Defining Types of Dementia

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Disclosures

I have no relevant disclosures.

The charge is to address four issues:

1. Diagnosis of different types of ADRD
2. Detection
3. Review the trajectory of each type of dementia
4. Racial and ethnic differences

5. Neurobiology of ADRD
6. Implications for risk factor associations

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Dementia is diagnosed when there are cognitive or neuropsychiatric symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder

Cognitive impairment is detected through a combination of:

1. History the patient and a knowledgeable informant and
2. An objective cognitive assessment

The cognitive or behavioral impairment involves two or more of the following domains

1. impaired ability to acquire and remember new information
2. Impaired reasoning and handling of complex tasks, poor judgment
3. Impaired visuospatial abilities
4. Impaired language functions
5. Changes in personality, behavior, or comportment

McKhann GM, et al. *Alzheimer's & Dementia*. 2011;7:263-269.

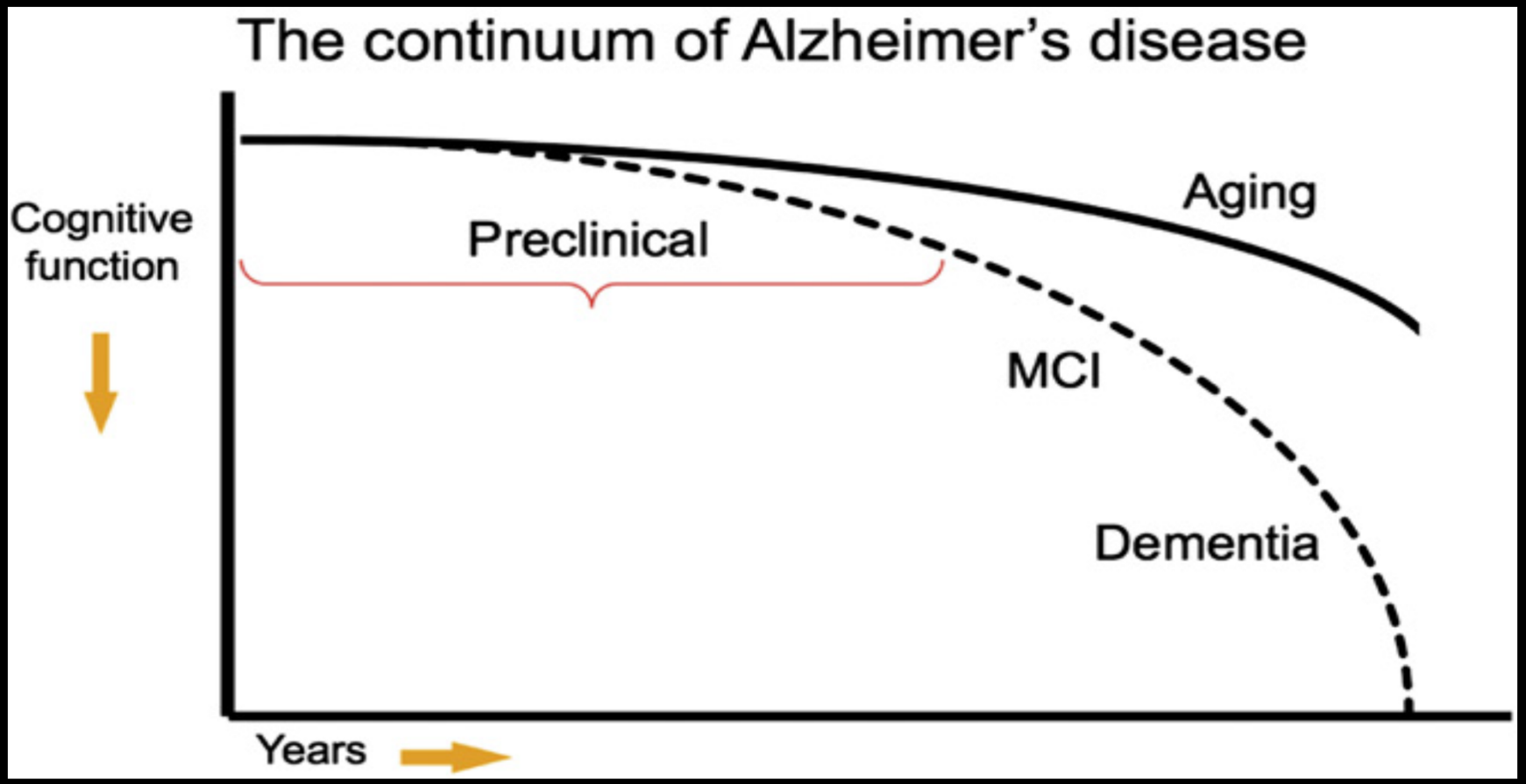
The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Diagnosis of MCI

1. Cognitive concern reflecting a change in cognition reported by patient or informant or clinician.
2. Objective evidence of Impairment in one or more cognitive domains.
3. Preservation of independence in functional abilities

Albert M, et al. *Alzheimer's & Dementia*. 2011;7:270-279.

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease



Sperling R, et al. *Alzheimer's & Dementia*. 2011;7:280-292.

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Meets criteria for dementia and has the following characteristics:

1. Insidious onset over months to years;
2. Clear-cut history of worsening of cognition by report or observation; and
3. The initial and most prominent cognitive deficits in one of the following: a. Amnesia; b. Non-amnestic presentations: Language, Visuospatial ability, Executive dysfunction

MCI due to AD Criteria is similar to AD except that it meets criteria for MCI rather than dementia.

McKhann GM, et al. *Alzheimer's & Dementia*. 2011;7:263-269.

Vascular Contributions to Cognitive Impairment and Dementia

Probable VaD

1. Cognitive impairment and imaging evidence of CVD, and
    1. Temporal relationship between a vascular event and onset of cognitive deficits, or
    2. Relationship between the severity and pattern of cognitive impairment and the presence of diffuse, subcortical CVD
2. No history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder

Gorelick PB, et al. *Stroke*. 2011;42:2672-2713.

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

McKeith IG, et al. *Neurology*. 2017;89:88-100.

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Rascovsky K, et al. *Brain*. 2011;134:2456-2477.

Diagnosis and Management of Dementia: A Review.

	DISEASE*			
	Alzheimer's disease (AD)	**Cerebrovascular Disease*** **	**Lewy body disease**	**Frontotemporal dementia**
PATHOLOGIC CHARACTERISTICS	Brain atrophy especially of the mesial temporal lobe; histologic hallmarks of neuritic plaques containing β amyloid and neurofibrillary tangles containing phosphorylated tau	Small, often cystic chronic infarcts (lacunar infarcts), multiple microinfarcts, or large infarcts including intracerebral hemorrhage; age of infarcts may be variable in the same person, including chronic and acute; cerebral vessel pathology such as atherosclerosis and arteriolosclerosis; white matter gliosis; focal brain atrophy	Brain atrophy, often generalized; intraneuronal Lewy body inclusions containing α synuclein, including in the neocortex (as opposed to inclusions restricted to the substantia nigra, as seen in Parkinson disease)	Focal brain atrophy affecting frontal**** and/or anterior temporal lobes, histologic hallmarks of phosphorylated Transactive response DNA-binding Protein 43 (TDP-43), microtubule-associated protein tau (MAPT), or fused-in-sarcoma (FUS) protein
ONSET AND COURSE	Slow onset and gradual progression over months or years	Temporal relation between acute vascular event (stroke) and onset of cognitive impairment, within minutes or days; stepwise course	Slow onset and gradual progression over months or years; fluctuations in levels of alertness and cognition	Slow onset and gradual progression over months or years
HISTORY, EXAM, AND COGNITIVE FEATURES IN THE *EARLY* STAGE**	History: presenting symptoms is typically short-term memory loss Exam and/or cognitive testing: episodic memory impairment accompanied by other subtle cognitive deficits, such as visuospatial problems and anomia	History: vascular risk factors (e.g., hypertension, diabetes) or prior stroke or other vascular events (myocardial infarction) Exam: focal neurologic deficits consistent with stroke such as unilateral weakness and hyperreflexia, Babinski sign Neuroimaging: evidence of cerebrovascular disease, such as infarcts or significant white matter changes (unilateral or bilateral) on magnetic resonance imaging (MRI)	History: Rapid Eye Movement (REM) Behavior Disorder (RBD) for years preceding the cognitive impairment; visual and other hallucinations Exam and/or cognitive testing: marked visuospatial problems with relative preservation of memory; parkinsonism, especially with bradykinesia and rigidity, but also stooped posture and slow and shuffling gait	History: marked changes in behaviors such as in personality (e.g., disinhibition, apathy) Exam and/or cognitive testing documenting disinhibition and inappropriate behaviors; in language variant, impaired fluency in speech, semantic paraphrasias; other significant executive or language problems, with relative preservation of memory

Arvanitakis Z, et al. *JAMA*. 2019;in press.

Cochrane Review Summary:
Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations

Community Studies

MMSE* at cut point 24 (indicating normal); 15 studies
sensitivity 0.85
specificity 0.90
dementia prevalence 7.4%
MMSE at cut point 25; 10 studies
sensitivity 0.87
specificity 0.82
dementia prevalence 8.4%
When adjusted for education; 7 studies (2 high risk of bias)
specificity was 0.70
sensitivity 0.97
dementia prevalence 13.8%

MMSE is proprietary

Trivedi D. *Prim Health Care res & Dev*. 2017;18:527-528.

Cognitive Tests to Detect Dementia
A Systematic Review and Meta-analysis

Clinic patients

11 screening tests were identified among 149 studies with 49,000+ participants

MMSE (n = 102) and included 10,000+ patients with dementia. sensitivity and specificity were 0.81 and 0.89

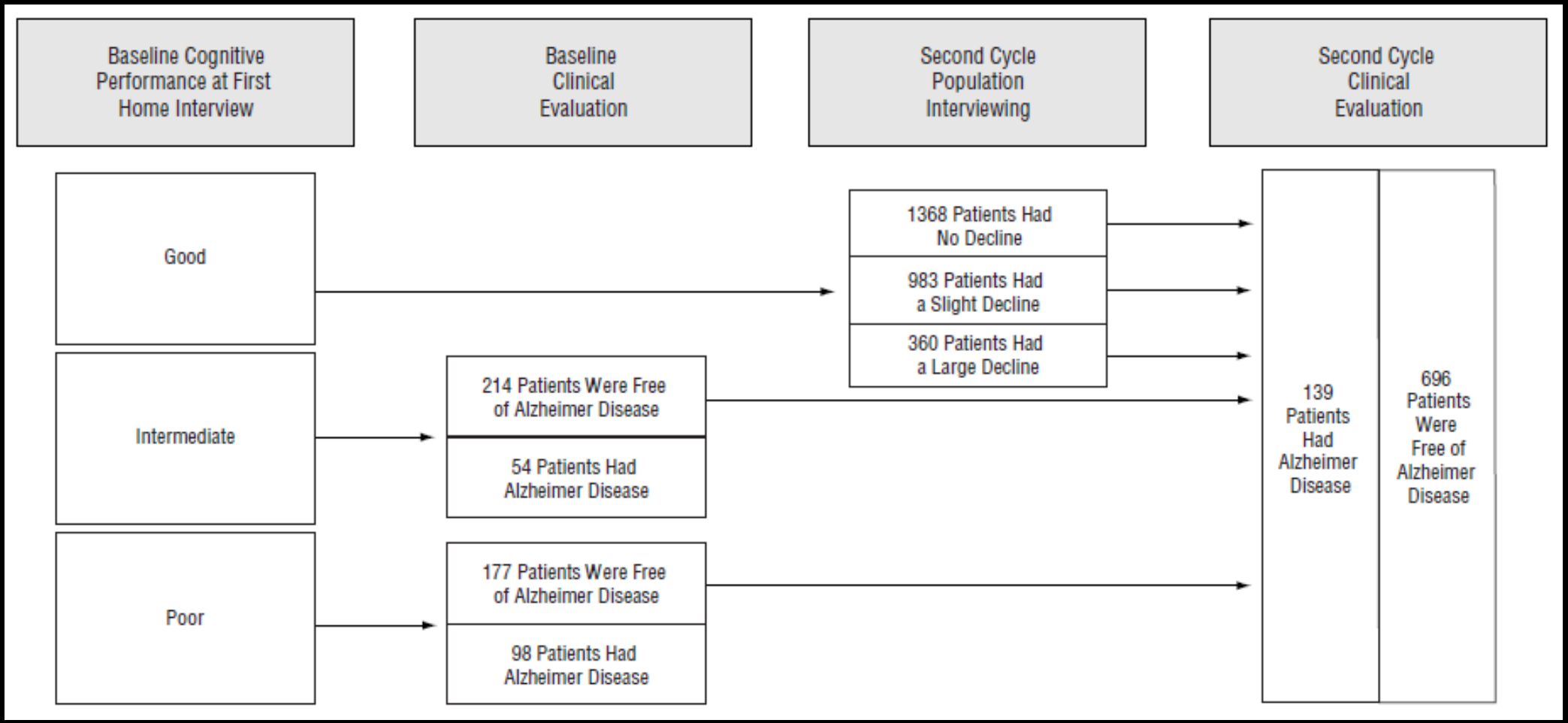
Mini-Cog, 0.91 sensitivity and 0.86 specificity for dementia

Addenbrooke's Cognitive Examination–Revised (ACE-R) 0.92 sensitivity and 0.89 specificity) for dementia

Montreal Cognitive Assessment (MoCA) 0.89 sensitivity and 0.75 specificity for MCI

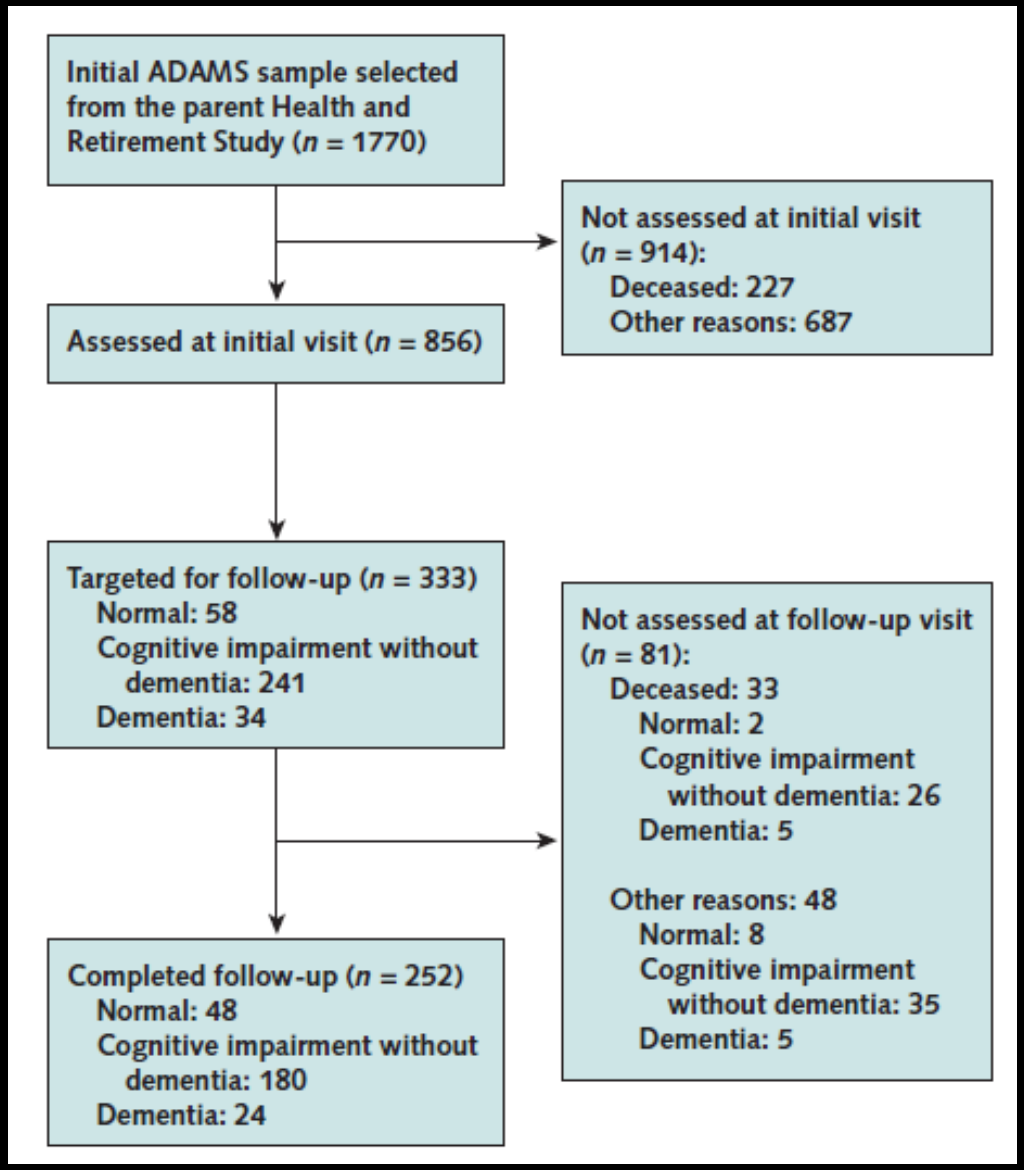
Tsoi KK, et al. *JAMA Int Med*. 2015;18:1450-1458.

Incidence of Alzheimer Disease in a Biracial Urban Community



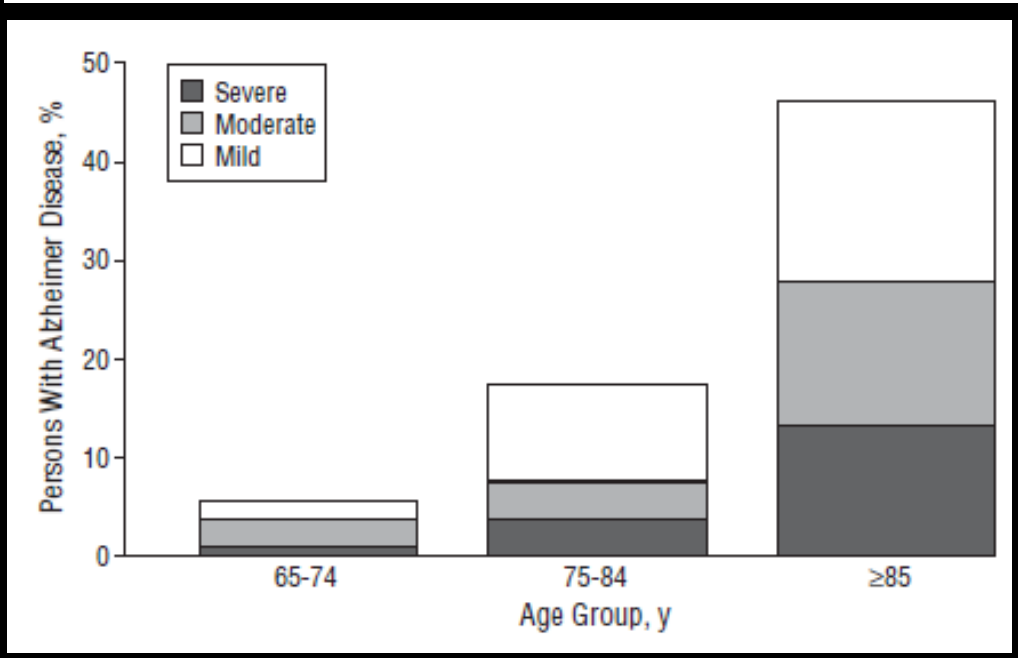
Evans DA, et al. *Arch Neurol*. 2003;60:185-189.

Prevalence of Cognitive Impairment without Dementia in the United States



Plassman BL, et al. *Ann Int Med*. 2008;148:427-434.

Alzheimer Disease in the US Population



Hebert LE, et al. *Arch Neurol*. 2003;60:1119-1122.

In 2000 4.5 million with AD age 65+
(half with mild dementia)

Dementia prevalence age 71+ = 13.9%, 3.4 million individuals in the USA
In 2002 AD was 9.7% and 2.4 million individuals
Prodromal AD (CIND) 2 million
Other CIND 3.4 million
Dementia prevalence increased from 5.0% 71–79 years to 37.4% 90+

Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study

Plassman BL, et al. Neuroep*idemiol*. 2007;29:125-132.

Sources of variability in estimates of the prevalence of Alzheimer's disease in the United States

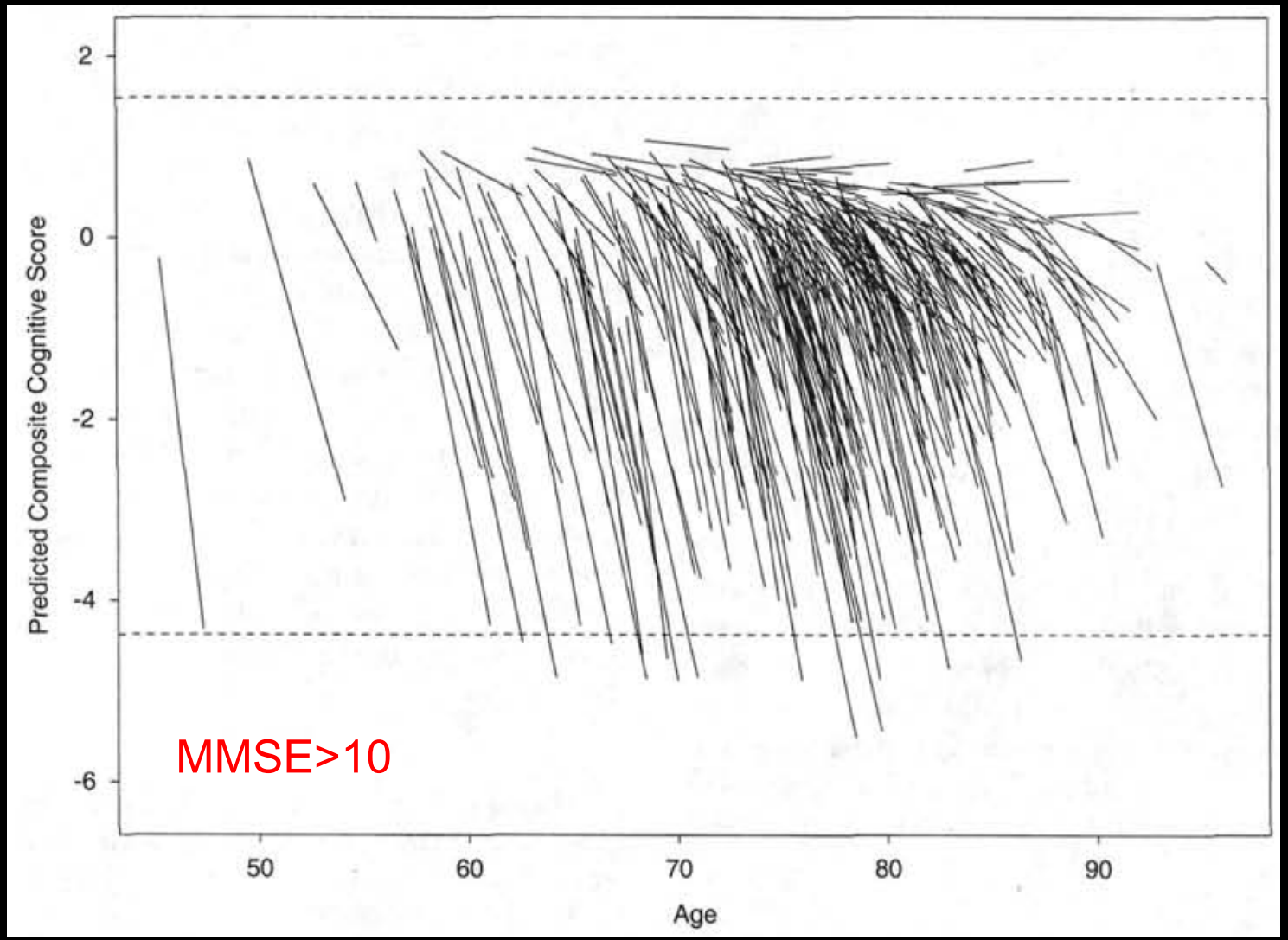
Conclusion:

"The diagnosis of AD in population studies is a complex process. When a diagnosis of AD excludes persons meeting criteria for vascular dementia,
when not all persons with dementia are assigned an etiology, and when a diagnosis of dementia requires an informant report of functional limitations,
the prevalence is substantially lower and the diagnosed cases most likely have a relatively higher level of impairment."

Wilson RS, et al. *Alz & Dement*. 2011;7:74-79.

Person-Specific Paths of Cognitive Decline in Alzheimer's Disease and Their Relation to Age

Clinic AD patients: Younger persons decline faster

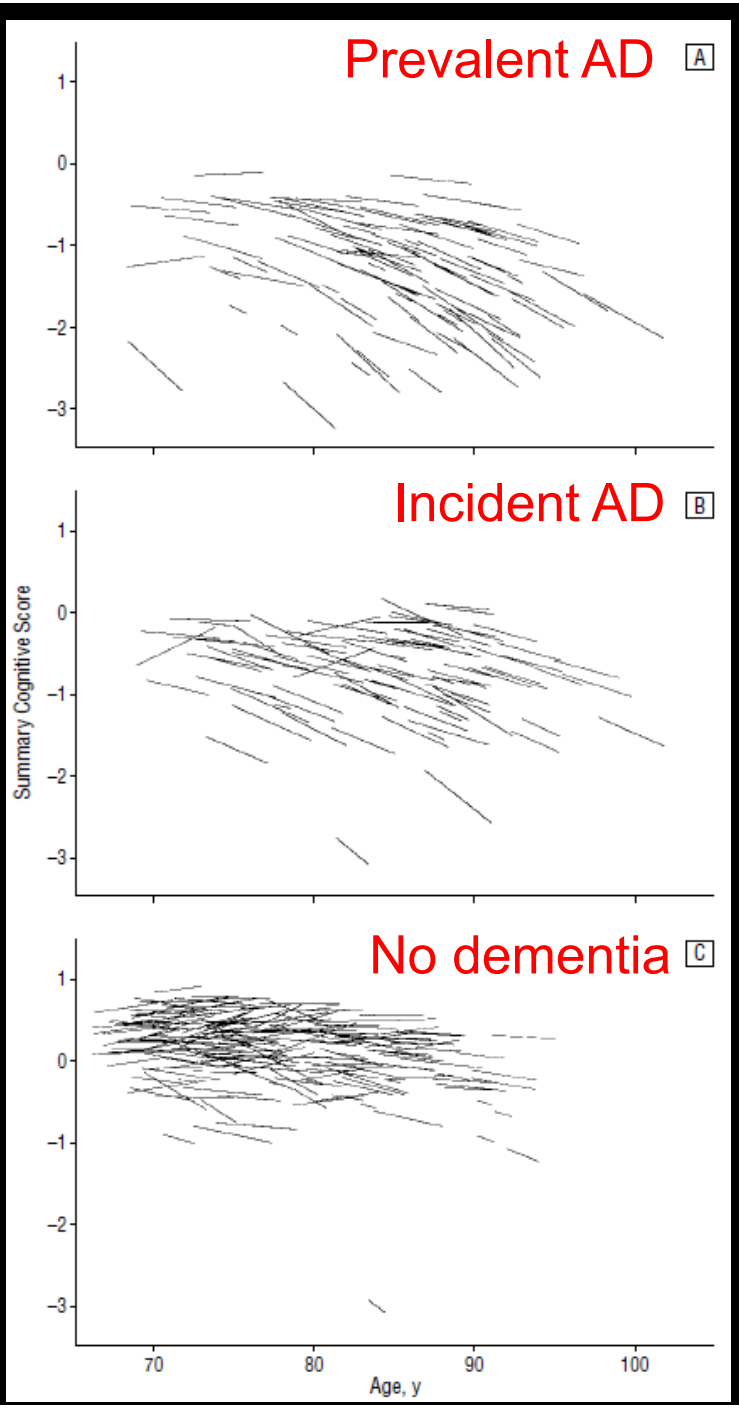


Wilson RS, et al. *Pscyh & Aging*. 2000;15:18-28.

Change in Cognitive Function in Older Persons From a Community Population

East Boston

Community AD participants:
Older persons decline faster



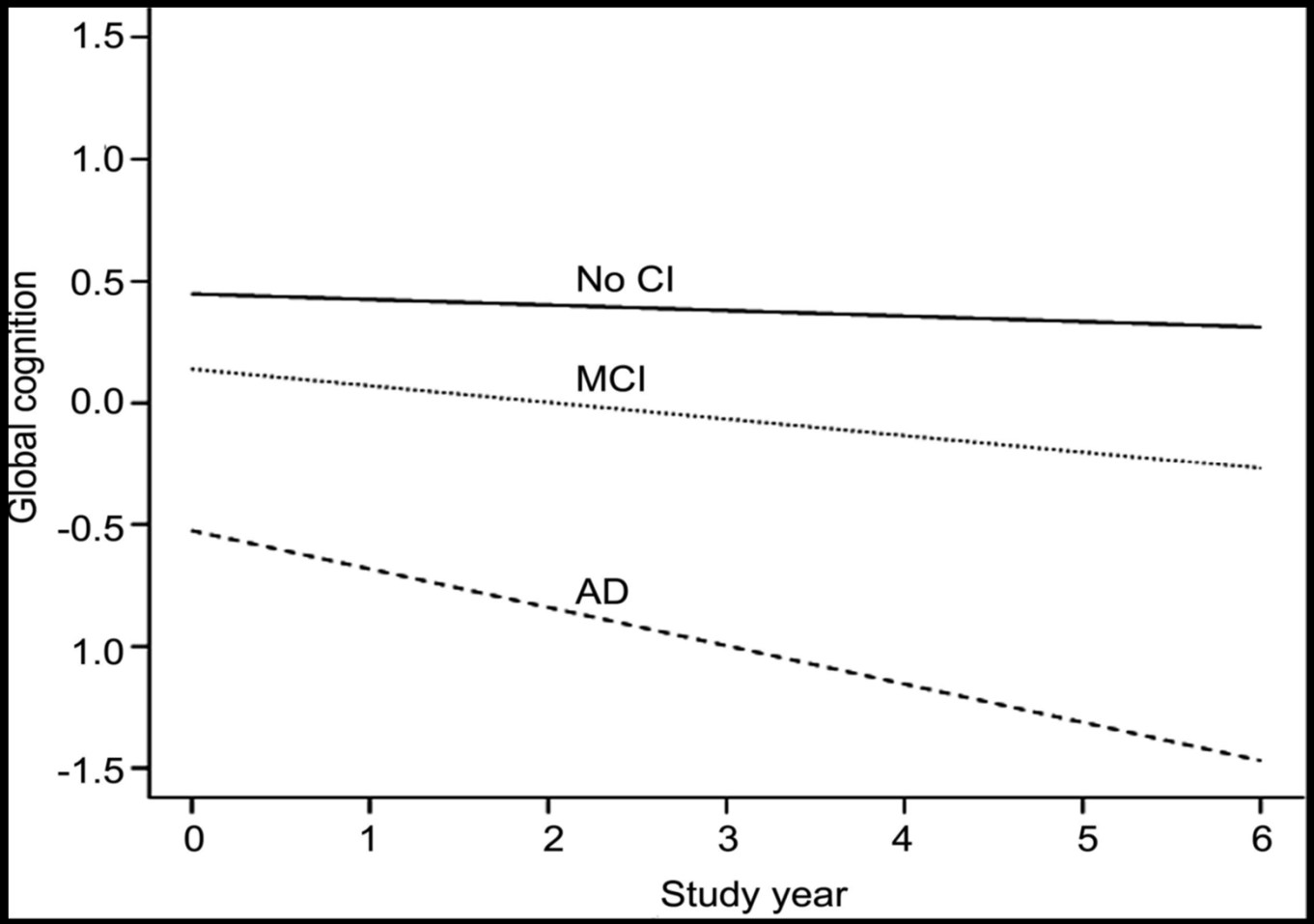
Wilson RS, et al. *Arch Neurol*. 1999;56:1274-1279.

Cognitive decline in incident Alzheimer disease in a community population

CHAP

Community AD participants: Older persons decline faster

Comparable effects in African American and white persons.

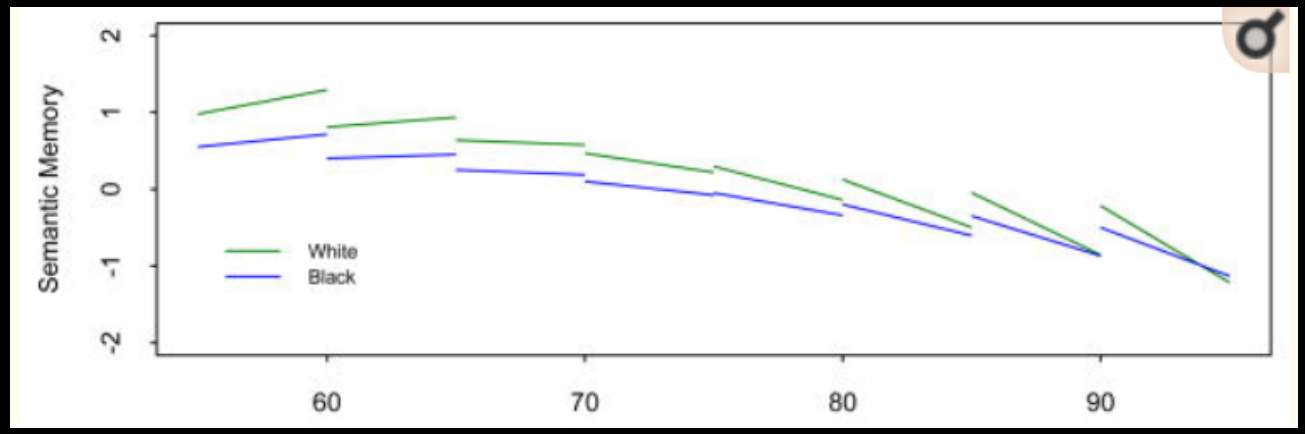


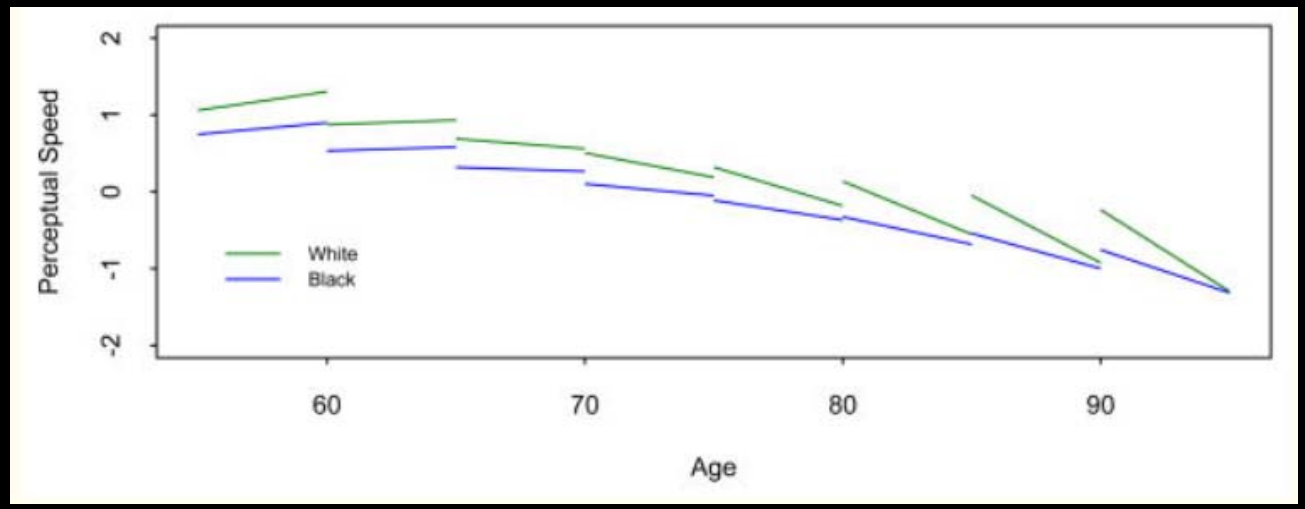
Wilson RS, et al. *Neurol*. 2010;74:951-955.

Cognitive Aging in Older Black and White Persons

CHAP

Baseline level of each ability lower in Blacks
Decline in episodic and working memory not related to race
Decline in semantic memory, perceptual speed, and visuospatial ability was slower in Blacks
in semantic memory and perceptual speed the effect was stronger in older participants.





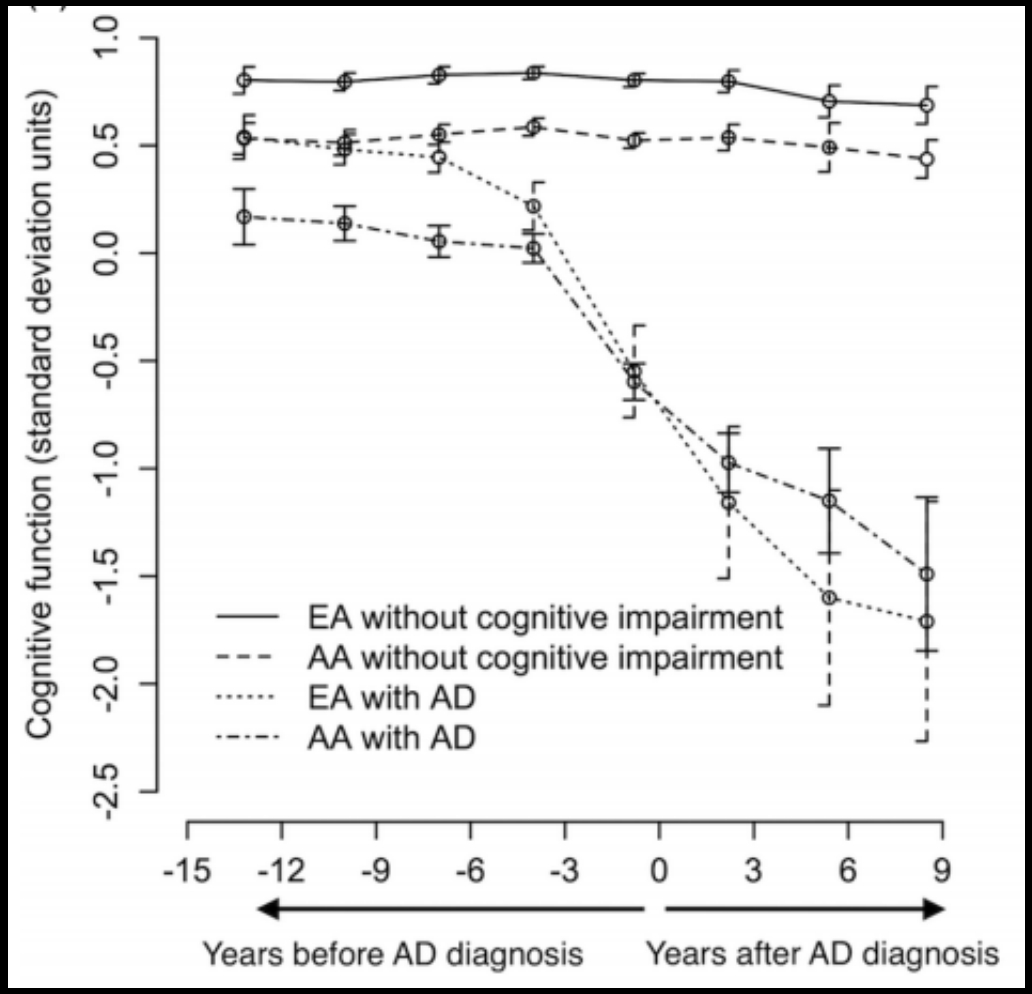
Adjusted for retest effects

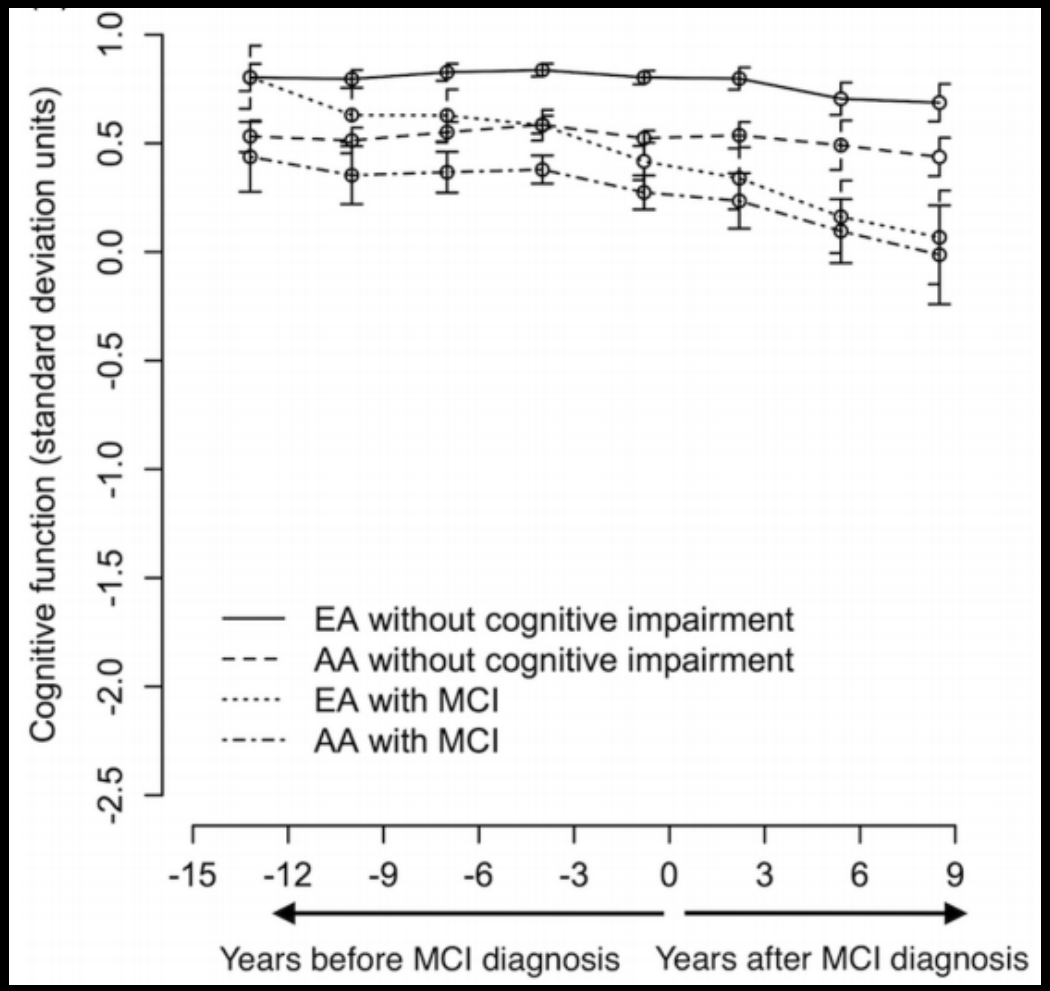
Wilson RS, et al. *Psych & Aging*. 2012;27:1008-1017.

A Cognitive Turning Point in Development of Clinical Alzheimer's Disease Dementia and Mild Cognitive Impairment: A Biracial Population Study

CHAP

Slope of cognitive decline after the change point is steeper among EAs than AAs.

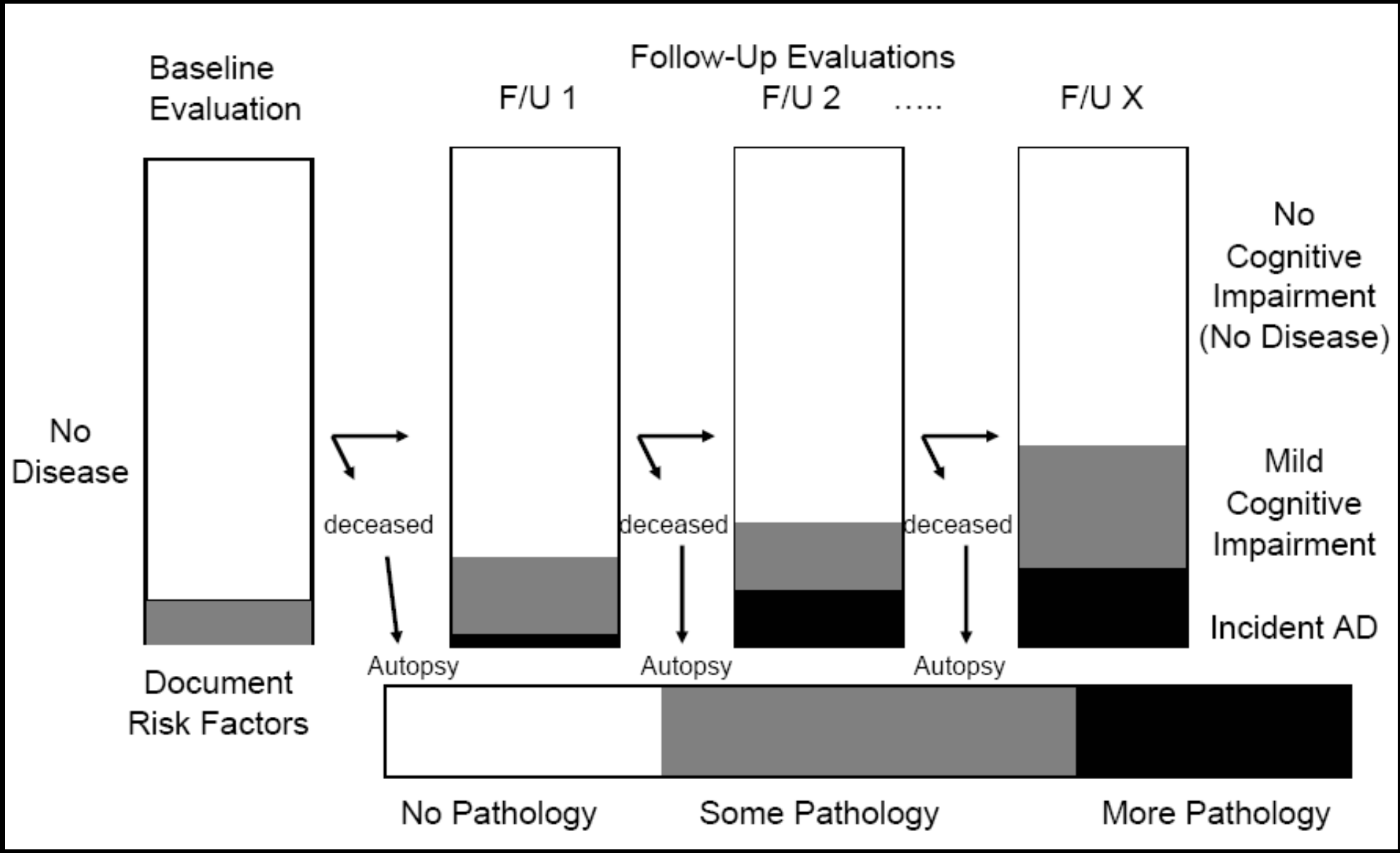




Kumar RB, et al. *JGMS*. 2017;72:424-430.

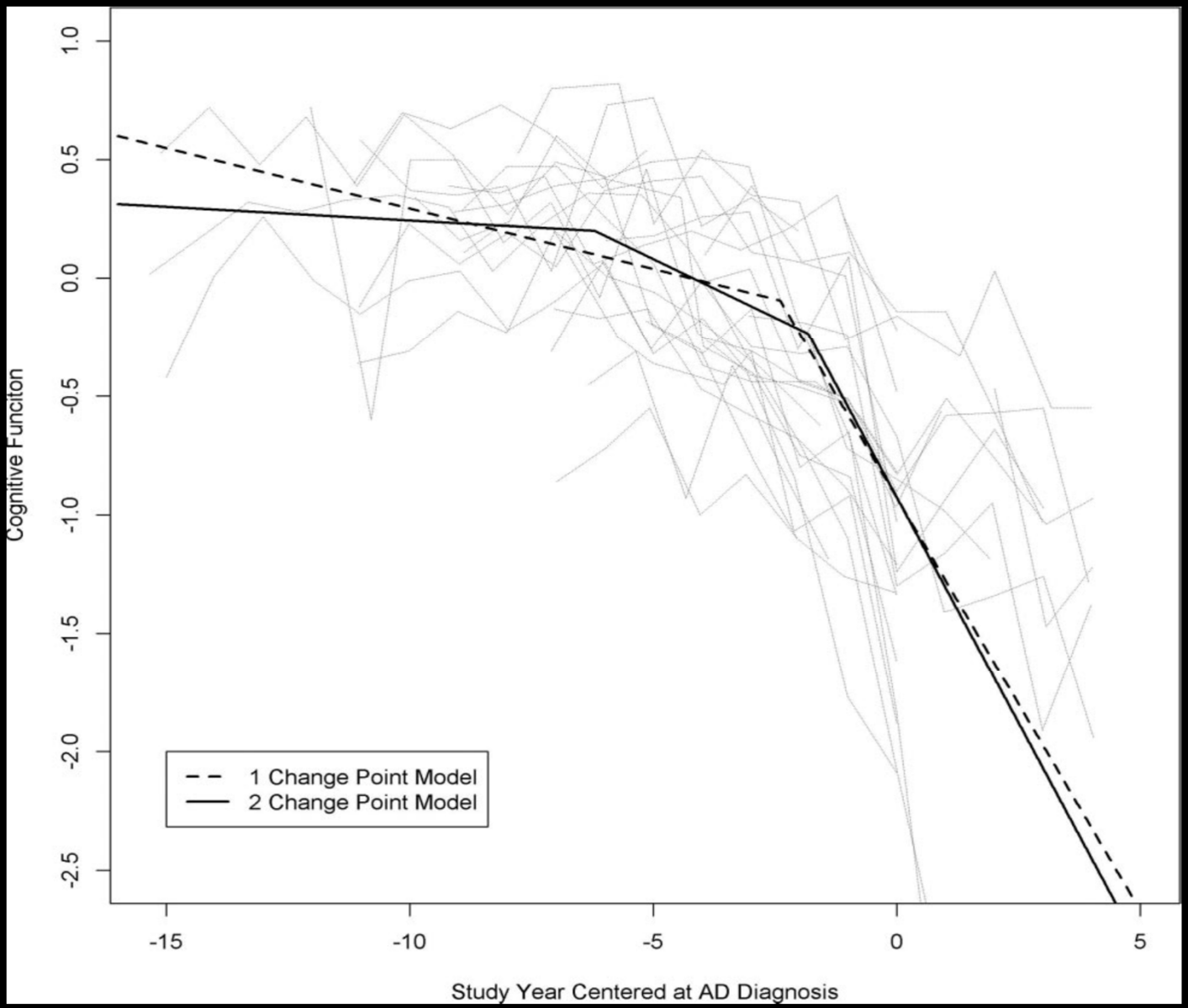
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort

Religious Orders Study and Rush Memory and Aging Project (ROSMAP)



Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

The Natural History of Cognitive Decline in Alzheimer's Disease



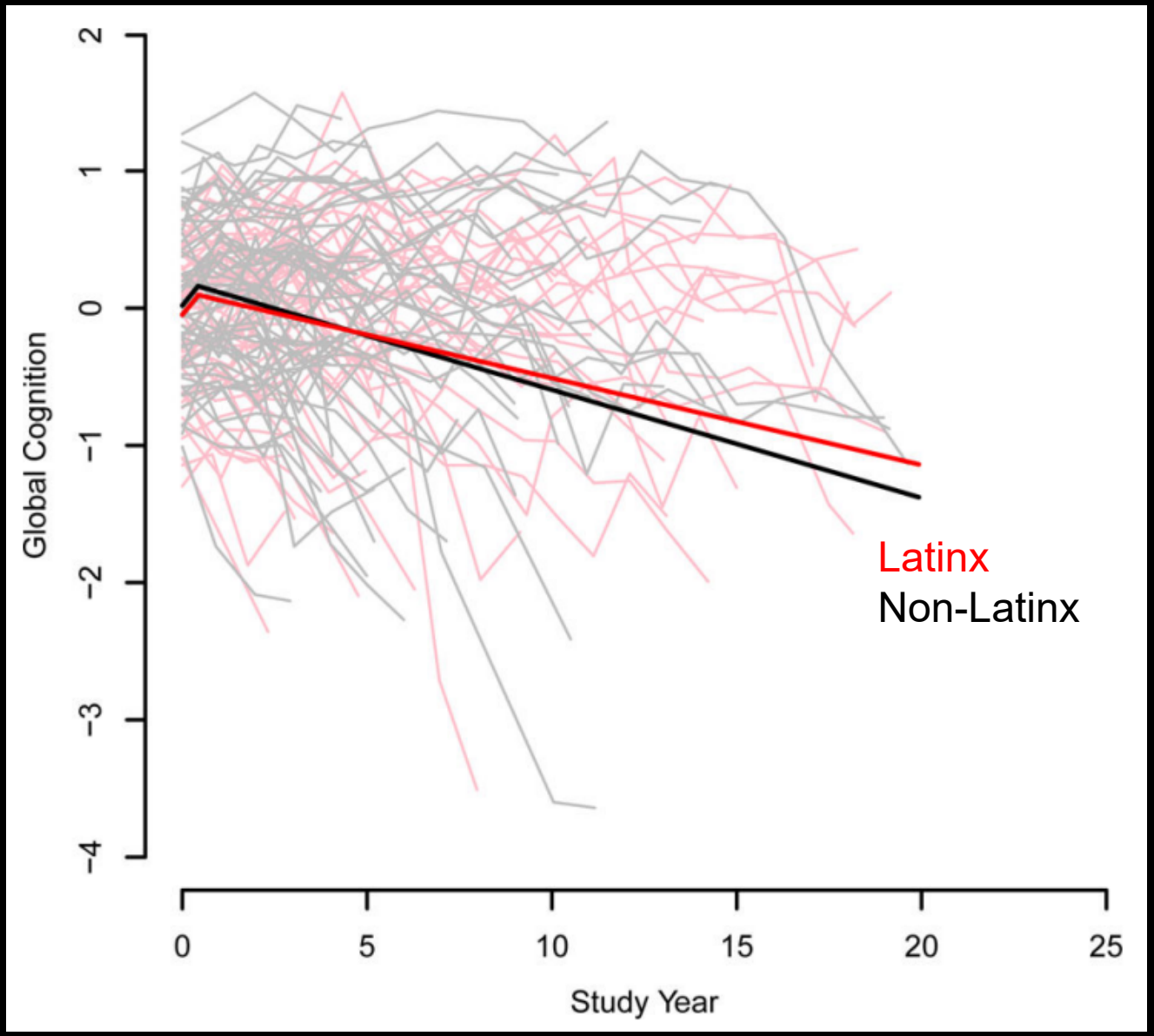
No change in cognitive function until 7.5 years before dementia diagnosis

Global cognitive measure declined 0.09-unit per year until 2.0 years before the diagnosis when it increased more than 4-fold to a mean loss of 0.37-unit per year

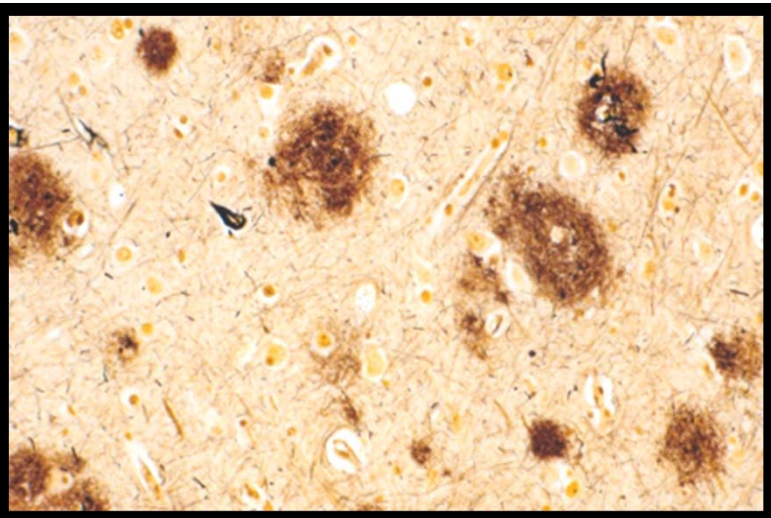
Wilson RS, et al. *Psych & Aging*. 2012;27:1008-1017.

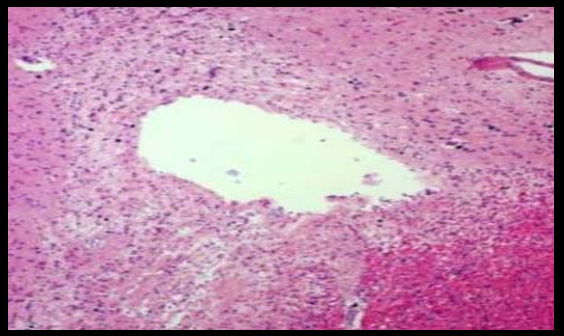
Change in Cognitive Abilities in Older Latinos

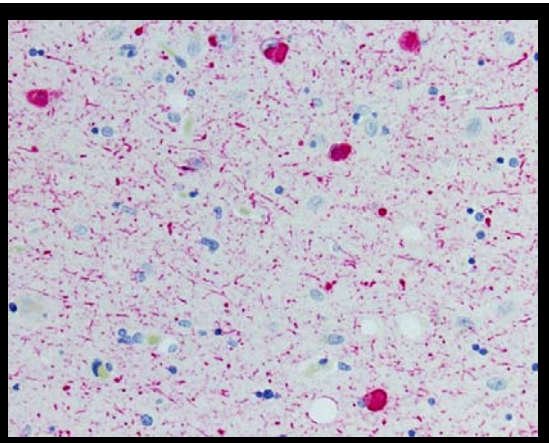
ROSMAP

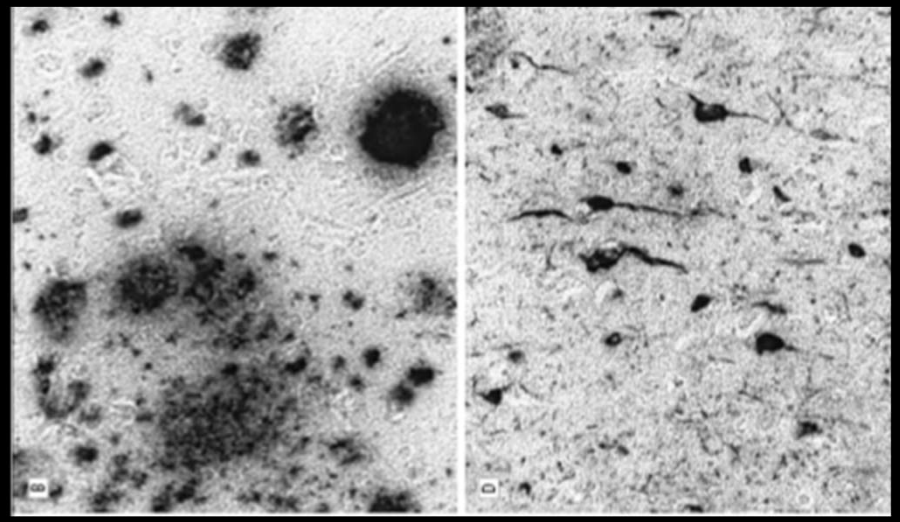


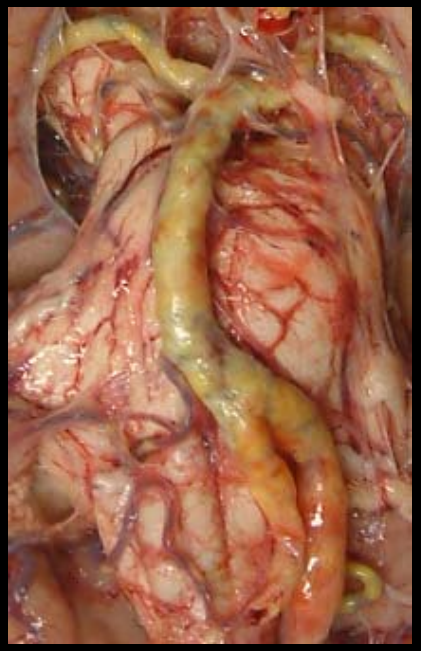
Wilson RS, et al. *JINS*. 2016;22:58-65.

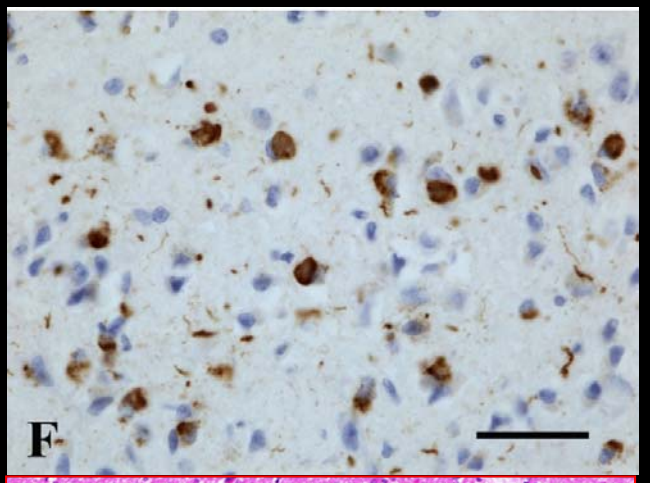








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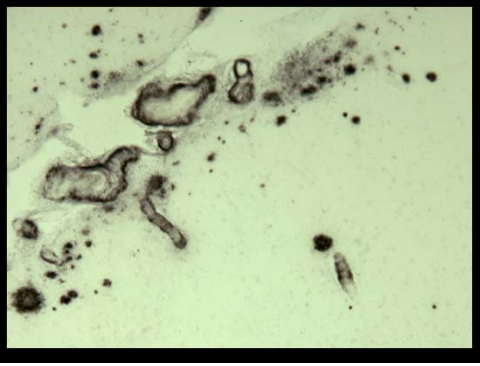

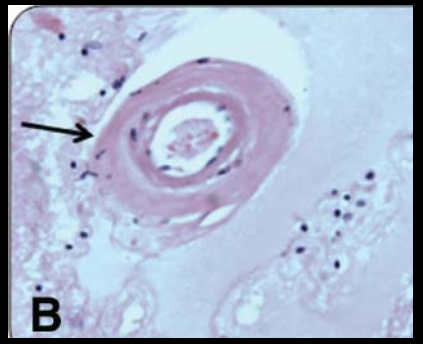
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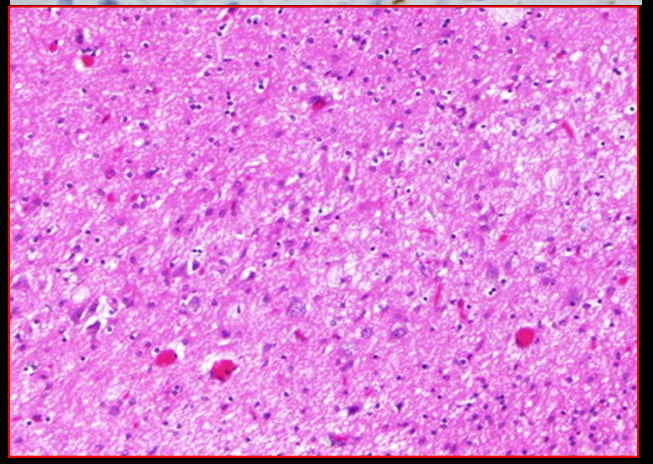
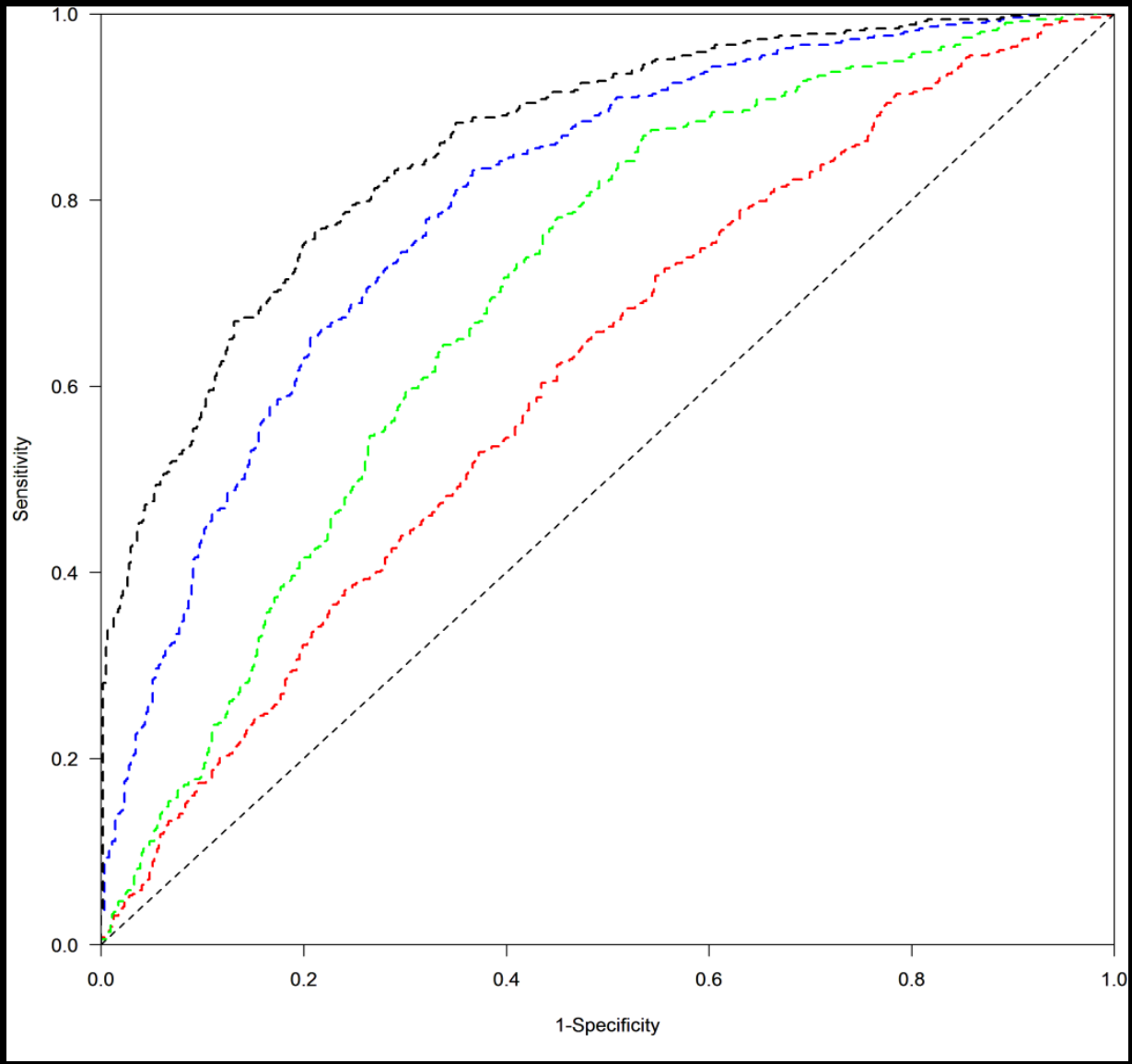


Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies

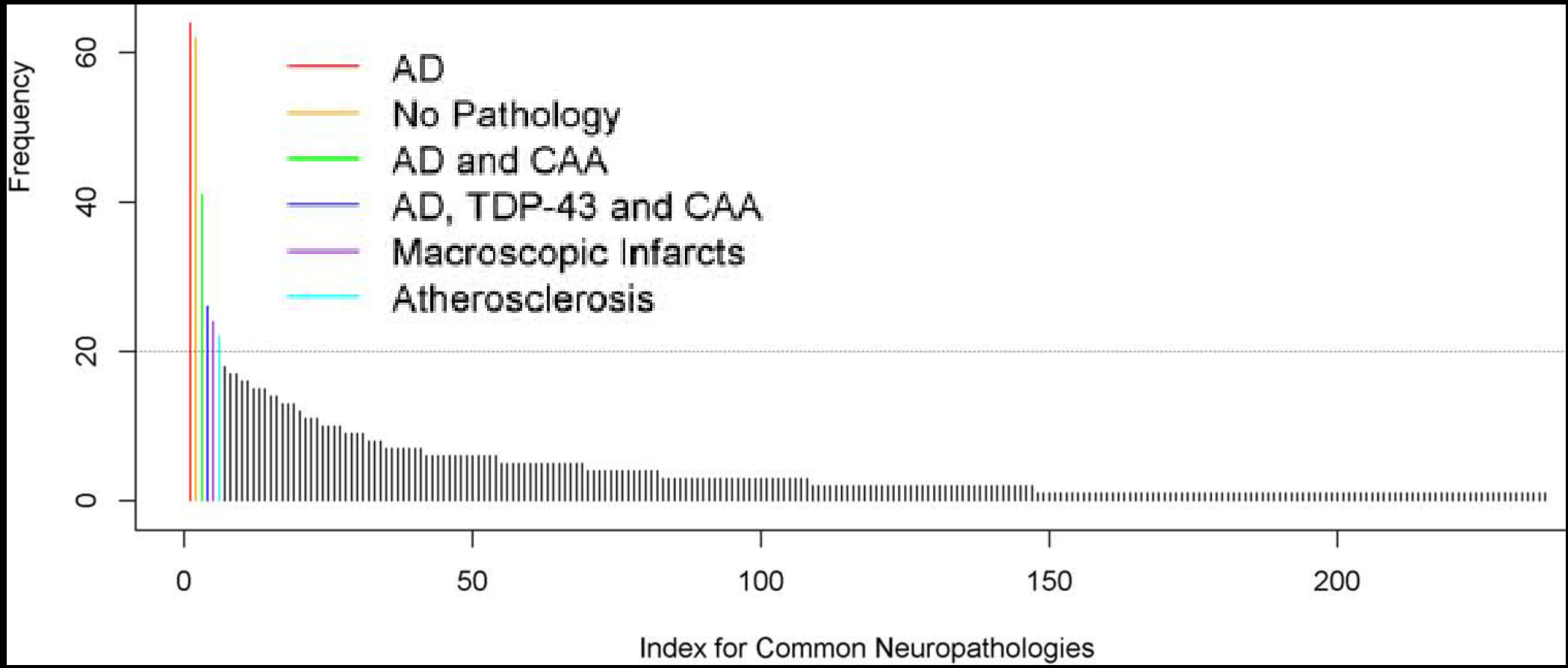
Demographics
And Pathologic AD
And 7 other pathologies
And an indicator for unaccounted AD dementia cases

67.5% AD dementia cases attributable all eight neuropathologic indices



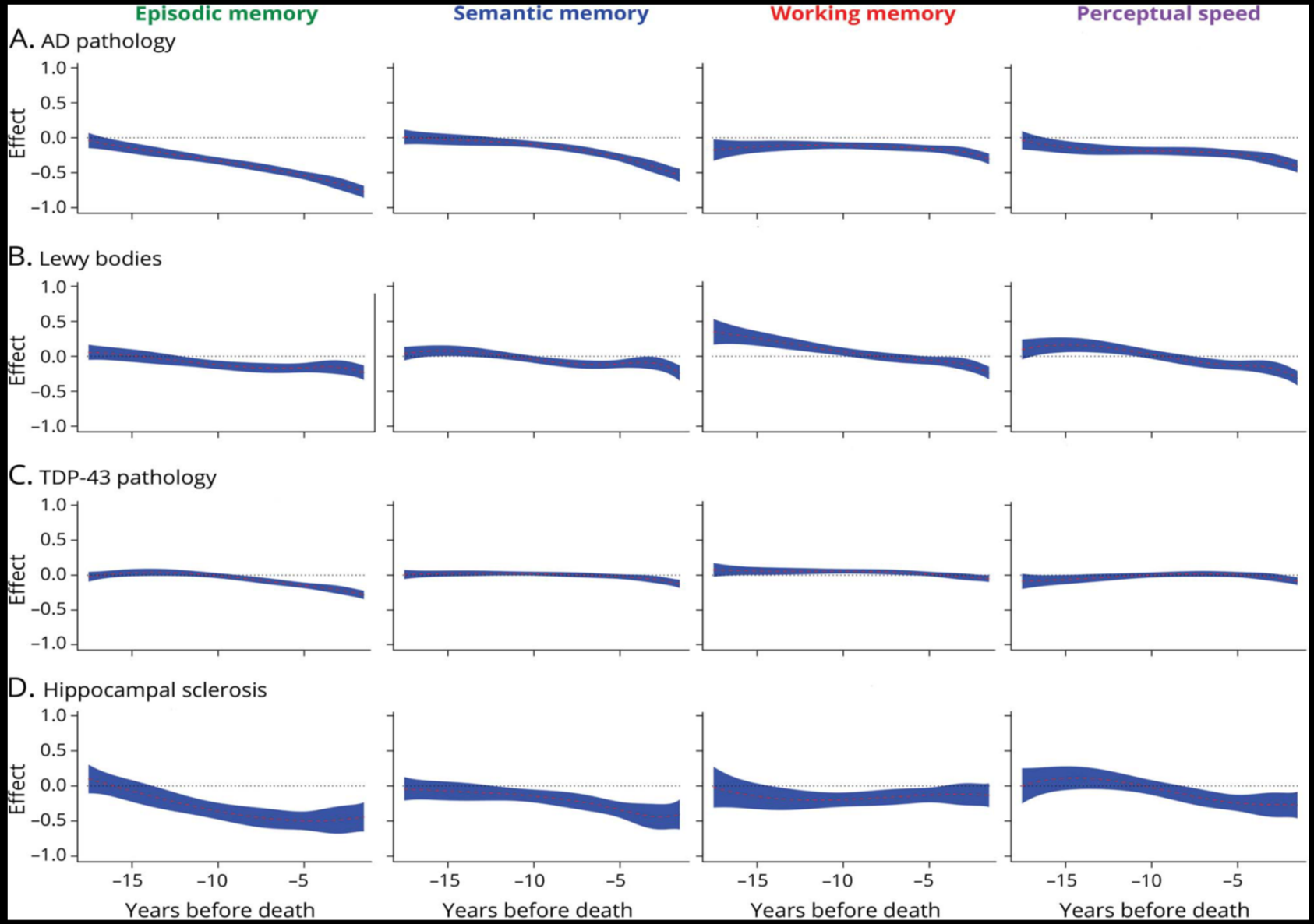
Boyle PA et al. *Ann Neurol*. 2019;85;114-124.

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age



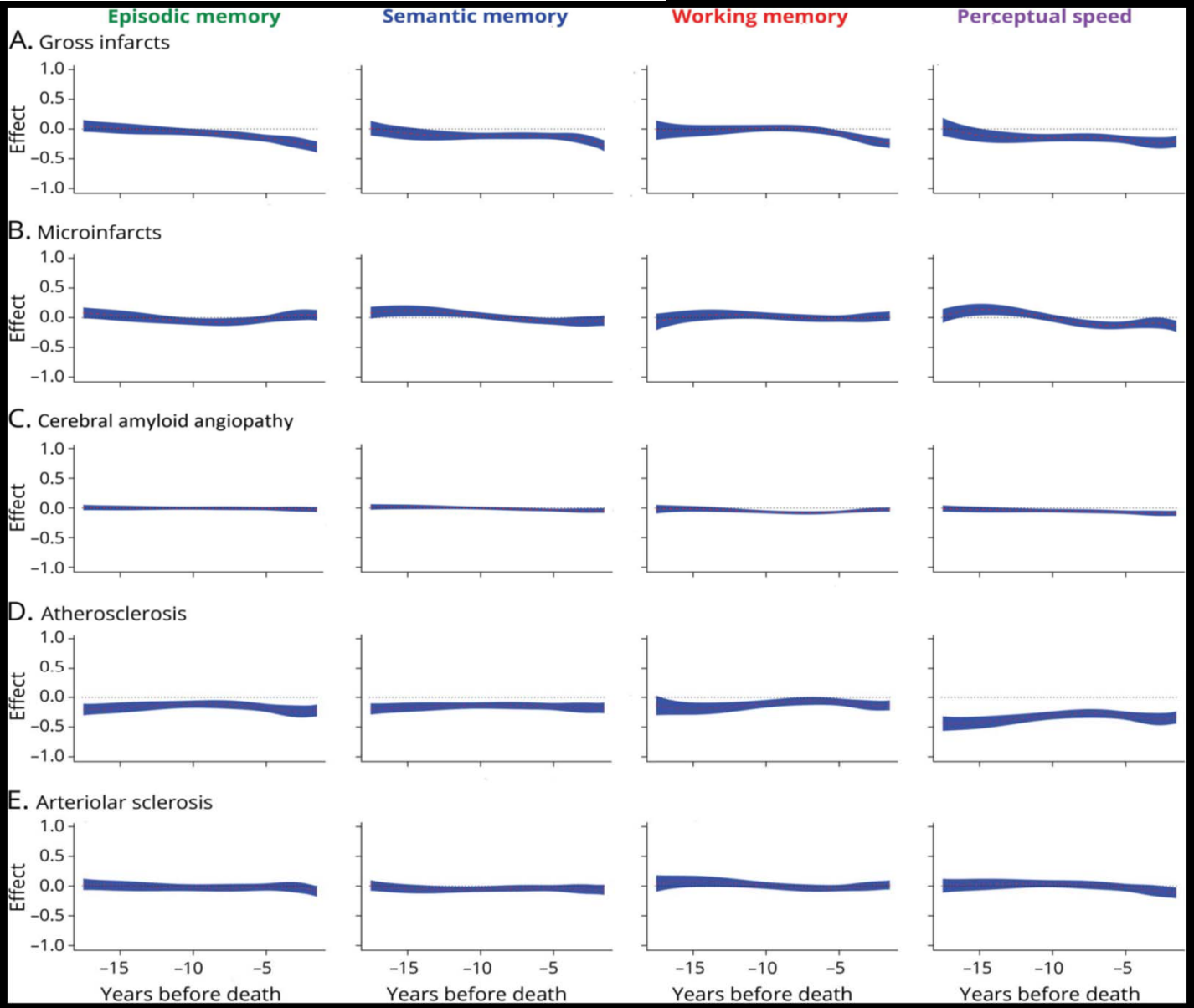
Boyle PA, et al. *Ann Neurol*. 2018;83:74-93.

Postmortem neurodegenerative markers and trajectories of decline in cognitive systems



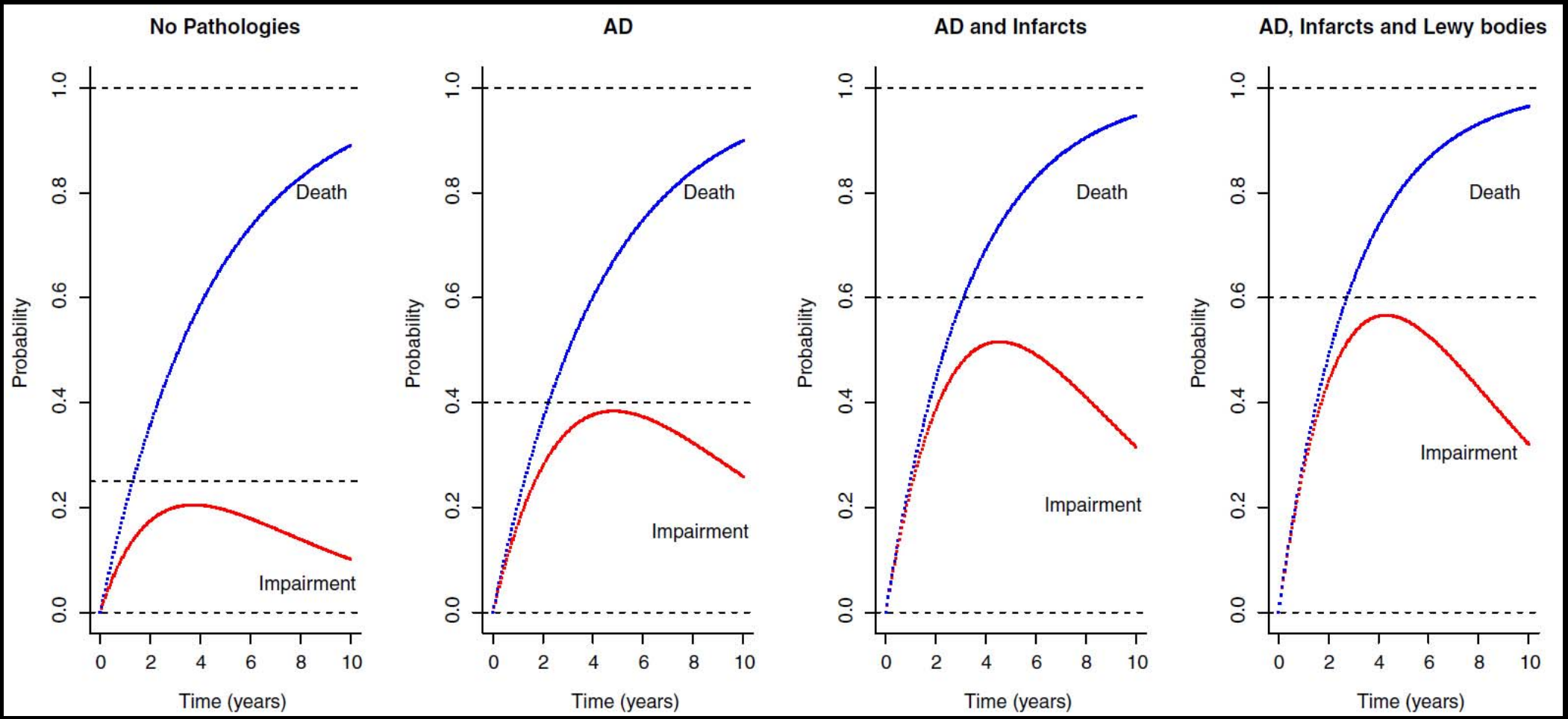
Wilson RS, et al. *Neurol*. 2019;92;e831-e840.

Postmortem neurodegenerative markers and trajectories of decline in cognitive systems



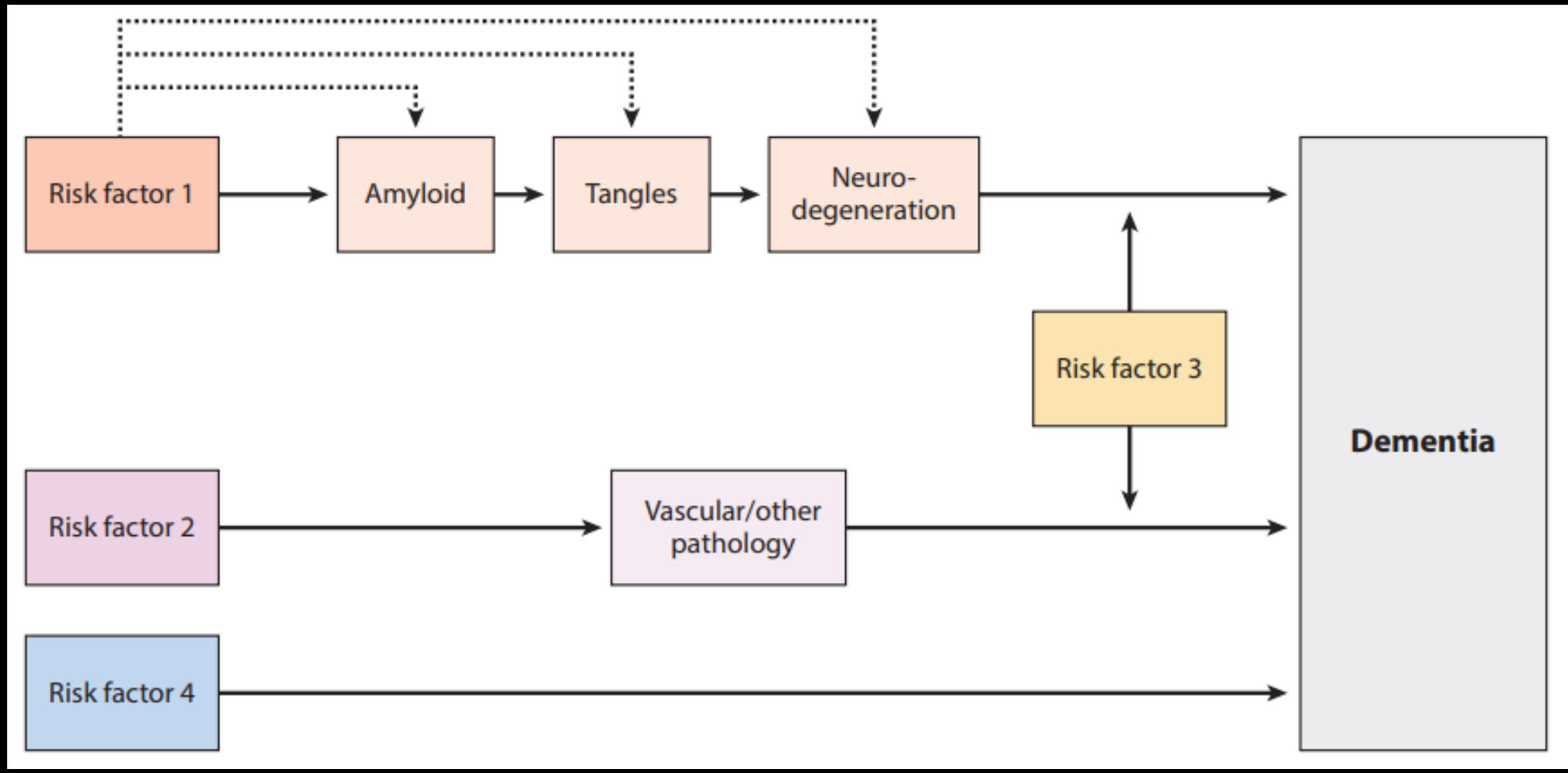
Wilson RS, et al. *Neurol*. 2019;92;e831-e840.

Effect of common neuropathologies on progression of late life cognitive impairment



Yu L, et al. *Neurobiol Aging*. 2015;36;2225-2231.

Causes and Patterns of Dementia: An Update in the Era of Redefining Alzheimer's Disease



James BD and Bennett DA. *Ann Rev Pub Health*. 2019;40;65-84.

Conclusions

- Accepted criteria for the clinical diagnoses of common dementia syndromes are made by and for clinical specialists
  - Need to be adapted for use in community-based studies
- Alzheimer's dementia is on a continuum
  - small differences in cut-points can result in very large differences in estimated prevalence
- Modest to large racial differences in level of performance but Blacks appear to decline more slowly
- Many brain pathologies in different combinations contribute to Alzheimer's dementia
  - yet much of Alzheimer's dementia remains unexplained
- Many brain pathologies contribute to loss of multiple cognitive domains making it impossible at this juncture to reliability distinguish different causes of dementia on a case by case basis
  - Blood biomarkers soon?
- In an era that now distinguishes AD from its clinical consequences, we need to rethink what it means to be a risk factor for AD

Preliminary Recommendations

- Need more data on regional, sex, racial, and ethnic differences in prevalence of cognitive impairment and dementia across the USA
  - I would not expend the effort at this time for differential diagnosis of ADRD
  - For political reasons I would diagnose Alzheimer's dementia
- Need to develop simple and inexpensive approaches to diagnoses
  - This will be particularly challenging across race and ethnicity
- Need to monitor trends over time
  - Age-specific incidence and prevalence of dementia may be declining (not discussed)
  - Data not convincing for the relatively short time horizon addressed
  - given other long term health trends it is likely to be true – but not equally true across the USA or in all subgroups (e.g., increasing mortality rates among lower SES whites)
- Need to consider competing risk
- Generalizability and internal validity compete for resources and studies that maximize the former may not be the best place to accomplish risk factor associations beyond select social determinants