Acknowledgments

Rush Alzheimer's Disease Center
Neelum Aggarwal, MD
Konstantinos Arfanakis, PhD
Zoe Arvanitakis, MD
Lisa Barnes, PhD
Patricia Boyle, PhD
Aron Buchman, MD
Ana Capuano, PhD
Bob Dawe, PhD
Jose Farfel, MD, PhD
Debra Fleischman, PhD
Chris Gaiteri, PhD
Crystal Glover, PhD
Fran Grodstein, ScD
Bryan James, PhD
Alifiya Kapasi, PhD

Rush Alzheimer's Disease Center
Namhee Kim, PhD
Melissa Lamar, PhD
Sue Leurgans, PhD
Rupal Mehta, MD
Sukriti Nag, MD, PhD
Shahram Oveisgharan, MD
Victoria Poole, PhD
Julie Schneider, MD
Raj Shah, MD
Bob Wilson, PhD
Shinya Tasaki, PhD
Yanling Wang, PhD
Jishu Xu, MS
Jingyun Yang, PhD
Lei Yu, PhD

Il buono il brutto e il cattivo, by Ennio Morricone

Acknowledgments

National Institutes of Health
State of Illinois
Alzheimer's Association

Study Participants:
Religious Orders Study
Rush Memory and Aging Project

Disclosures

I am a co-author on the Framework and the prior A/T/N paper

The Good,

The Framework for the first time clearly distinguishes between the underlying disease – Alzheimer's disease
and its cognitive consequences – cognitive decline and cognitive impairment

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]**:** Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

Jack CR, et al. *Alz & Dementia*. 2018;14:535-562.

Ecclesiastes 1:9

“That which hath been is that which shall be, and that which hath been done is that which shall be done; and there is nothing new under the sun.”

What Is- Atherosclerosis?

Atherosclerosis is a disease in which plaque builds up inside your arteries.

What are symptoms of Atherosclerosis?

Typically NONE!

It needs to severely narrow or totally block an artery

Coronary arteries

angina, myocardial infarction, arrythmia

Carotid arteries

TIA, stroke

Femoral arteries

claudication

Renal arteries

chronic kidney disease

NIH National Heart, Lung, and Blood Institute

Consumption

Coughing pain, coughing up blood, chest pain, weight loss, fatigue, fever, chills, night sweats

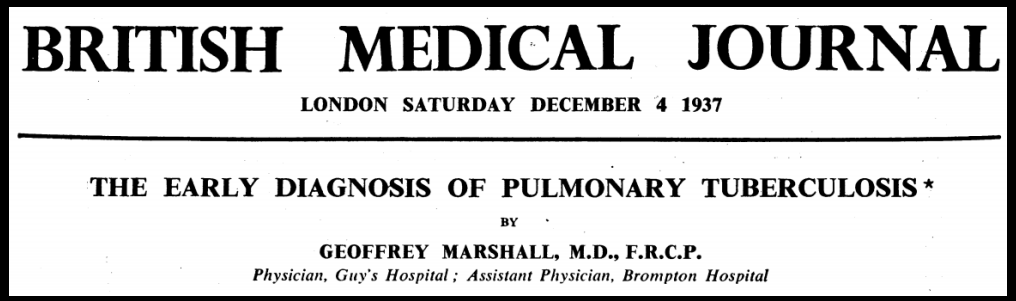
Pott's disease

Back pain, fever, weight loss

Scrofula

Painless swelling of cervical lymph nodes and other areas of the body, sweating, fever..

1882 - Robert Koch discovered the cause of tuberculosis
1908 - Clemens von Pirquet and Charles Mantoux developed the TB skin test - PPD



BRITISH MEDICAL JOURNAL

LONDON SATURDAY DECEMBER 4 1937

THE EARLY DIAGNOSIS OF PULMONARY TUBERCULOSIS*

BY

GEOFFREY MARSHALL, M.D., F.R.C.P.

Physician, Guy's Hospital; Assistant Physician, Brompton Hospital

"I have heard physicians state that they could diagnose pulmonary tuberculosis in its earliest stages by physical examination of the chest. At the time I received the statement with scepticism, and now I know that it deserved flat disbelief….

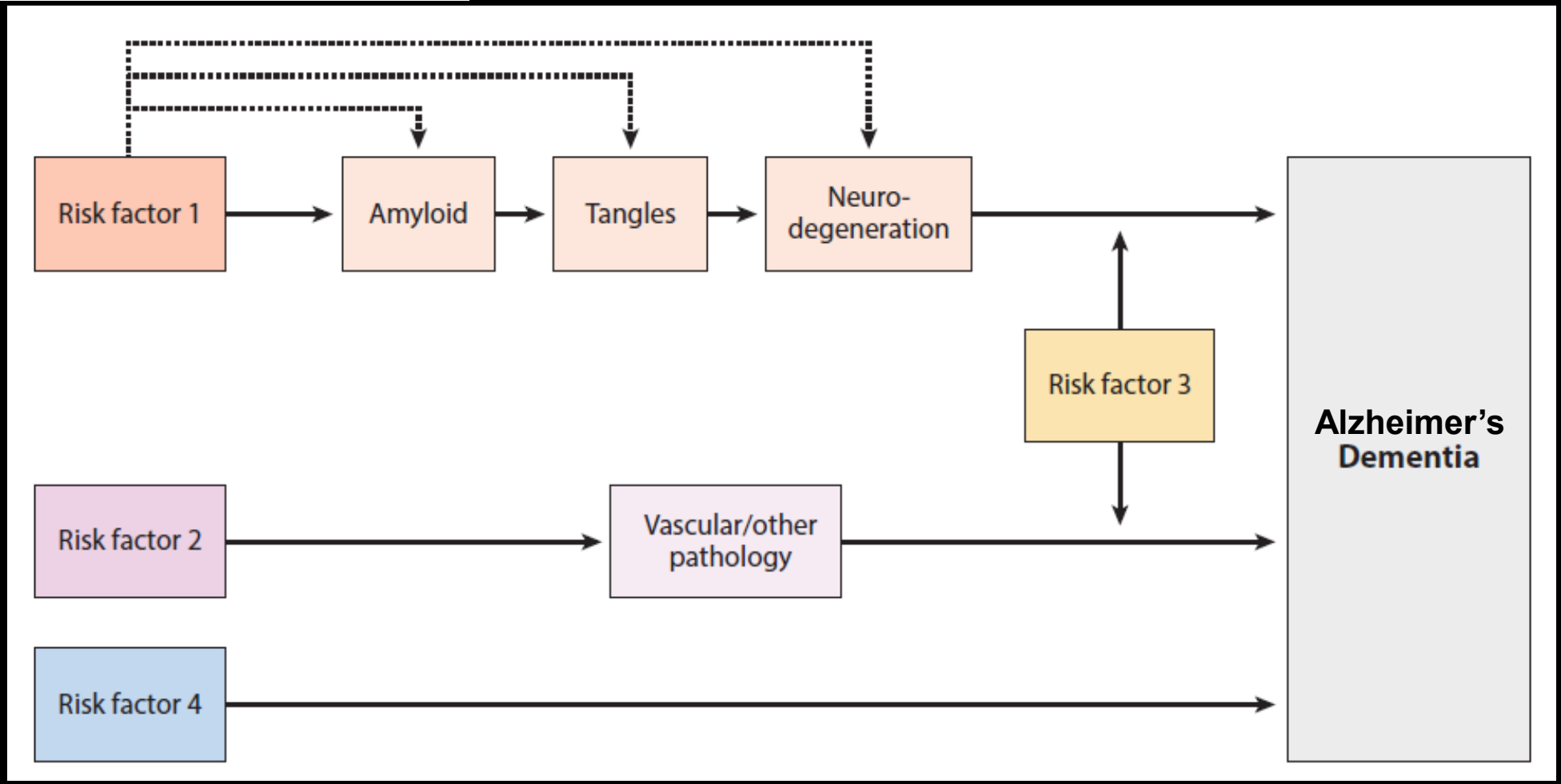
"in early diagnosis the method of physical examination alone would be completely unreliable…

"… but … there are the various tuberculin testscutaneous, subcutaneous, or conjunctival.

"These tests are still held in great respect by our veterinary colleagues …"

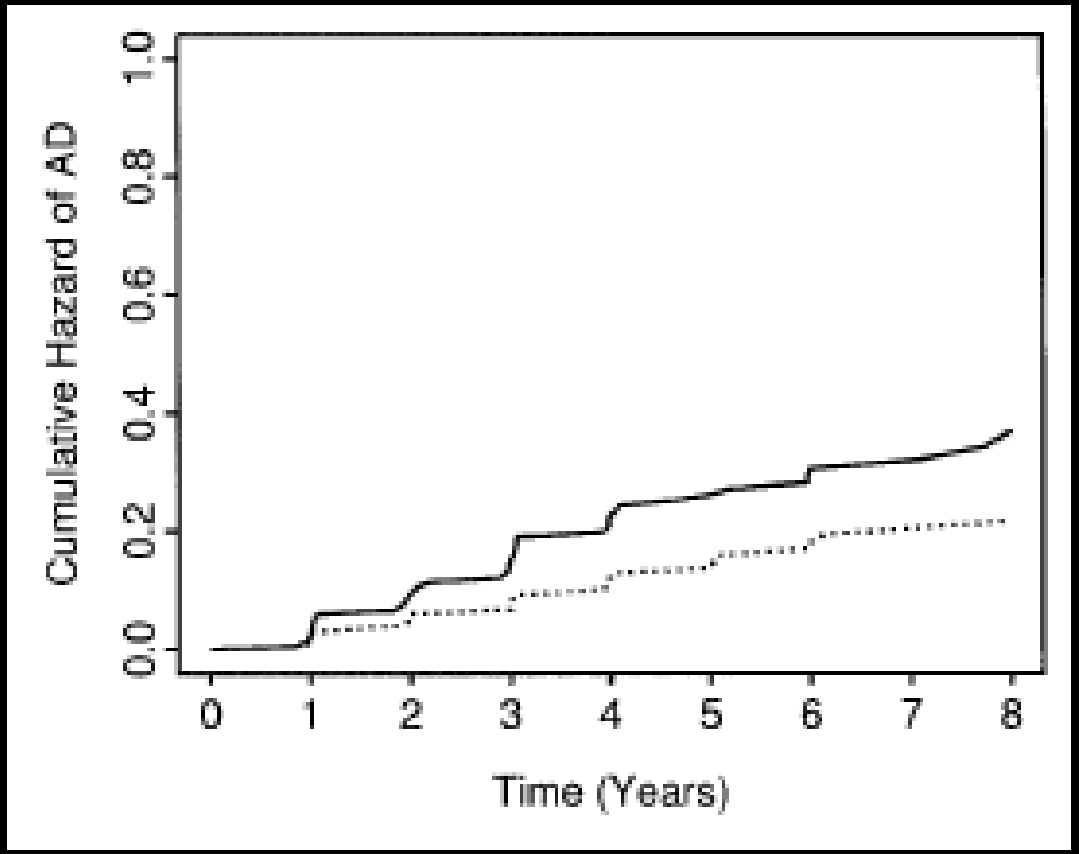
1943 - streptomycin developed by Selman Waksman, Elizabeth Bugie, and Albert Schatz (Waksman received the 1952 Nobel prize)

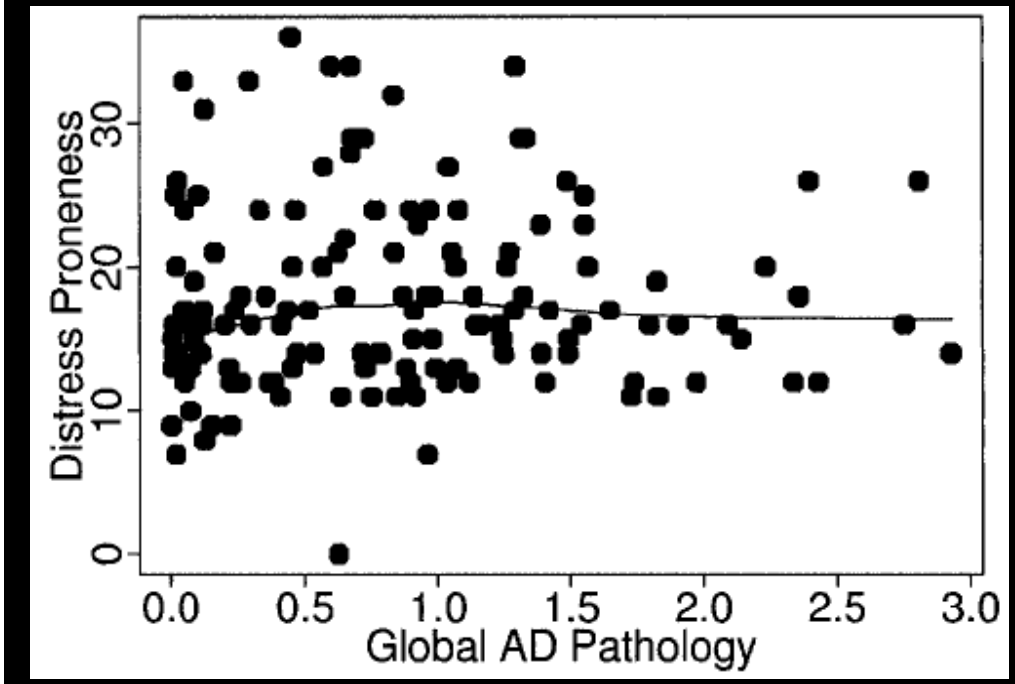
Causes and Patterns of Dementia: An Update in the Era of Redefining Alzheimer's Disease



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

Proneness to psychological distress is associated with risk of Alzheimer's disease





Wilson RS, et al. *Neurology* 2003;61:1479-1485.

The relation of cognitive activity to risk of developing Alzheimer's disease

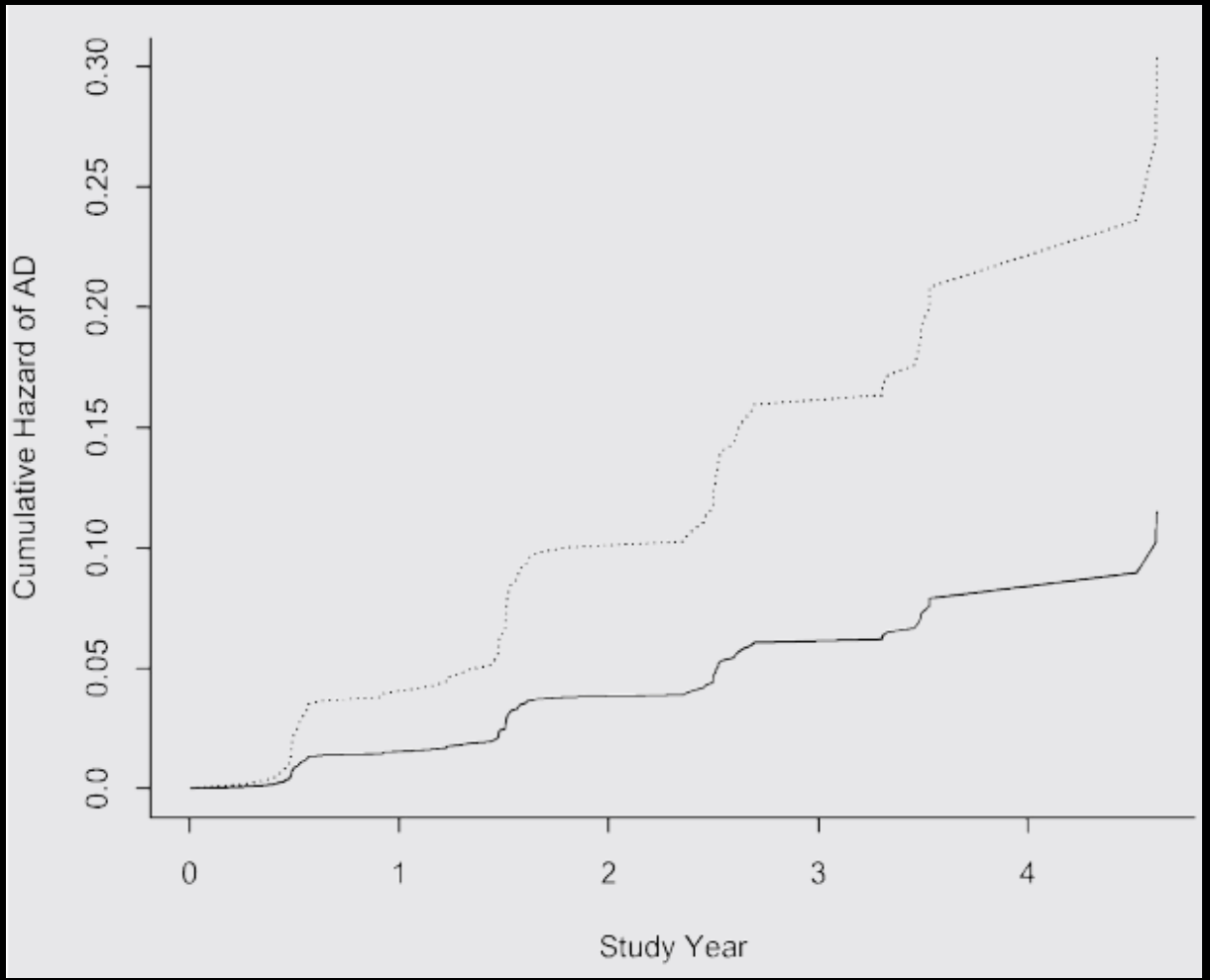
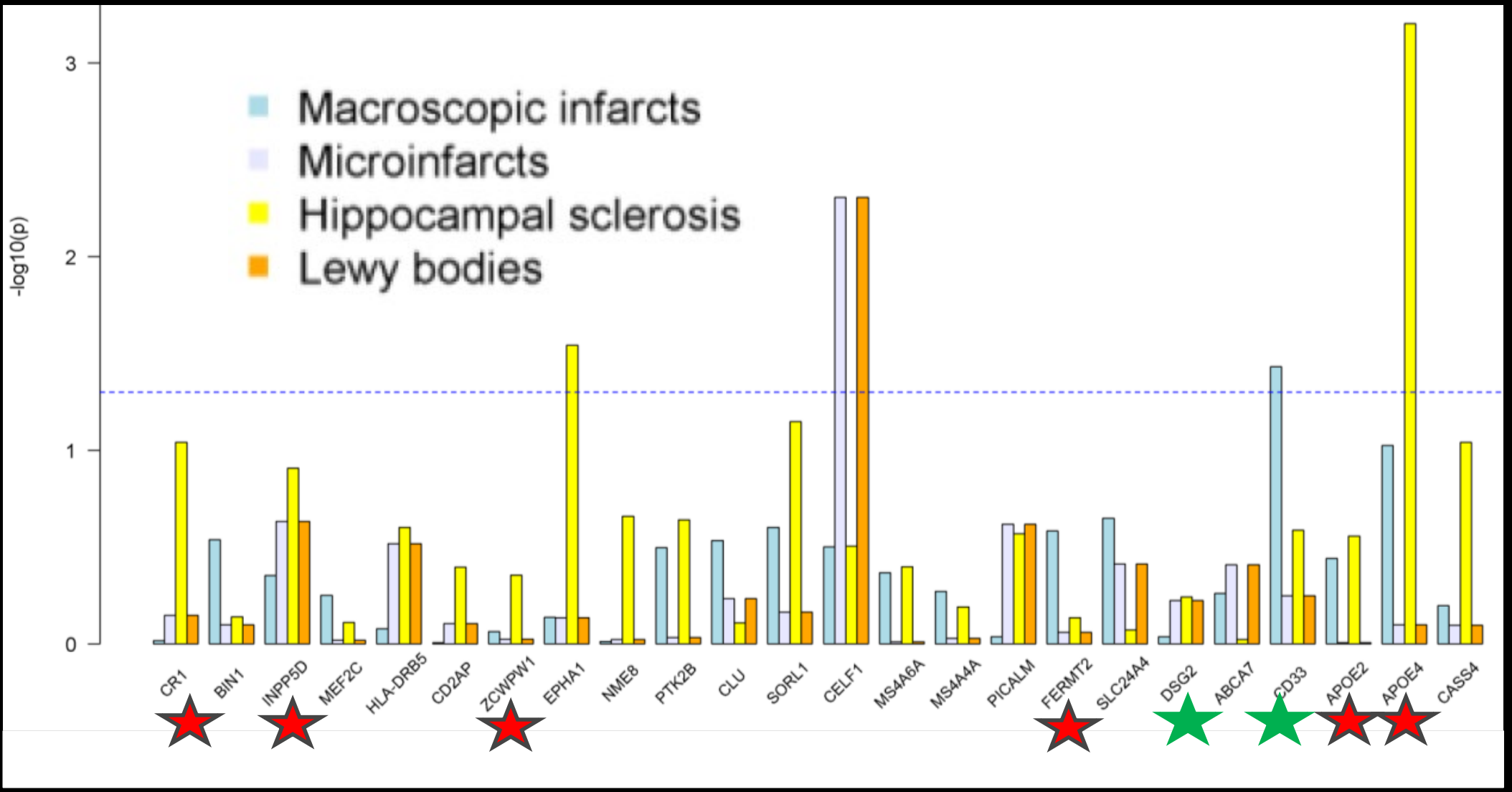


Table 4 Relation of neuropathology to frequency of participation in cognitively stimulating activities at study onset*

Model term	Estimate	SE	*p*
Amyloid burden	0.002	0.028	0.943
Tangle density	−0.016	0.014	0.229
Braak stage	0.003	0.066	0.964
Lewy bodies	−0.130	0.222	0.561
One infarction	−0.304	0.229	0.188
Multiple infarction	−0.037	0.206	0.859

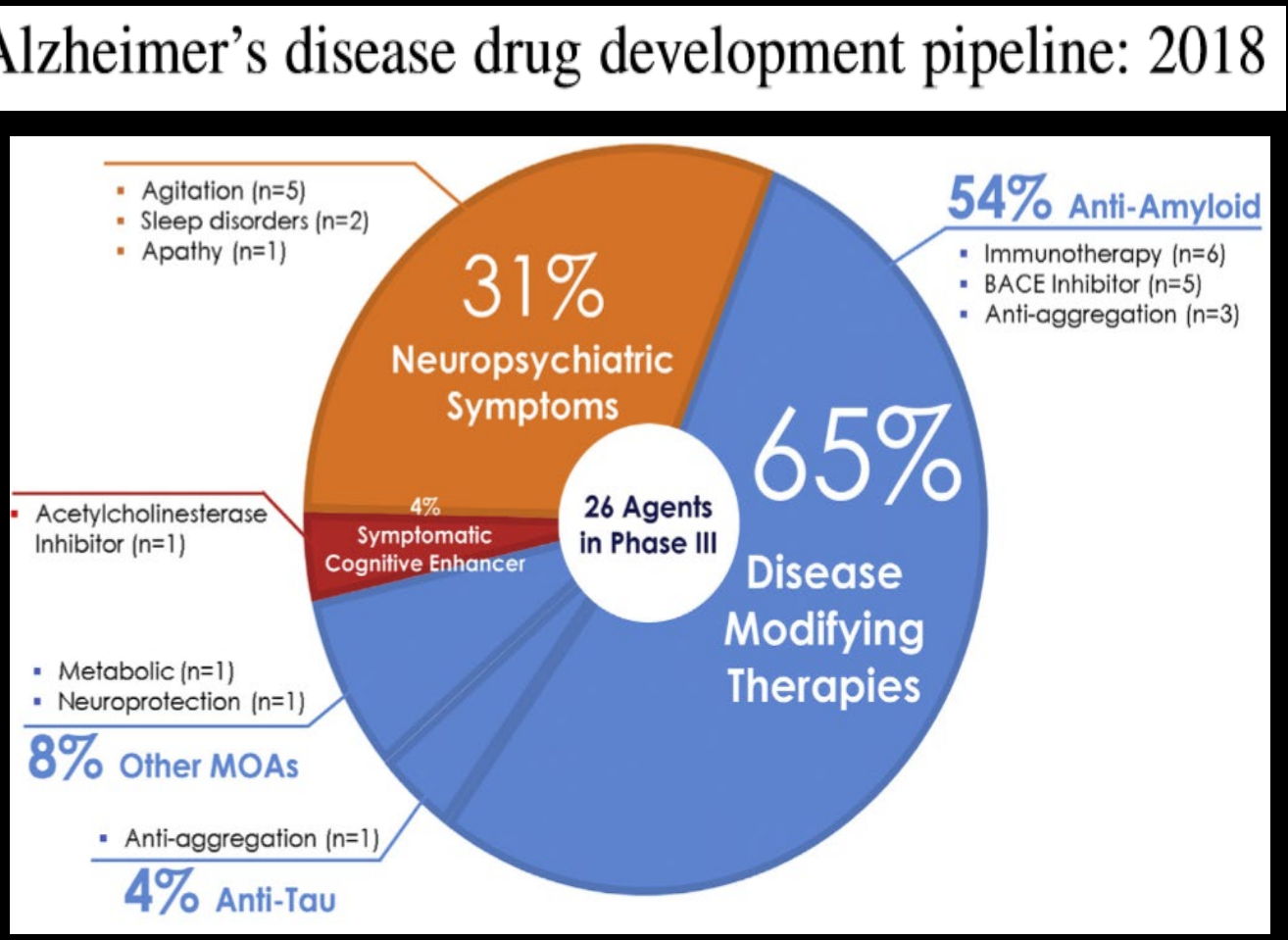
Wilson RS, et al. *Neurology* 2007;69:1911-20.

Relation of genomic variants for Alzheimer disease dementia to common neuropathologies



Farfel JM, et al. *Neurology*. 2016;87:489-496.

The Bad,



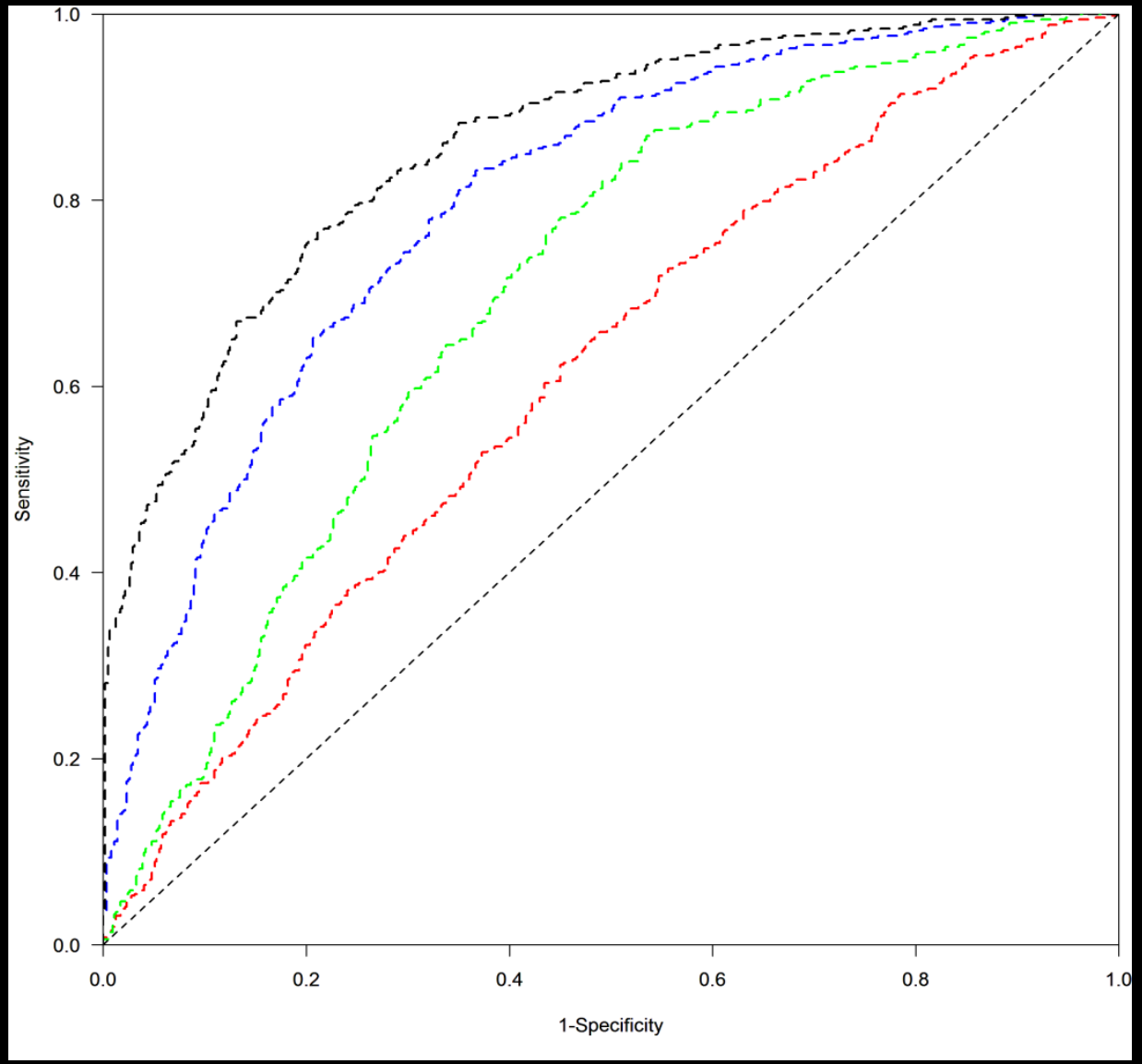
Cummings J, et al. *Alz & Dement.: TR & CI* 2018;4:195-214.

So, if we reduce or even eliminate AD pathology, what is the expected reduction of Alzheimer's dementia?

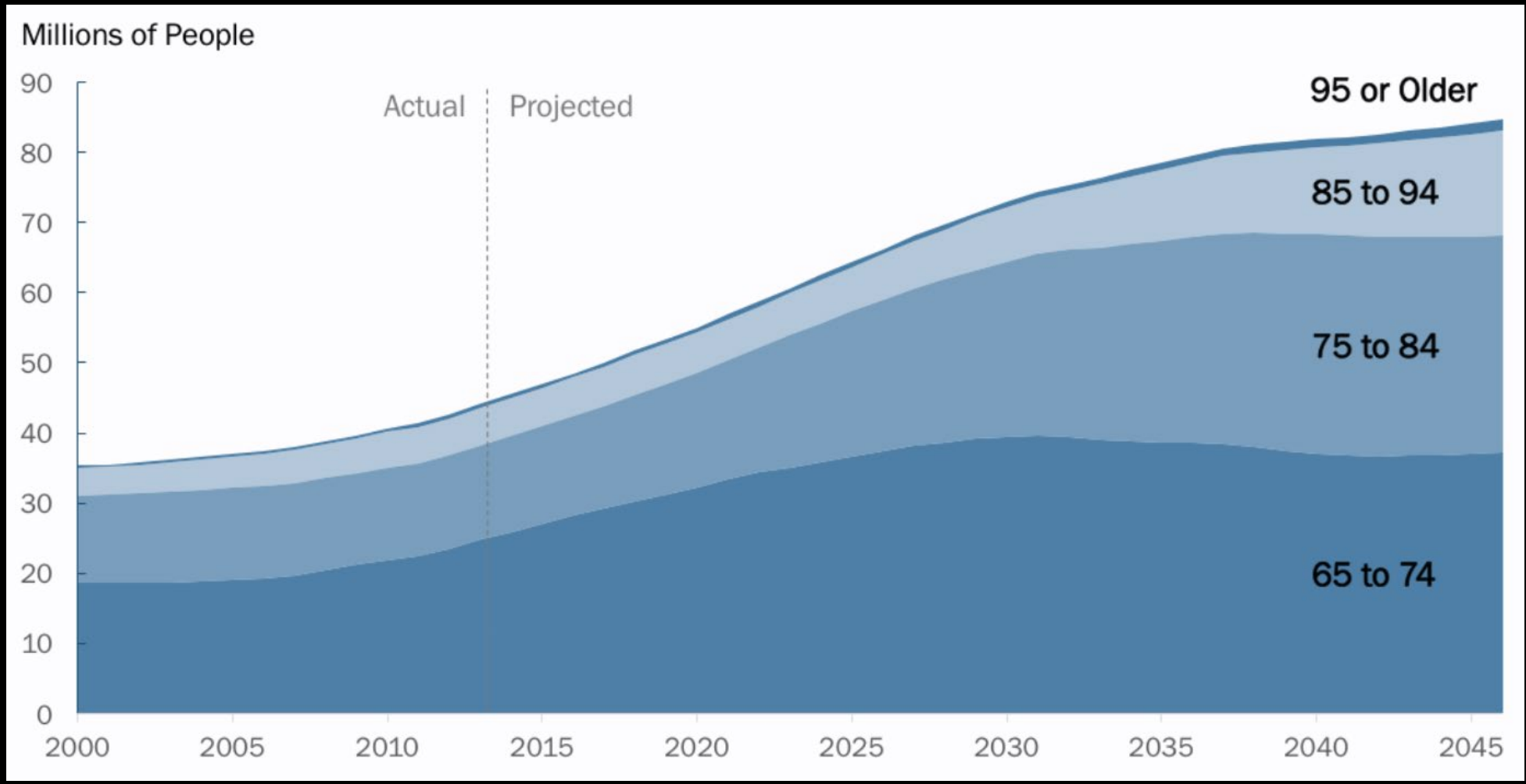
Attributable risk of Alzheimer's dementia attributed to age-related neuropathologies

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

One third attributable to AD
One third other pathologies
One third… other things



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



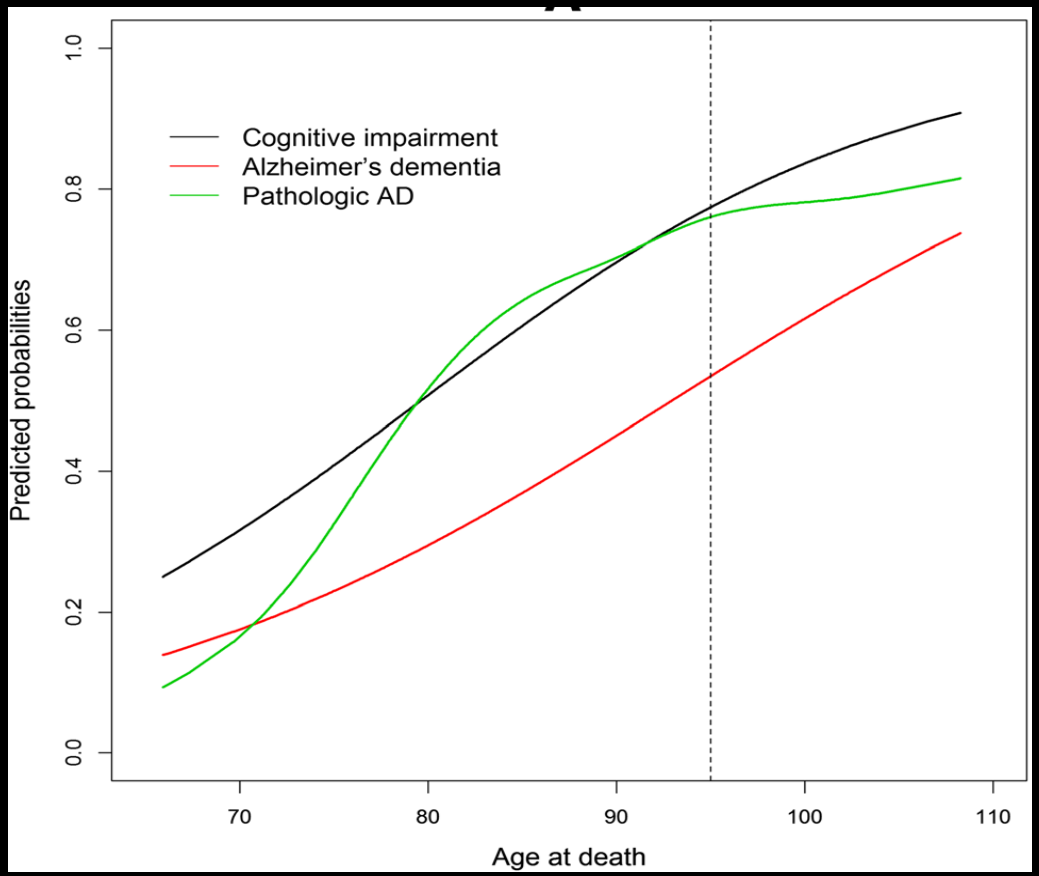
Congressional Budget Office.

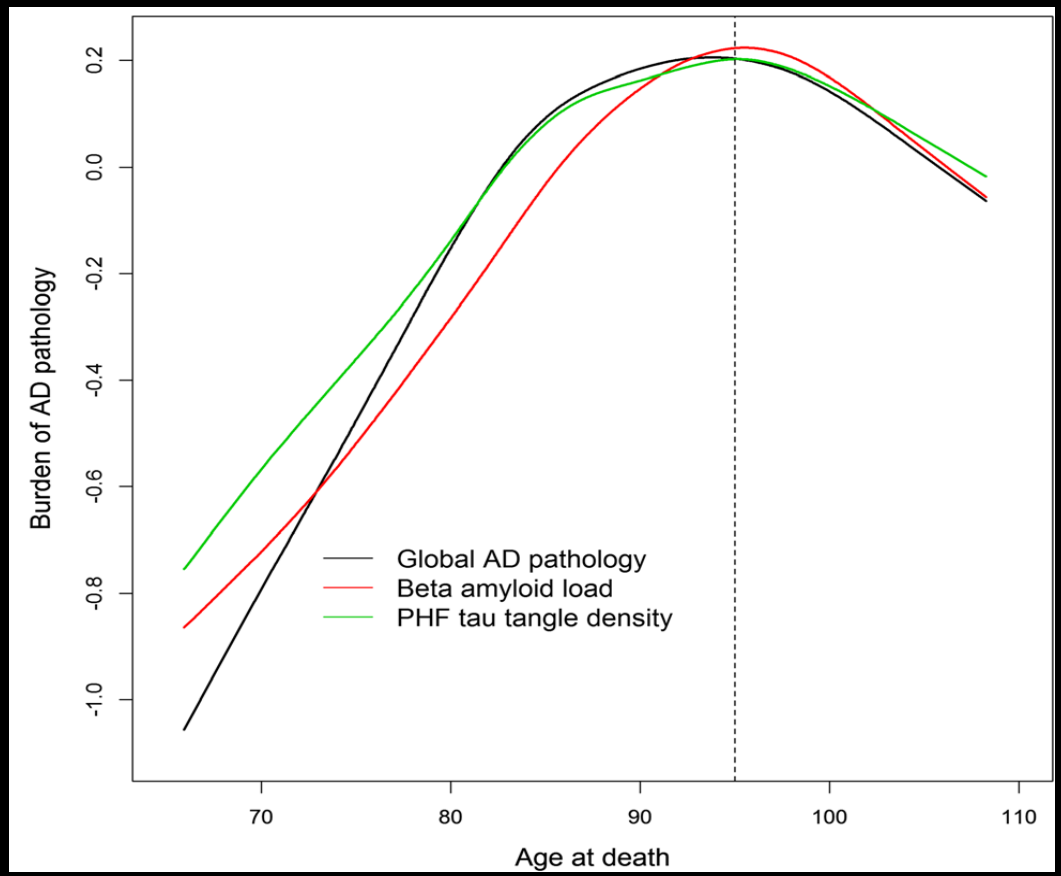
Dementia From Alzheimer Disease and Mixed Pathologies in the Oldest Old

"…the relationship between a pathological diagnosis of AD and dementia was significantly attenuated in the oldest old compared with the old…".

James BD, et al. *JAMA.* 2012;307:1798-1800.

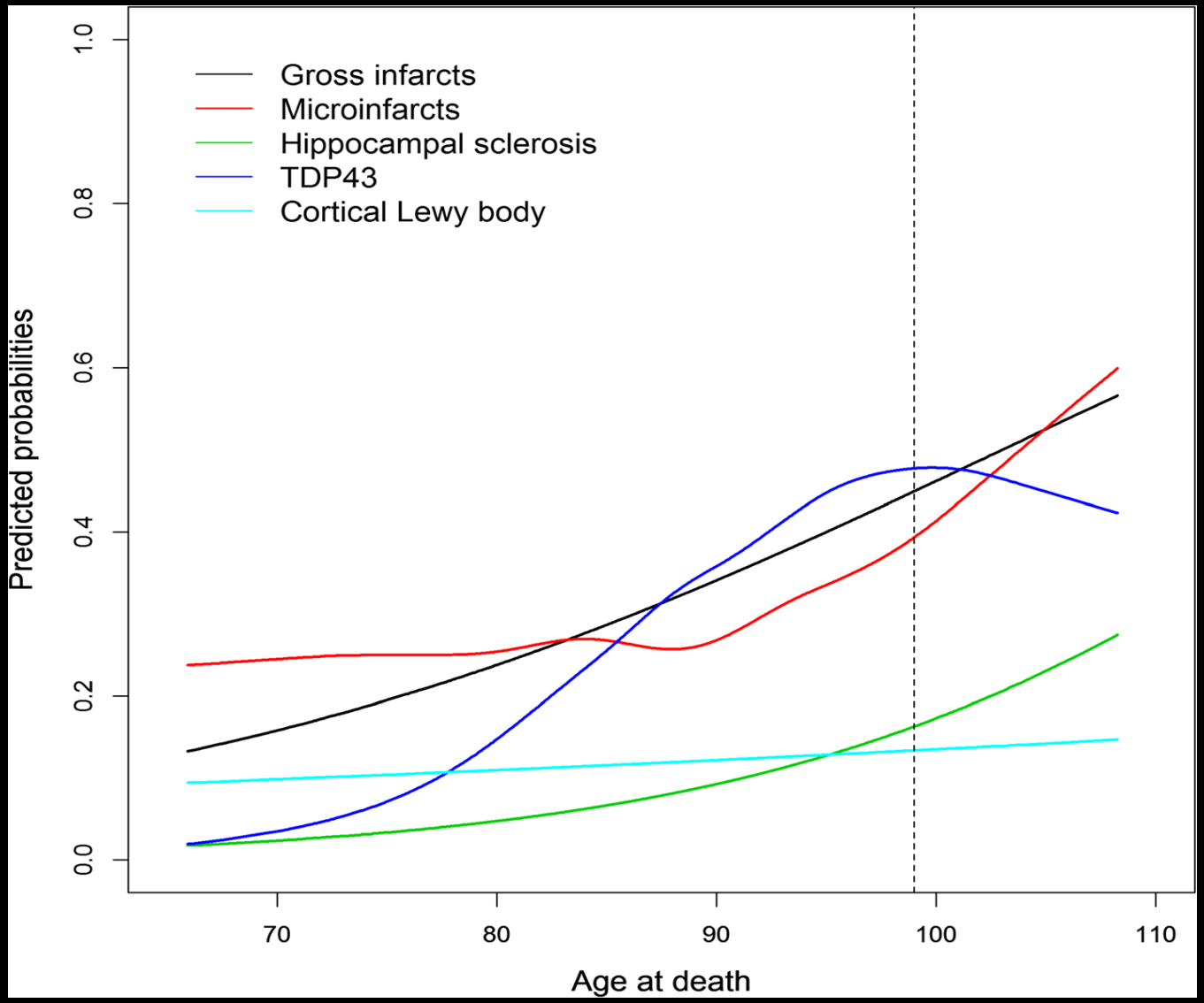
Alzheimer's disease frequency peaks in the tenth decade and is lower afterwards





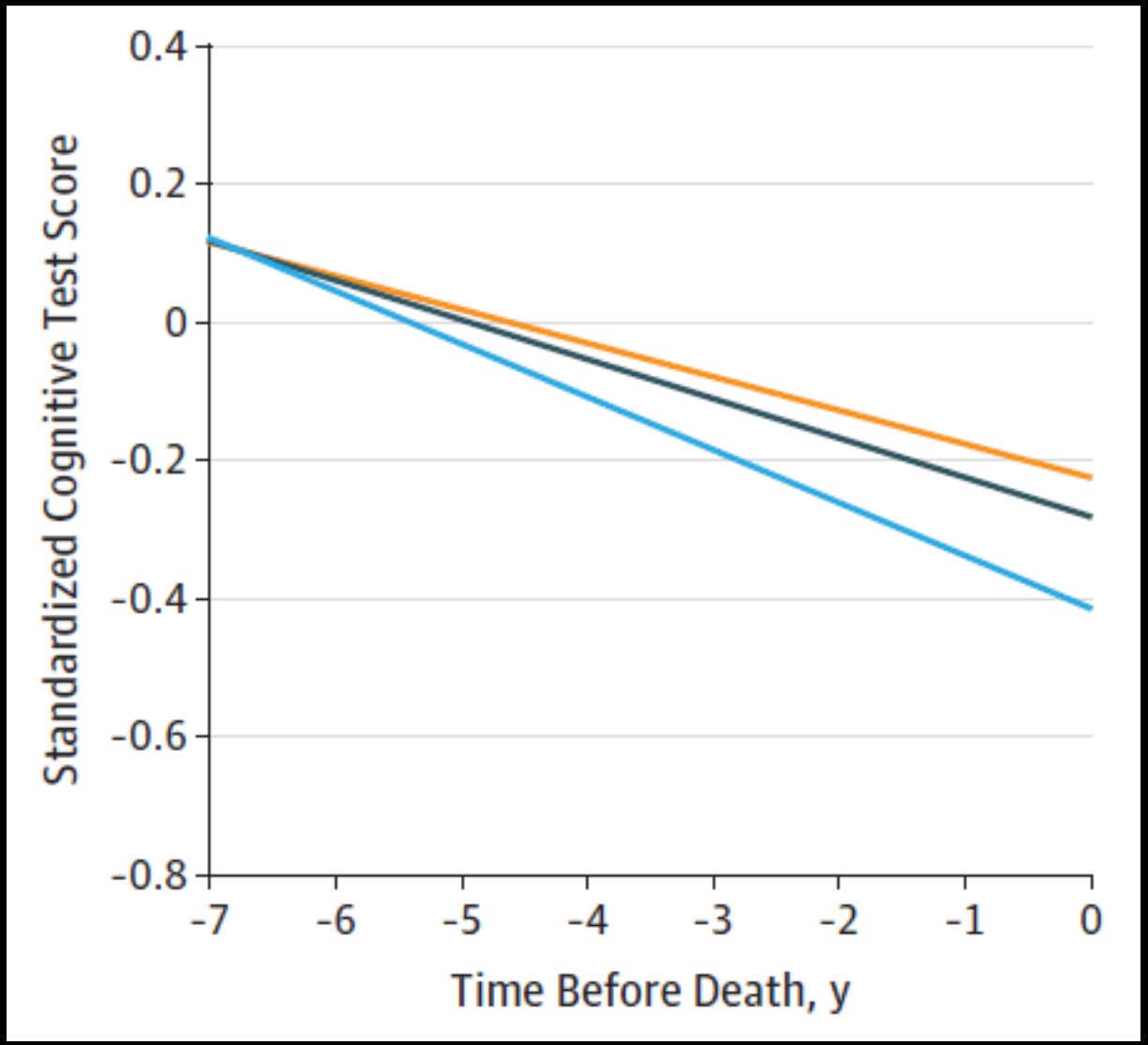
Farfel JM, et al. *Acta Neuropath Comm*. 2019;7:104.

Alzheimer's disease frequency peaks in the tenth decade and is lower afterwards



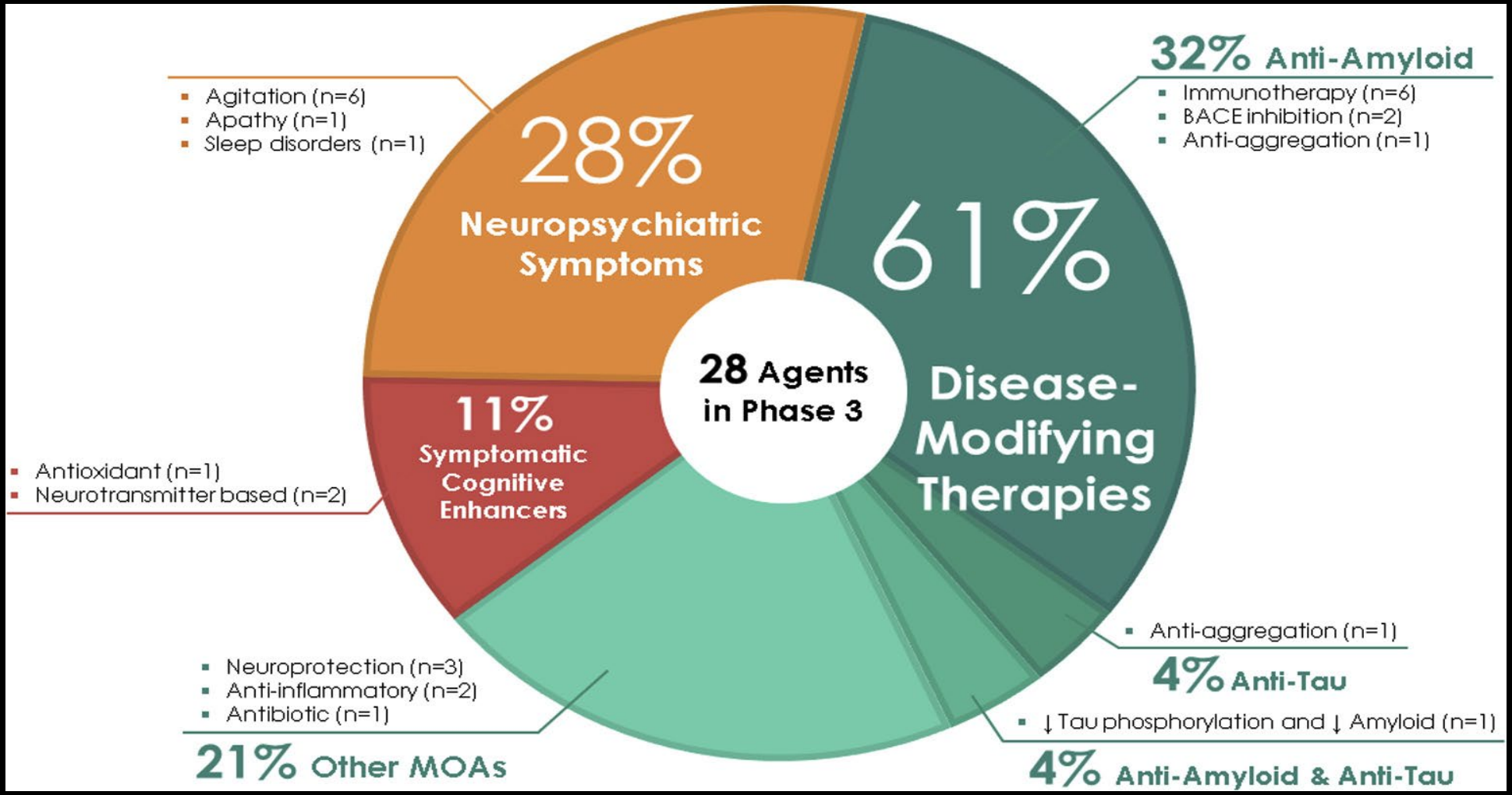
Farfel JM, et al. *Acta Neuropath Comm*. 2019;7:104.

Association of Cortical β-Amyloid Protein in the Absence of Insoluble Deposits With Alzheimer Disease



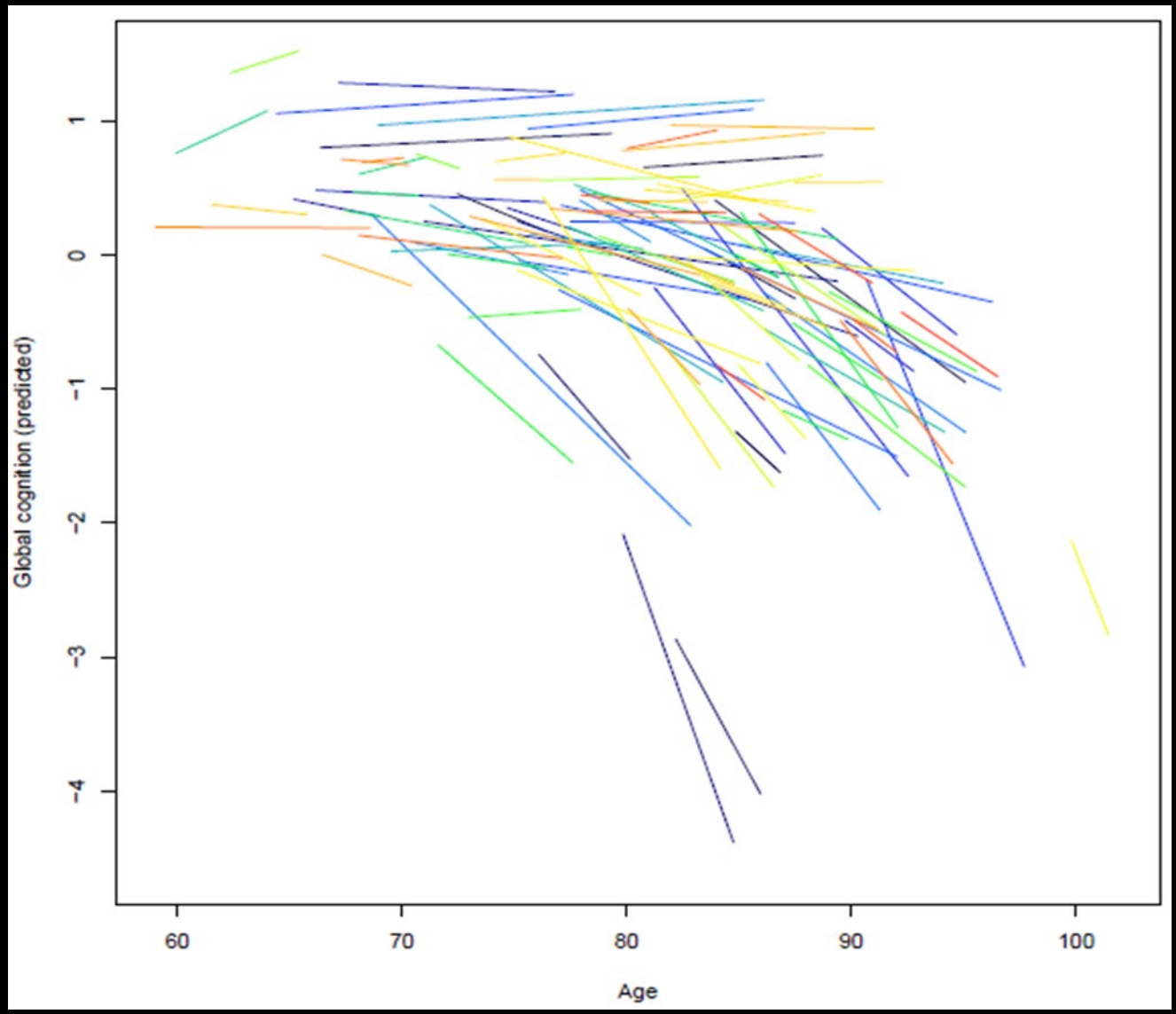
Yu L, et al. *JAMA Neurol.* 2019;76:818-26.

Alzheimer's disease drug development pipeline: 2019

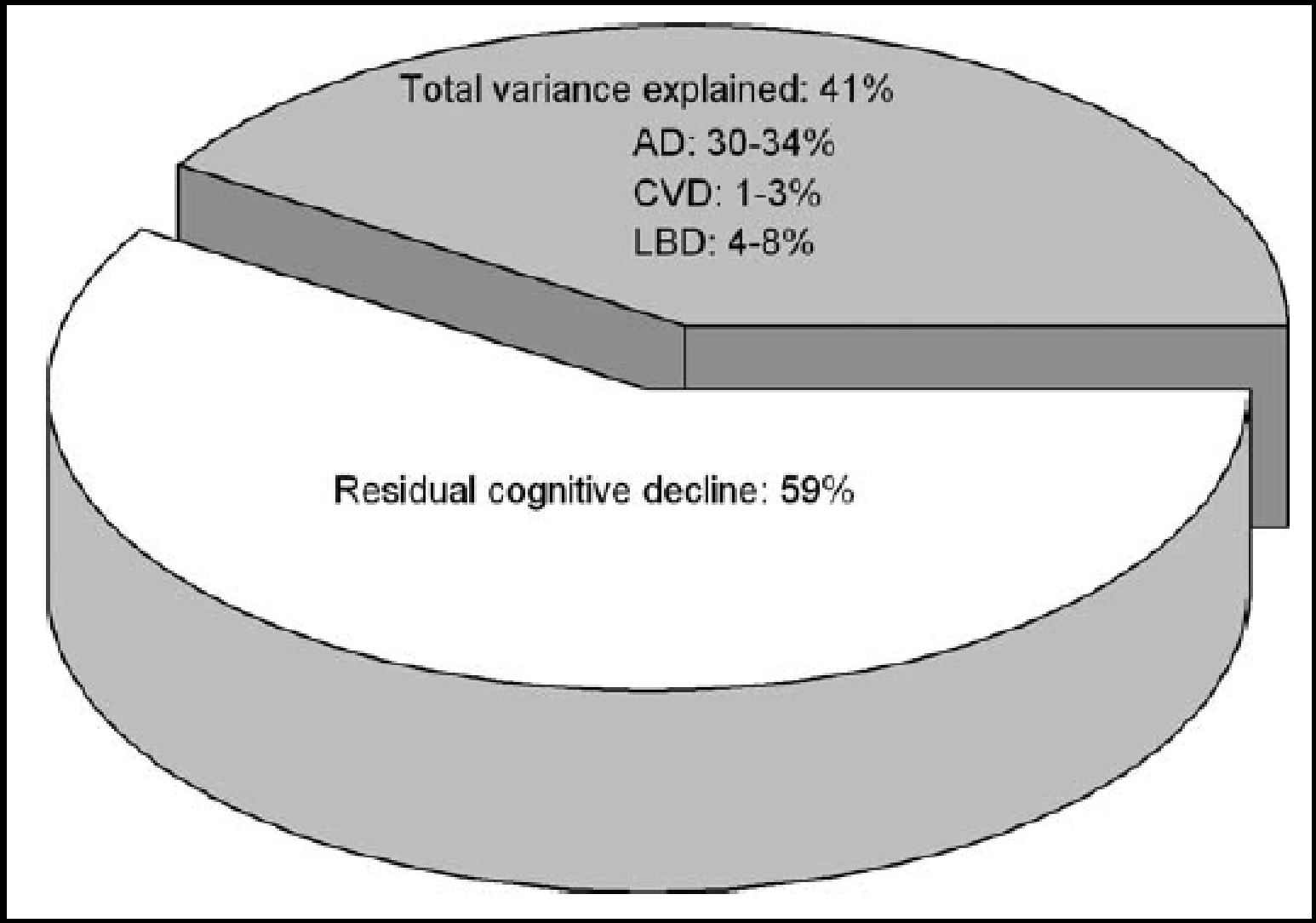


Cummings J, et al. *Alz & Dement.: TR & CI* 2019;5:272-293.

The Ugly,

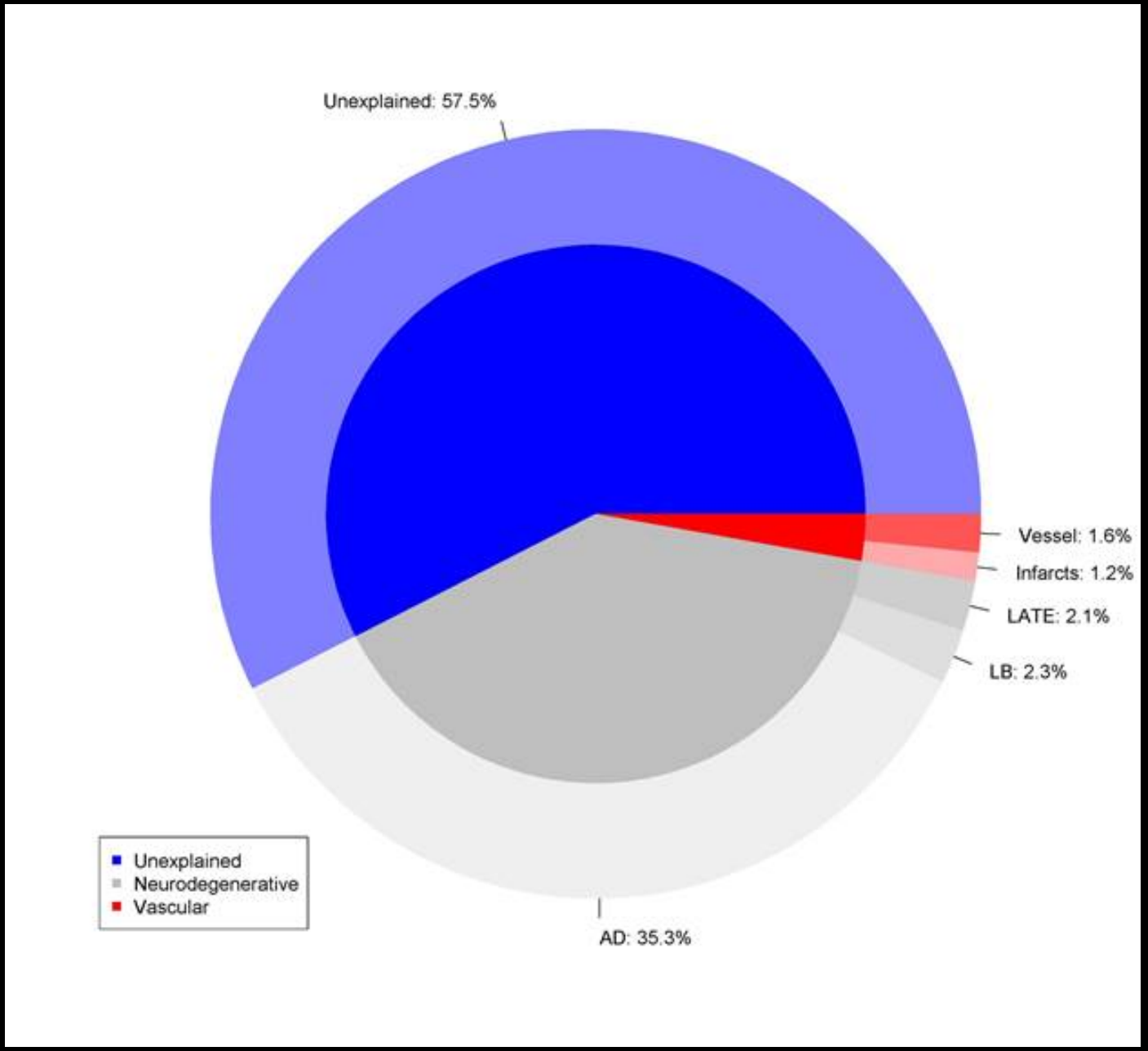


Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

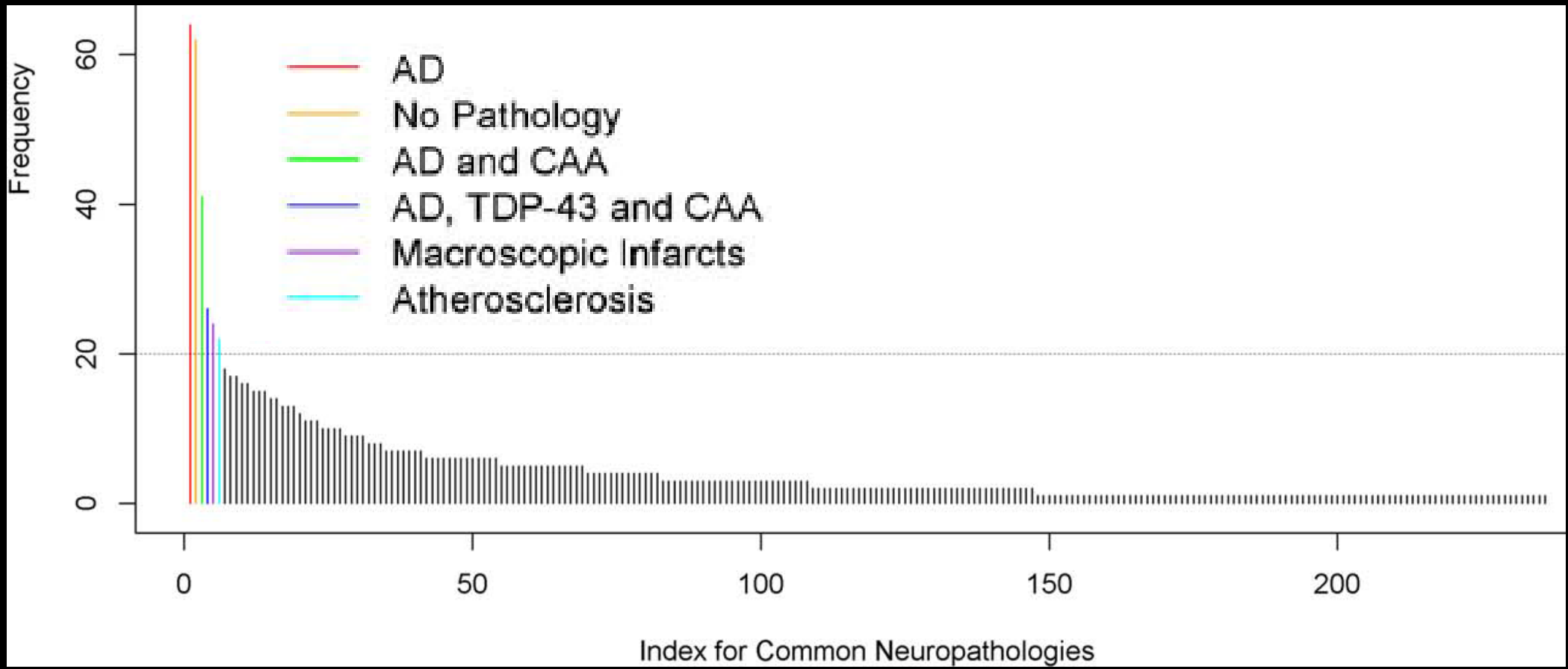


Boyle PA, et al. *Annals Neurology.* 2013;74:478-89

David, there are a lot more pathologies!

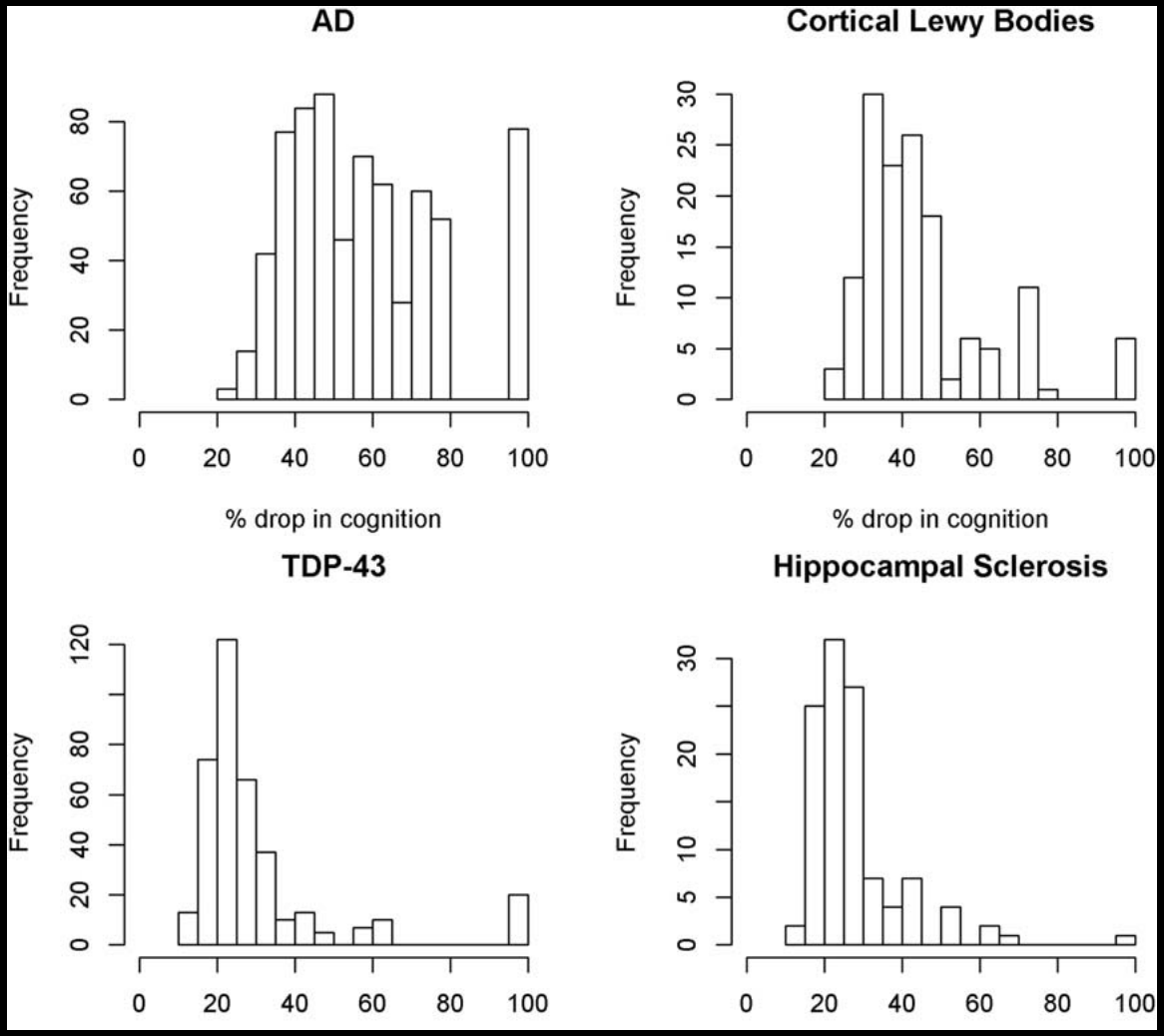


Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

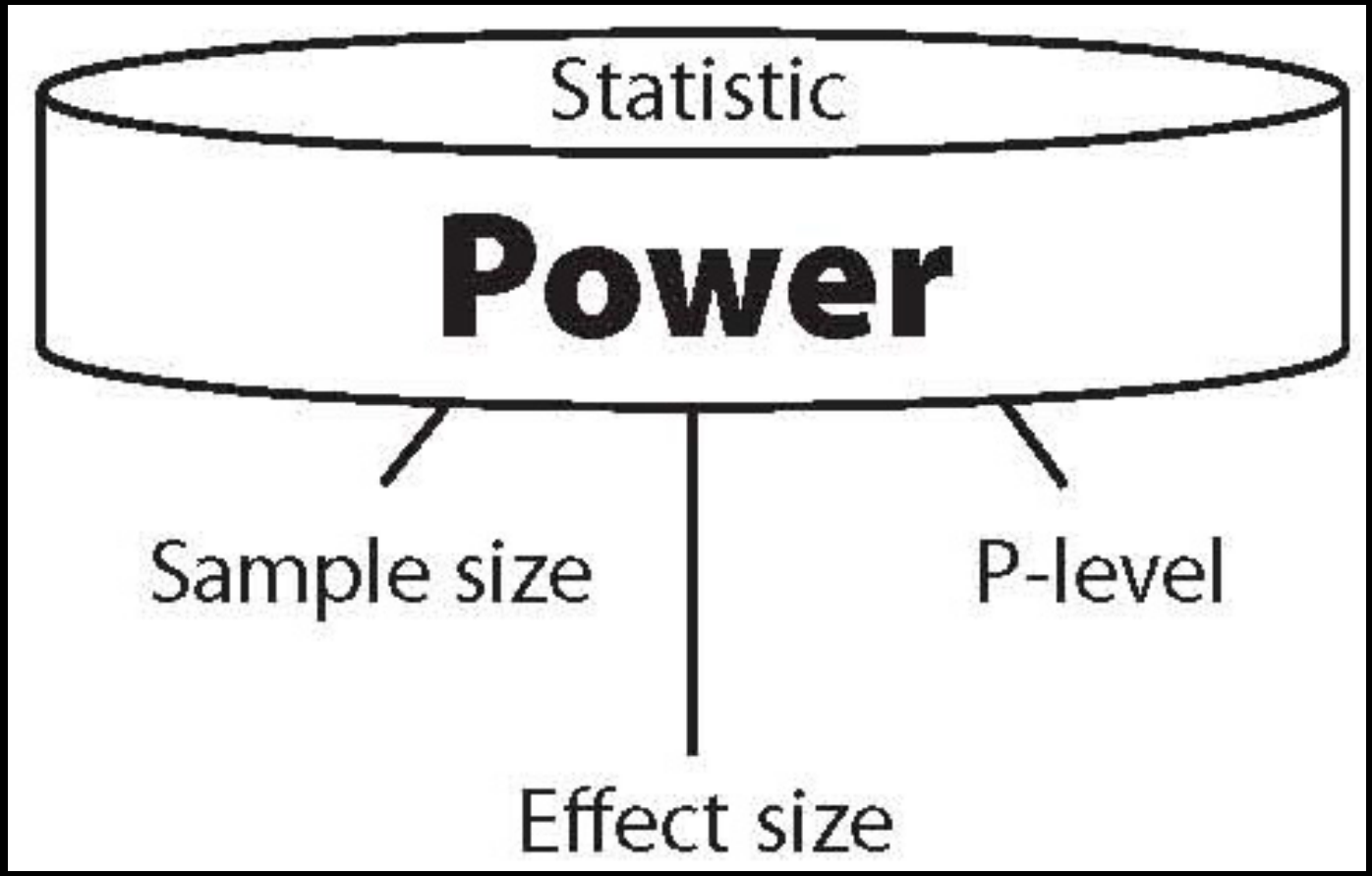


Boyle PA, et al. *Ann Neurol*.2018;83:74-93.

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



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


Statistic
Power
Sample size
Effect size
P-level

Summary

- **The Good**
  - Distinct terms for AD pathology and its consequences allows us to separate risk factors for AD from risk factors for other causes of cognitive impairment

Summary

- **The Good**
  - Distinct terms for AD pathology and its consequences allows us to separate risk factors for AD from risk factors for other causes of cognitive impairment
- **The Bad**
  - AD only accounts for about a third of Alzheimer's dementia cases
  - Less so for the oldest old
  - AD pathology goes down after age 95 despite increasing dementia

Summary

- **The Good**
  - Distinct terms for AD pathology and its consequences allows us to separate risk factors for AD from risk factors for other causes of cognitive impairment
- **The Bad**
  - AD only accounts for about a third of Alzheimer's dementia cases
  - Less so for the oldest old
  - AD pathology goes down after age 95 despite increasing dementia
- **The Ugly**
  - Given the number of mixed pathologies and the limited variance of cognitive decline explained, we are likely markedly under-powered in the current slate of anti-amyloid therapeutic trials

RADC Research Resource Sharing Hub

www.radc.rush.edu

Looking for a new opportunity? Email:
David_A_Bennett@Rush.edu