

Opportunities for Drug and Behavioral Interventions

David A. Bennett, M.D.

Director, Rush Alzheimer's Disease Center

Robert C. Borwell Professor of Neurological Sciences

Rush University Medical Center

Chicago, IL

Innovative Perspectives to Advance AD/ADRD Multidisciplinary Research

Boston, MA

November 11, 2025

Objectives

- Completed Drug and Behavioral Interventions for AD
- Ongoing Drug and Behavioral Interventions for AD
- Thought Experiment

Completed Drug and Behavioral Interventions

- Onder G, et al. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *Br J Psychiatry* 2005; 187: 450-5.
- Quintana-Hernández DJ, et al. Mindfulness in the Maintenance of Cognitive Capacities in Alzheimer's Disease: A Randomized Clinical Trial. *Journal of Alzheimer's disease : JAD* 2016; 50(1): 217-32.
- Bottino CM, et al. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. *Clin Rehabil* 2005; 19(8): 861-9.
- Aguiar P, et al. Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomized clinical trial. *Curr Alzheimer Res* 2014; 11(6): 532-7.
- Bergamaschi S AG,. One-year repeated cycles of cognitive training (CT) for Alzheimer's disease. *Aging Clin Exp Res* 2013; 25(4): 421.
- D'Onofrio G, et al. A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2015; 30(9): 965-75.

Completed Drug and Behavioral Interventions

- Onder G, et al. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *Br J Psychiatry* 2005; 187: 450-5.
- Quintana-Hernández DJ, et al. Mindfulness in the Maintenance of Cognitive Capacities in Alzheimer's Disease: A Randomized Clinical Trial. *Journal of Alzheimer's disease : JAD* 2016; 50(1): 217-32.
- Bottino CM, et al. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. *Clin Rehabil* 2005; 19(8): 861-9.
- Aguiar P, et al. Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomized clinical trial. *Curr Alzheimer Res* 2014; 11(6): 532-7.
- Bergamaschi S AG,. One-year repeated cycles of cognitive training (CT) for Alzheimer's disease. *Aging Clin Exp Res* 2013; 25(4): 421.
- D'Onofrio G, et al. A pilot randomized controlled trial evaluating an integrated treatment of rivastigmine transdermal patch and cognitive stimulation in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2015; 30(9): 965-75.

Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial

- Randomly assigned 79 of 156 patients on donepezil to a reality orientation programme (person-centered approach with consistent reminders about time, place, and person through conversation, environmental cues)
- Caregivers trained to perform the programme at home
- Main Outcome: MMSE and ADAS–Cog
- Duration: 3 days a week, 30min/day, 25 consecutive weeks; 70 completed as did 67 controls
- Results: Significant differences in favor of the treatment group were seen at the end

Mindfulness in the Maintenance of Cognitive Capacities in Alzheimer's Disease: A Randomized Clinical Trial

- 168 patients on donepezil with MMSE \geq 18 randomized to four groups
 - 43 donepezil
 - 42 donepezil + mindfulness (defined as “paying attention in a particular way: on purpose, in the present moment, and non-judgmentally”)
 - 38 donepezil + cognitive stimulation
 - 45 donepezil + muscle relaxation
- Main Outcome: MMSE and CAMCOG
- Duration: weekly group sessions of 90 min for two years; 288 sessions in 96 weeks; 29, 41, 38, 33 completed
- Results: Mindfulness was significantly better than control or muscle relaxation, and equivalent to cognitive stimulation

Bridging the gap: Efficacy of combined therapies for cognitive, behavioral, and functional outcomes in Alzheimer's disease - results from a systematic review and network meta-analysis

Donepezil plus cognitive therapy, and rivastigmine plus cognitive rehabilitation were the most effective treatments for improving cognitive outcomes. Rivastigmine plus cognitive stimulation ranked highest for both behavioral and functional outcomes, while exercise remains an important strategy for supporting daily functioning in patients with AD.

Objectives

- Completed Drug and Behavioral Interventions for AD
- Ongoing Drug and Behavioral Interventions for AD
- Thought experiment

Prevention of cognitive decline in subjective cognitive decline APOE ϵ 4 carriers after EGCG and a multimodal intervention (PENSA): Study design

- 200 APOE4+ persons with subjective cognitive decline (SCD)
- Randomized into four treatment arms
 - multimodal intervention + epigallocatechin gallate (green tea extract) or placebo
 - lifestyle recommendations + epigallocatechin gallate or placebo
 - Plus a non-randomized arm
- Main Outcome. Change in ADCS-PACC
- Duration: 12 months

A multimodal lifestyle intervention complemented with epigallocatechin gallate to prevent cognitive decline in APOE- ϵ 4 carriers with Subjective Cognitive Decline: a randomized, double-blinded clinical trial (PENSA study)

- 129 participants enrolled in the two control groups
 - 52 multimodal intervention (MLI) + epigallocatechin gallate (EGCG)
 - 52 multimodal intervention + placebo
 - 25 non-randomized
- 12-month washout
- They were compared to 25 non-randomized persons
- Main Outcome. Change in ADCS-PACC+
- Duration: Interim 12-month analyses
- Results: No difference observed between MLI+EGCG and MLI+placebo in the PACC-exe ($p=0.061$)

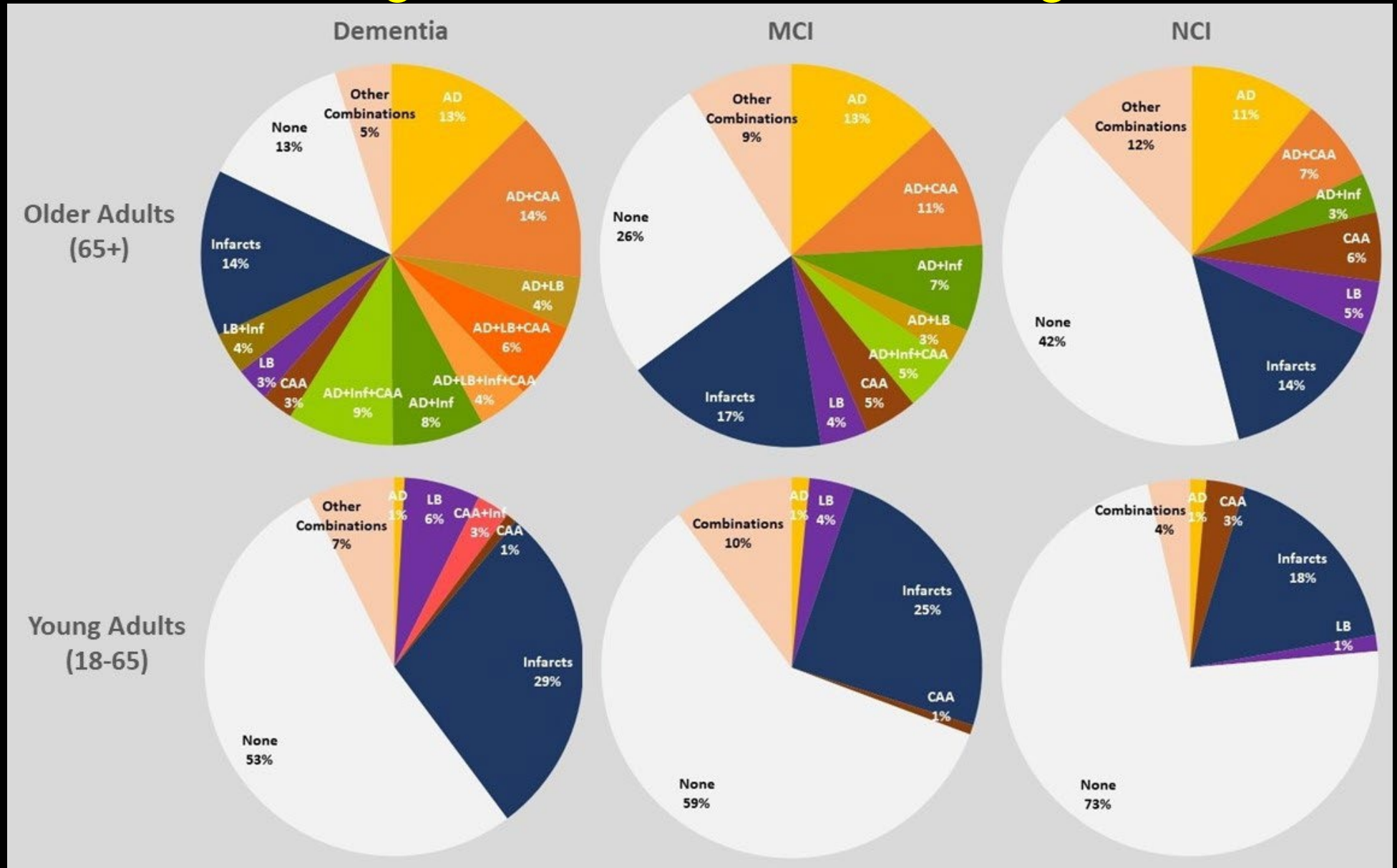
A multimodal precision-prevention approach combining lifestyle intervention with metformin repurposing to prevent cognitive impairment and disability: the MET-FINGER randomised controlled trial protocol

- Recruitment ongoing
- 600 older persons at risk for dementia
- Randomly assigned 1:1 to either a self-guided multidomain lifestyle intervention or to the FINGER 2.0 multidomain lifestyle-based intervention
- Within the FINGER 2.0
 - participants at increased risk of diabetes, will be randomly assigned 1:1:1 to either the metformin 2000mg/day, metformin 1000mg/day, or placebo group (double blinded).
- Duration: 24 months

Objectives

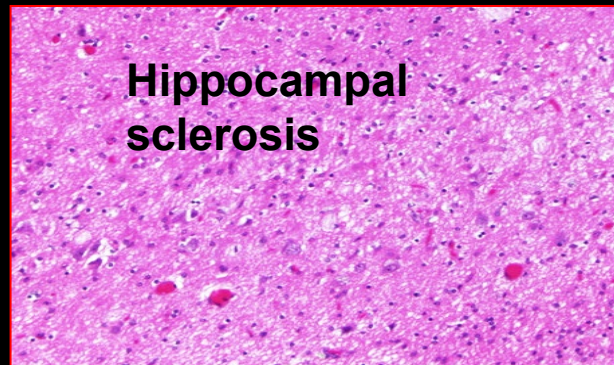
- Completed Drug and Behavioral Interventions for AD
- Ongoing Drug and Behavioral Interventions for AD
- Thought experiment

Mixed Brain Pathologies in 5300+ Brazilian adults age 18+





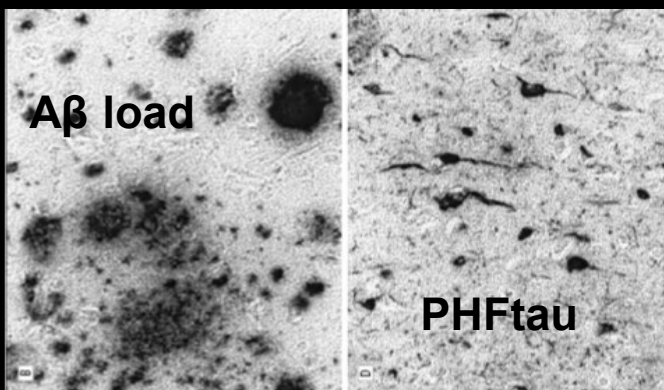
AD silver stain



Hippocampal sclerosis

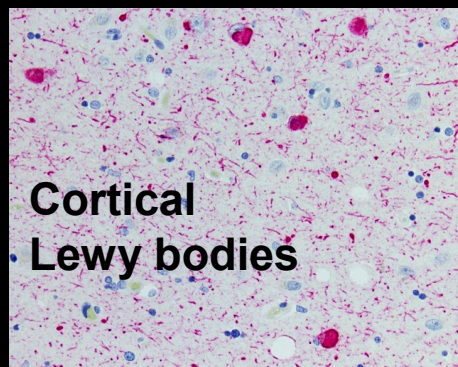


Atherosclerosis



Aβ load

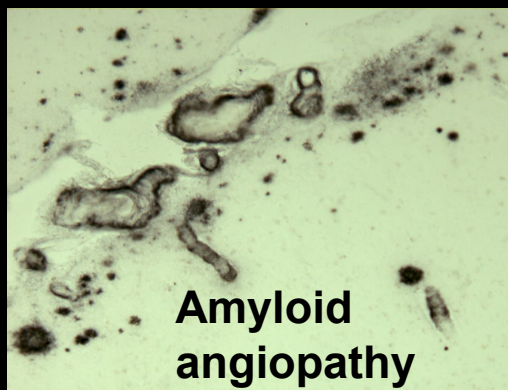
PHFtau



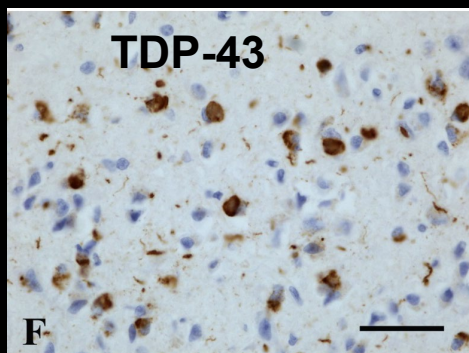
Cortical Lewy bodies



Arteriosclerosis



Amyloid angiopathy



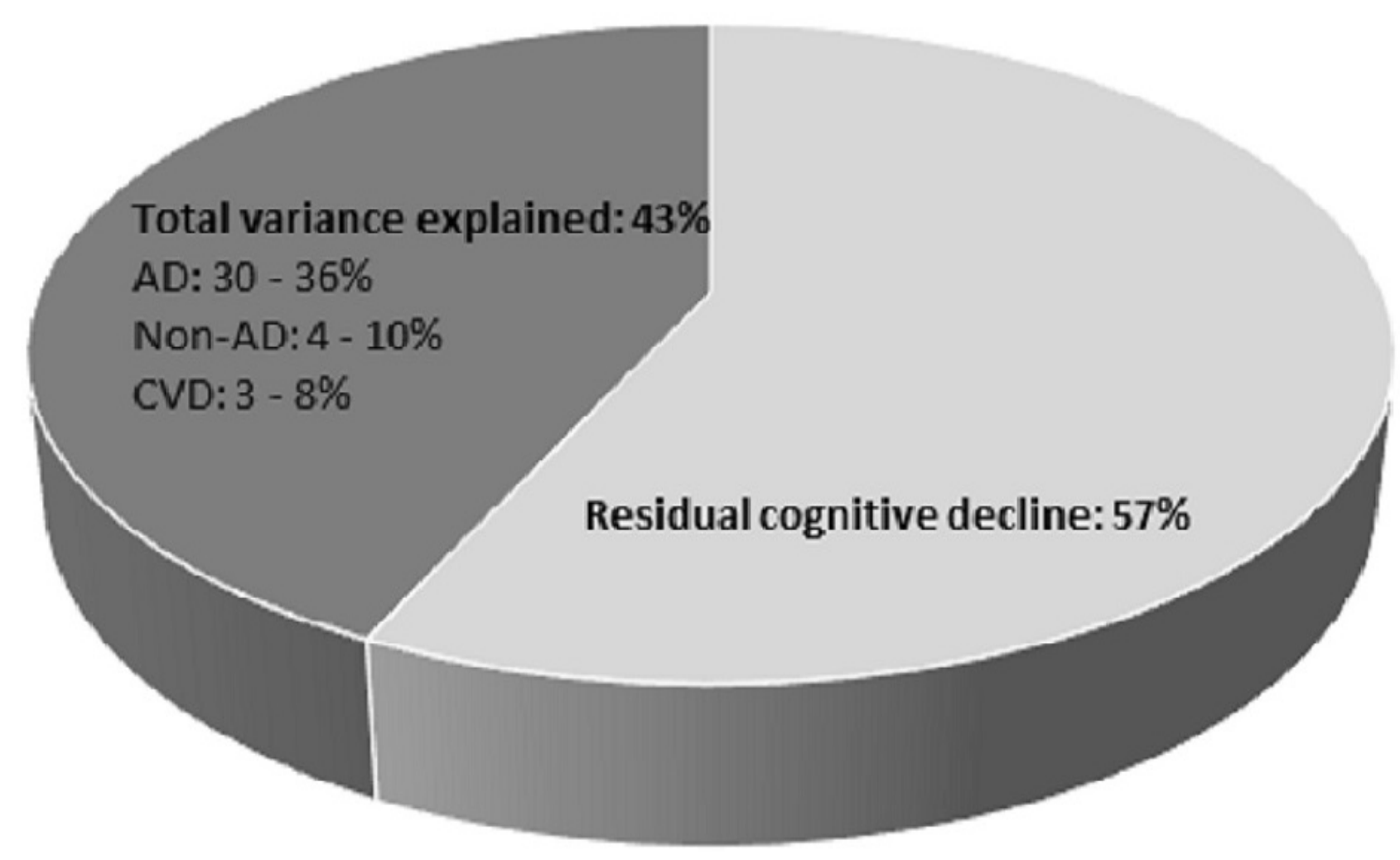
TDP-43

F

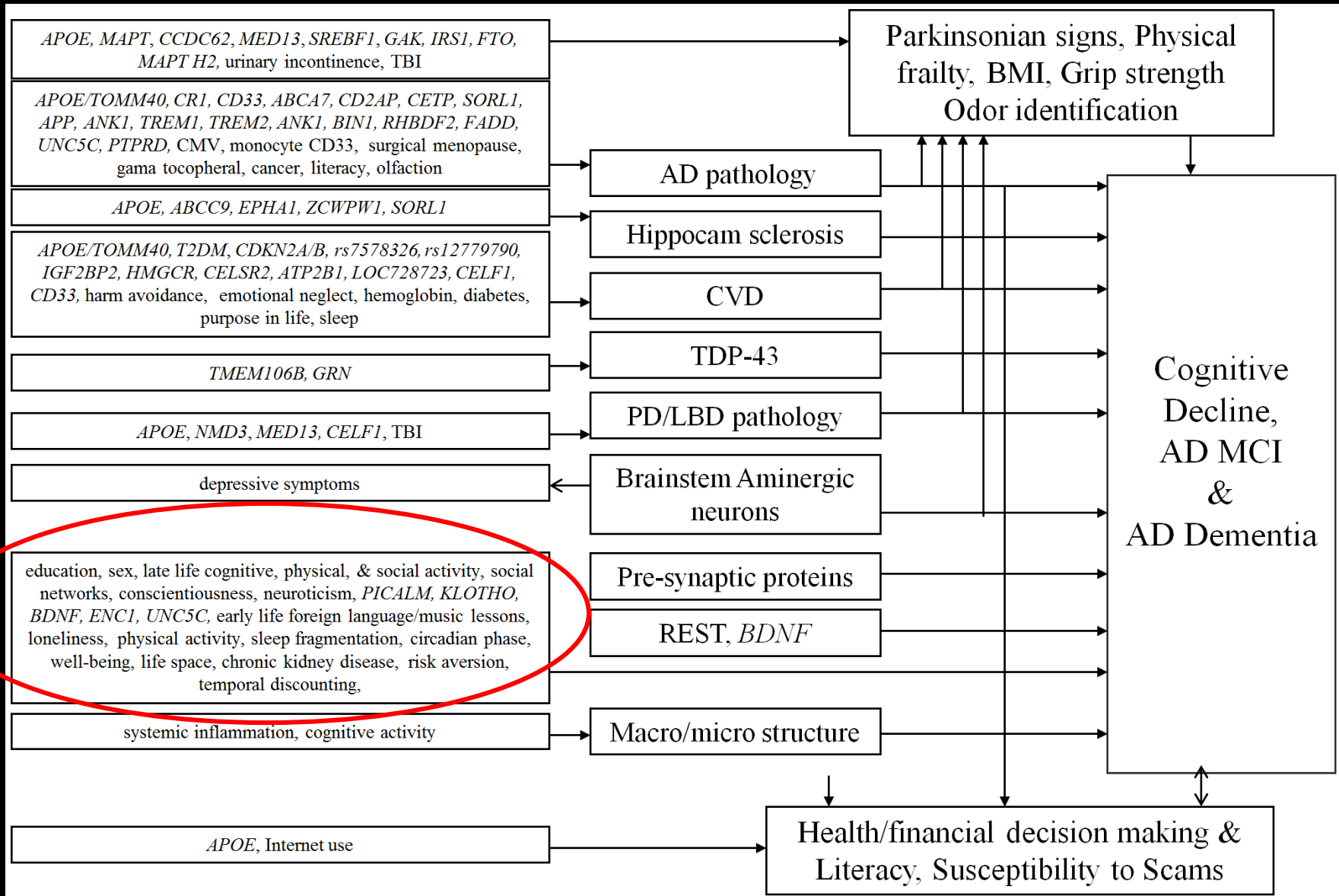


Infarct

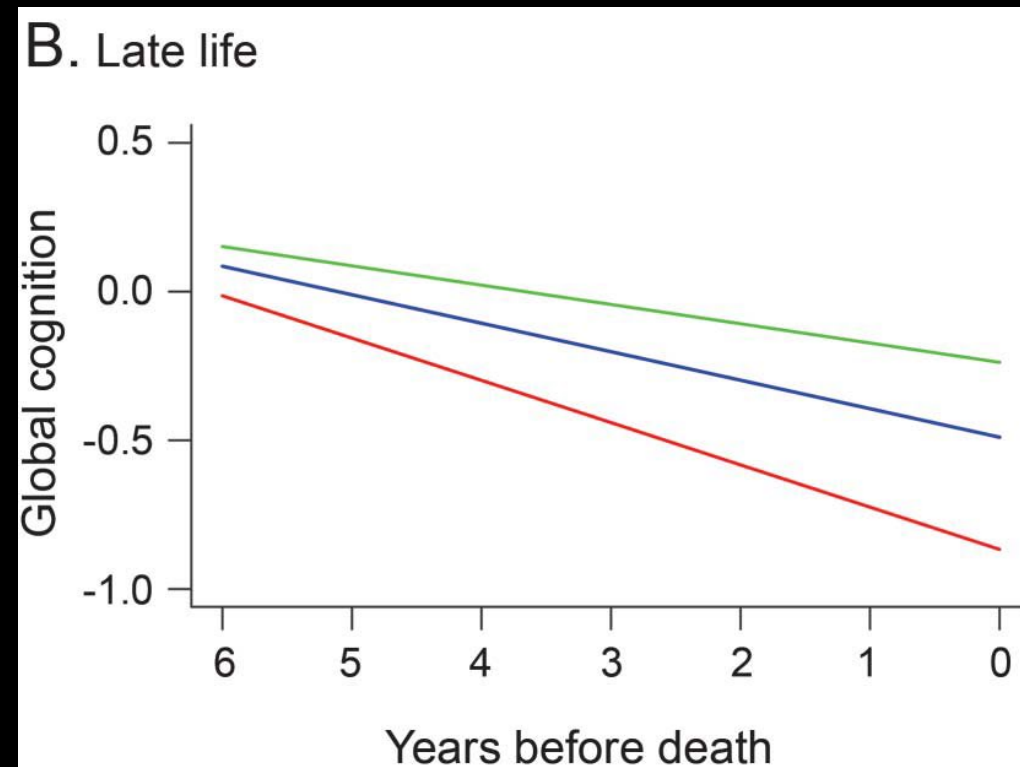
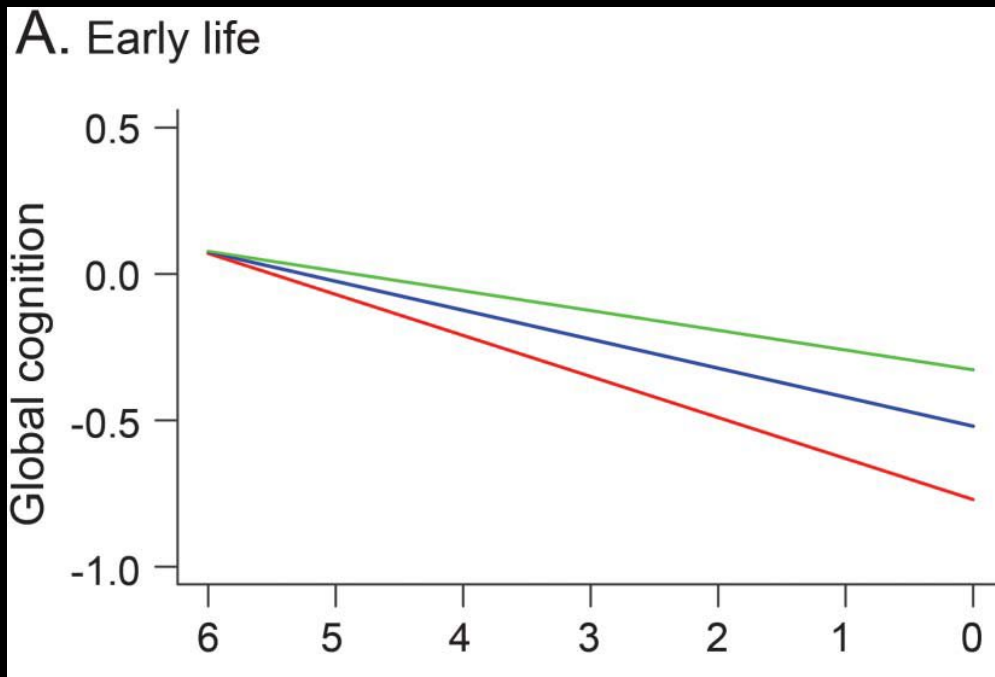
Variance of cognitive decline explained by common brain pathologies



Religious Orders Study and Rush Memory and Aging Project



Life-span cognitive activity, neuropathologic burden, and cognitive aging

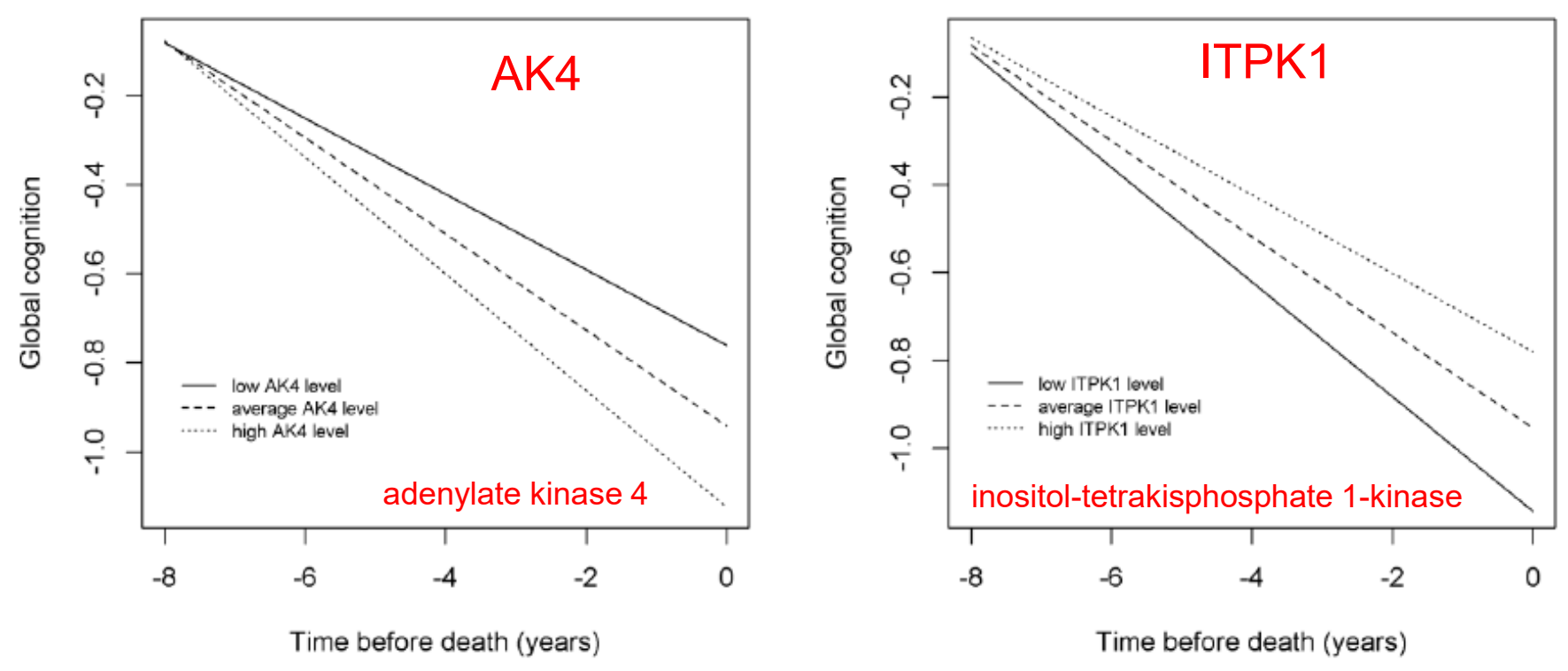


Controlled for demographics and common pathologies and early- or late-life.

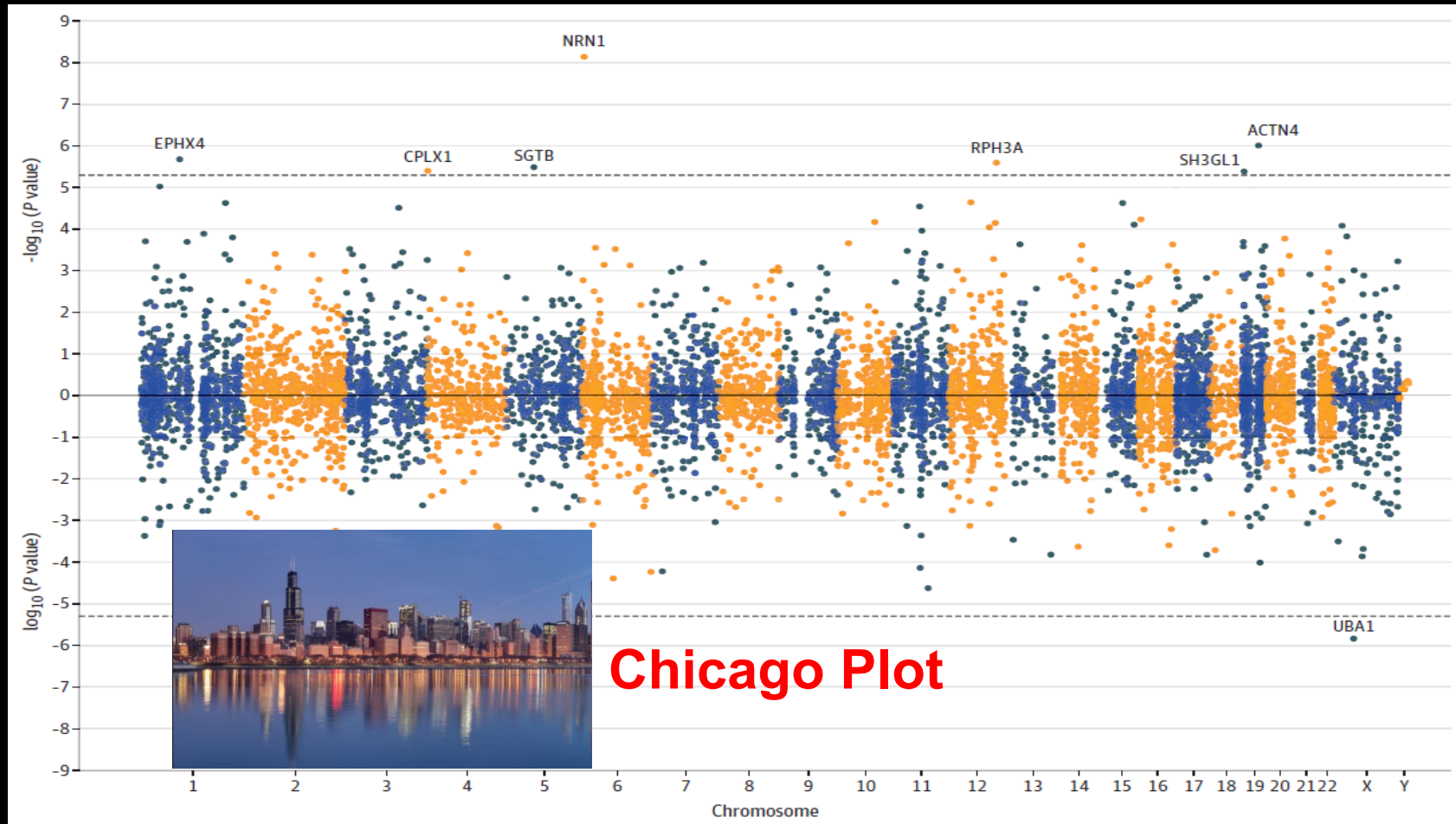
Thought Experiment

- Multiple pathologies contribute to cognitive decline
- The field is diligently working to identify
 - biomarkers for each pathology
 - A drug cocktail targeting each pathology
- The public health imperative is disease prevention
- Imagine surveilling 150 million at risk Americans with numerous biomarkers over time and then offering them one, two, three or more cocktails for prevention?
 - No country can afford that!
- Most cognitive decline is not related to extant pathologies
- Many risk factors, in particular cognitive, physical, and social activities protect against cognitive decline but are not related to any brain pathology – they promote resilience
- Targeting resilience is the most cost-effective approach to prevention
- But is resilience druggable?

By leveraging the full spectrum of resilience, we can find proteins a/w with less (AK4) and more (ITPK1) resilience



Proteome-wide association study finds proteins associated with more (top) and less (bottom) resilience



Summary

- Most drug and behavioral interventions for AD were randomized behavior intervention as an adjunct to standard medication use
 - Most show some additional benefit of the intervention
- Two modest size ongoing behavioral intervention trials one with nutraceutical and one drug
- The scientific community should complement work on pathologies with work on identifying drugs for resilience
- A drug for resilience would pair well with the kinds of behavioral interventions that have been, are, and will be done