Barbara B. Bendlin, PhD

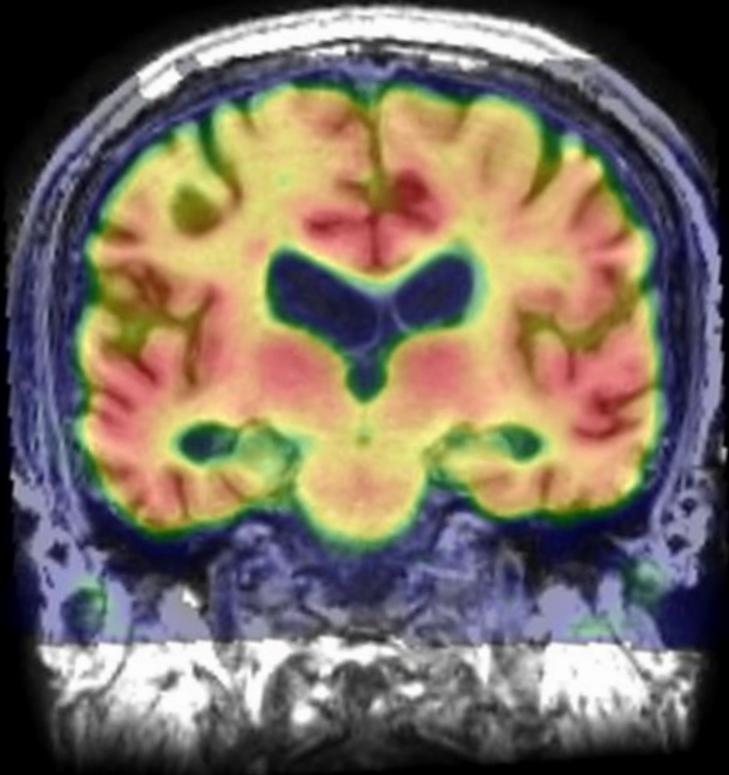
Associate Professor Medicine
University of Wisconsin-Madison



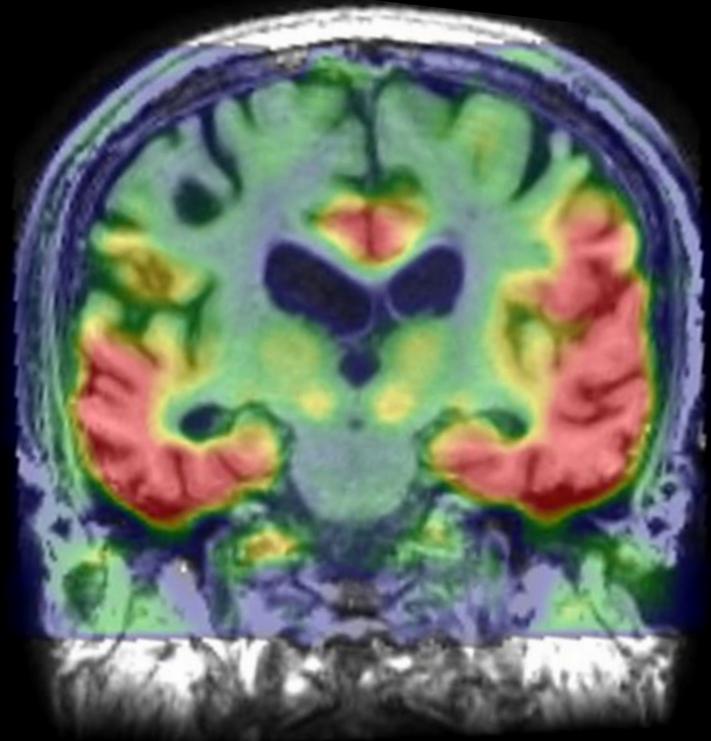
What happens to the brain in Alzheimer's



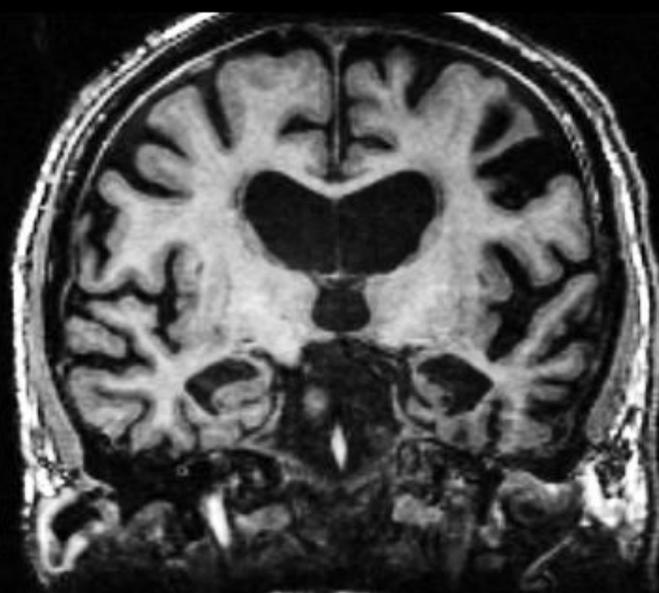
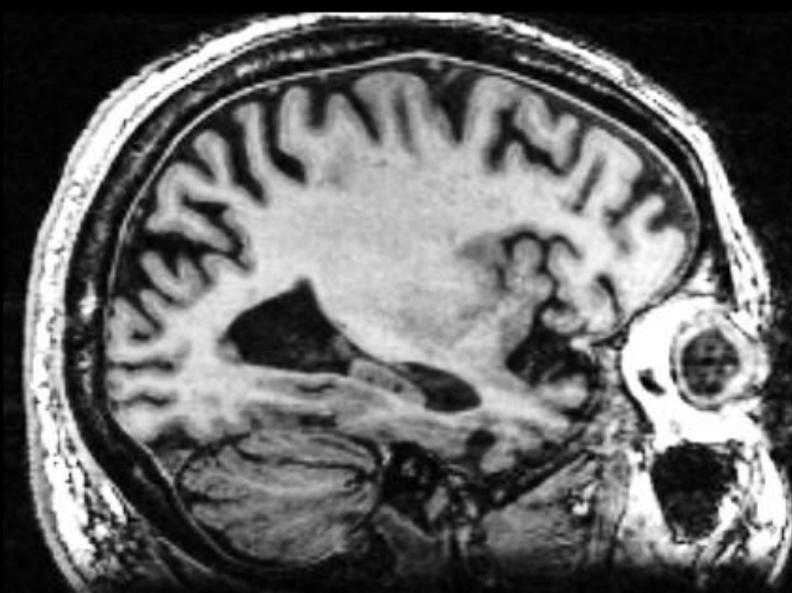
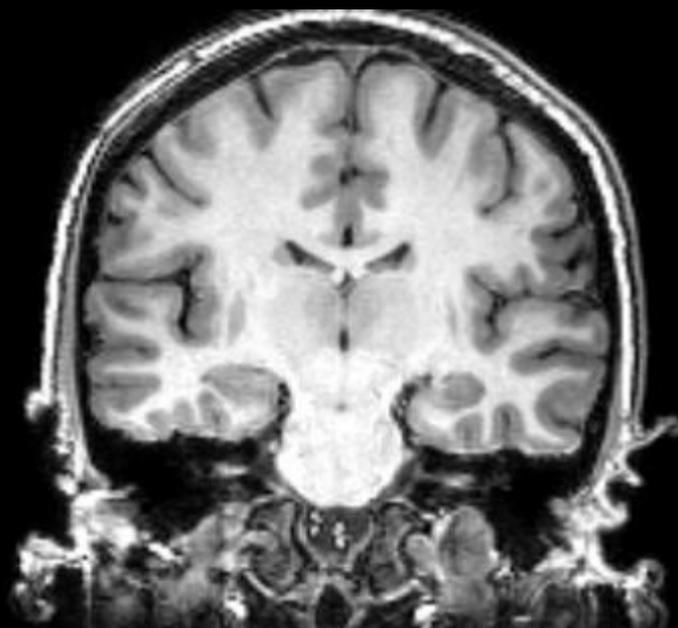
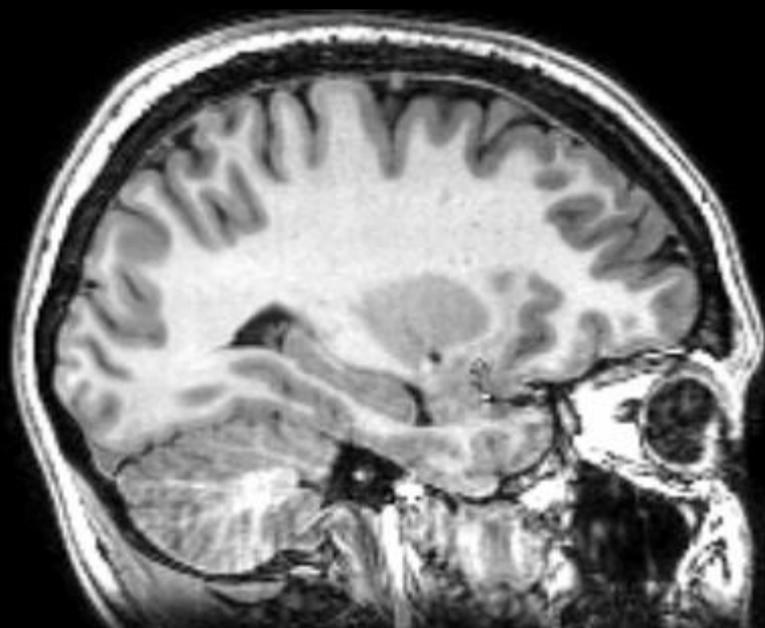
Courtesy Shahriar Salamat, MD PhD



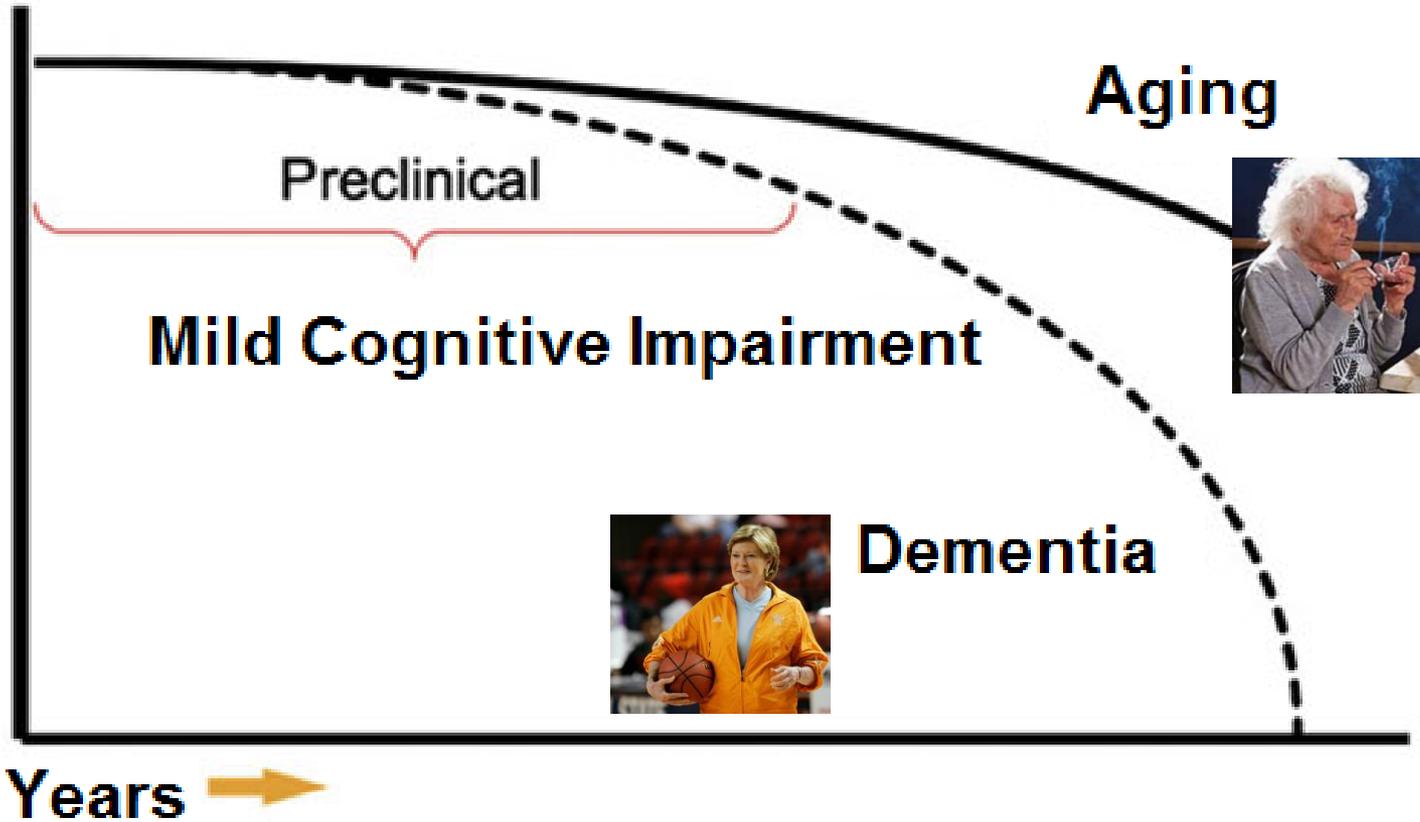
Amyloid Plaque



Tau pathology



Cognitive function





- Genetics
- Parental history
- Age
- Sex
- Race/Ethnicity

- High blood pressure
- Abnormal cholesterol
- Obesity
- High blood sugar
- Exercise
- Diet
- Sleep
- Education
- Cognitive/social engagement
- Air Pollution
- Smoking
- Stress
- Neighborhood



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MRI



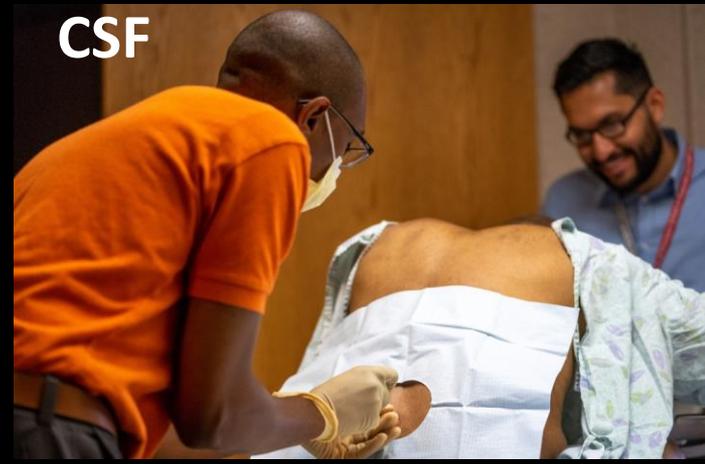
PET



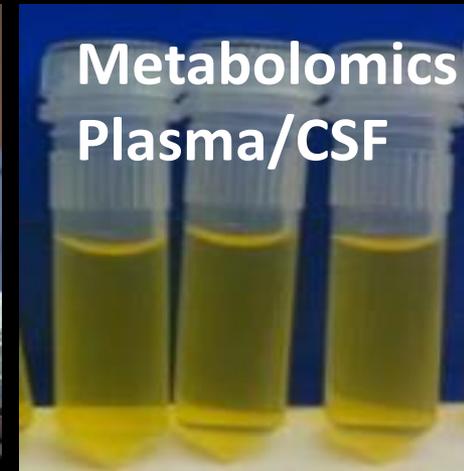
Cognitive Evaluation



CSF

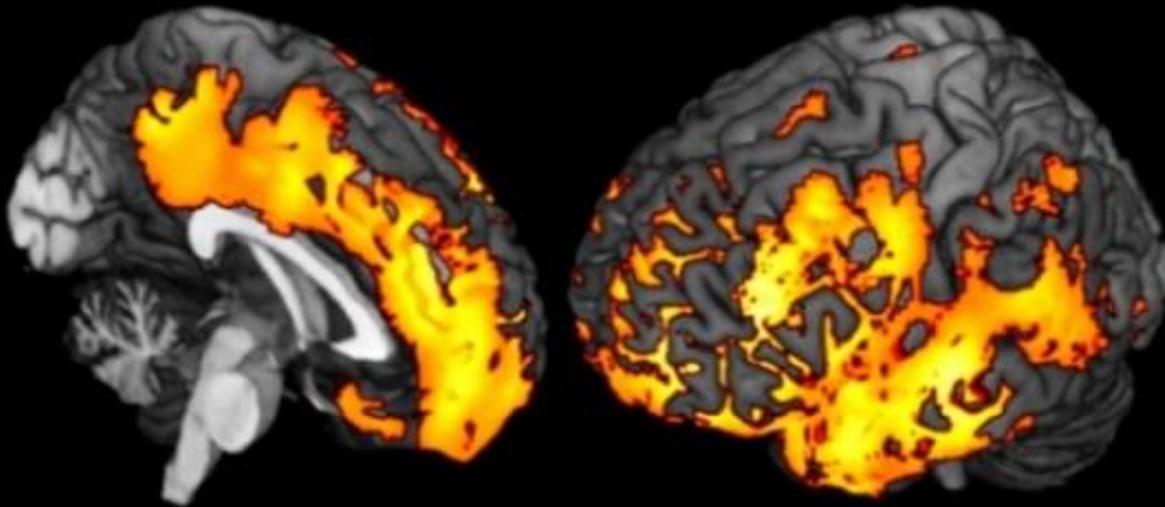


**Metabolomics
Plasma/CSF**



Vascular risk factors at midlife

- High blood pressure
- Abnormal cholesterol
- Central obesity
- High blood sugar and insulin



Low Cerebral Blood Flow is Associated with Lower Memory Function in Metabolic Syndrome

Alex C. Birdsill^{1,2}, Cynthia M. Carlsson^{1,2}, Auriel A. Willette³, Ozioma C. Okonkwo^{1,2}, Sterling C. Johnson^{1,2}, Guofan Xu^{1,2}, Jennifer M. Oh^{1,2}, Catherine L. Gallagher^{2,4,5}, Rebecca L. Kosciak⁶, Erin M. Jonaitis⁶, Bruce P. Hermann⁶, Asenath LaRue⁶, Howard A. Rowley^{2,7}, Sanjay Asthana^{1,2}, Mark A. Sager^{2,6} and Barbara B. Bendlin^{1,2}

Obesity



12 week carbohydrate restricted diet and exercise
intervention to improve brain blood flow

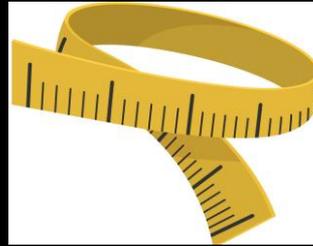
ClinicalTrials.gov Identifier: NCT03117829

- Recruited from the Wisconsin ADRC
- 45 Years to 65 Years
- Pre-diabetic or similar
- Exclusion criteria: active lifestyle (exercise >1 hour/wk)
- Enrolled 29 participants
- Supervised moderate intensity aerobic exercise for 50 minutes 3X weekly
- Unsupervised exercise 2X weekly
- Behavioral change classes 1X weekly
- At the end of the intervention, participants were instructed to maintain the regimen for an additional six months

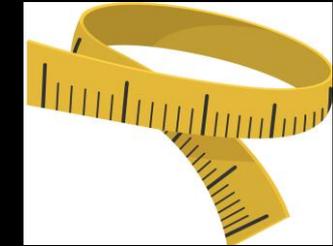




Baseline



Month 3



Month 6



MRI



Cognitive Evaluation



BLOOD LABS



Fitness

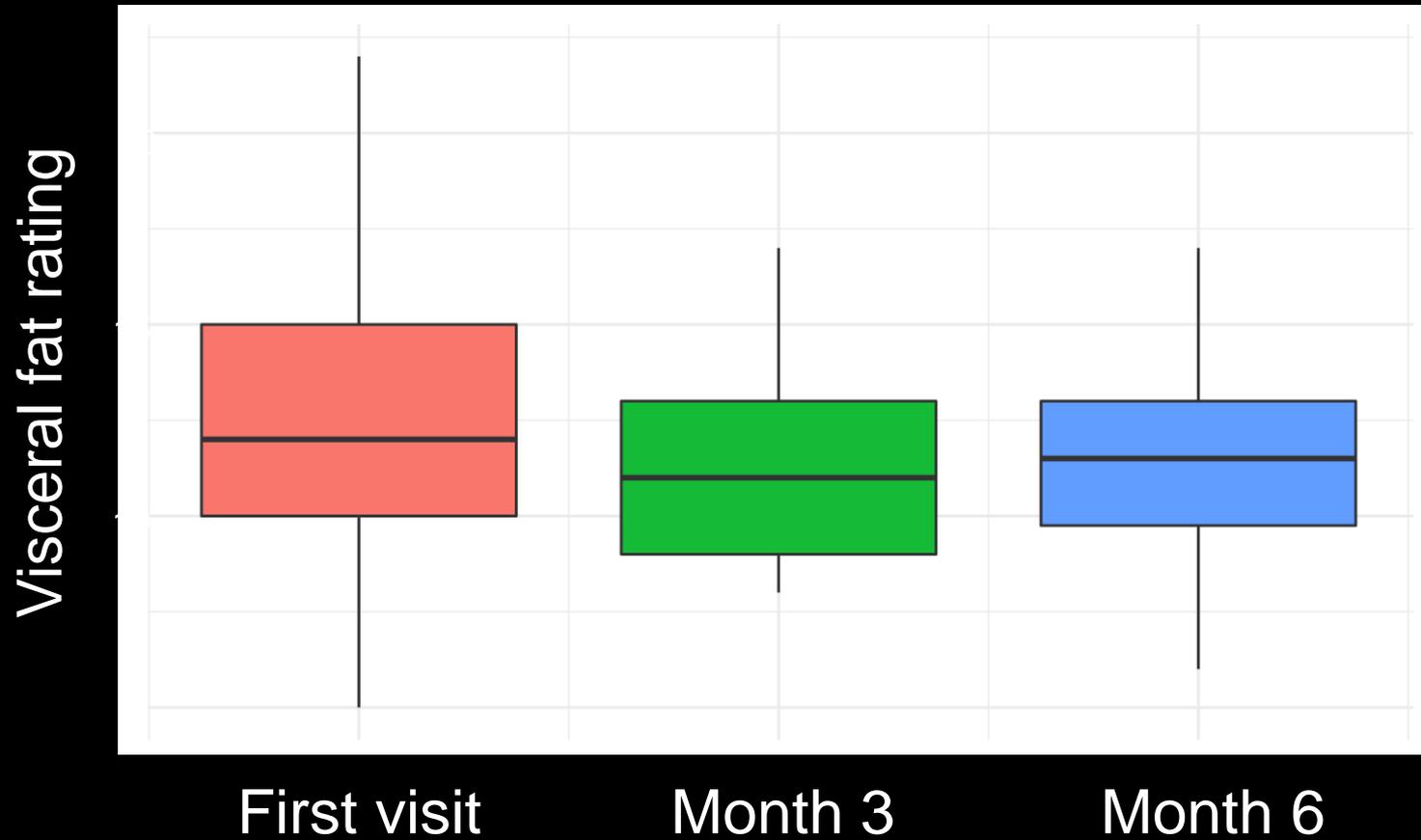


SUPERVISED EXERCISE

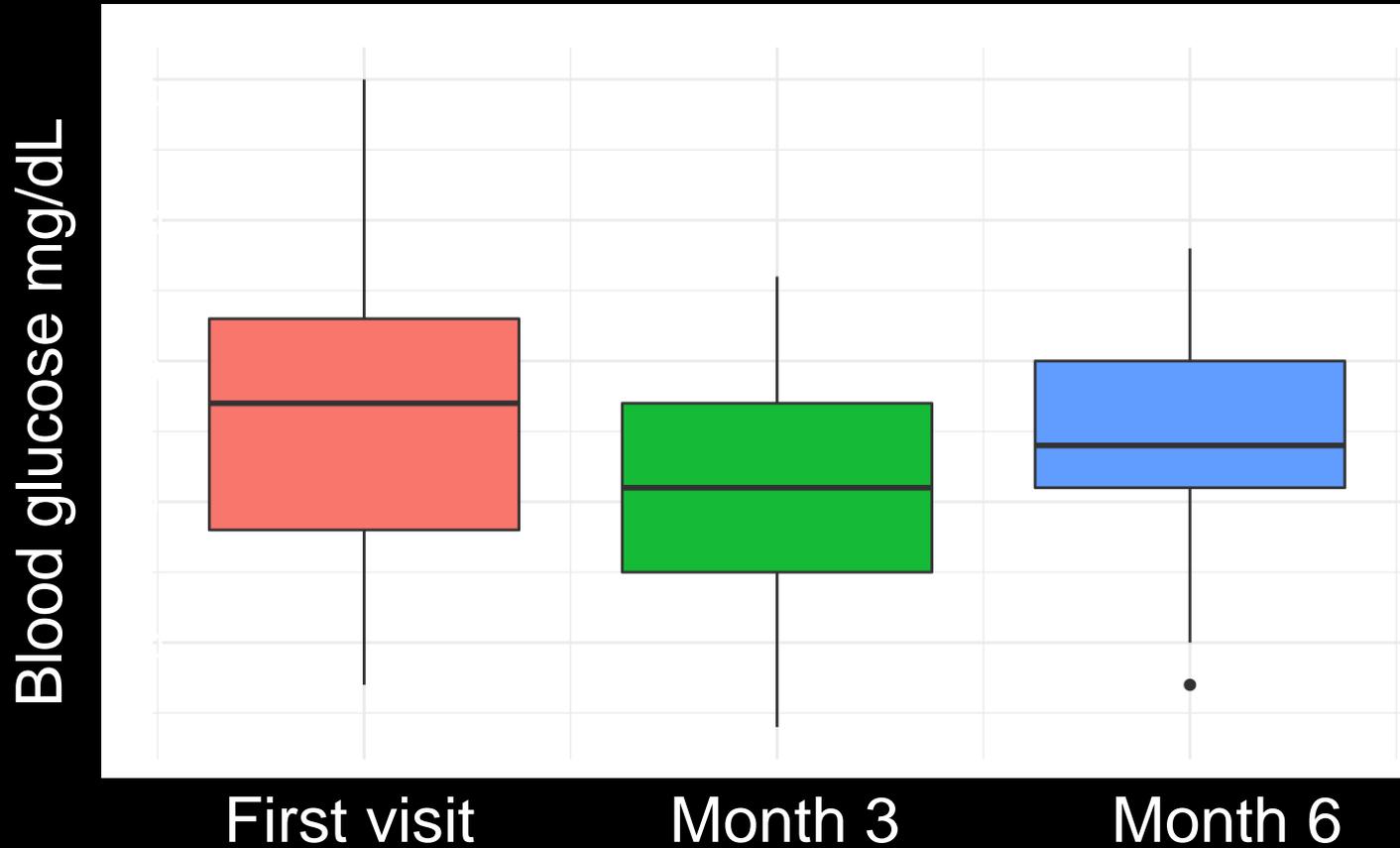


CRD DIET

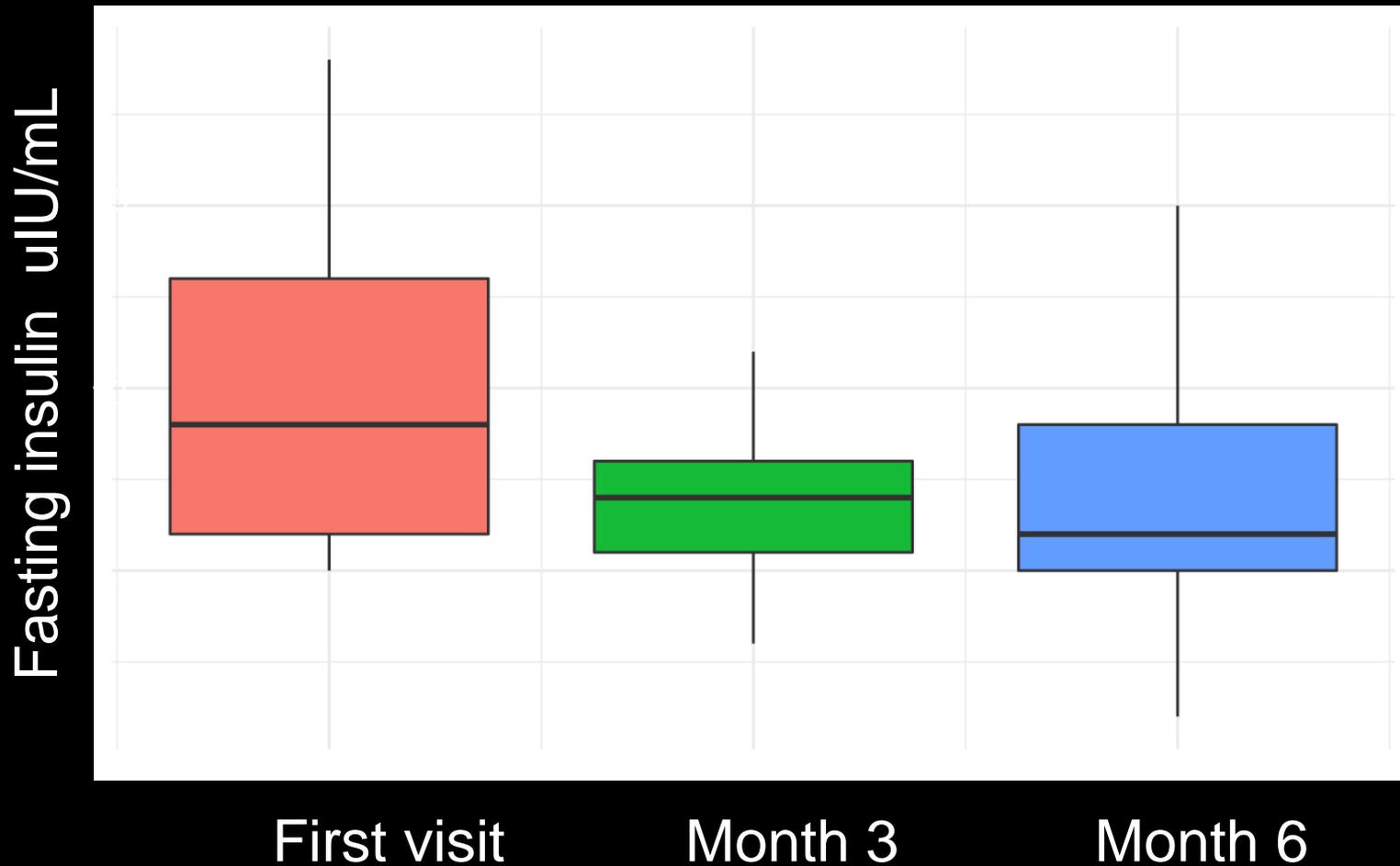
Central obesity significantly decreased



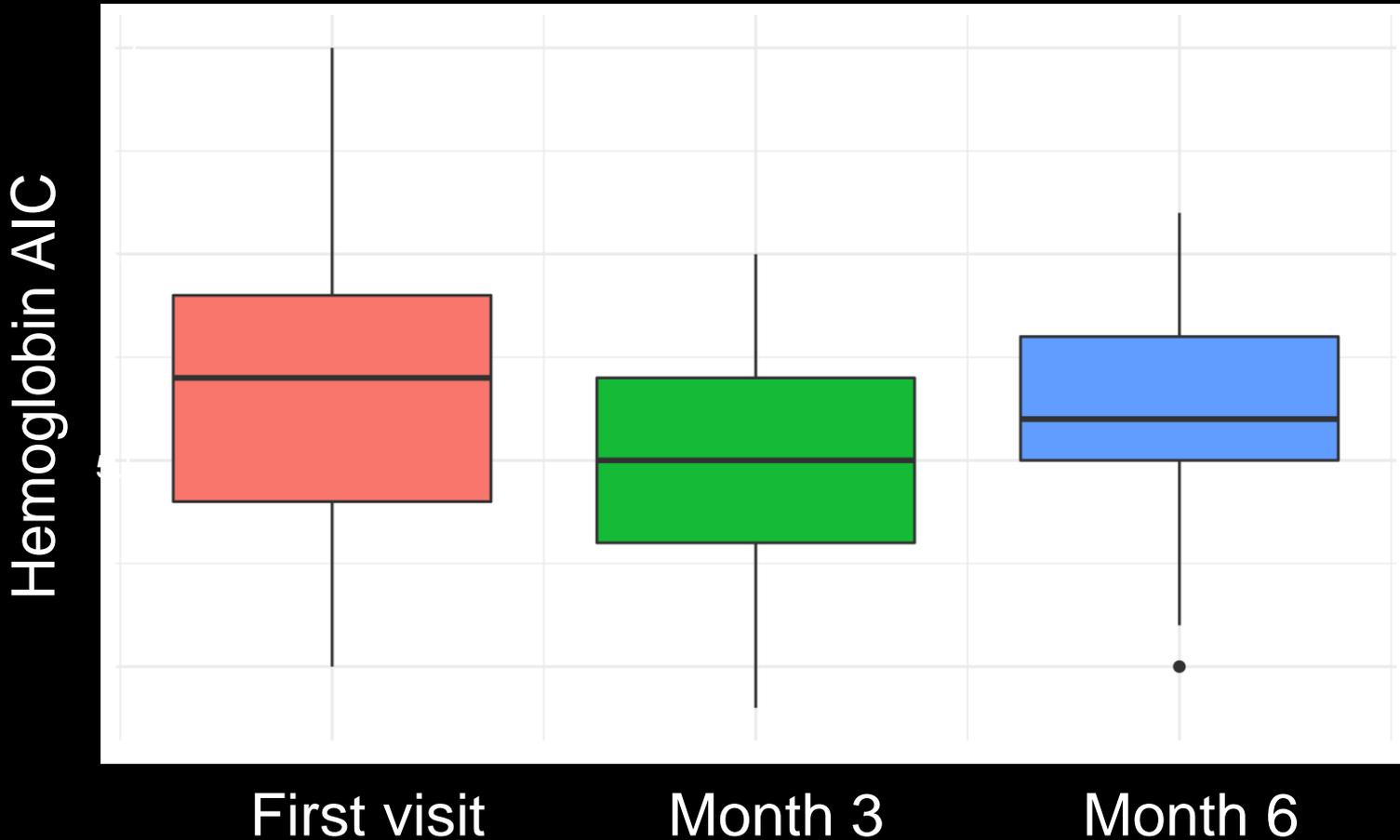
Blood sugar level significantly decreased



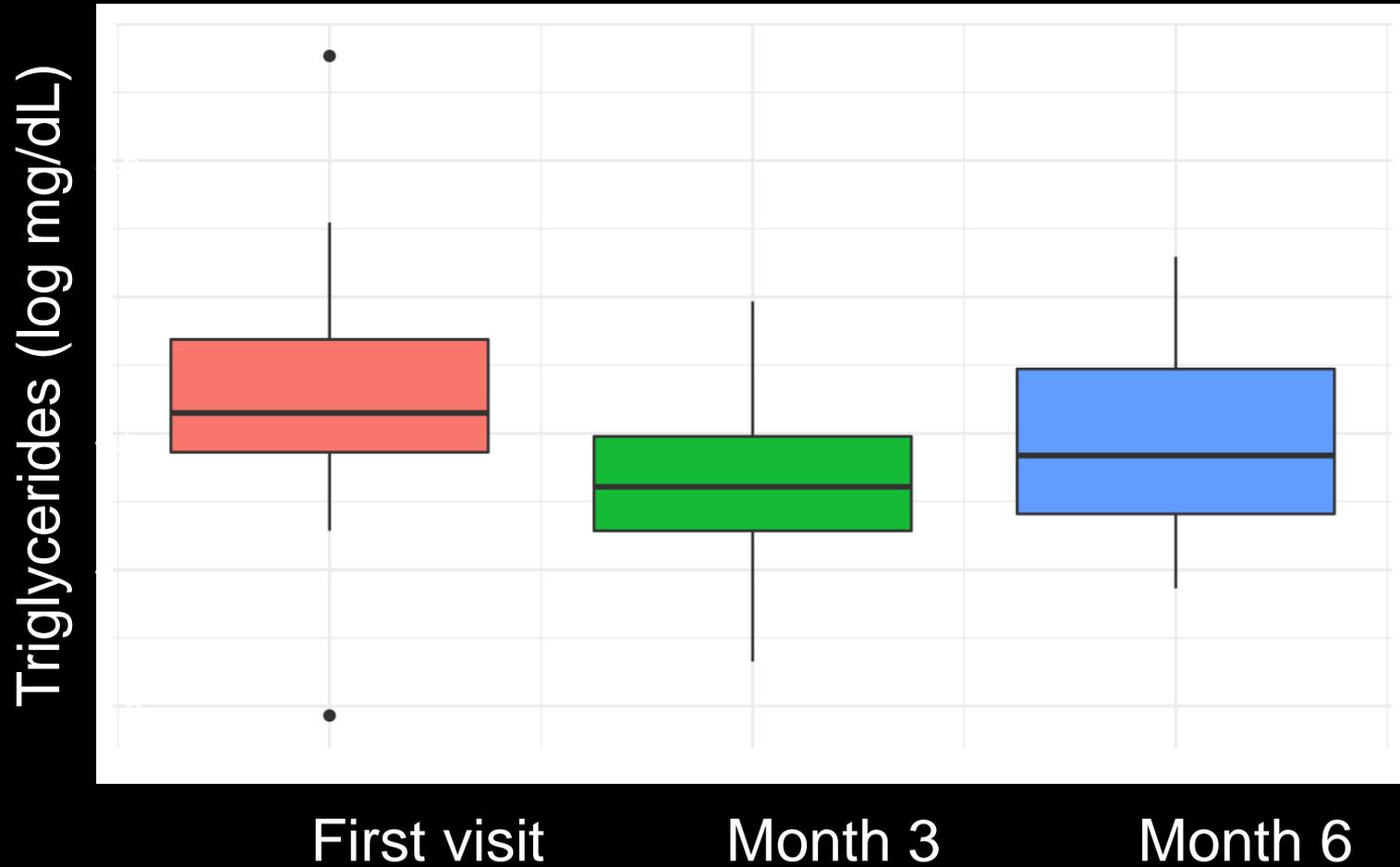
Blood insulin level significantly decreased



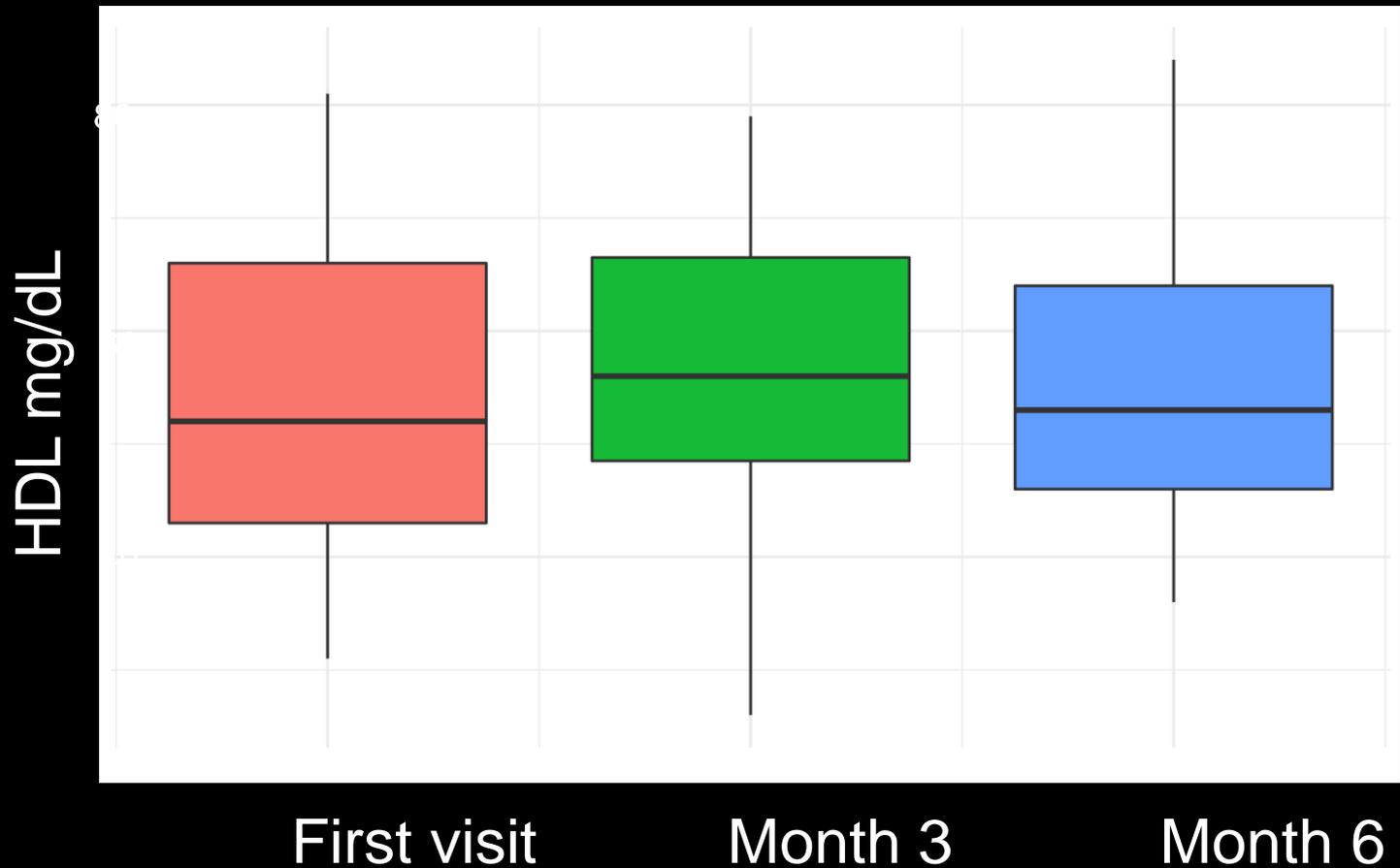
Hemoglobin A1C significantly decreased



Triglycerides significantly decreased

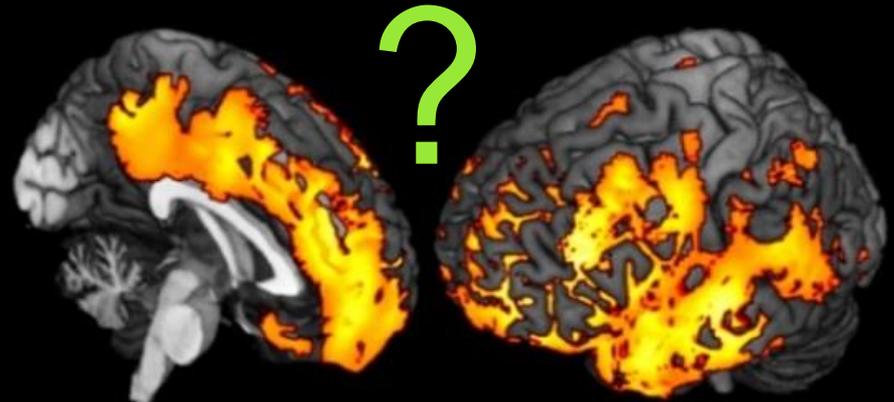
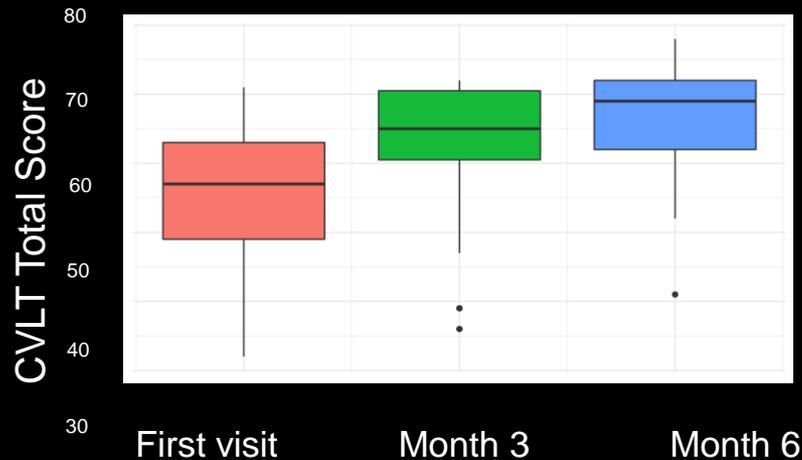


HDL significantly increased



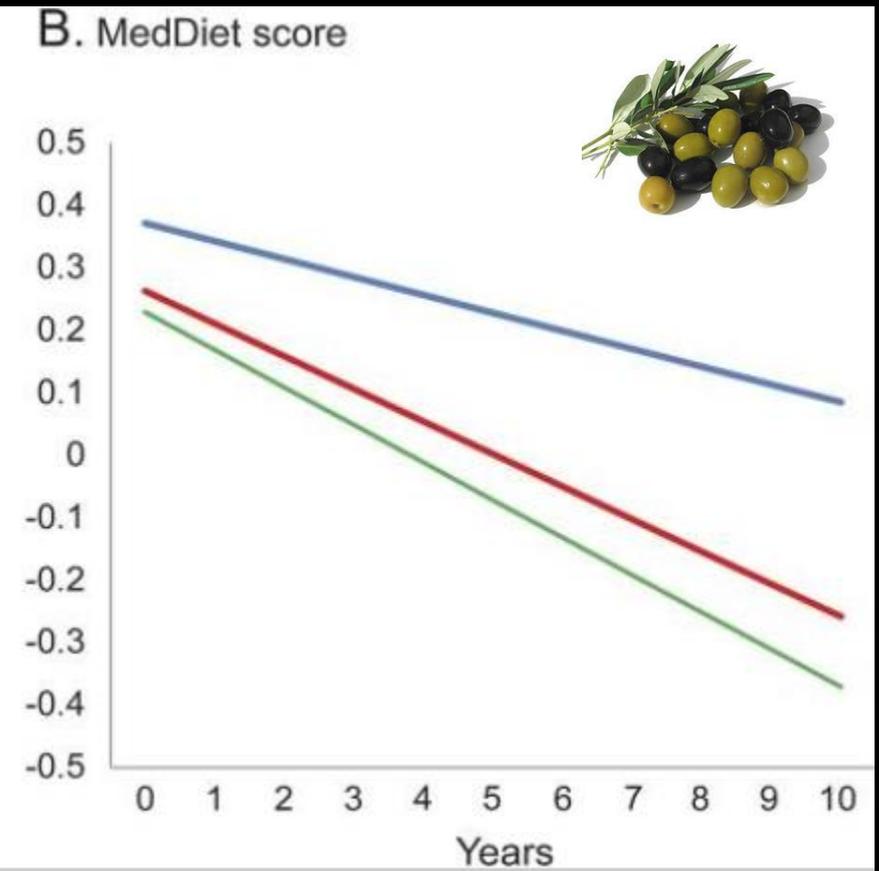
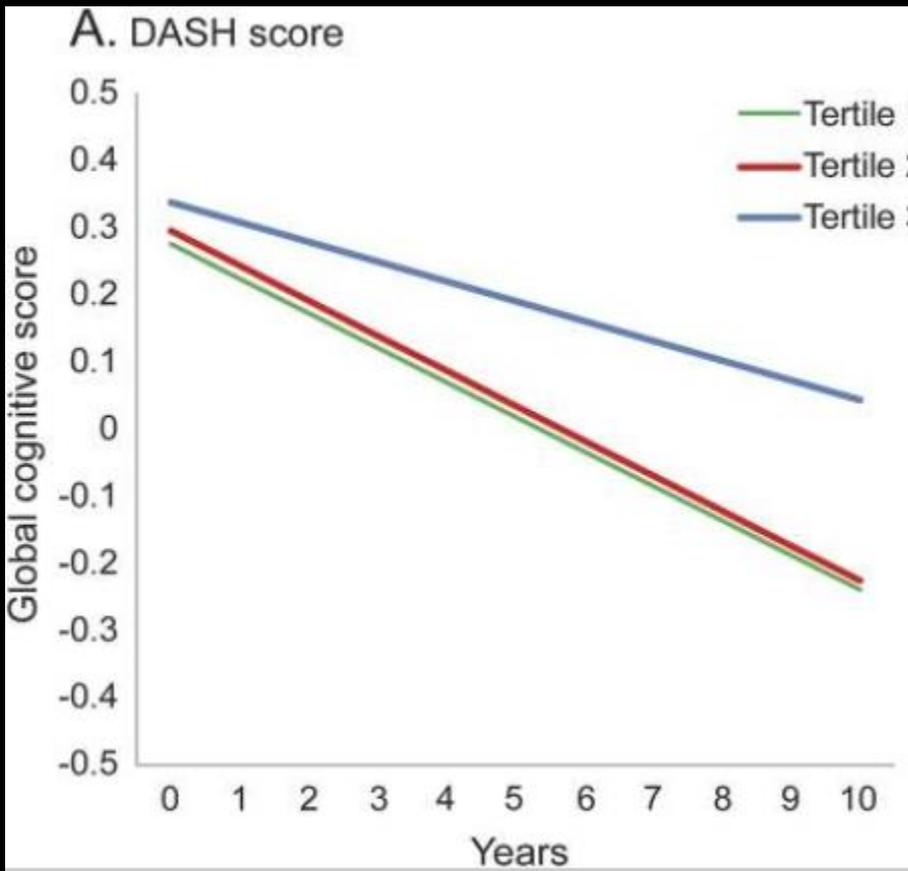
Cognitive function significantly improved

- Memory improvement
- Faster motor and processing speed





Mediterranean diet and similar are associated with slower cognitive decline over time.



Examined whether accordance to the DASH (Dietary Approach to Stop Hypertension) and Mediterranean diets is associated with slower cognitive decline in a prospective Chicago cohort study of older persons, the Memory and Aging Project.

MIND Diet

10 brain-healthy foods:

Green leafy vegetables

Other vegetables

Nuts

Berries

Beans

Whole grains

Fish

Poultry

Olive oil

Wine

Unhealthy:

Red meats

Butter and stick margarine

Cheese

Pastries and sweets

Fried or fast food



MIND Diet Intervention and Cognitive Decline (MIND)

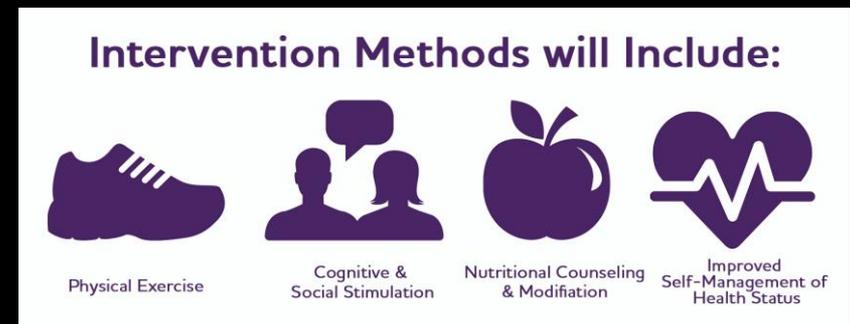


Phase III randomized controlled trial designed to test the effects of a 3-year intervention of the MIND diet (Mediterranean-DASH Intervention for Neurodegenerative Delay) on cognitive decline and brain neurodegeneration among 600 individuals 65+ years without cognitive impairment who are overweight and have suboptimal diets.

Emphasis on natural plant-based foods and limited animal and high saturated fat foods; uniquely specifies green leafy vegetables and berries.

U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (POINTER)

- Modeled after the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study
- Multidomain intervention that involves a structured program of diet, physical and cognitive exercise, and management of cardiometabolic risks
- 2000 participants
- Age 60 Years to 79 Years
- Stay tuned...



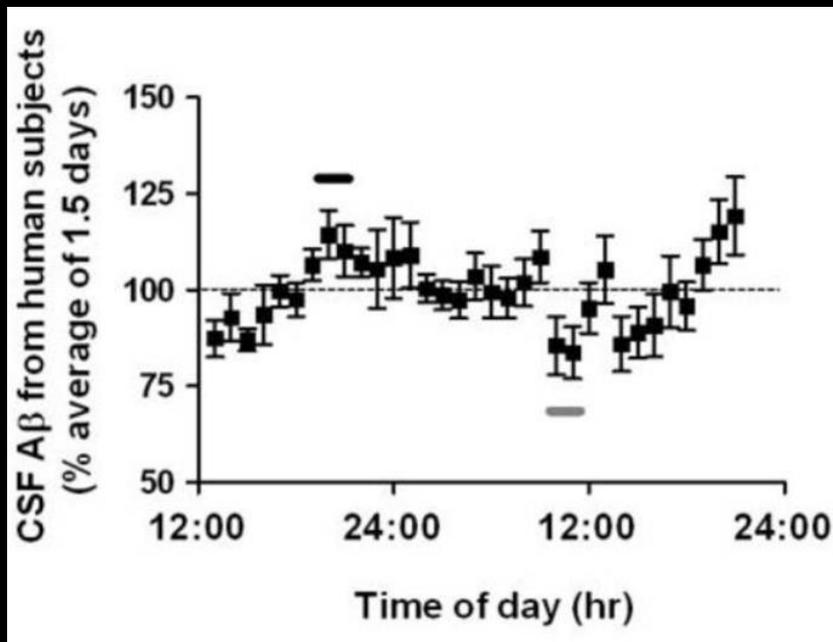
Sleep



- Insomnia at night
- Agitated behavior at sunset
- Excessive sleeping during the daytime
- Sleep is fragmented, with frequent awakenings
- Reversal of the day–night sleep pattern

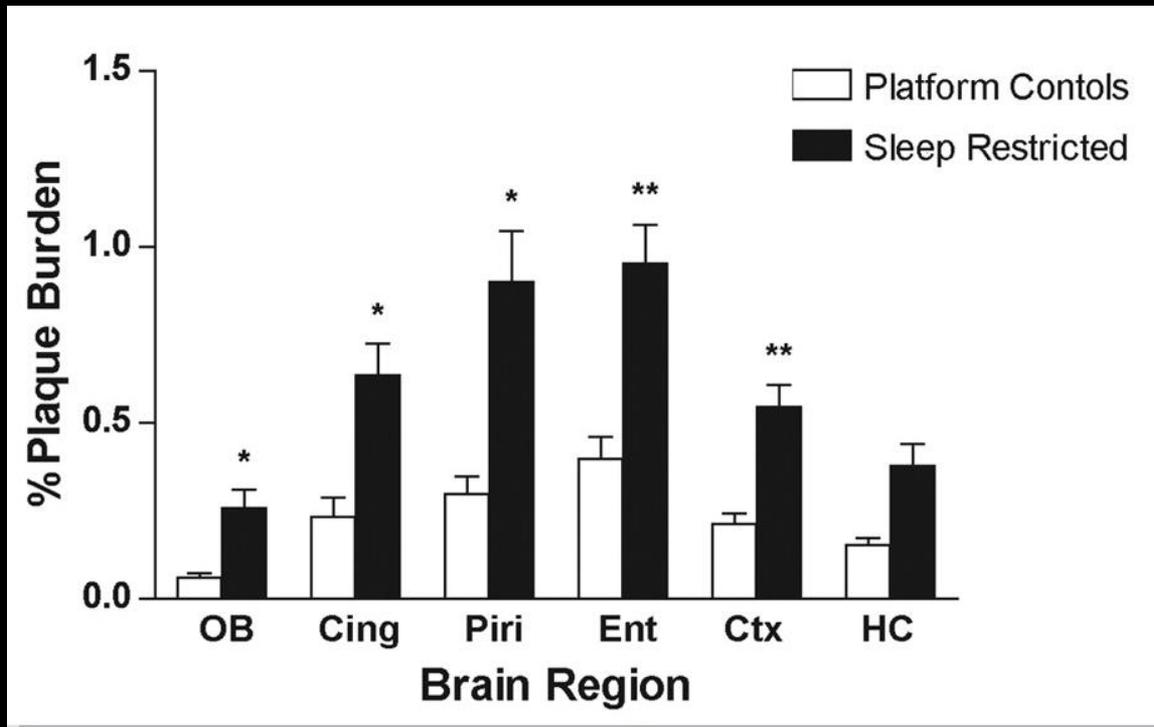
Sleep tied to brain pathology?

- Soluble amyloid- β is released into interstitial space during synaptic activity
- A β levels in the CSF drop during a normal night's sleep (people and mice).



Kang et al. Science. 2009
Nov 13;326(5955):1005-7.

A β plaque deposition after chronic sleep restriction



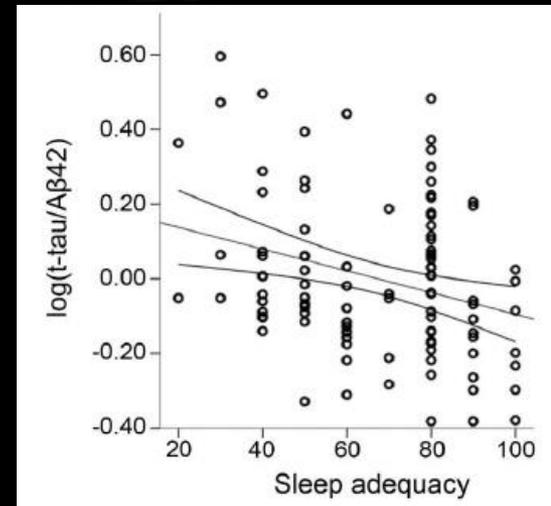
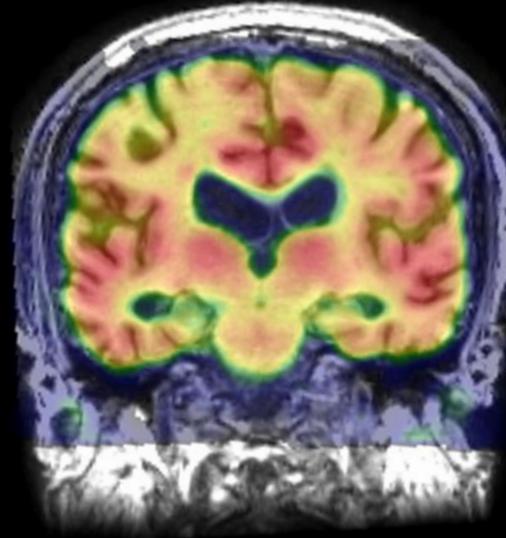
Kang et al. Science. 2009
Nov 13;326(5955):1005-7.

Connection between sleep and AD before dementia onset in our research participants?

Sleep Quality: MOS Sleep Scale

	Sleep Adequacy	Somnolence	Sleep Problems Index	Snoring
<i>During the past 4 weeks...</i>				
1. How long did it usually take for you to fall asleep? ^a			○	
2. On the average, how many hours did you sleep each night? ^b				
<i>How often did you...^c</i>				
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?			●	
4. get enough sleep to feel rested upon waking in the morning?	●		○	
5. awaken short of breath or with a headache?			●	
6. feel drowsy or sleepy during the day?		●	●	
7. have trouble falling asleep?			●	
8. awaken during your sleep time and have trouble falling asleep again?			●	
9. have trouble staying awake during the day?		●	●	
10. snore during your sleep?				●
11. take naps (5 minutes or longer) during the day?		●		
12. get the amount of sleep you needed?	●		○	

Lack of restorative sleep and brain amyloid



Sprecher et al. *Neurobiology of Aging*. 2014. 36(9):2568-76.
Sprecher et al. *Neurology*. 2017 Aug 1;89(5):445-453.

Sleep Apnea

- Abnormal breathing during sleep
- Systematic review and meta-analysis including 4 288 419 participants
- People with SDB were 26% more likely to develop cognitive impairment
- Executive function decline



JAMA Neurol. 2017 Oct 1;74(10):1237-1245

OSA associated with diabetes, obesity, cardiovascular health... also linked with dementia risk.

Alzheimer's disease neuropathology in people with obstructive sleep apnea

- 34 people with OSA (18 females, 16 males)
- Examined A β plaques
- OSA severity was a significant predictor of A β plaque burden in the hippocampus after controlling for age, sex, body mass index (BMI), and continuous positive airway pressure (CPAP) use



Neighborhood Disadvantage

Fundamental cause of US health disparities
and drives proximal health risks

Social determinants of health are the conditions in the environments where people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning, and quality-of-life outcomes and risks.



<https://health.gov/healthypeople/objectives-and-data/social-determinants-health>

Neighborhood disadvantage and dementia

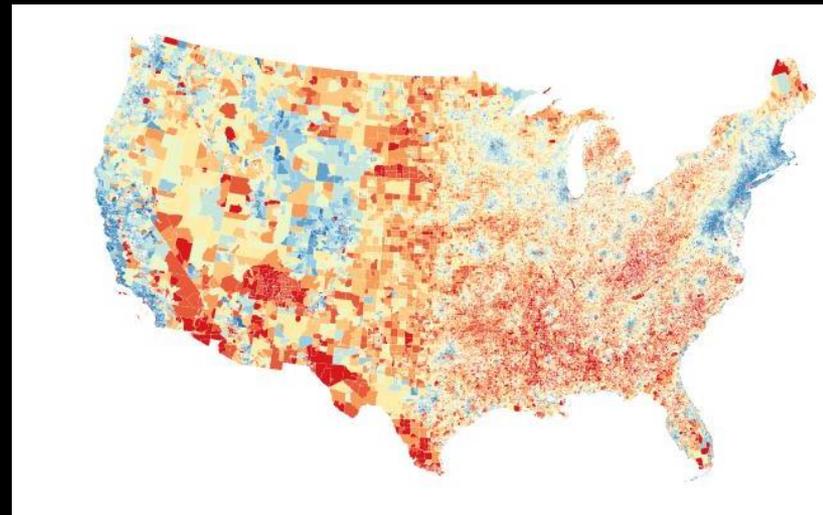
- Living in a disadvantaged US neighborhood is strongly linked to increased mortality and disease, even after accounting for individual-level SES factors
[Kind et al, Annals of Int Med, 2014; Link & Phelan, J Health Soc Behav, 1995; House et al, Milban Q, 1990; and others]
- Neighborhood disadvantage influences many factors including health behaviors, access to food, toxic exposures and personal safety
[Link & Phelan, J Health Soc Behav, 1995; House et al, Milban Q, 1990; Franco et al, Am J Prev Med, 2008; and others]
- Dementia disproportionately impacts populations exposed to neighborhood disadvantage
[Al Hazzouri et al, Am J Epi, 2011; Yaffe et al, BMJ, 2013; Barnes et al, Health Aff, 2014; Mayeda et al, Alz Dem 2016]
- Markers of neighborhood disadvantage can be employed to quantify contextual-level social determinants of health

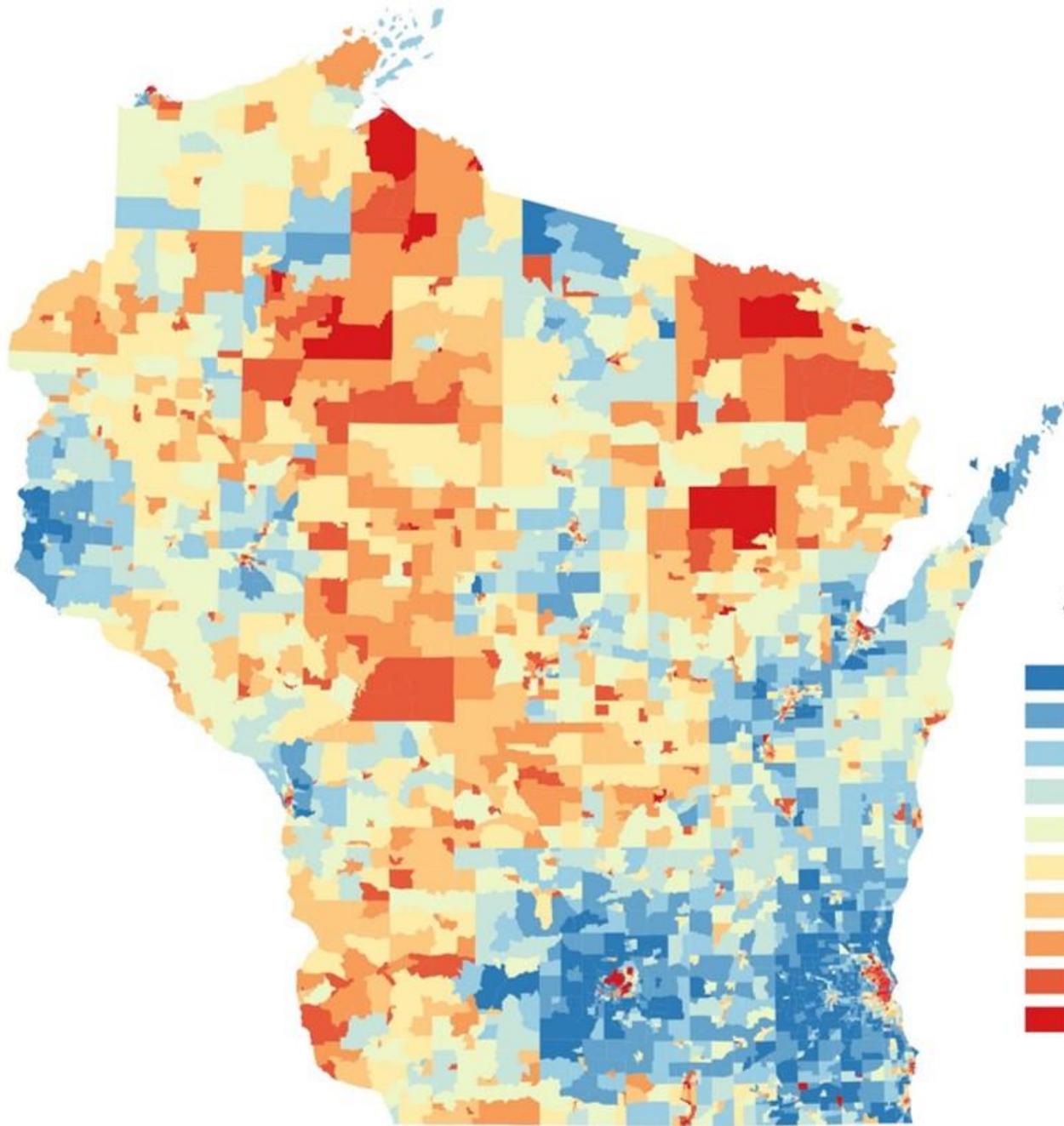
Neighborhood Disadvantage - Area Deprivation Index

- 17 education, employment, housing-quality and poverty measures drawn from American Community Survey conducted by the Census Bureau
- Refined to census block-group level (i.e. “neighborhood” ~ 1,500 persons) to precisely measure exposure
- Validated across US
- Created, refined, validated and disseminated by the Kind team via the Neighborhood Atlas platform
 - Kind and Buckingham, *New England Journal of Medicine*, 2018



Amy Kind, MD, PhD



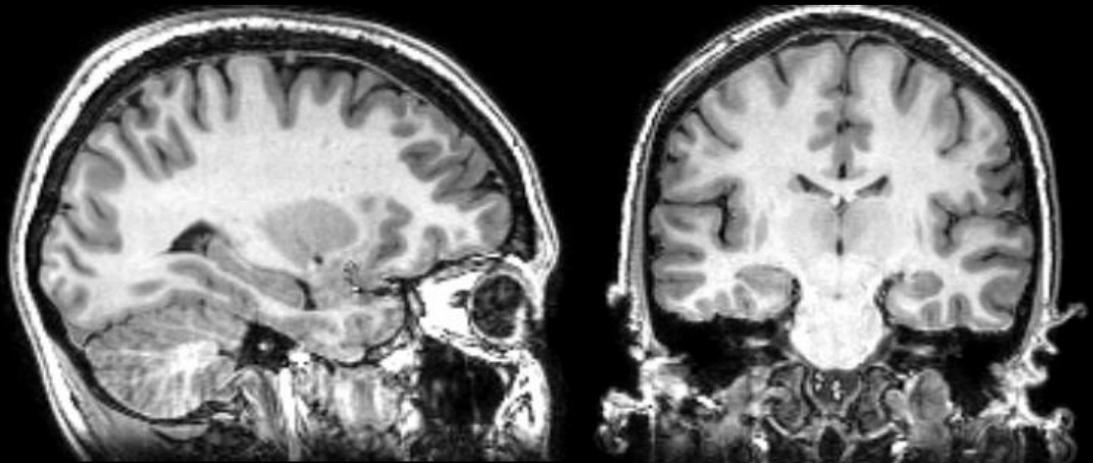


Area Deprivation Index

- Decile 1 (Least Disadvantaged)
- Decile 2
- Decile 3
- Decile 4
- Decile 5
- Decile 6
- Decile 7
- Decile 8
- Decile 9
- Decile 10 (Most Disadvantaged)

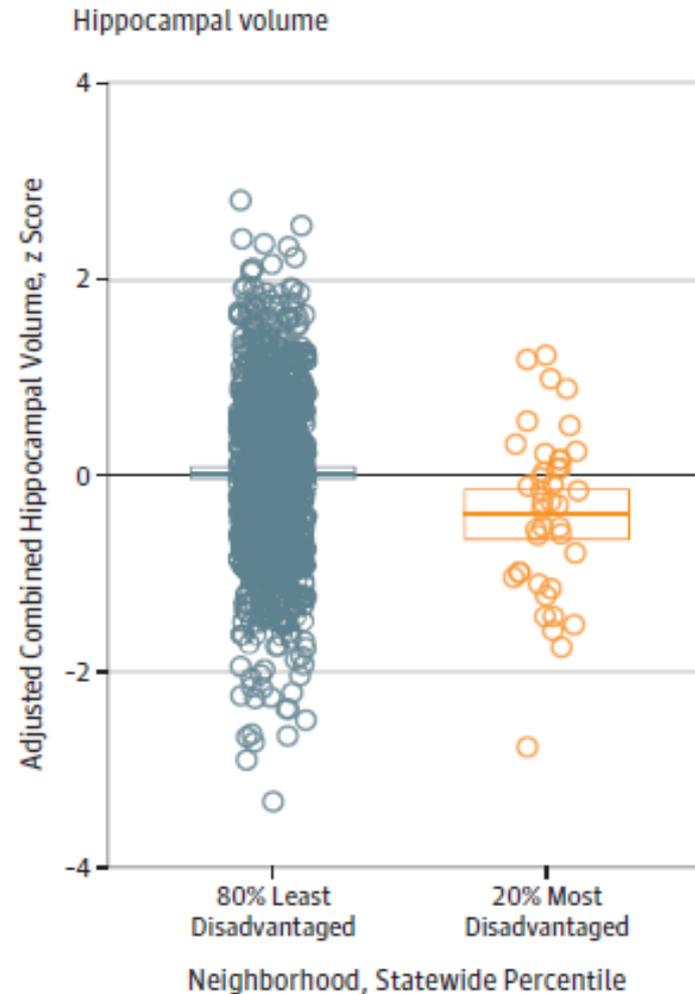
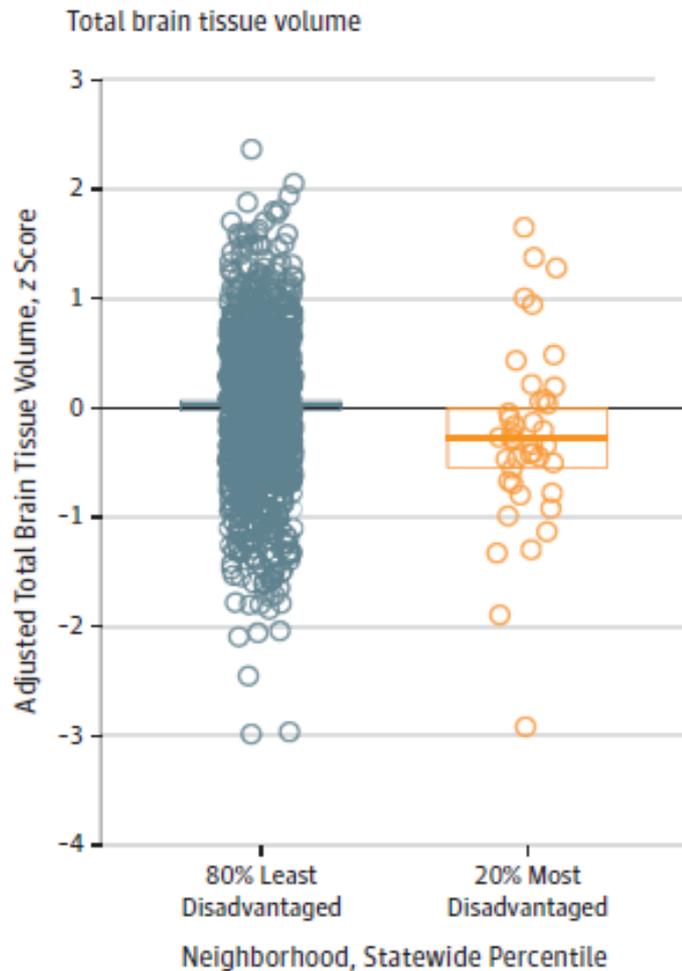
Neighborhood disadvantage associated with brain?

- N=951 cognitively unimpaired participants from Wisconsin Registry for Alzheimer's Prevention and Wisconsin ADRC
- Residential address geocoded, linked to neighborhood disadvantage by ADI
- MRI measures of hippocampal and total brain tissue volume



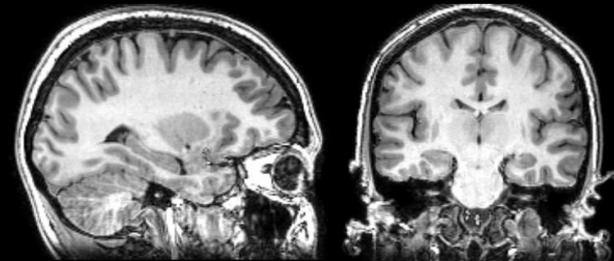
Association of Neighborhood-Level Disadvantage With Cerebral and Hippocampal Volume

Jack F. V. Hunt, BA; William Buckingham, PhD; Alice J. Kim, BA; Jennifer Oh, BS; Nicholas M. Vogt, BA; Erin M. Jonaitis, MS, PhD; Tenah K. Hunt, MPH, PhD; Megan Zuelsdorff, PhD; Ryan Powell, PhD; Derek Norton, MS; Robert A. Rissman, PhD; Sanjay Asthana, MD; Ozioma C. Okonkwo, PhD; Sterling C. Johnson, PhD; Amy J. H. Kind, MD, PhD; Barbara B. Bendlin, PhD



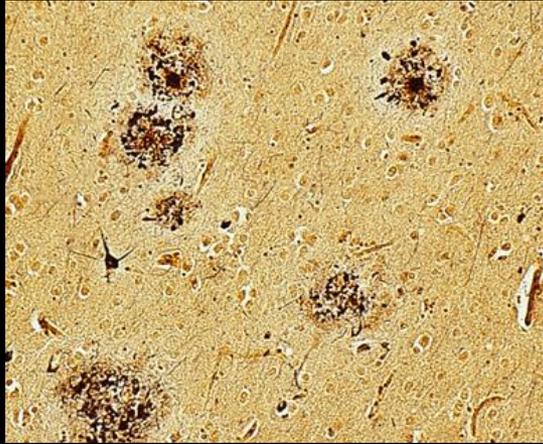
Findings

- Neighborhood disadvantage was associated with brain volumes in cognitively unimpaired older middle-aged adults, independent of individual socioeconomic factors
 - Equivalent to +7 years of age-associated hippocampal atrophy



- Cardiovascular risk mediated the association for total brain tissue volume but not for hippocampal volume
- Residential location may increase risk for volume loss

Neighborhood Disadvantage and AD Neuropathology



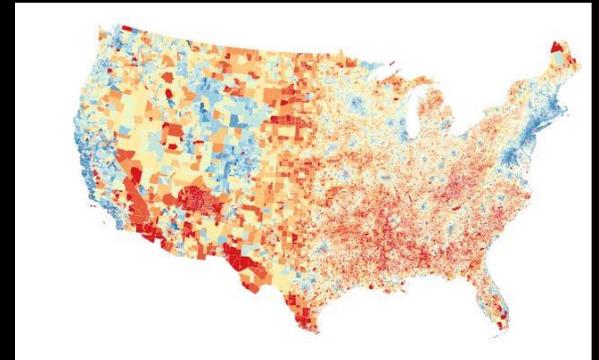
- N=453 decedents with documented addresses who donated their brain to Wisconsin or University California San Diego (UCSD) ADRC brain banks, 1993-2016
- No social factor characterization, linkage otherwise available at these brain banks
- Residential address at death geocoded, linked to neighborhood disadvantage by ADI
- Neuropathologic features drawn from National Alzheimer's Coordinating Center (NACC) and autopsy reports



Neuropath Confirmed AD

- Higher neighborhood disadvantage was associated with 8.1% increase in the odds of AD neuropathology for every decile change on the ADI rank index
- Living in the most disadvantaged neighborhood decile was associated with a 2.18 increased odds of AD neuropathology
- Social determinants of health, including neighborhood disadvantage, are fundamental drivers of health and health disparities

<https://www.neighborhoodatlas.medicine.wisc.edu/>



Summary

- Modifiable factors affect the brain aging
- Some effects may be through AD process
- Some effects due to non-AD processes
- Potentially modifiable factors for dementia include vascular (and related physical activity and diet behaviors), sleep, and neighborhood
- Social determinants of health impact the brain
- Multifactorial

