The Impact of Cognitive Reserve on CSF Biomarkers of AD

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DISCLOSURES

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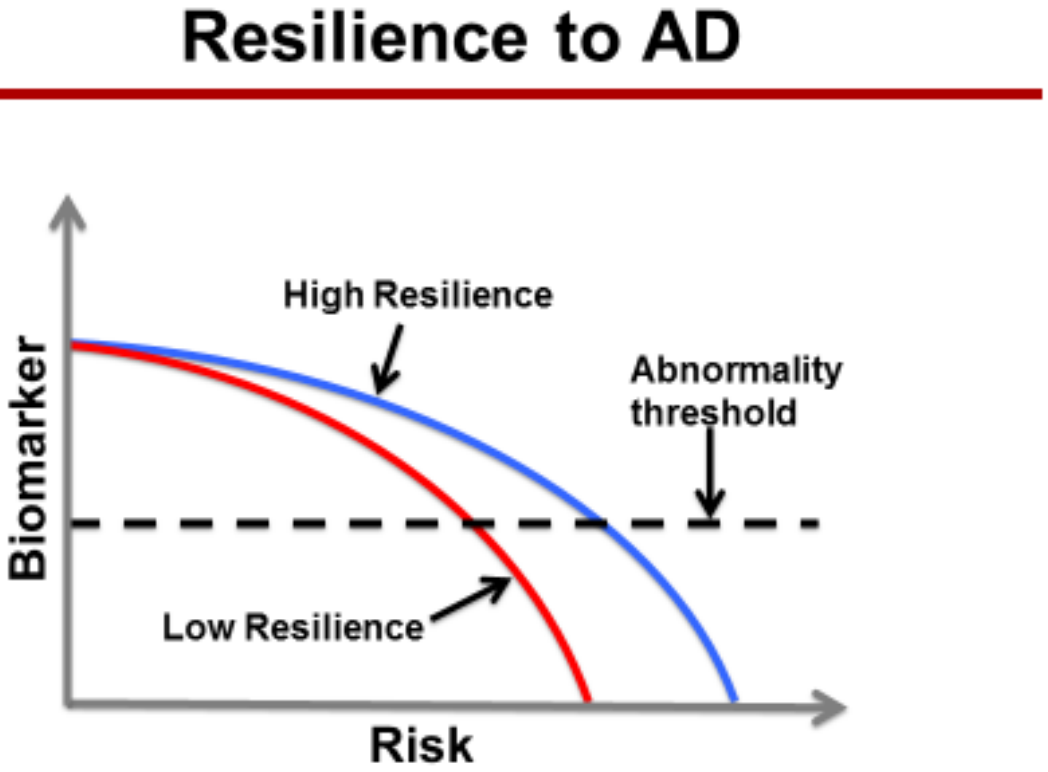
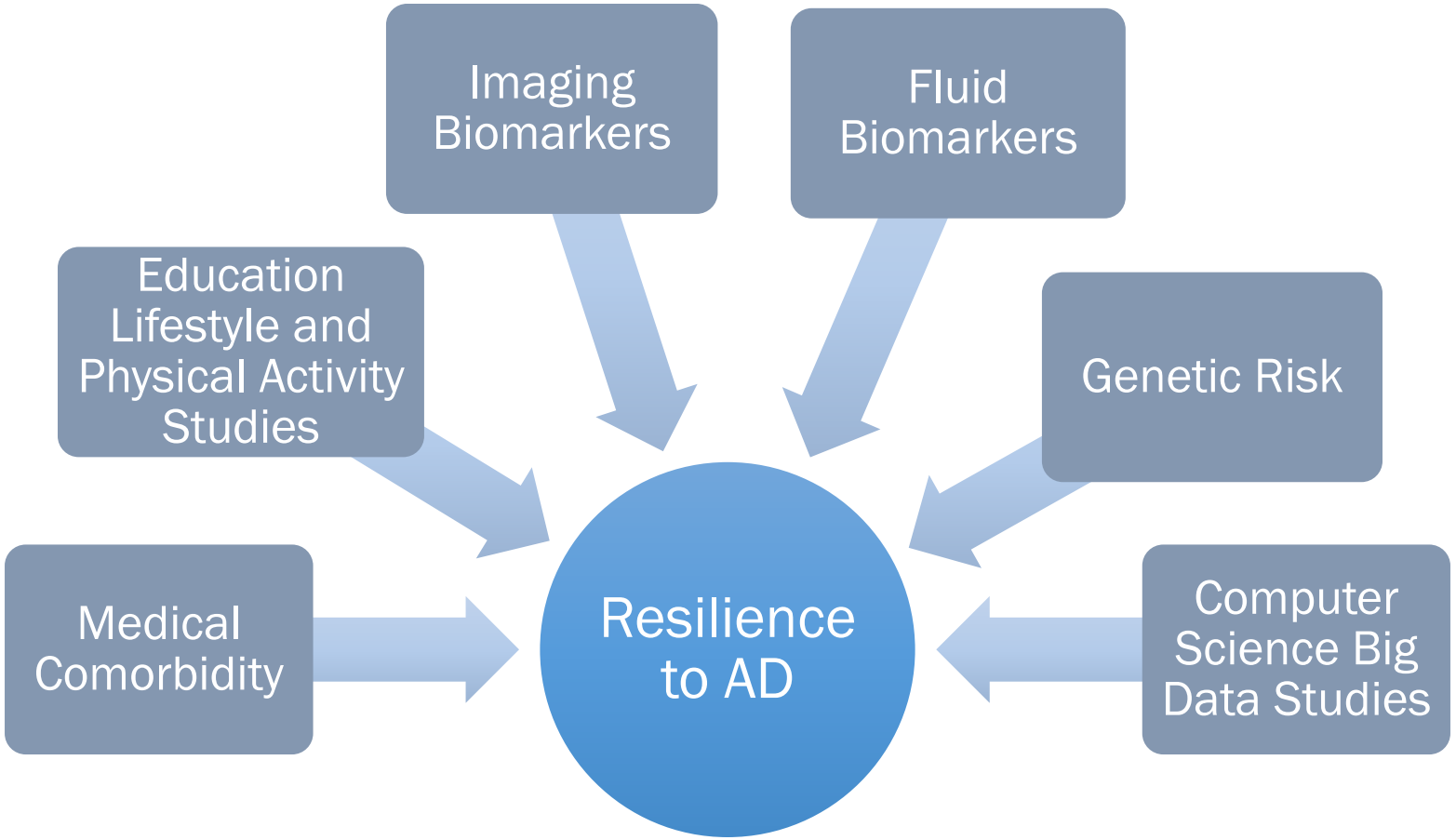
- Department of Veterans Affairs
- State of Wisconsin
- John A. Hartford Foundation
- Alzheimer's Association
- UW-Madison and UW School of Medicine and Public Health
- Pharmaceutical companies (Merck, Pfizer, Lundbeck, Toyoma Chemical, Eli Lilly, Wyeth, Parke Davis, Ciba-Geigy)

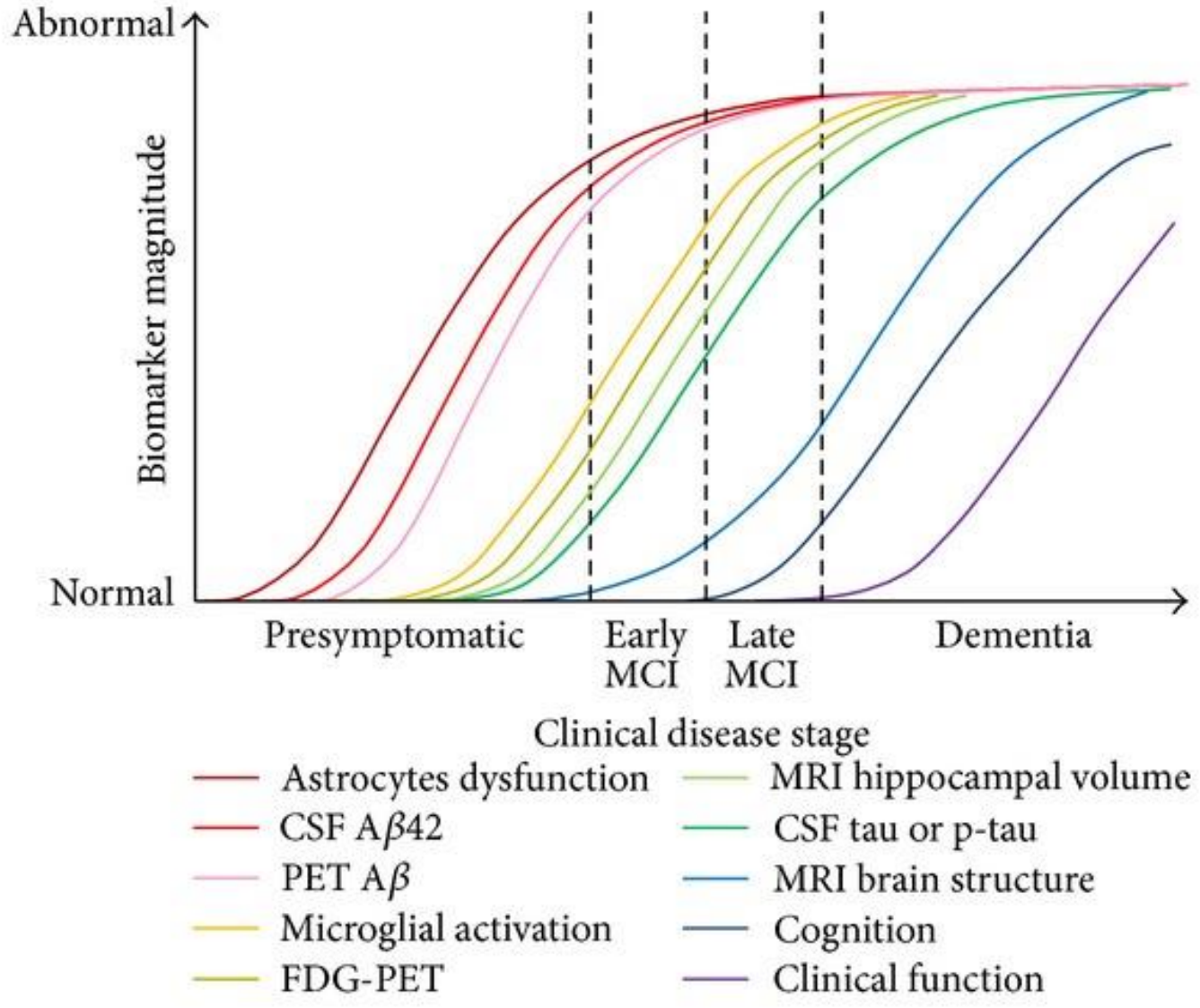
Cognitive Reserve: Resilience to AD



Approaches to AD Resilience Research



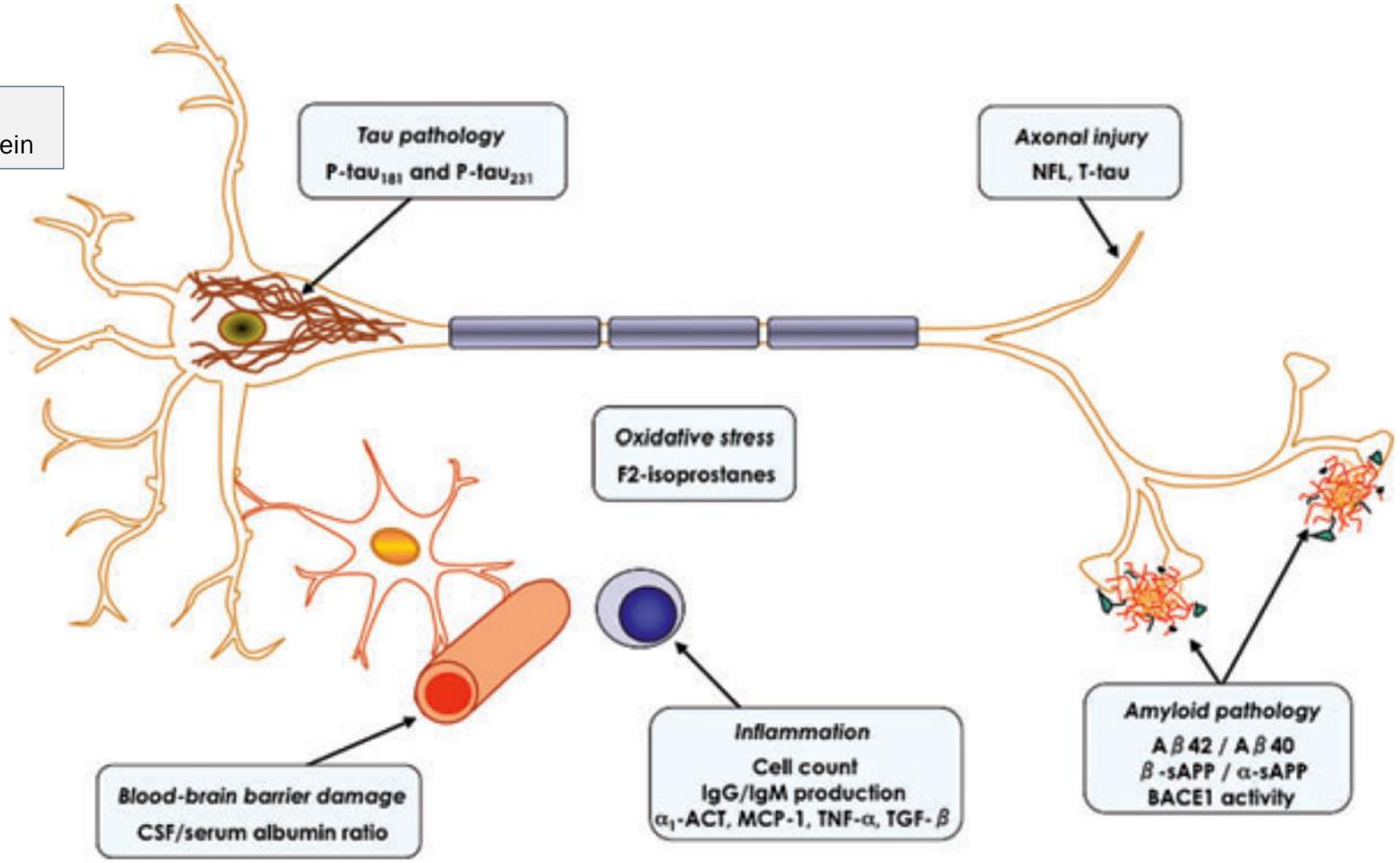
Biomarkers of Alzheimer's Disease



Adapted from Jack et al. Lancet Neurology (2013)

Molecular Neurobiology of AD: CSF Biomarkers

BDNF / TDP 43 /
Neurogranin / α Synuclein



Mattson et al. Ann NY Acad. Sci. (2009)

CSF Biomarkers of Alzheimer's Disease

AD Pathology-Related Mechanism	CSF Measure
Amyloid Deposition	Aβ40, Aβ42, sAPPα, sAPPβ, Aβ oligomers, BACE1 levels/activity, ratios e.g., Aβ42/p-Tau, Aβ40/Aβ42, N-terminal truncated Aβ42 APLP-1
Neurodegeneration	Total Tau, p-Tau, oligomeric forms of Tau
Neuronal/Axonal Damage and White Matter Integrity	Neurofilament L (NFL),
Synaptic Function/Damage	Neurogranin, SNAP25, Visinin-like-protein 1 (VLP1),
Neuroinflammation	YKL-40, MCP1, Soluble form of TREM2, cytokines, chemokines, com3, S-100

Potential CSF Biomarkers of Cognitive Reserve

Cognitive Reserve-Related Mechanisms	CSF Measure
Reduced amyloid deposition	Aβ40, Aβ42, sAPPα, sAPPβ, Aβ oligomers, BACE1 levels/activity, ratios e.g., Aβ42/p-Tau, Aβ40/Aβ42, N-terminal truncated Aβ42 APLP-1
Decreased neuronal and axonal damage	Total Tau, p-Tau, oligomeric forms of Tau
Neurogenesis	BDNF, GDF 15, Osteopontin (OPN)
Synaptogenesis	Neurogranin, SNAP25, Visinin-like-protein 1 (VLP1), MMP3
Reduced neuroinflammation	YKL-40, MCP1, Soluble form of TREM2, cytokines, chemokines, com3, S-100

Potential Limitations and Sources of Inconsistency in CSF Biomarkers of AD and Cognitive Reserve

Pre-analytical

- Subject selection & clinical diagnosis
- CSF Collection
- Sample processing, storage and shipment

Analytical

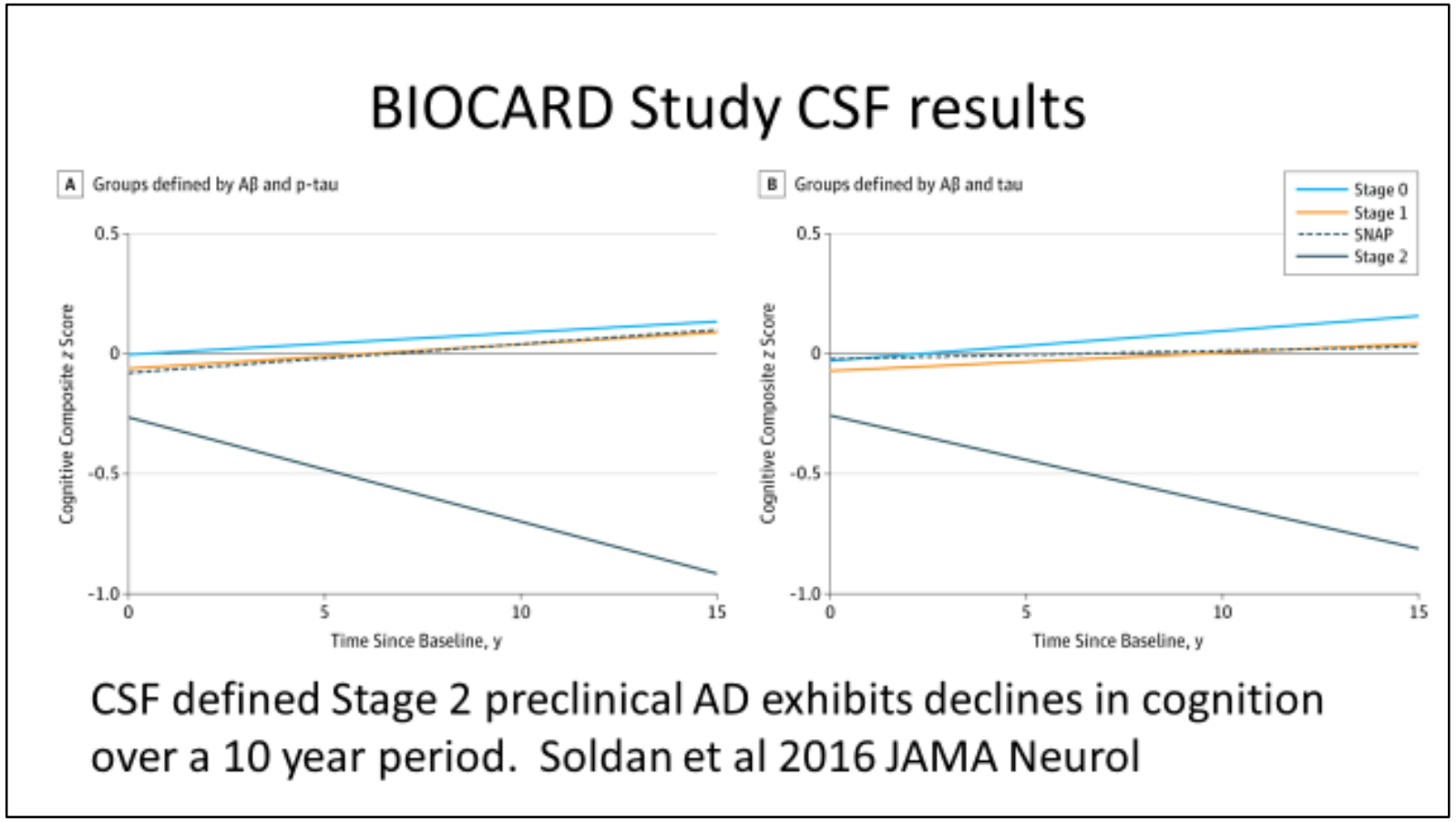
- Assay technique
- Reagents used
- Analytical procedures
- Equipment

Meta-analysis of CSF Biomarkers of AD

- Olsson et al. analyzed CSF data from 231 studies involving over 15,600 patients with AD, and more than 13,000 healthy controls
- Four CSF biomarkers – total tau, p-tau, neurofilament light chain (NFL) and Aβ-42 emerged as the most robust measures differentiating AD from controls
- Moderate effect sizes were observed for VILIP-1, neuron-specific enolase (NSE), YKL-40 and heart fatty acid-binding protein (HF-ABP)
- AD and controls could not be differentiated on CSF levels of Aβ-38, Aβ-40, sAPP α or β, MCP-1, GFAP and CSF-plasma ratio of albumin

Olsson B, Lancet Neurol. June 15(7), 673-694, 2016

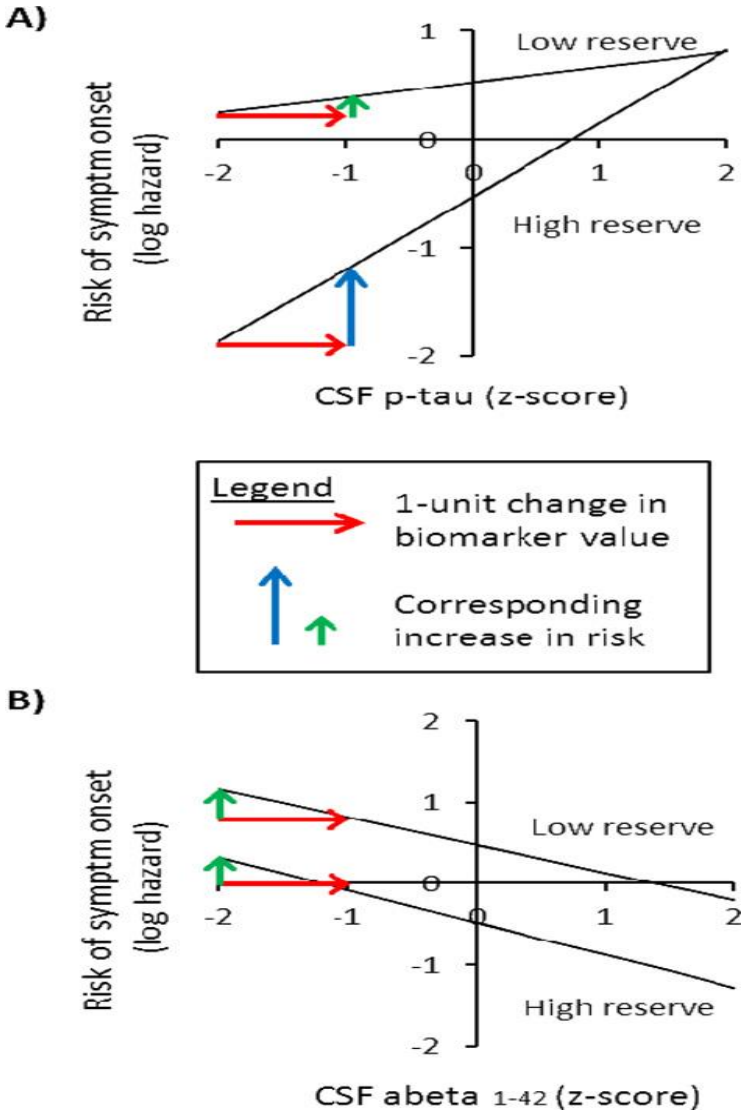
BIOCARD: CSF Biomarkers and Longitudinal Cognitive Change



- 222 subjects (mean age-57yrs; range: 22-85) followed for 18 years. Baseline CSF used to create 4 hypothetical preclinical stages of AD
- Stage 2 individuals showed greater cognitive decline than those in Stage 0, 1 and SNAP; APOE4 did not affect the rate of cognitive decline

Soldan et al., JAMA Neurol; 73(6): 698-705, 2016

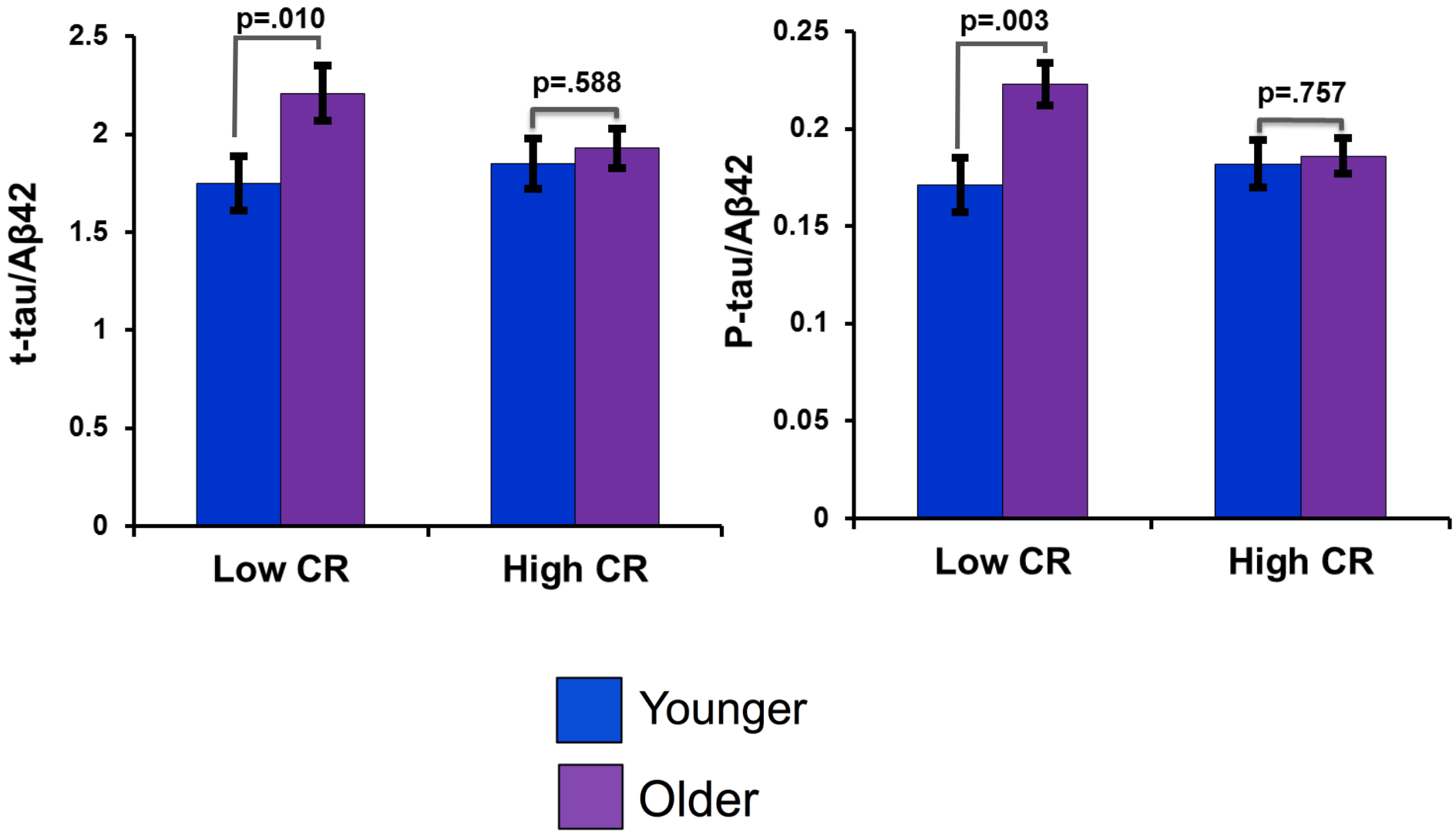
BIOCARD Study – Cognitive Reserve and CSF Biomarkers of Preclinical AD



- 239 participants (mean age - 57.2 yrs) from BIOCARD followed for 17 years
- Cognitive reserve (CR) measured by NART, vocabulary and years of education
- Increased risk of progressing from normal to symptom onset was found in those with lower CR, lower CSF Aβ levels and higher p-tau

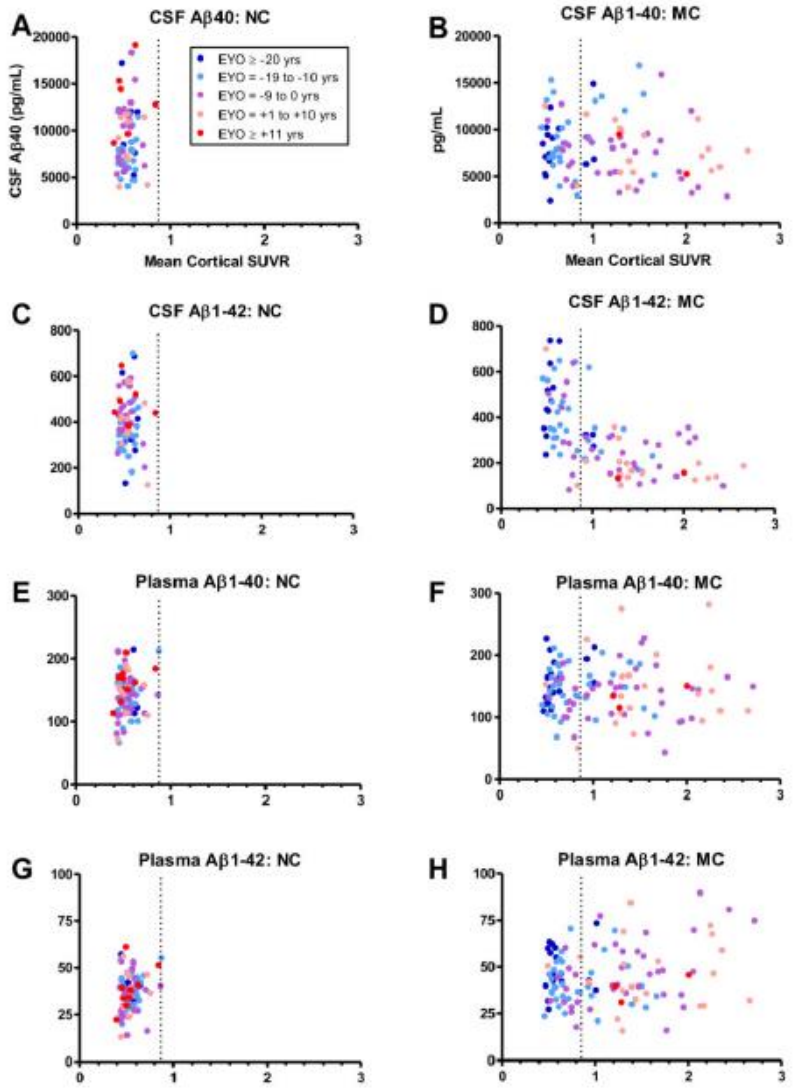
Soldan et al. Neurobiol Aging, 34(12), December 2013

Wisconsin ADRC: Cognitive Reserve and CSF Biomarkers of AD



DIAN Study: CSF Biomarkers

Association between fluid Aβ measures and mean cortical PiB retention in NCs and MCs (A to H). Concentrations of CSF Aβ-40 (A & B) and Aβ-42 (C & D) and Concentrations of plasma Aβ-40 (E & F) and Aβ-42 (G & H) for NCs (left panels)
and MCs (right panel)

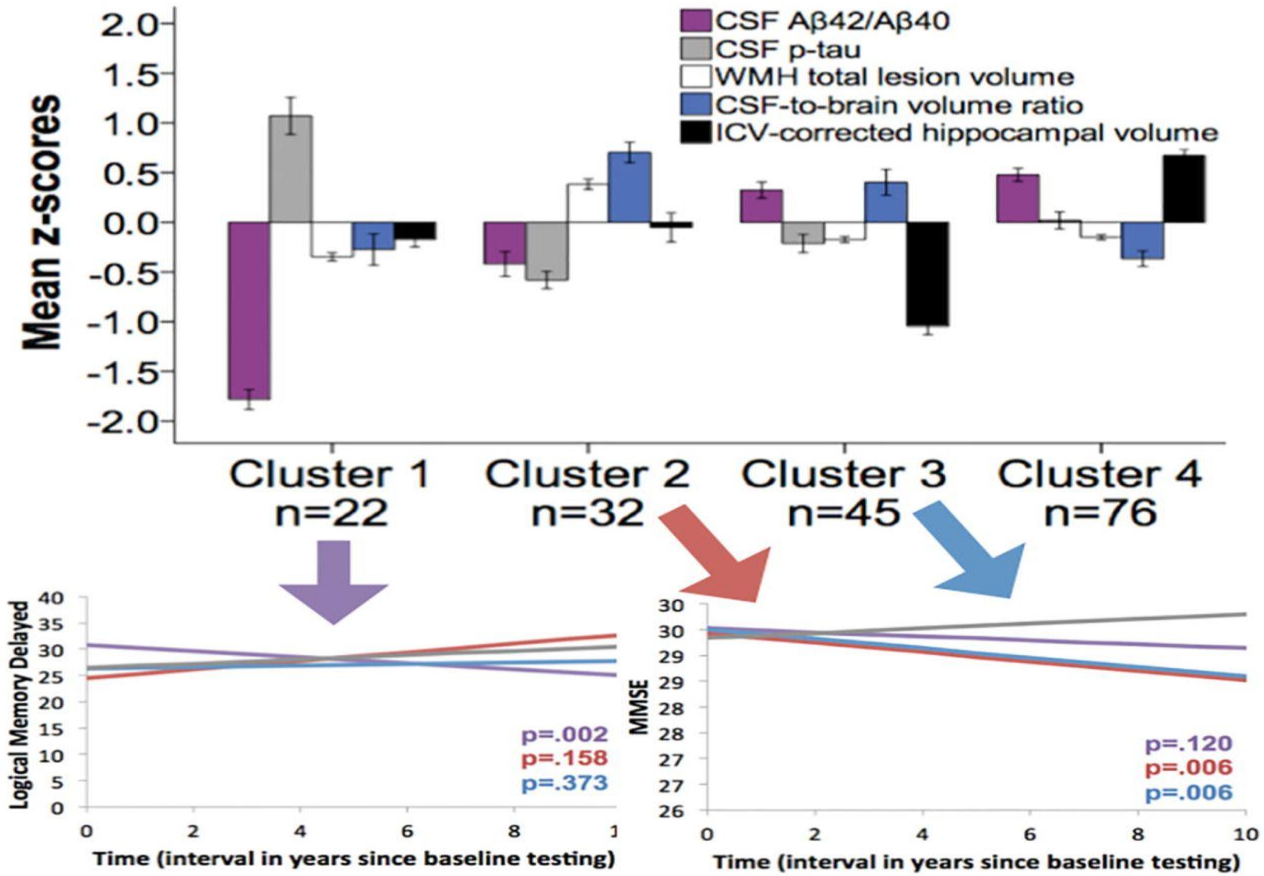


Anne M. Fagan et al., Sci Transl Med; 6(226):226ra30.

Wisconsin Cohorts on Preclinical AD

	University of Wisconsin Alzheimer's Disease Program	
	NIH Wisconsin ADRC	
Cohort	**IMPACT**	**WRAP**
Cohort characteristics	Ages 45-65 years at baseline AD parental history positive (PH+, 75%) and negative (PH-, 25%)	Ages 45-65 years at baseline AD parental history positive (PH+, 70%) and negative (PH-, 30%)
Sample size	n=450	n=1560
Year started	2009	2001
Visit frequency	Every other year	Every other year
Cognitive battery	NACC (National Alzheimer's Coordinating Centers) cognitive battery & additional tests	Extensive cognitive battery
Computerized cognitive battery	NIH Toolbox cognitive battery	Cogstate computerized battery
Questionnaires	Medical history, medications, lifestyle factors, sleep, cognitive activities, physical activity	Medical history, medications, lifestyle factors, sleep, cognitive activities, physical activity
Cerebrospinal fluid (CSF) samples	Baseline CSF samples in consented subjects; as of 2015, CSF collected every 2 years	Baseline and follow-up CSF samples in subset
Neuroimaging	Structural MRI, perfusion, 4-D flow, DTI	ADRC MRI, amyloid PET, tau PET

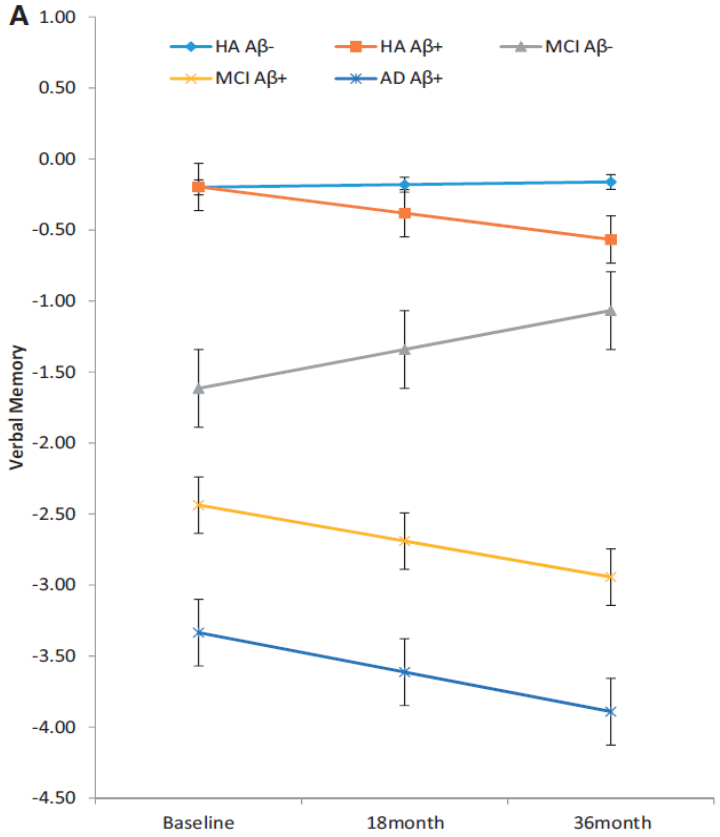
Wisconsin ADRC: Clinical Utility of CSF Biomarker Data – AD Risk Prediction
Wisconsin ADRC Data



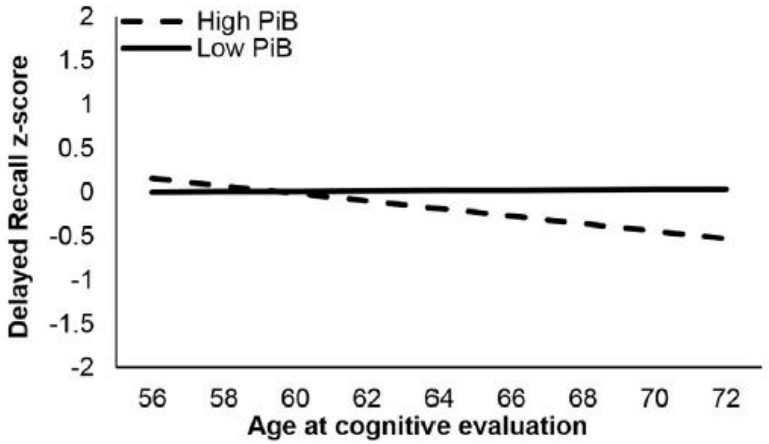
Annie M. Racine et al. Brain 2016;139:2261-2274

BRAIN A JOURNAL OF NEUROLOGY

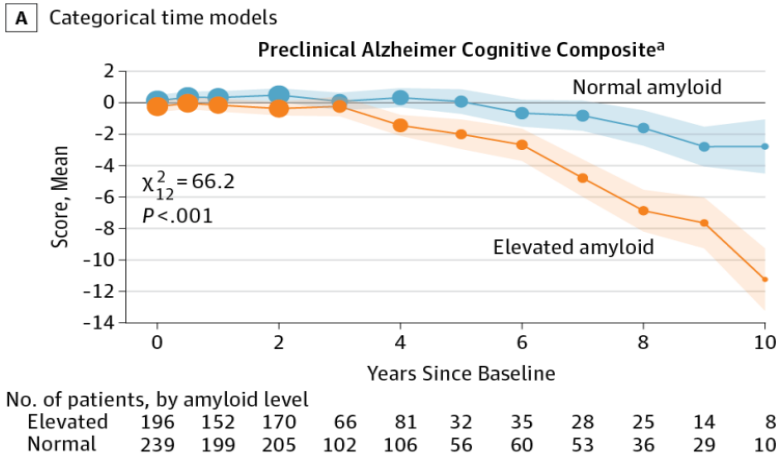
β-amyloid Burden in Cognitively Healthy Adults is Associated with Subtle Cognitive Decline



AIBL; Lim et al., 2014 BRAIN



WRAP; Clark et al., 2016 A&D



ADNI; Donohue et al., 2017 JAMA

Supported by recent meta-analyses

- Small to moderate differences observable on measures of global cognition, memory, language, visuospatial ability, processing speed, and executive functioning

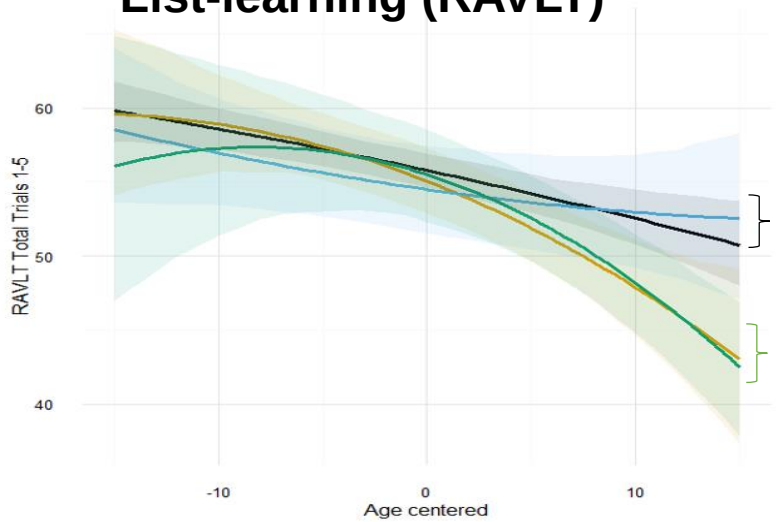
Baker et al., 2017; Alzheimer's & Dementia (DADM)
Han et al., 2017; Neuropsychology Review

Wisconsin ADRC: Aβ+ only and Aβ+/Tau+ Groups - Greater Rates of Non-Linear Cognitive Decline with Age on List-Learning and Set-Shifting

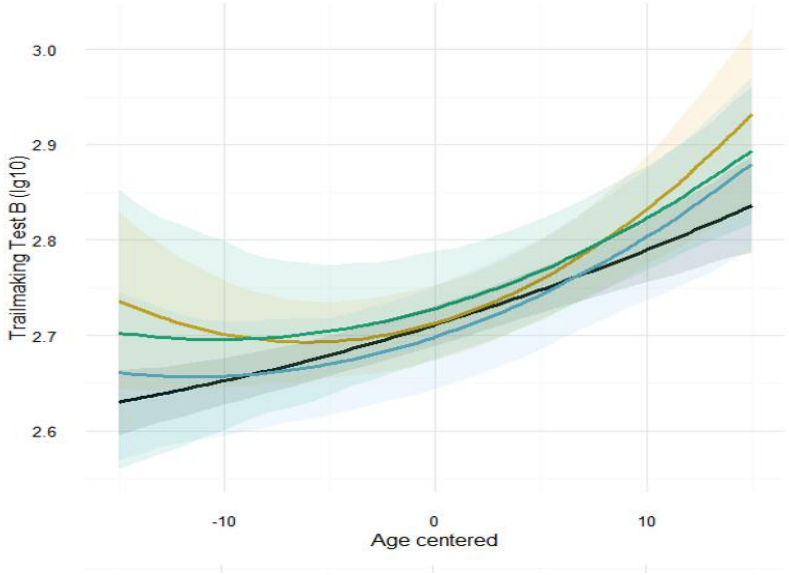
Fixed Effects:
Biomarker Group
Time (age at each visit – linear + quadratic)
Gender
Education
Practice Effects
Biomarker Group x Age at each visit (linear + quadratic)

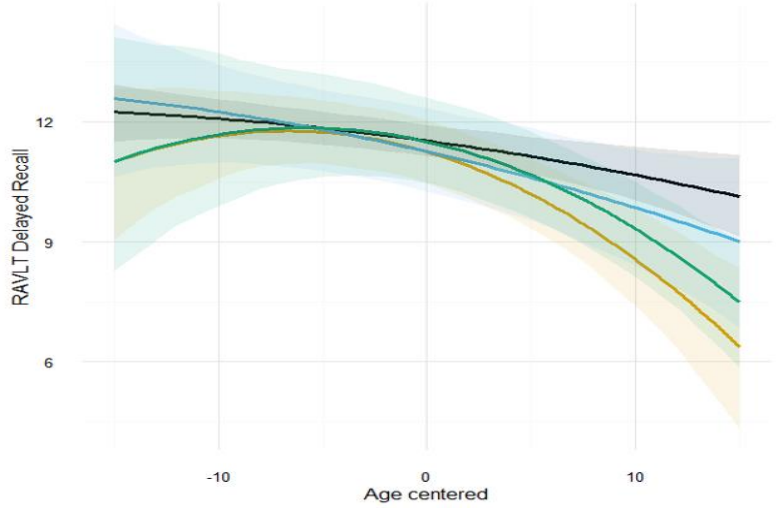
Random Effects:
Intercept
Slope

List-learning (RAVLT)



Executive Functioning (TMTB)



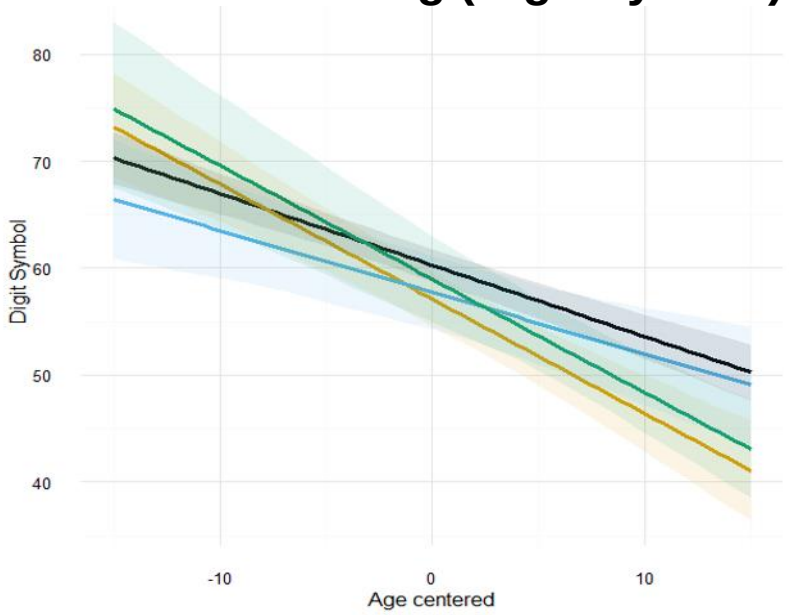


Time ⟶

Mixed-effects regression models (R lme4)

Wisconsin ADRC: CSF Biomarkers and Cognitive Function Trajectories in At Risk Study Participants

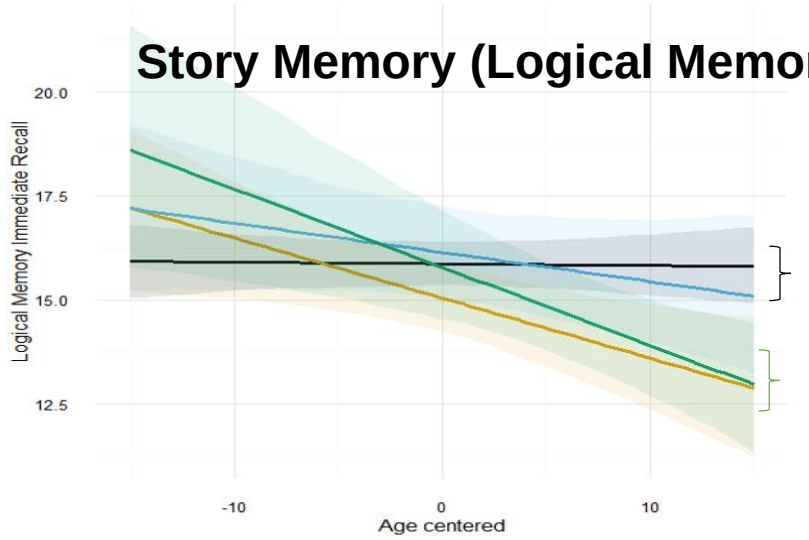
Executive Functioning (Digit Symbol)

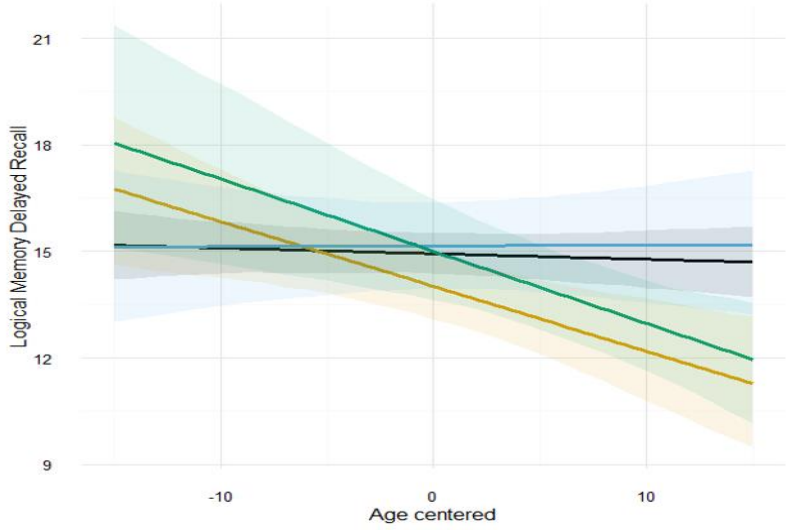


Fixed Effects:
Biomarker Group
Slope (Age at each visit)
Gender
Education
Practice Effects
Biomarker Group x Age at each visit

Random Effects:
Intercept
Slope

Story Memory (Logical Memory)



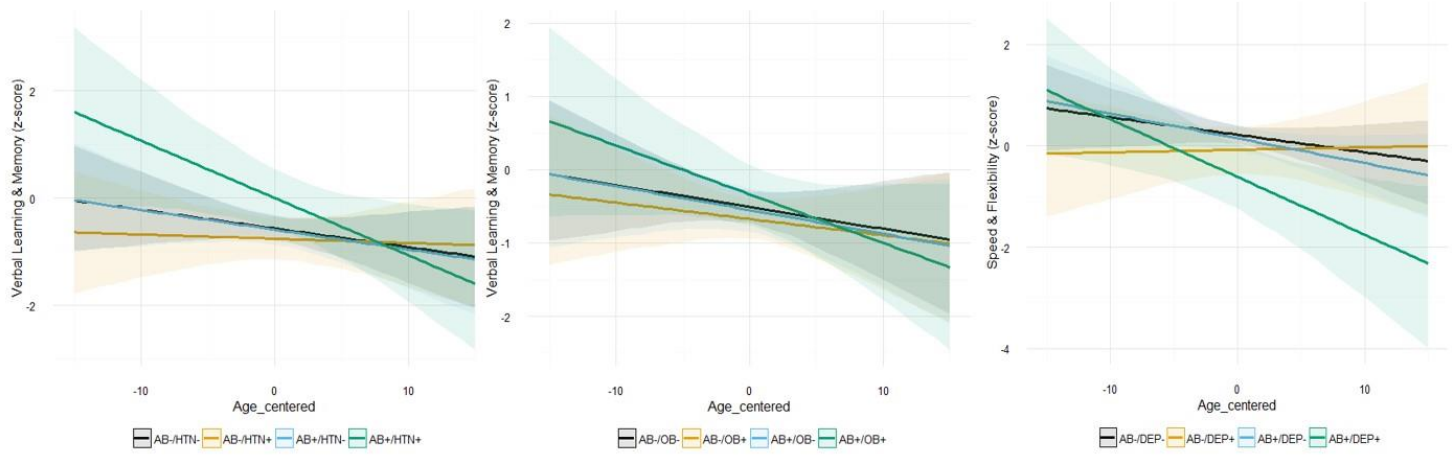


Time ⟶

Mixed-effects regression models (R lme4)

Wisconsin ADRC: CSF Positive Biomarker Groups & Modifiable Risk Factors

Modifiable factors that are differentially related to cognitive decline in biomarker positive subjects in late midlife



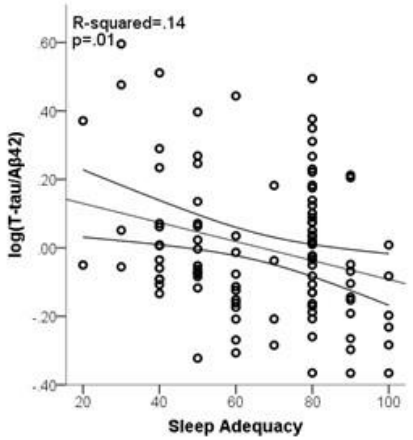
Hypertension | Obesity | Depression

Clark et al in review

Wisconsin ADRC: Healthy Behaviors and CSF and Imaging Markers of AD

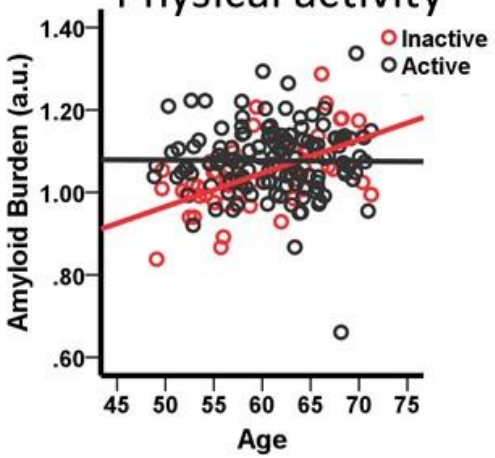
Health Behaviors and AD pathology / risk

Sleep



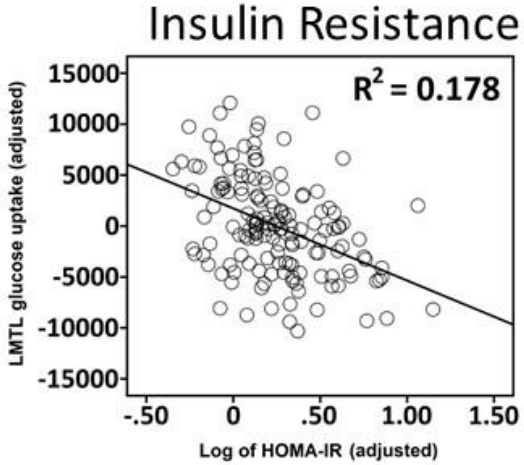
Associations with sleep and AD pathology
Sprecher et al *Neurology* (2017—in press)
Sprecher et al neurobiology of aging (2015)

Physical activity



Okonkwo et al 2014, *Neurology*
Greater phys activity --> lower amyloid burden with age

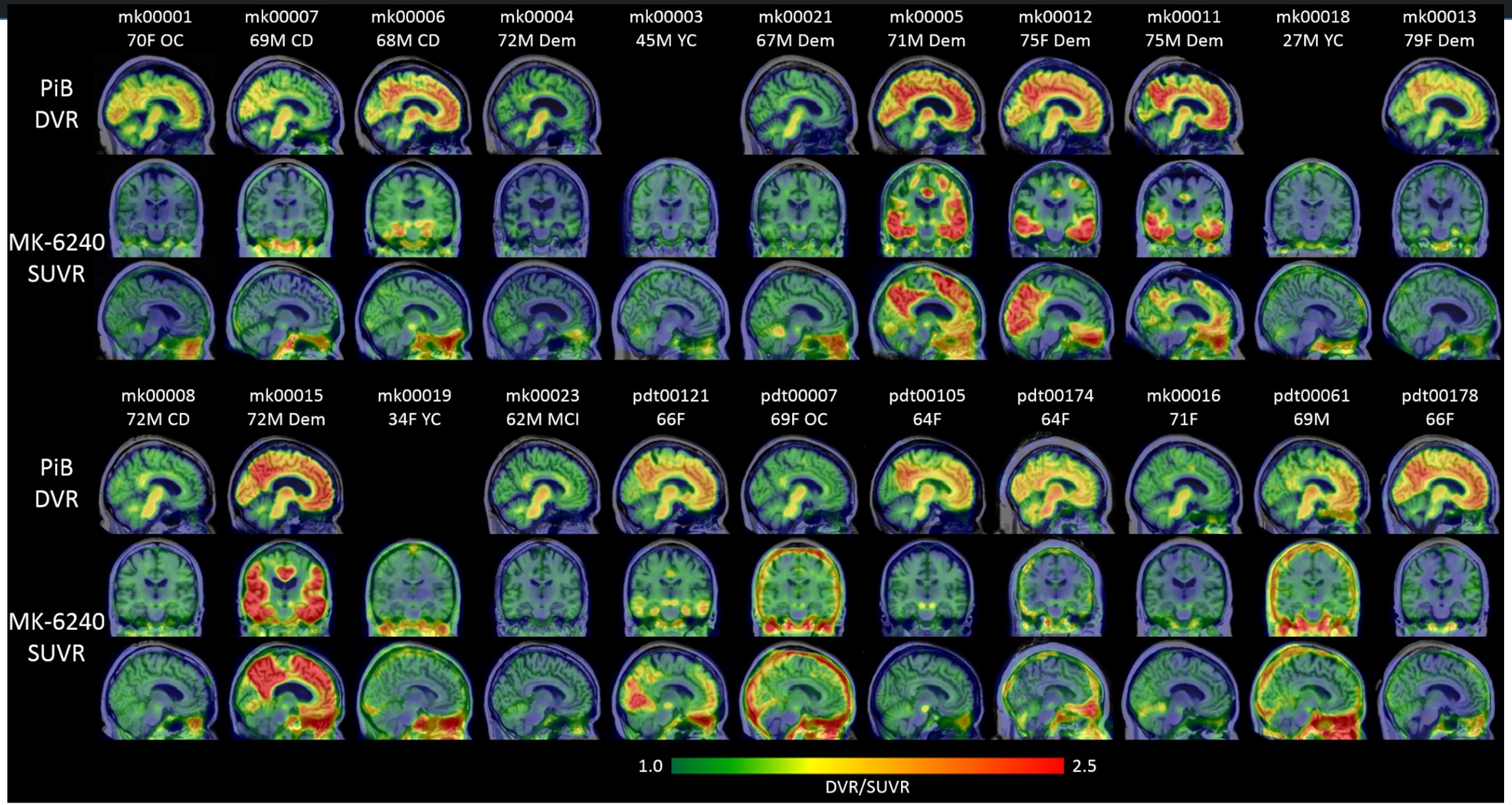
Insulin Resistance



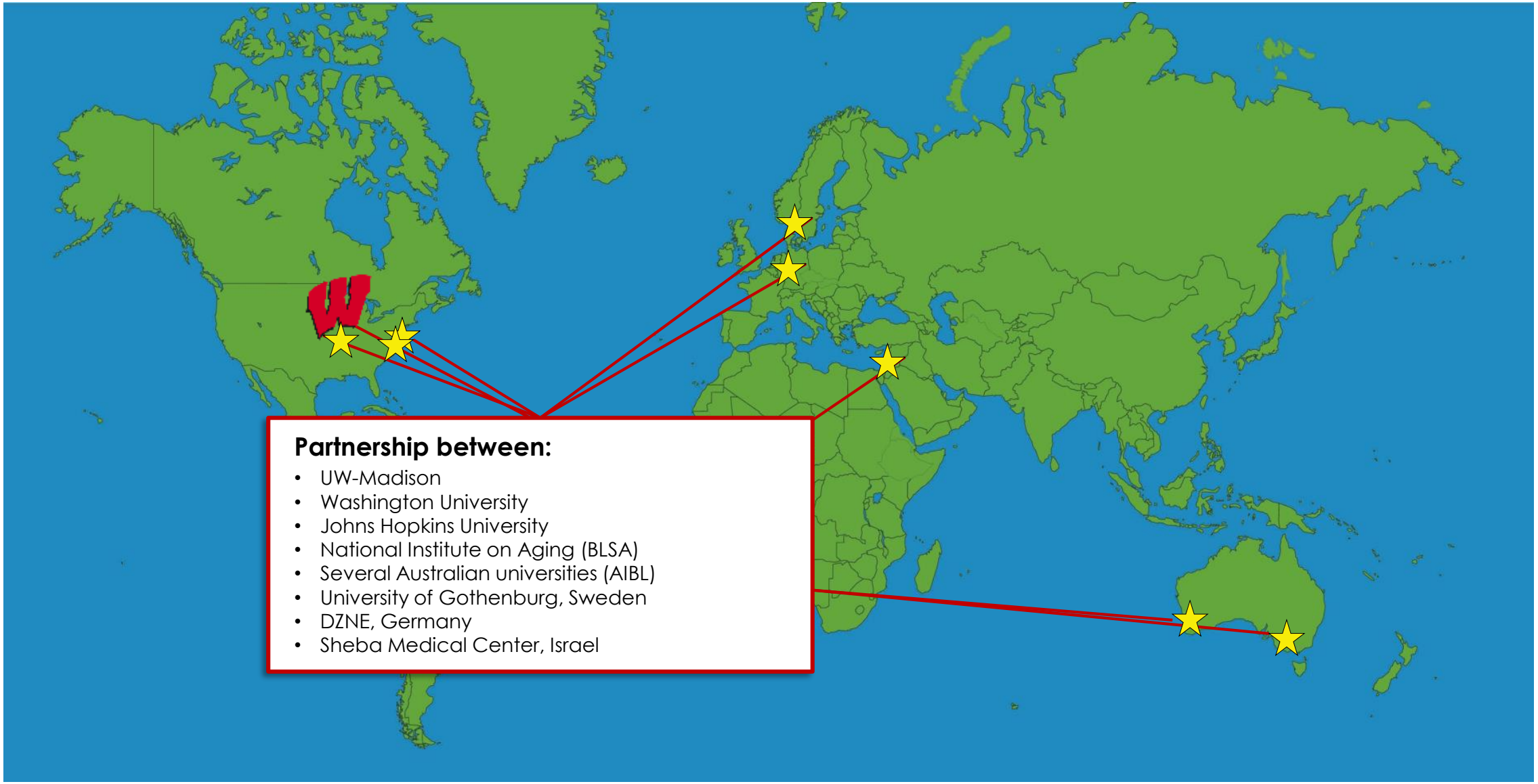
Insulin resistance is associated with FDG
Willette et al 2015 JAMA Neurol

Similar findings seen with amyloid
Willette et al 2013

Wisconsin ADRC: PIB amyloid and [F-18]MK6240 tau PET Ligands Across the AD Spectrum



Wisconsin Global Partnerships and Preclinical AD Consortium



Partnership between:

- UW-Madison
- Washington University
- Johns Hopkins University
- National Institute on Aging (BLSA)
- Several Australian universities (AIBL)
- University of Gothenburg, Sweden
- DZNE, Germany
- Sheba Medical Center, Israel

Conclusions

- The field of CSF Biomarkers of AD is rapidly expanding with the potential discovery of new mechanism-driven biomarkers
- An important caveat in interpretation of CSF biomarker data is variability in sample processing, storage, shipment and analytical techniques between studies and sites
- Better understanding of who is amyloid and tau positive and if they develop clinical symptoms will be key to understanding cognitive reserve and resilience to AD
- Beneficial effects of healthy behaviors on resilience and risk for AD could be assessed through CSF biomarkers
- CSF biomarkers of cognitive reserve have a high potential to predict and represent resilience to AD; they will become an important component of multimodal approaches to predict conversion from preclinical to clinical stages of AD
- The validity and clinical utility of newer CSF cognitive reserve and AD biomarkers has to be systematically evaluated