Aging and Alzheimer's Disease: Findings from the Religious Orders Study

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Rush University Medical Center
Chicago, IL

Psychometric Workshop
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Alzheimer's Association; Illinois Department Public Healt

Objectives:

- Background to Religious Orders Study (ROS)
- ROS Study Design
  - Introduction to the Rush Memory and Aging Project for combined cohort analyses
- Distributions of neuropathology
- Relation of risk factors to:
  - Incident MCI and incident AD
  - Change in cognitive function
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Background to Religious Orders Study: Name that year

- March - Windows 3.1 released
- April - The Great Chicago Flood
- May - Jay Leno becomes the new host of NBC's Tonight Show
- July - Ex-Soviet Republic of Georgia joins UN
- August – Hurricane Andrew hits south Florida
- October – Dr. David Bennett and colleagues submit grant for Religious Orders Study to NIH

Background to Religious Orders Study:

- Year: 1992
- Epidemiology – the study of the distribution and determinants of disease in human populations
- Diseases of cognition such as AD are defined clinically
  - However, it has long been known that the pathology underlying AD is heterogeneous

Clinical, Pathological, and Neurochemical Changes in Dementia: A Subgroup with Preserved Mental Status and Numerous Neocortical Plaques

Robert Katzman, MD,* Robert Terry, MD,* Richard DeTeresa, BS,* Theodore Brown, PhD,†
Peter Davies, PhD,‡§ Paula Fuld, PhD,‖ Xiong Renbing, MA,† and Arthur Peck, MD¶

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- Epidemiology – the study of the distribution and determinants of disease in human populations
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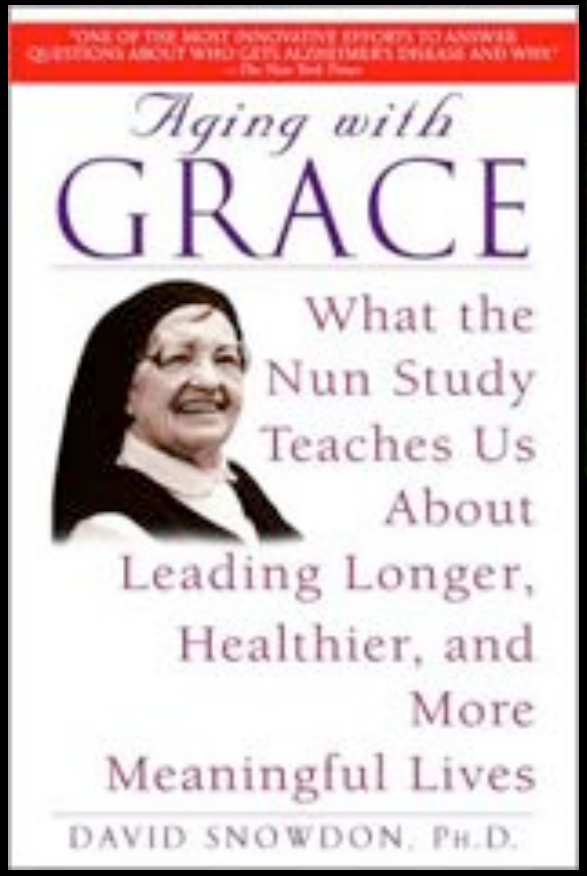
- Recent studies were beginning to address this heterogeneity by incorporating neuropathologic indices into epidemiologic studies o aging and dementia



Honolulu-Asia Aging Study

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- Diseases of cognition such as AD are defined clinically
  - However, it has long been known that the pathology underlying AD is heterogeneous
- Recent studies were beginning to address this heterogeneity by incorporating neuropathologic indices into epidemiologic studies o aging and dementia
- The overall goal of ROS is to identify risk factors for cognitive decline and dementia and examine the neurobiologic pathways linking risk factors to clinical phenotypes

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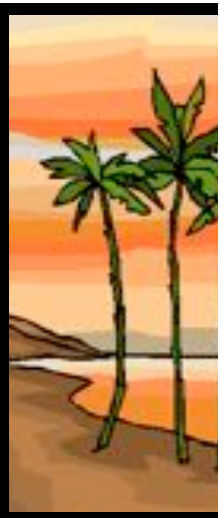
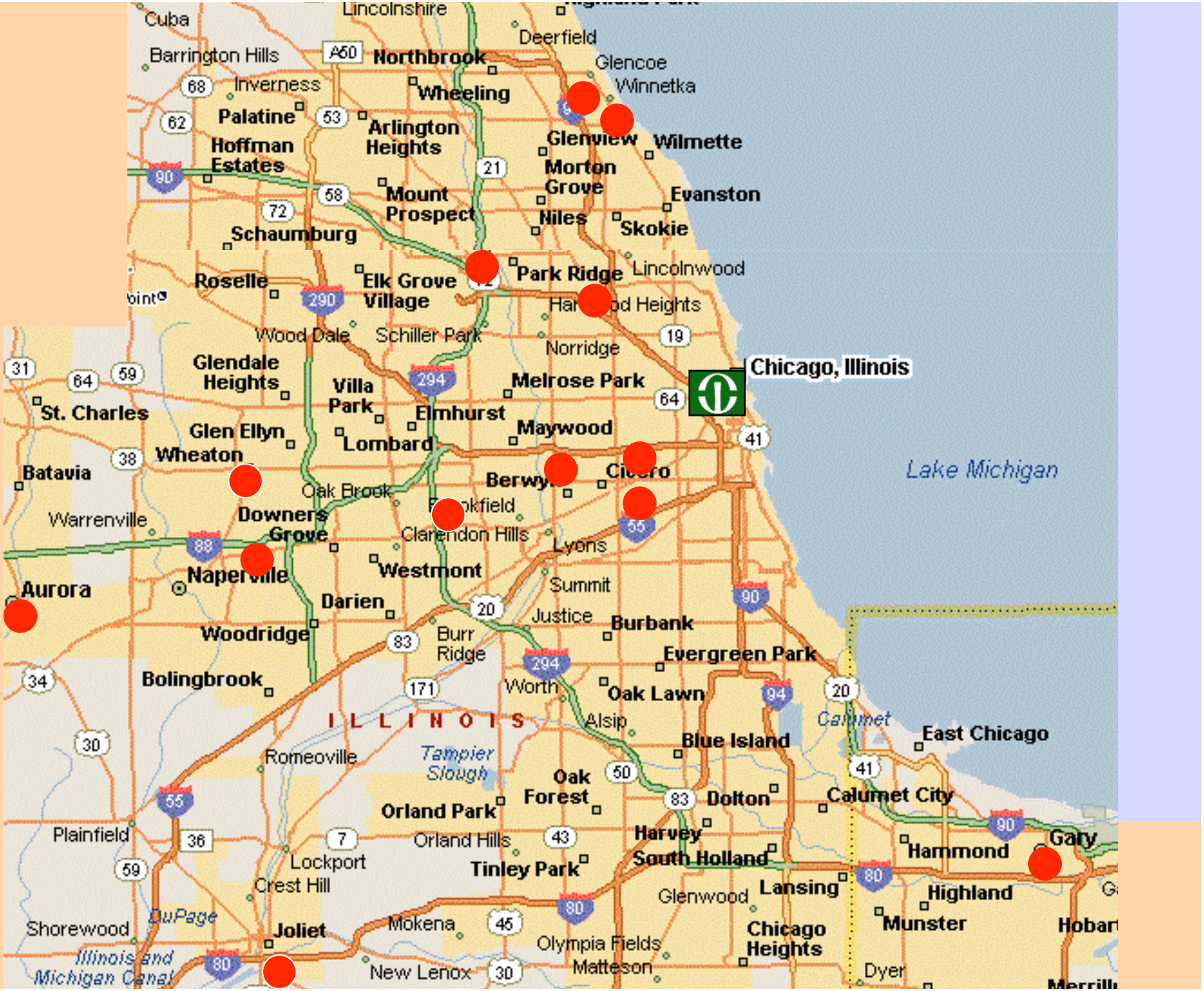
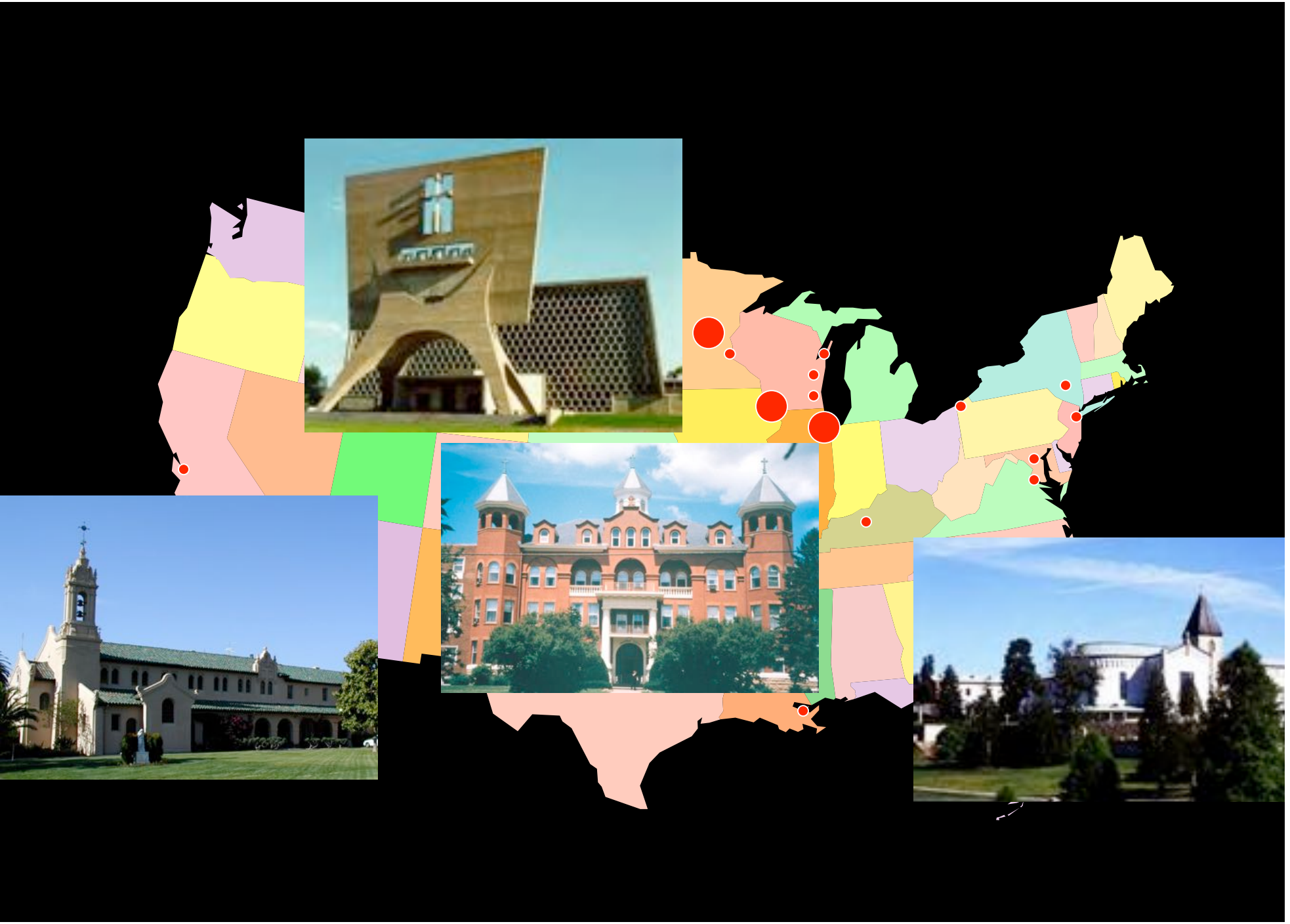
The Religious Orders Study

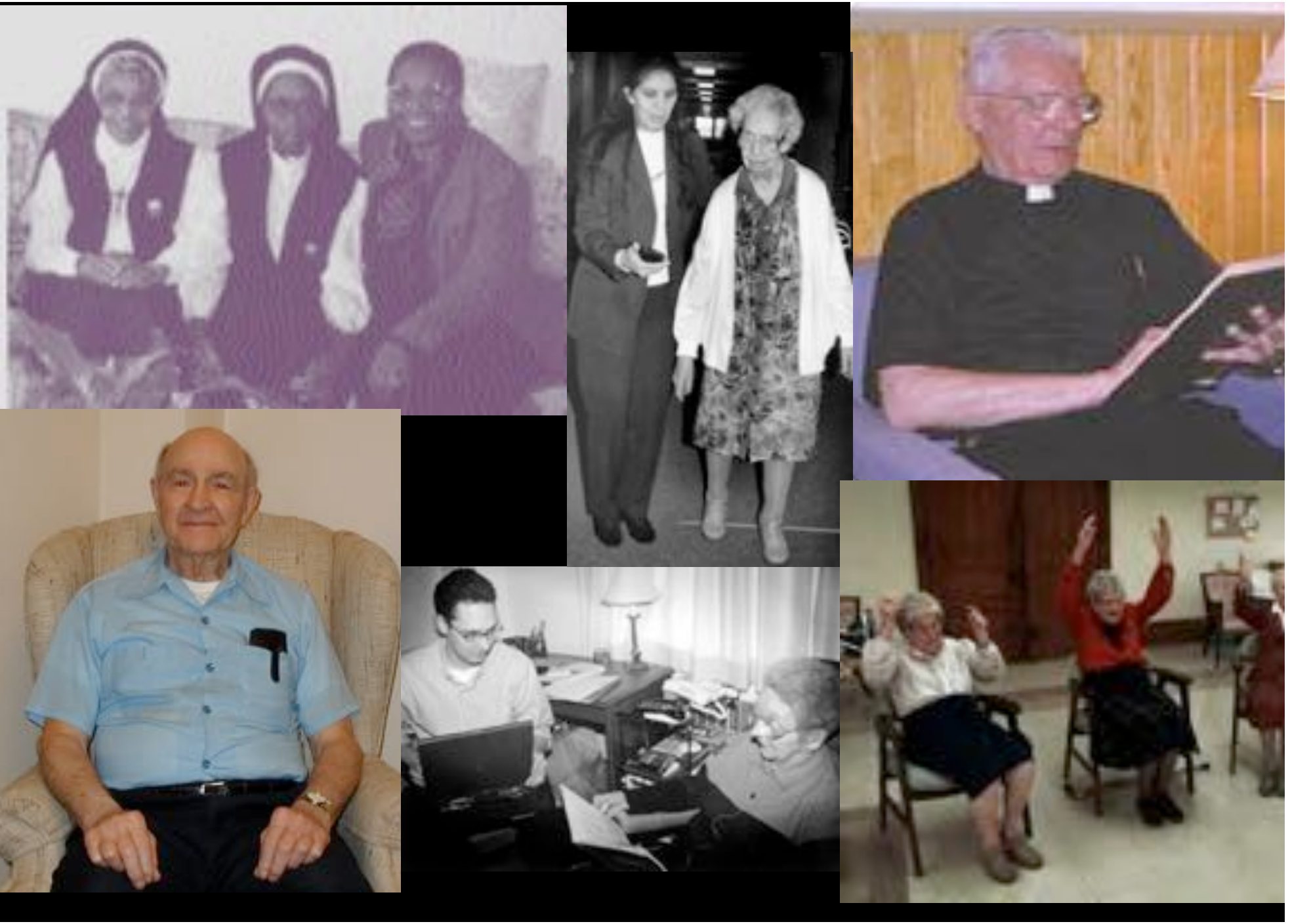


- Began enrollment in 1994
- > 1,100 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing
- All agreed to brain donation at the time of death
- > 95% follow-up of survivors
- > 350 incident MCI and > 250 incident AD cases
- ~ 95% autopsy rate with > 425 brain autopsies


Chicago, Illinois
Lake Michigan
ILLINOIS
Lincolnshire
Deerfield
Barrington Hills
Northbrook
Glencoe
Winnetka
Inverness
Wheeling
Palatine
Arlington Heights
Glenview
Wilmette
Hoffman Estates
Morton Grove
Evanston
Mount Prospect
Niles
Skokie
Schaumburg
Park Ridge
Lincolnwood
Roselle
Elk Grove Village
Wood Dale
Schiller Park
Norridge
Glendale Heights
Melrose Park
St. Charles
Villa Park
Elmhurst
Maywood
Glen Ellyn
Lombard
Wheaton
Batavia
Cicero
Oak Brook
Downers Grove
Warrenville
Clarendon Hills
Lyons
Naperville
Westmont
Aurora
Darien
Summit
Justice
Burbank
Woodridge
Burr Ridge
Evergreen Park
Bolingbrook
Worth
Oak Lawn
Alsip
Blue Island
East Chicago
Calumet
Romeoville
Tampier Slough
Oak Forest
Orland Park
Dolton
Calumet City
Plainfield
Orland Hills
Harvey
Hammond
Gary
Lockport
Tinley Park
South Holland
Crest Hill
Glenwood
Lansing
Highland
DuPage
Shorewood
Joliet
Mokena
Olympia Fields
Chicago Heights
Munster
Illinois and Michigan Canal
New Lenox
Matteson
Dyer

Religious Orders Study: Participating Sites





Strengths and Weaknesses:

- Strengths
  - Large numbers of persons enroll without dementia
  - Participants comparable in terms of lifestyle factors
  - Cohort enriched with genetic variants for dementia
  - High rates of follow-up participation and autopsy
  - Volunteer cohort permits great depth and breadth of data collection
- Weaknesses
  - Cohort not representative of older persons in US
  - Truncated variance of lifestyle factors limits ability to investigate the relation of these factors to dementia
  - Geographic dispersion limits clinical and post-mortem data collection

The Rush Memory and Aging Project

… because memories should last a lifetime

- Began enrollment in 1997
- > 1,200 residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive and motor testing, and blood draw
- All agreed to donate brain, spinal cord, muscle, and nerv at the time of death
- > 95% follow-up of survivors
- > 250 incident MCI and > 175 incident AD cases
- ~ 85% autopsy rate with > 250 autopsies to date


MapPoint.net
Antioch
Zion
Lindenhurst
Beach Park
Waukegan
Fox Lake Hills
Spring Grove
Alden
Chemung
Round Lake Beach
Gurnee
McHenry
Gages Lake
North Chicago
BOONE
M C H E N R Y
L A K E
Woodstock
Libertyville
Fremont Center
Belvidere
Mundelein
Marengo
Crystal Lake
Fox River Grove
Lake Barrington
Lake Michigan
Highwood
Lake in the Hills
Algonquin
Lake Zurich
Highland Park
Northbrook
Carpentersville
West Dundee
Palatine
Wheeling
Glencoe
Genoa
Hoffman Estates
Arlington Heights
Wilmette
Elgin
Evanston
Schaumburg
Niles
Lincolnwood
Sycamore
Bartlett
C O O K
Park Ridge
Roselle
De Kalb
I L L I N O I S
Melrose Park
Carol Stream
Villa Park
Chicago
Cortland
St. Charles
Lombard
Oak Park
D E K A L B
Wheaton
Maywood
Cicero
Batavia
Downers Grove
Oak Brook
Berwyn
K A N E
Warrenville
Hinckley
Sugar Grove
Westmont
Willowbrook
Aurora
Naperville
Burbank
Shabbona
Darien
Little Rock
Bolingbrook
D U P A G E
Oak Lawn
East Chicago
Bristol
Lemont
Worth
Calumet
Sandwich
Plano
Oswego
W I L L
Robbins
Dolton
LAKE
Yorkville
Romeoville
Harvey
Hammond
Leland
Somonauk
Orland Park
Gary
LA SALLE
KENDALL
Plainfield
Lockport
Tinley Park
Crest Hill
Munster
Highland
Sheridan
Shorewood
Joliet
Chicago Heights
INDIANA
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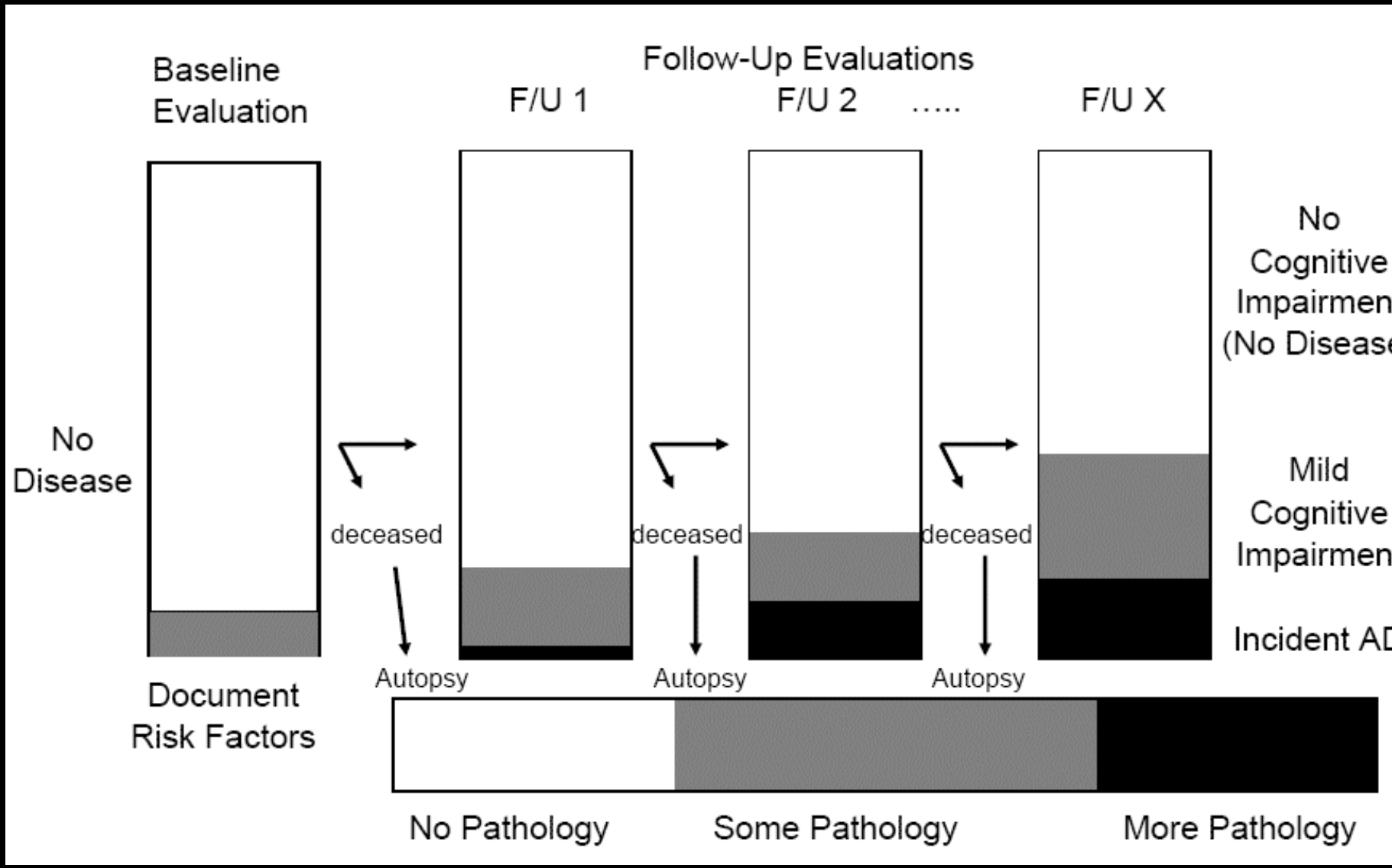
The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort



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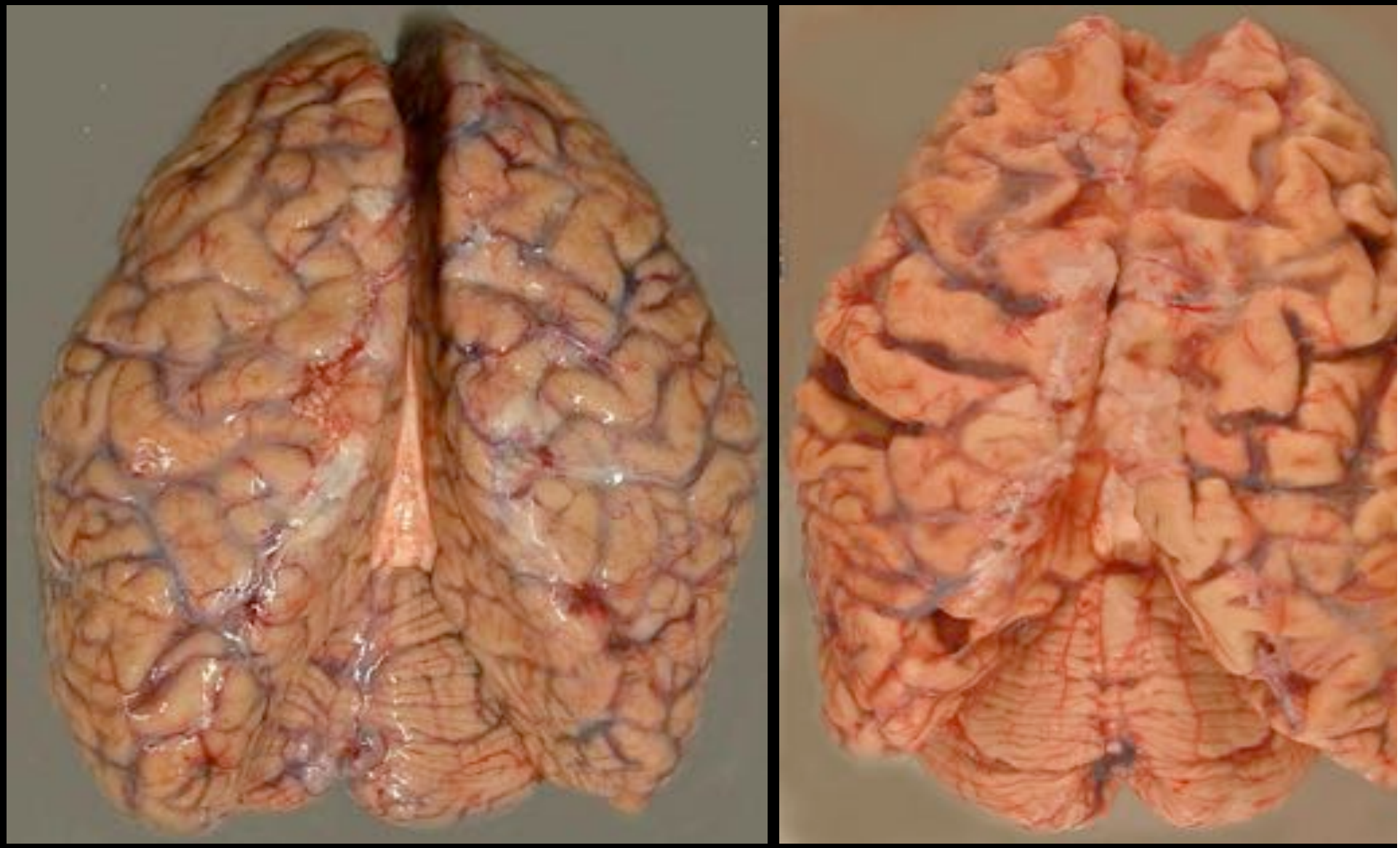

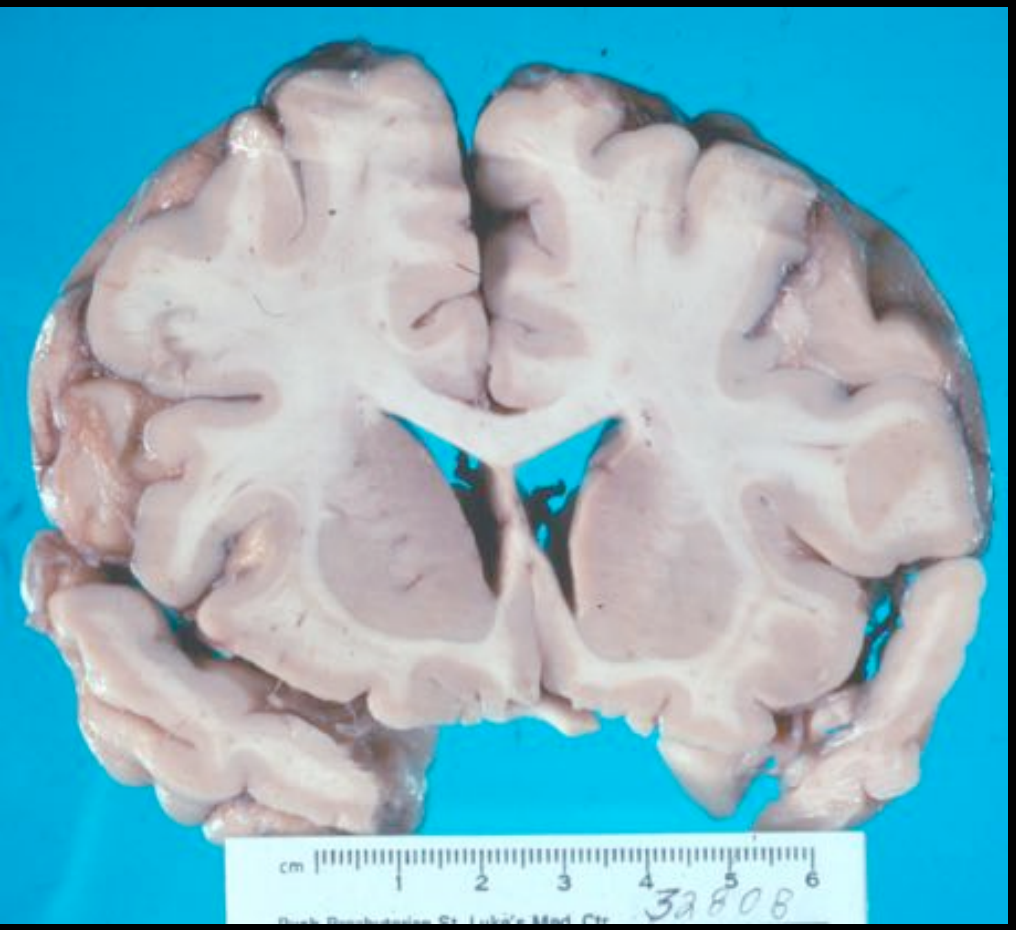
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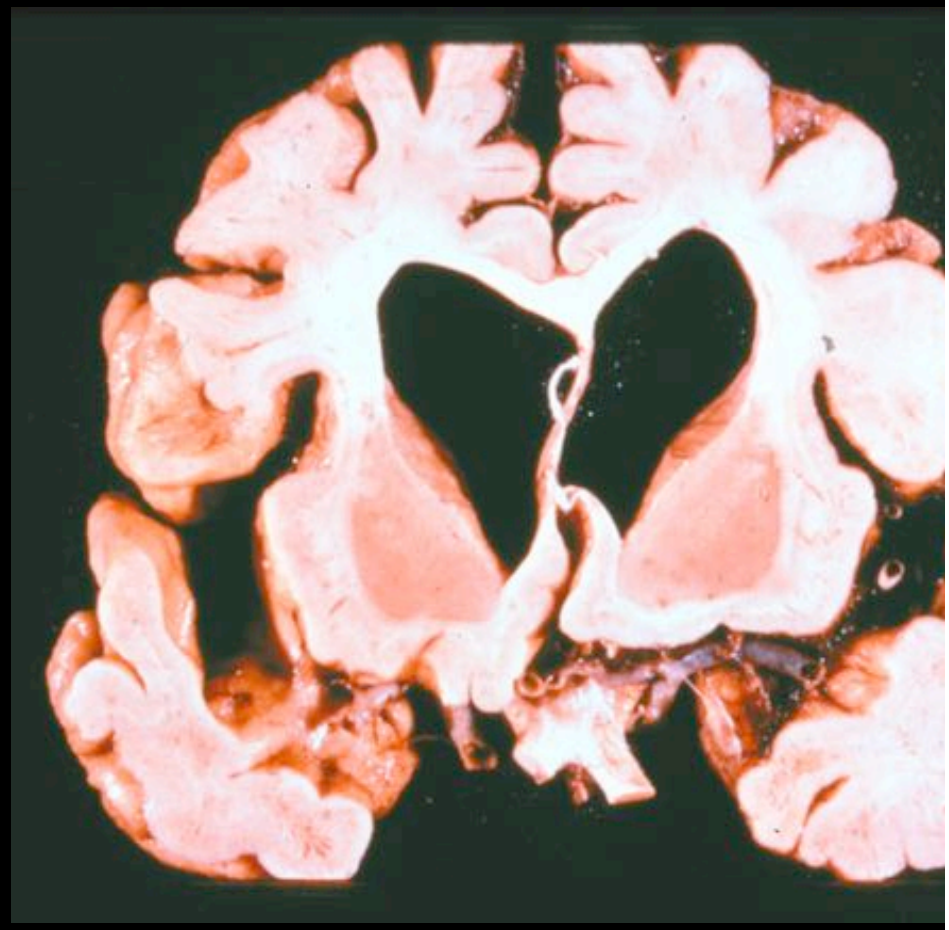
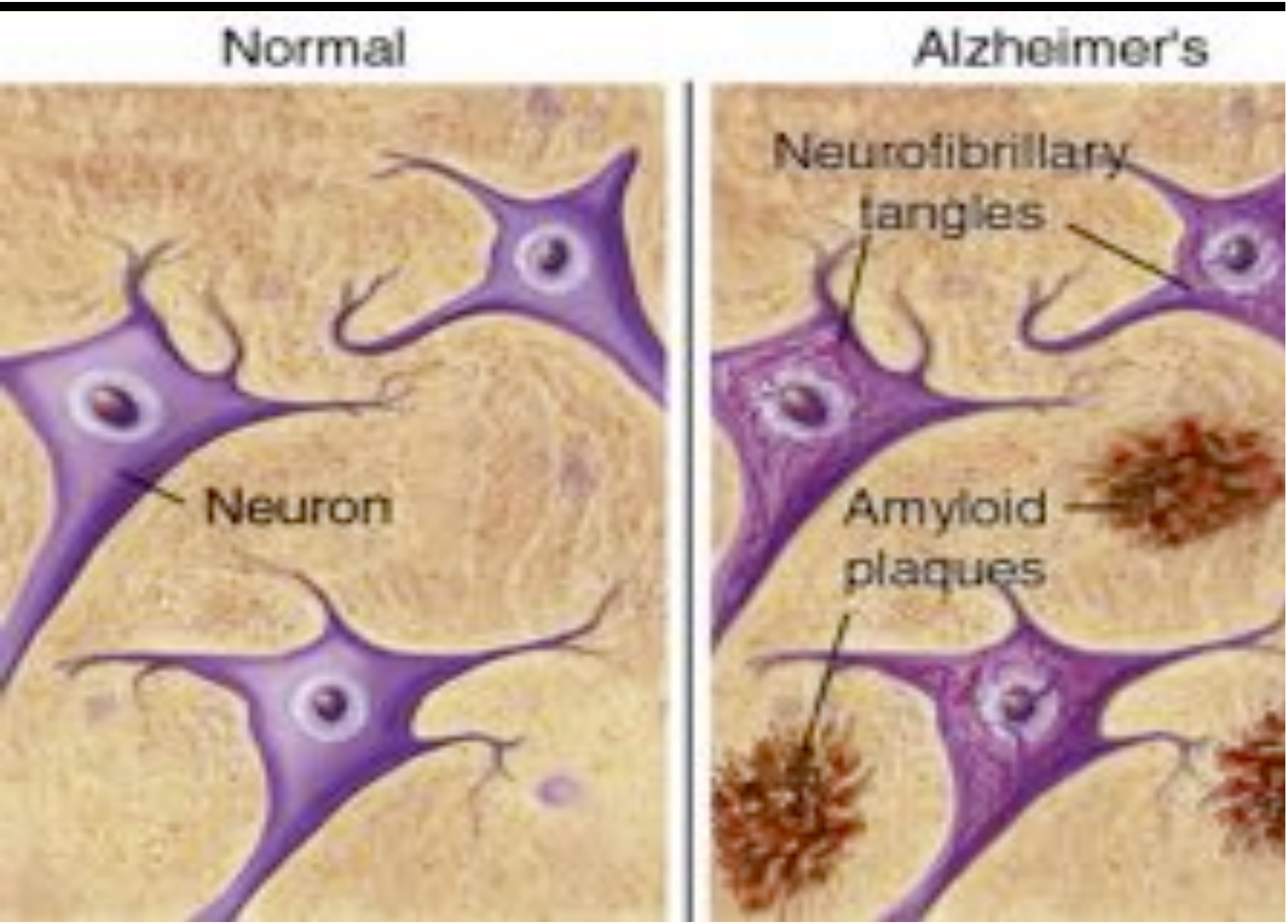
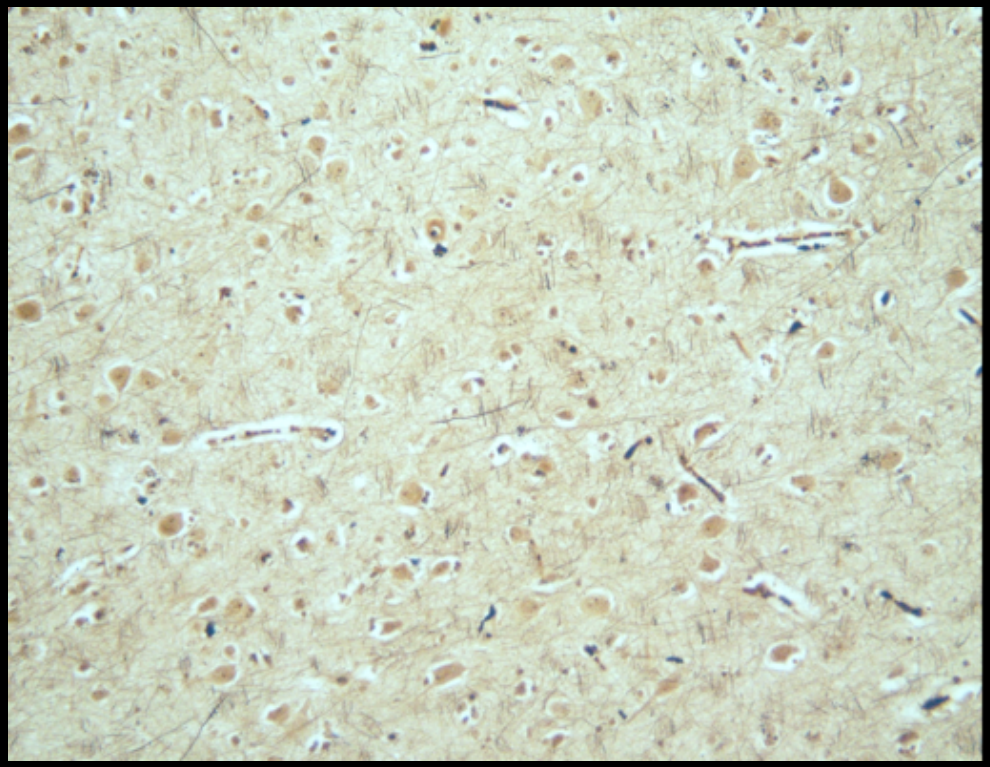
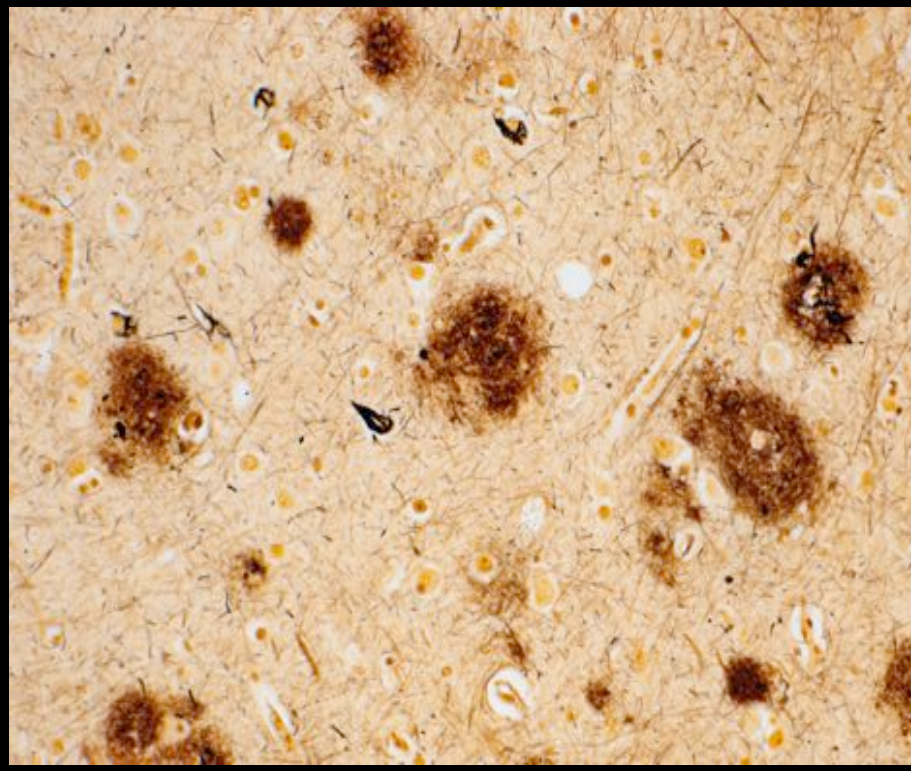
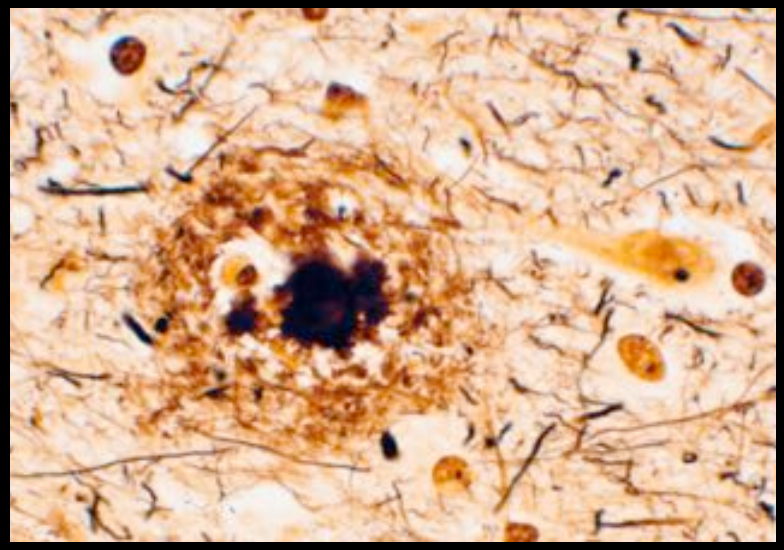
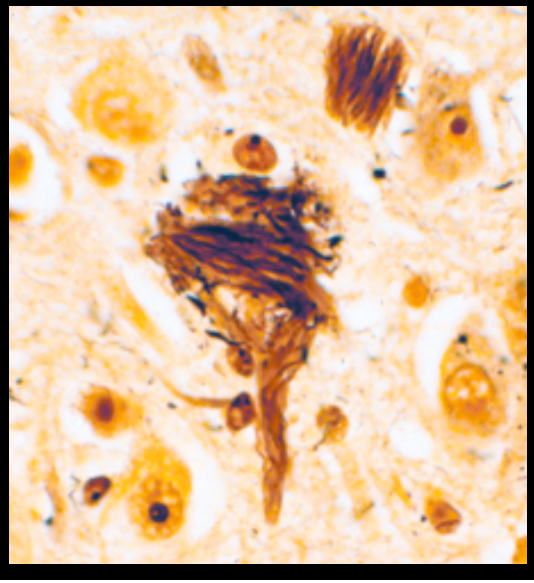



Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

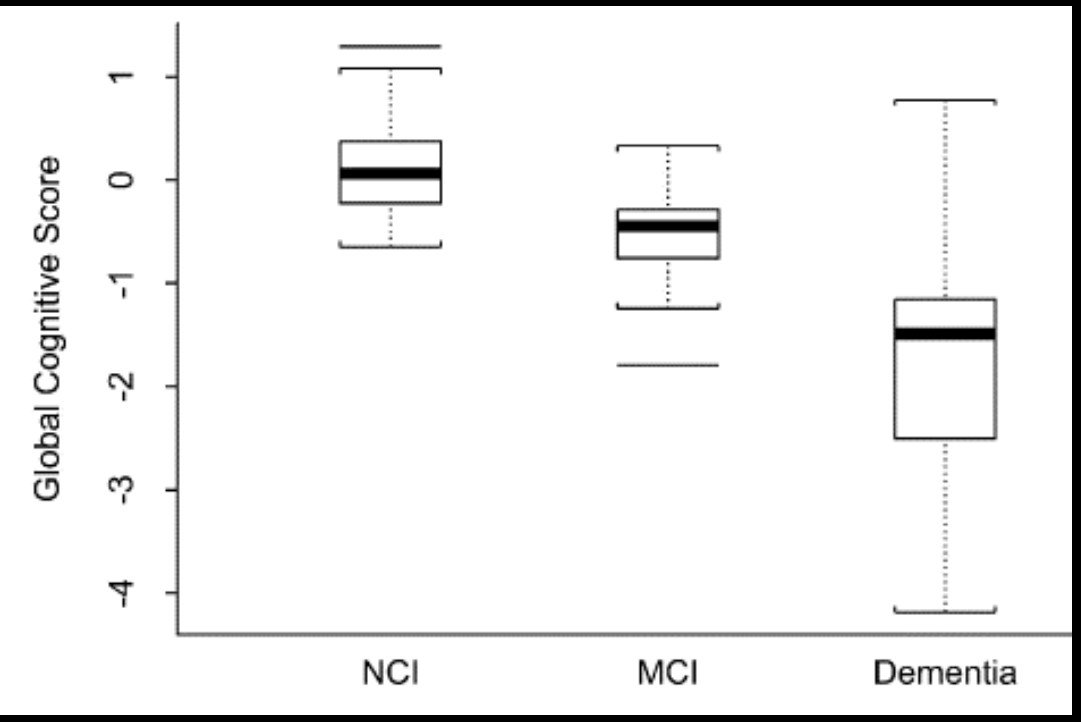


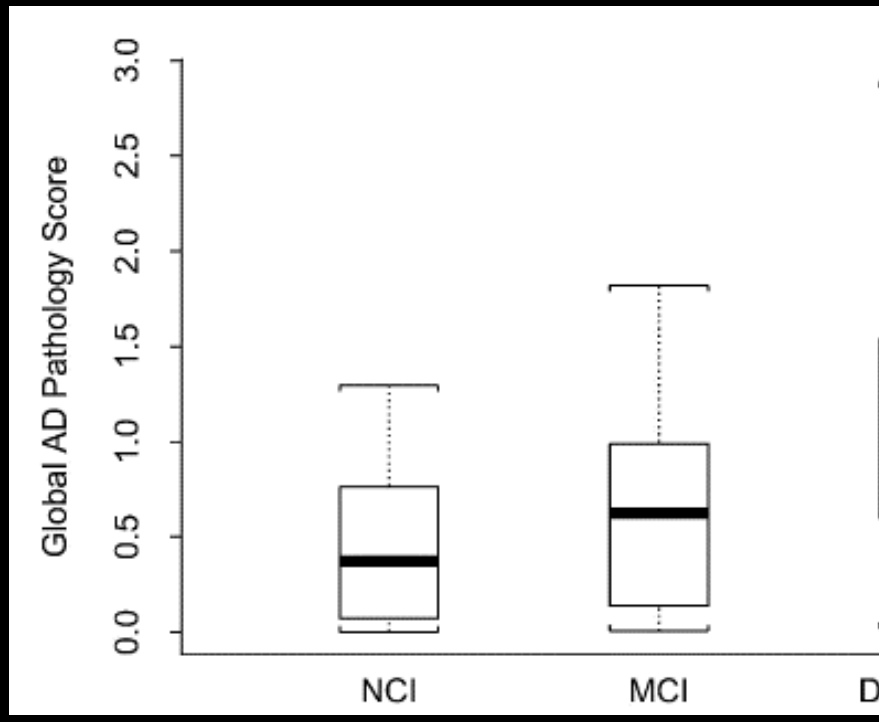






Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions





Bennett DA, et al. *Neurology* 2005;64:834-842.

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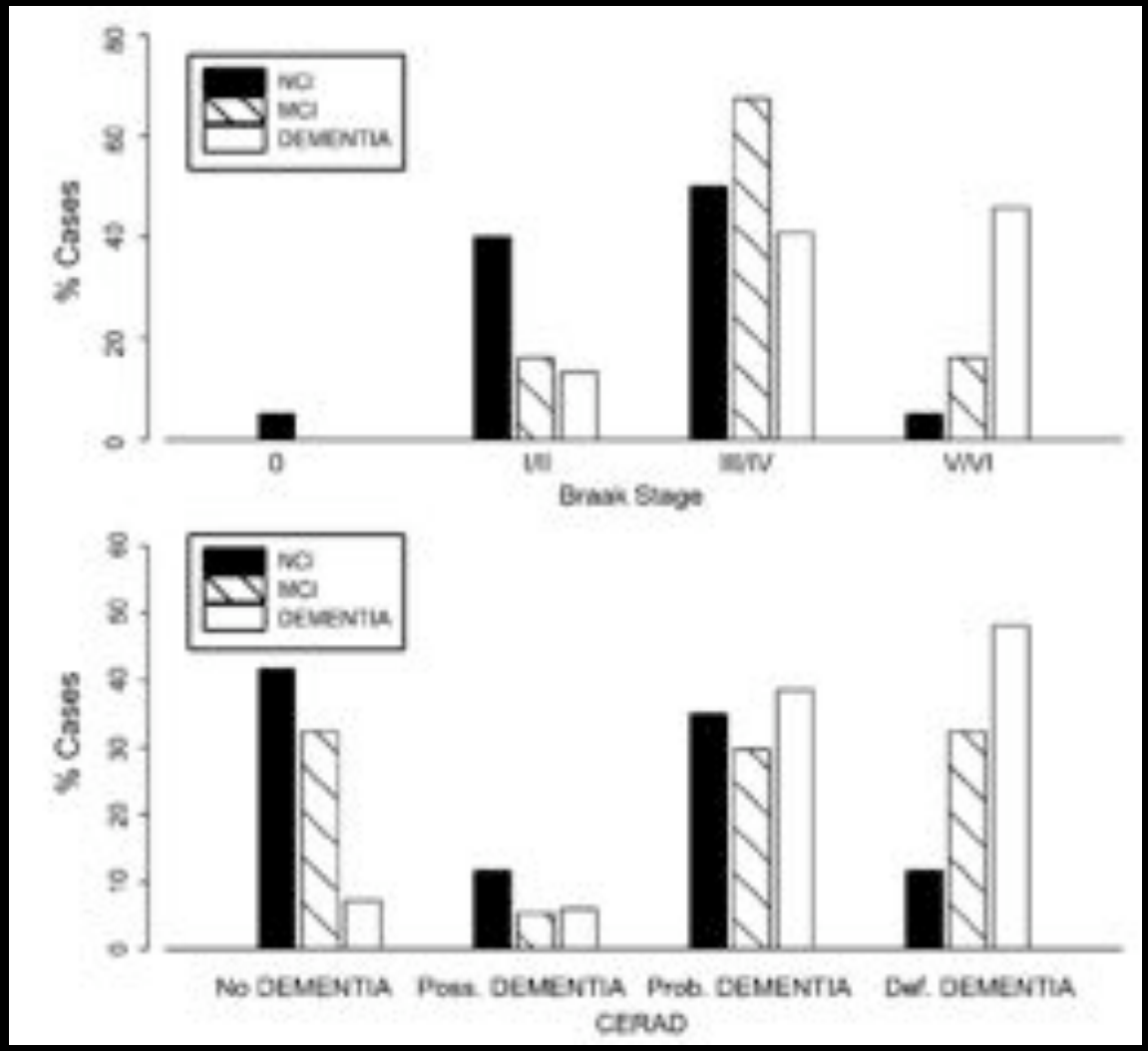

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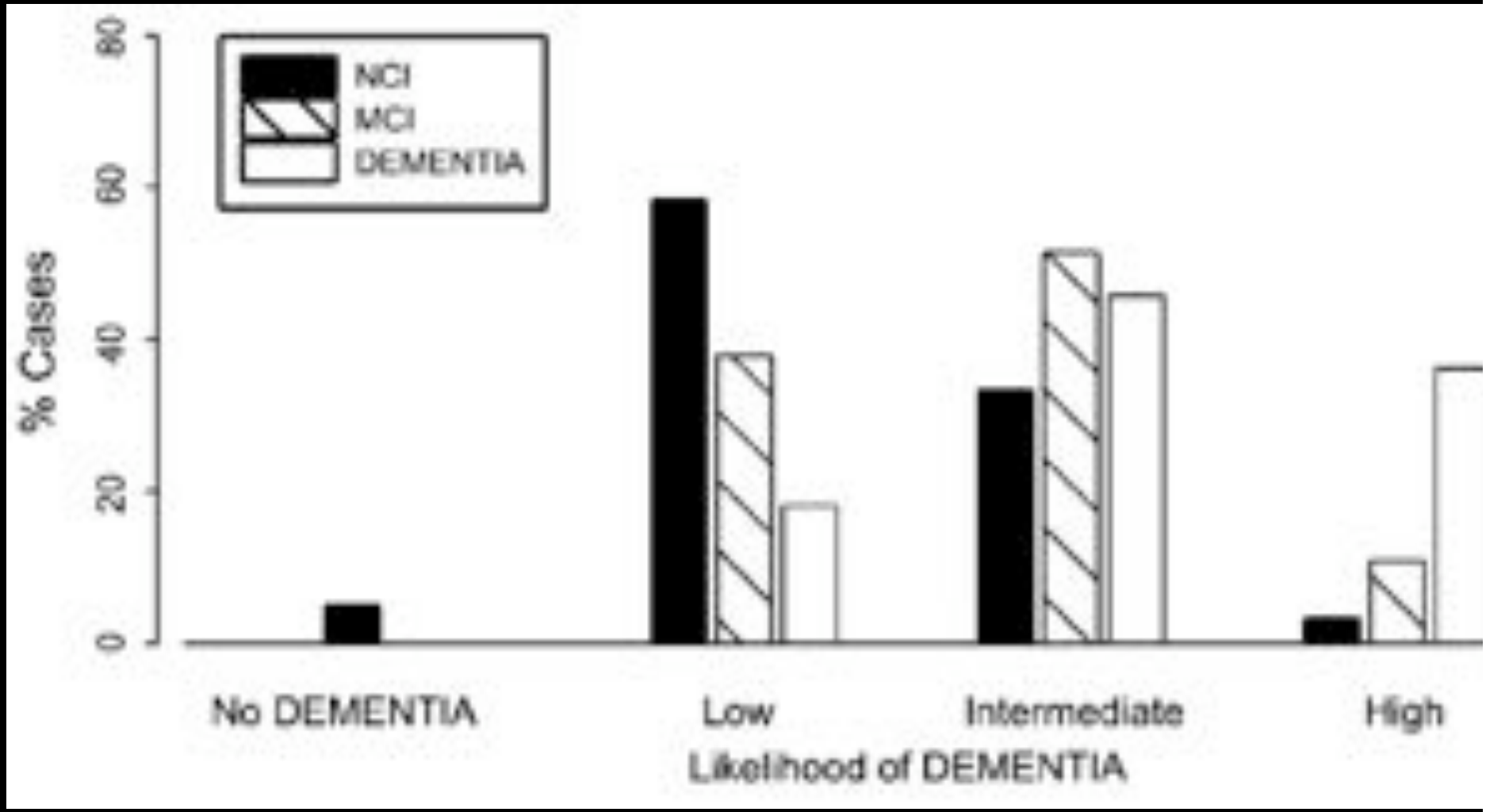

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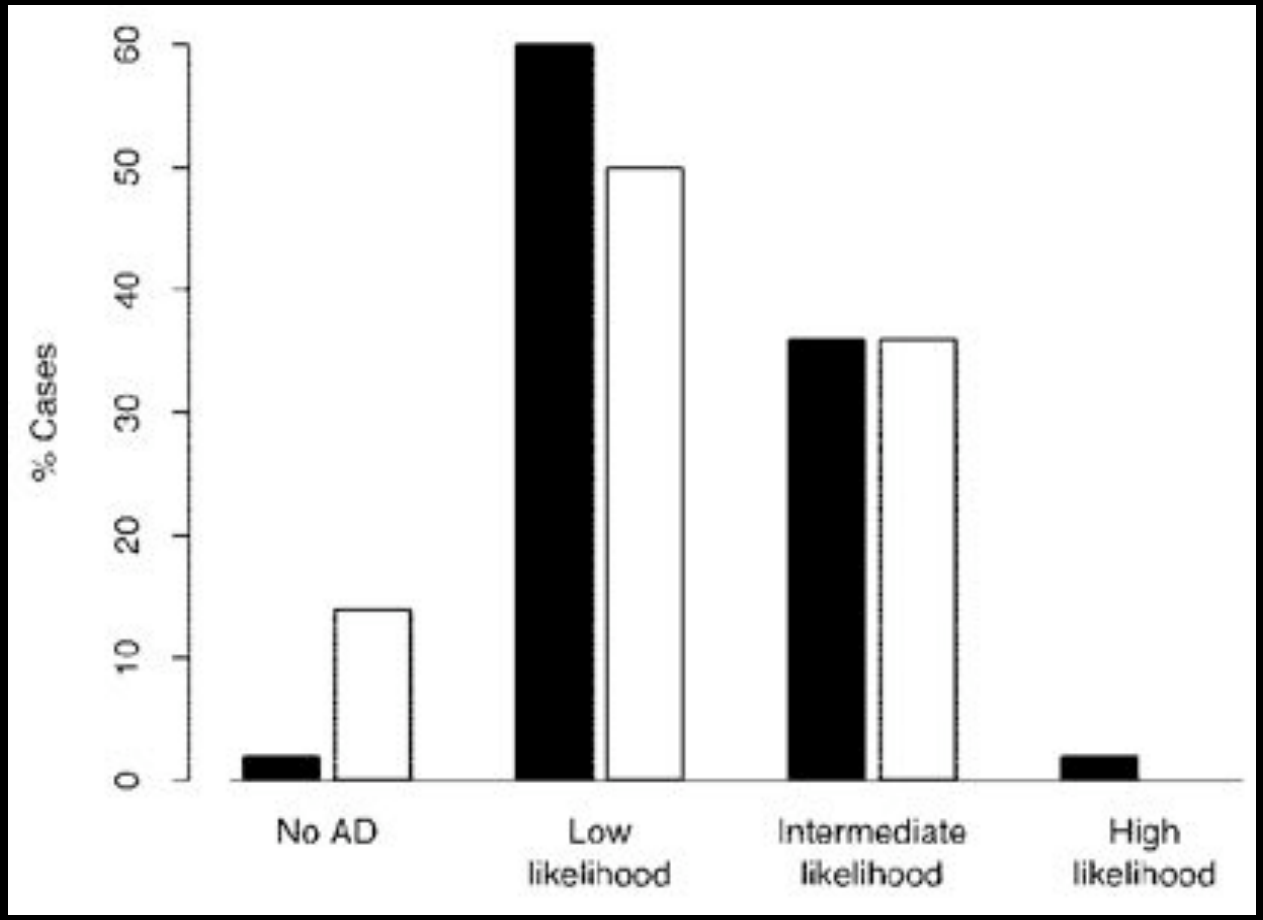
Neuropathology of older persons without cognitive impairment from two community-based studies

MMSE proximate to death	28.4 (1.4)	28.2 (1.6)



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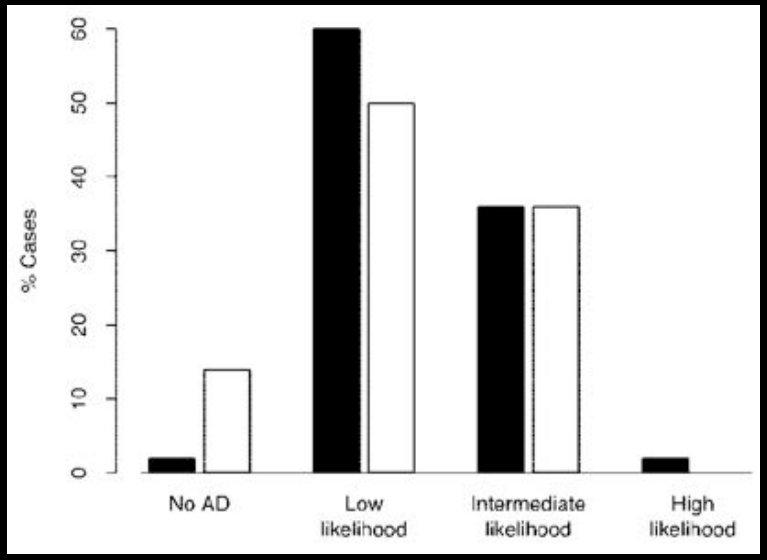
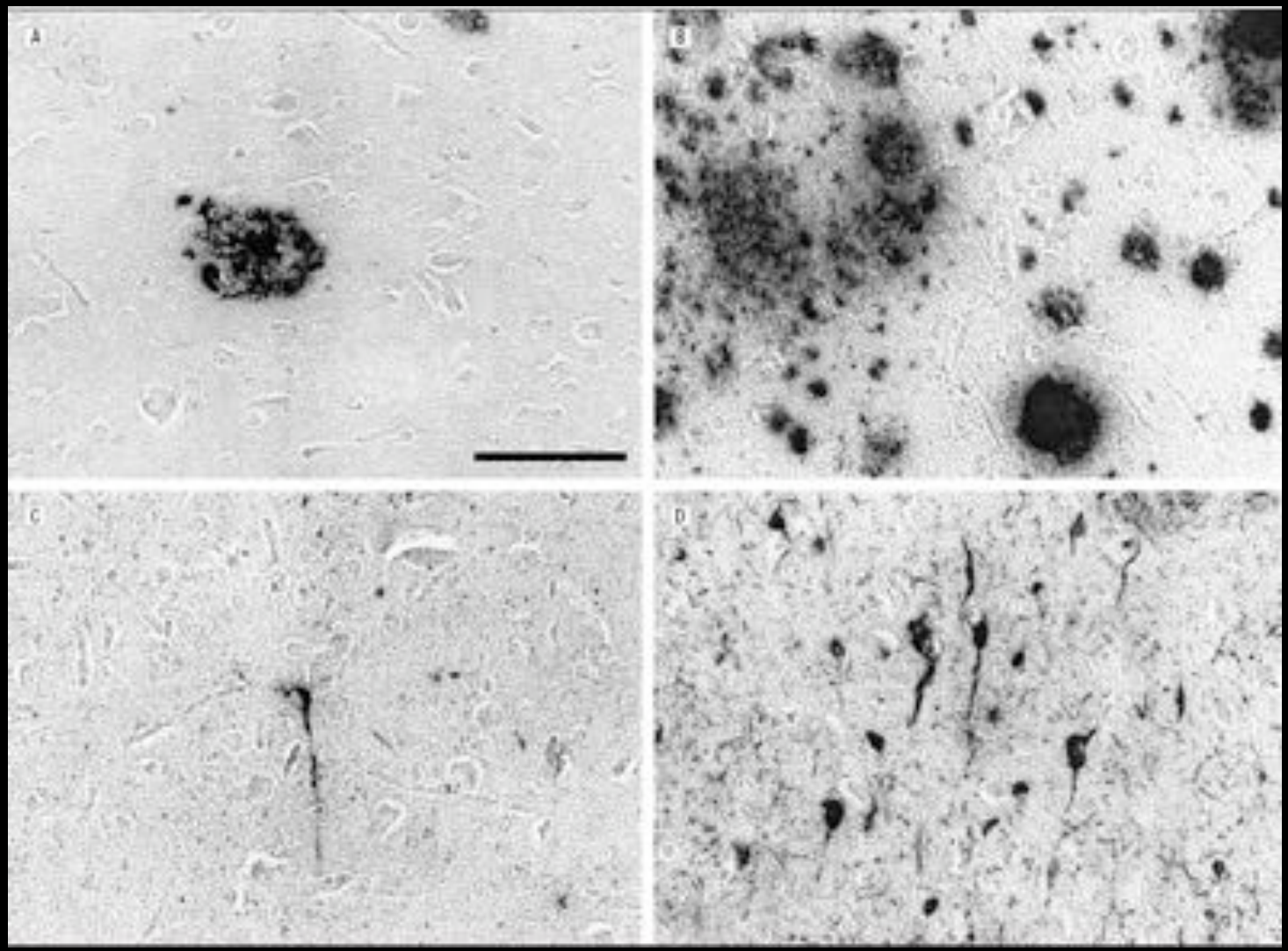


	NIA-Reagan pathologic AD		*p* V
	No	Yes	Model 1
Episodic memory	0.44 (0.45)	0.18 (0.46)	0.01
Semantic memory	0.11 (0.47)	–0.05 (0.50)	0.16
Working memory	0.18 (0.71)	0.00 (0.58)	0.12
Perceptual speed	–0.15 (0.92)	–0.27 (0.77)	0.62
Visuospatial ability	0.03 (0.62)	0.12 (0.59)	0.26

Bennett DA, et al. *Neurology* 2006;66:1837-44.

Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function



Bennett DA, et al. *Arch Neurol* 61:378-384

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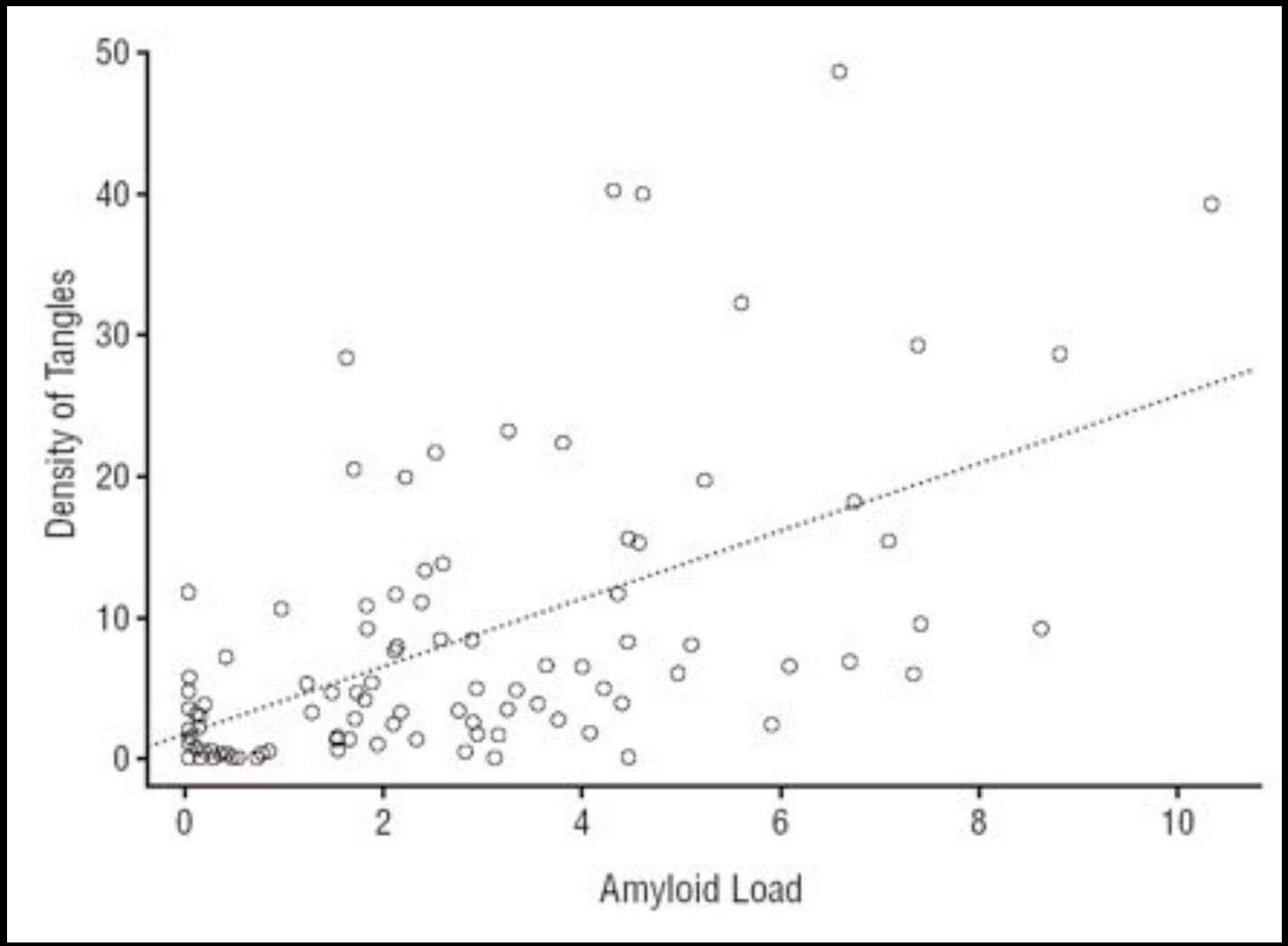

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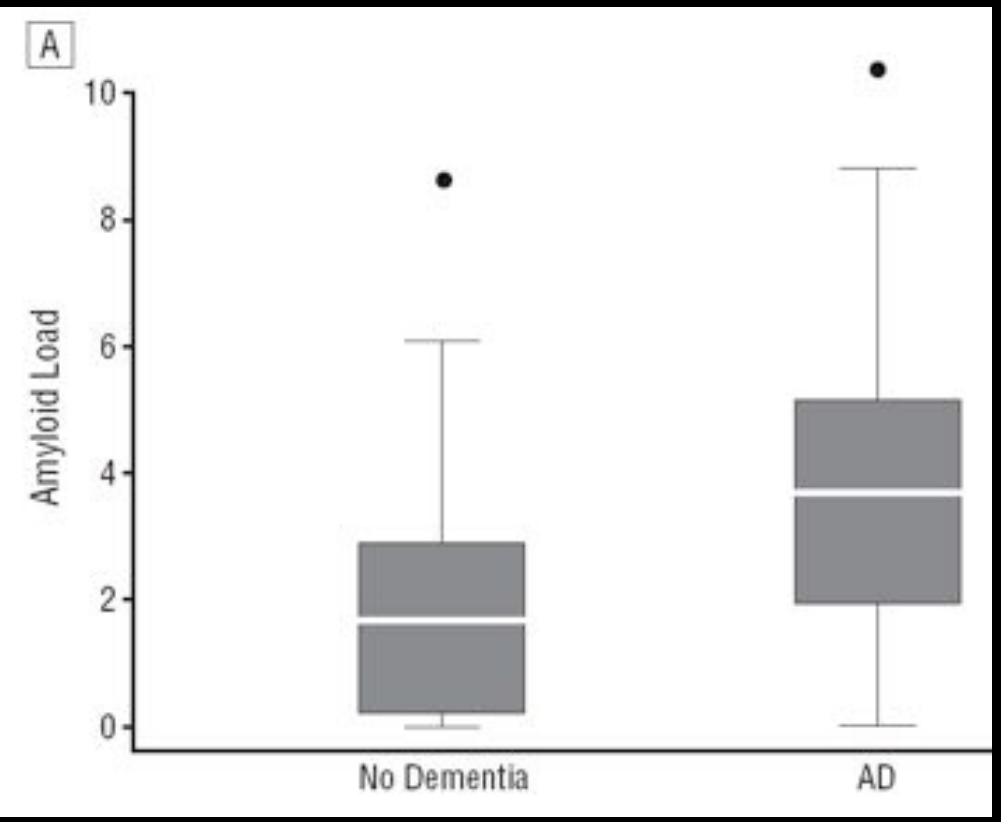

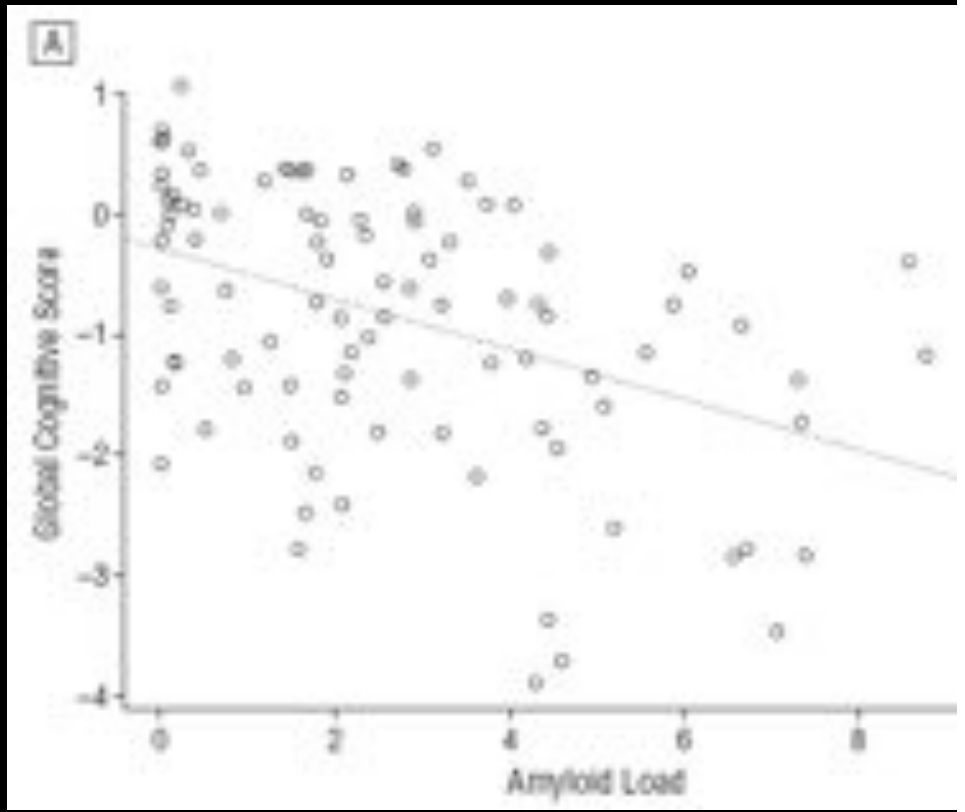

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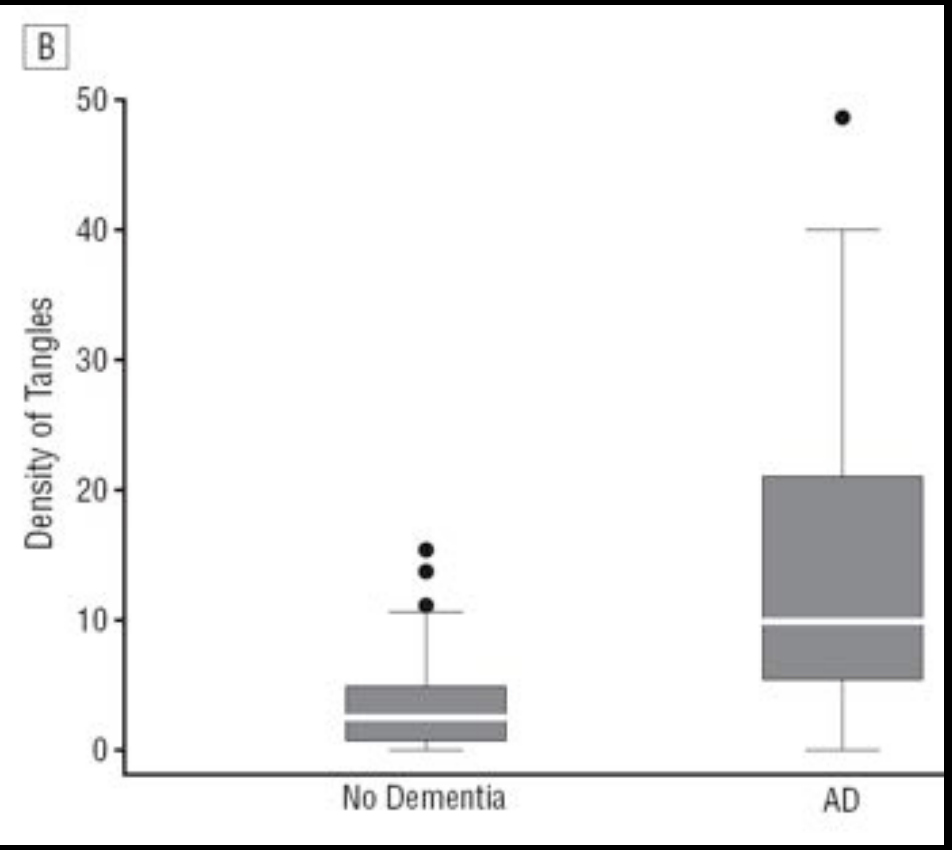

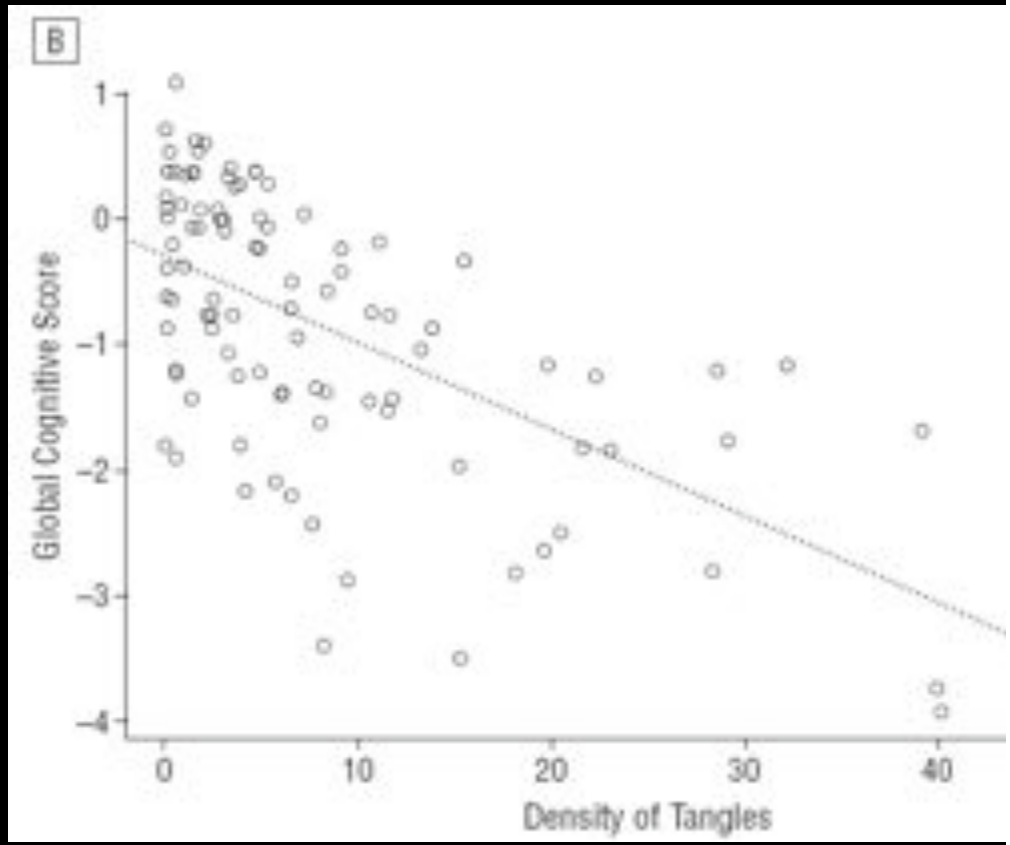

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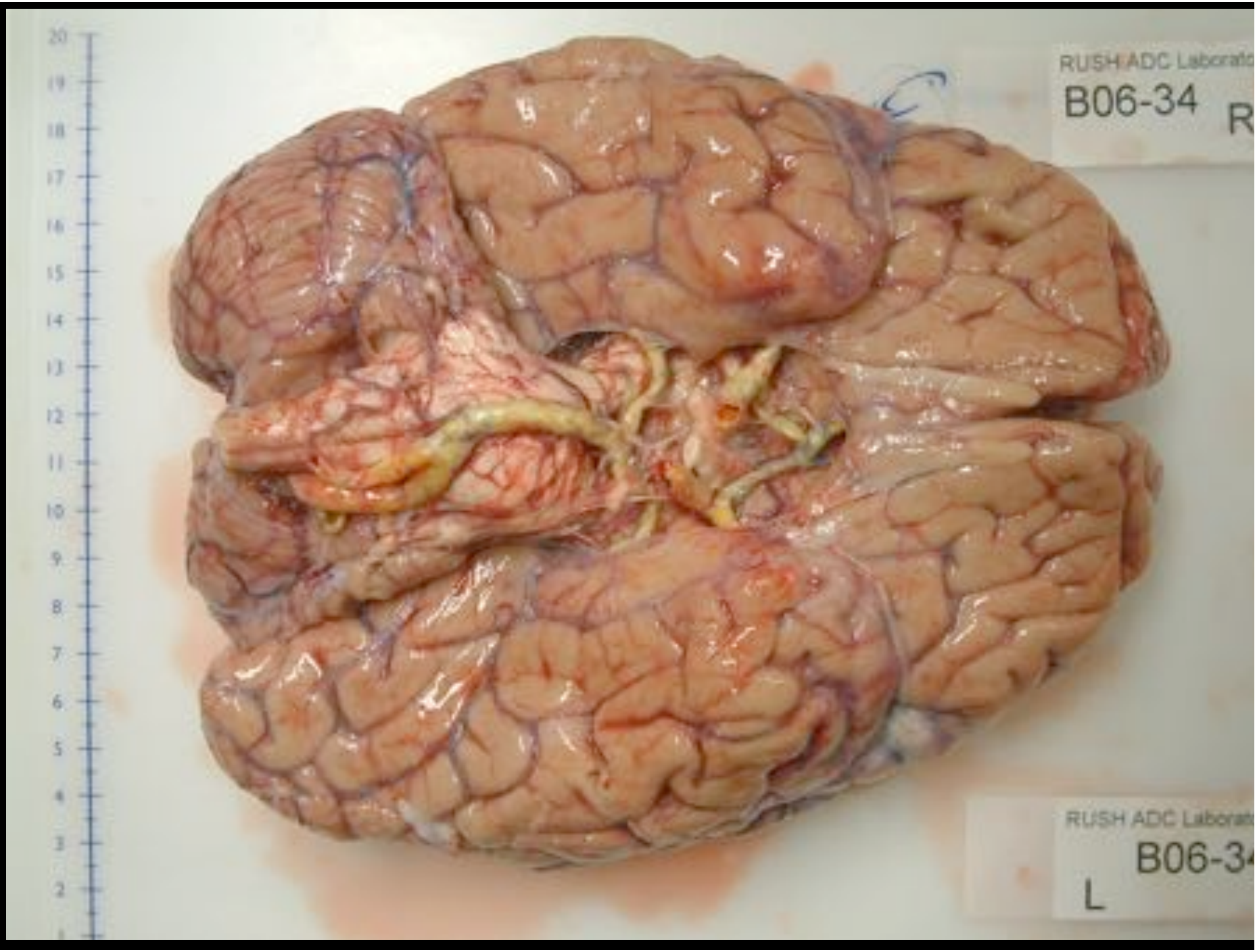
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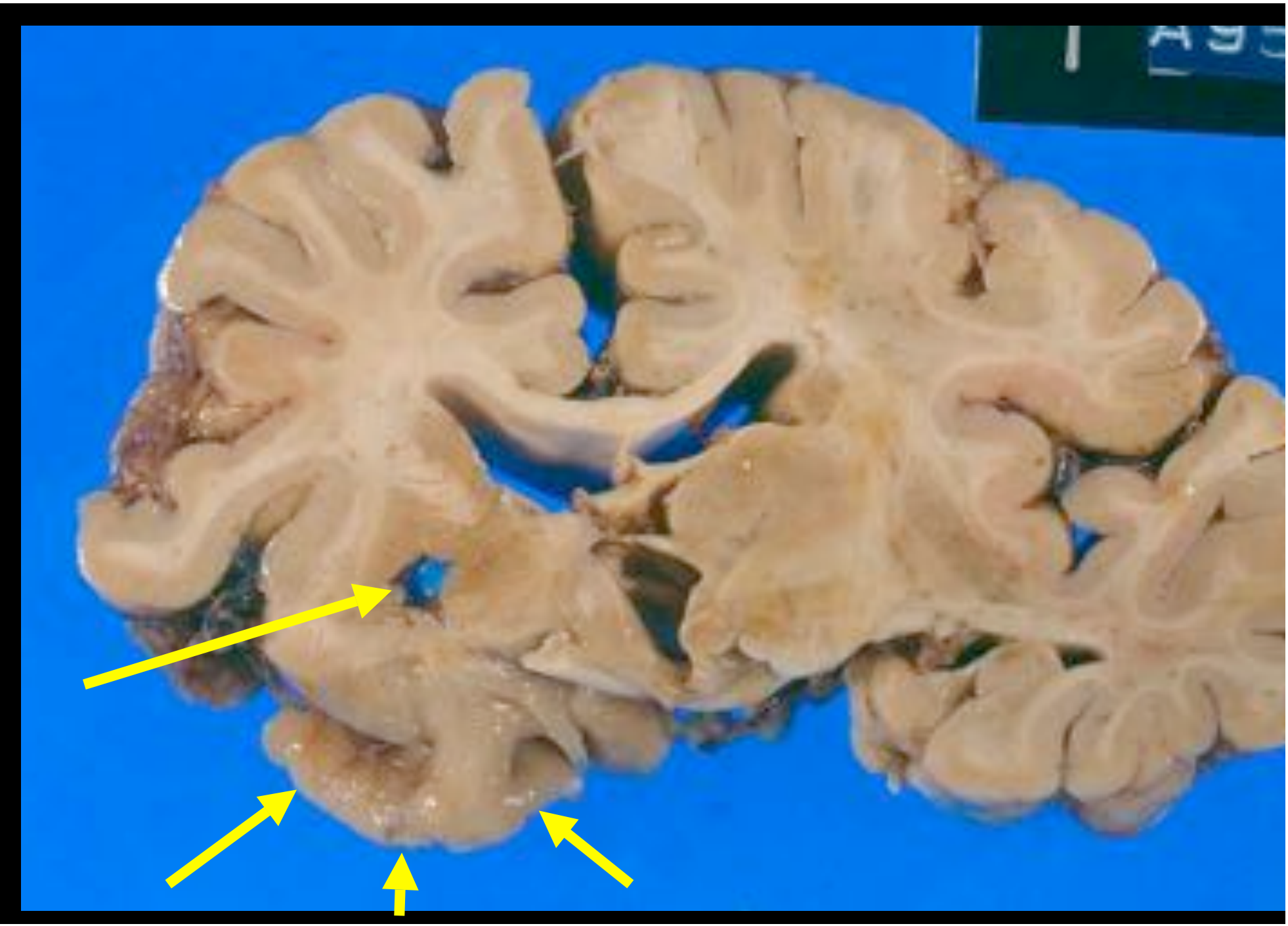
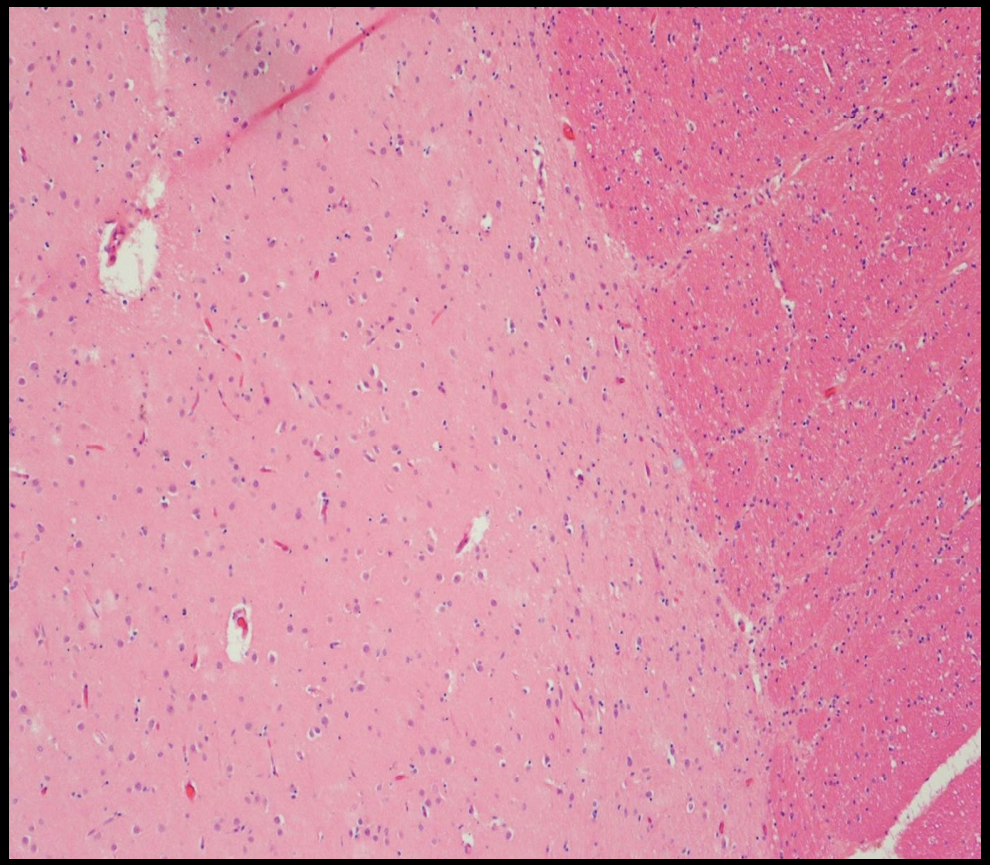
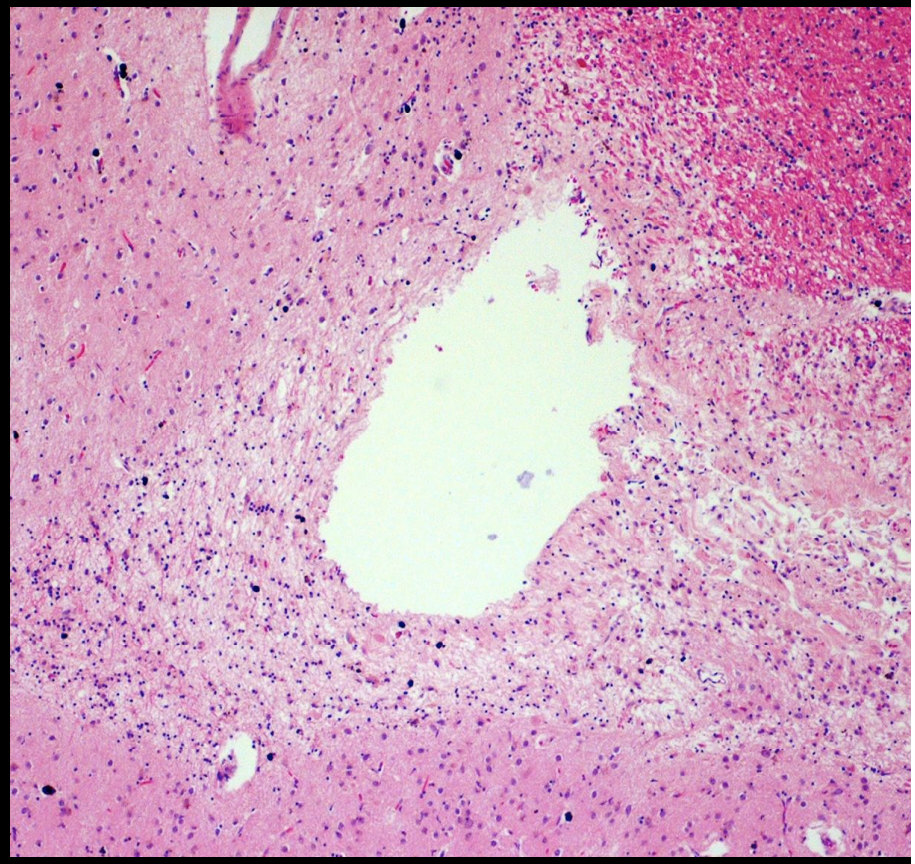
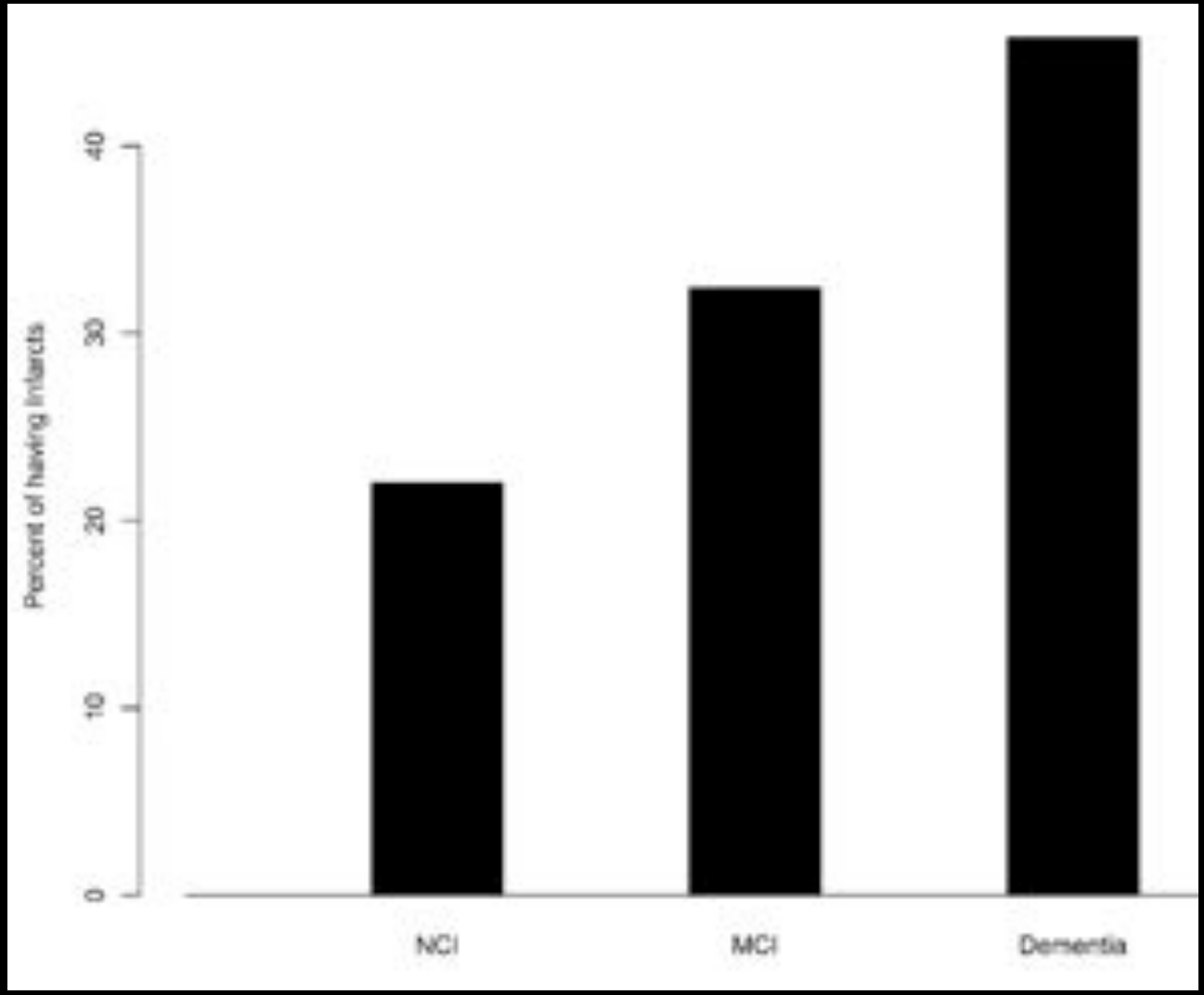






Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions



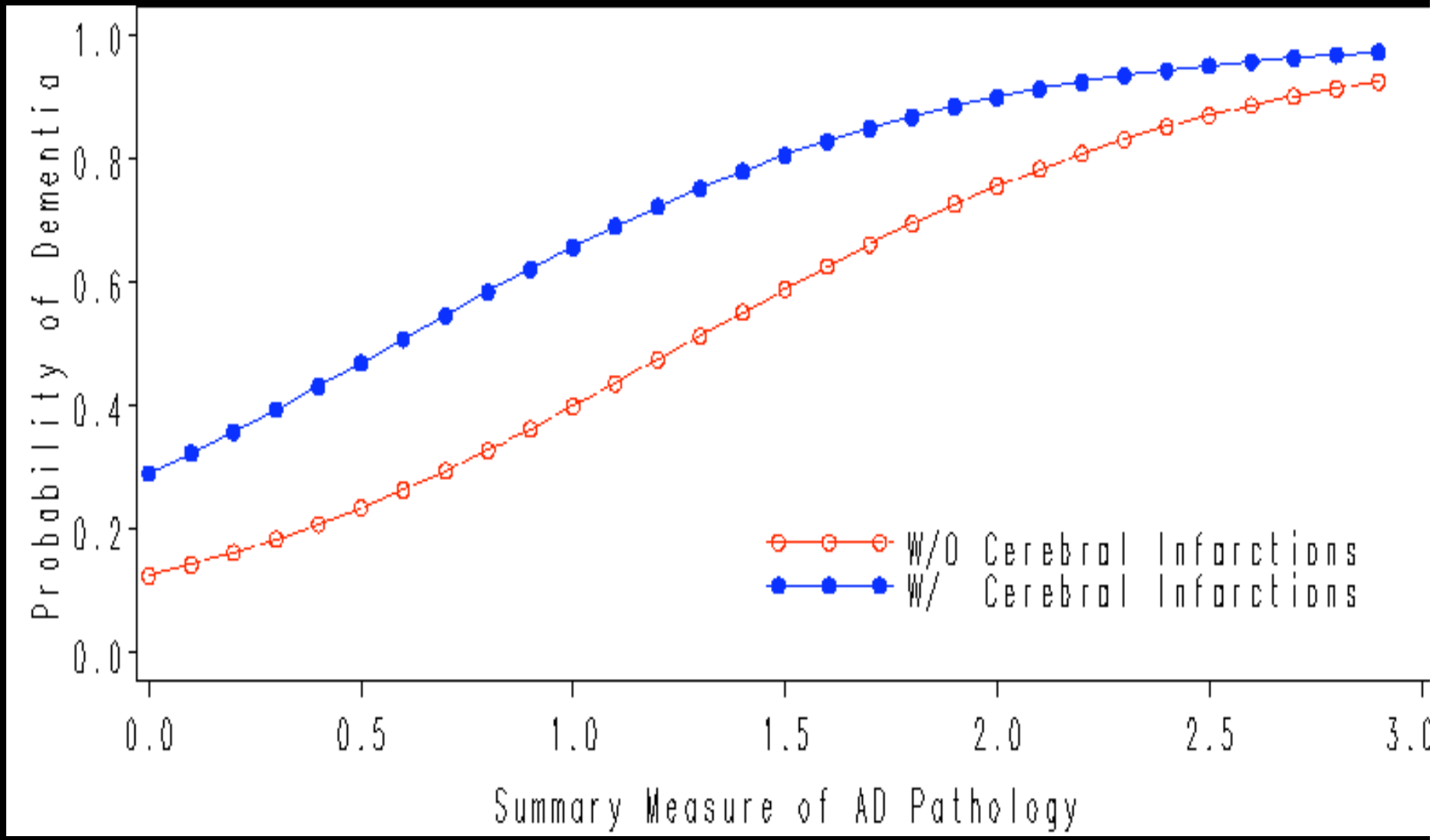
Bennett DA, et al. *Neurology* 2005;64:834-842.

Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology

Model, predictors*	Odds of dementia	95% C
1. One unit AD pathology†	4.40	2.33–8.3
2. One unit of AD pathology	4.62	2.41–8.8
Presence of macroscopic infarctions	2.80	1.26–6.2

Schneider JA, et al. *Neurology* 2004;62:1148-1155.

Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology



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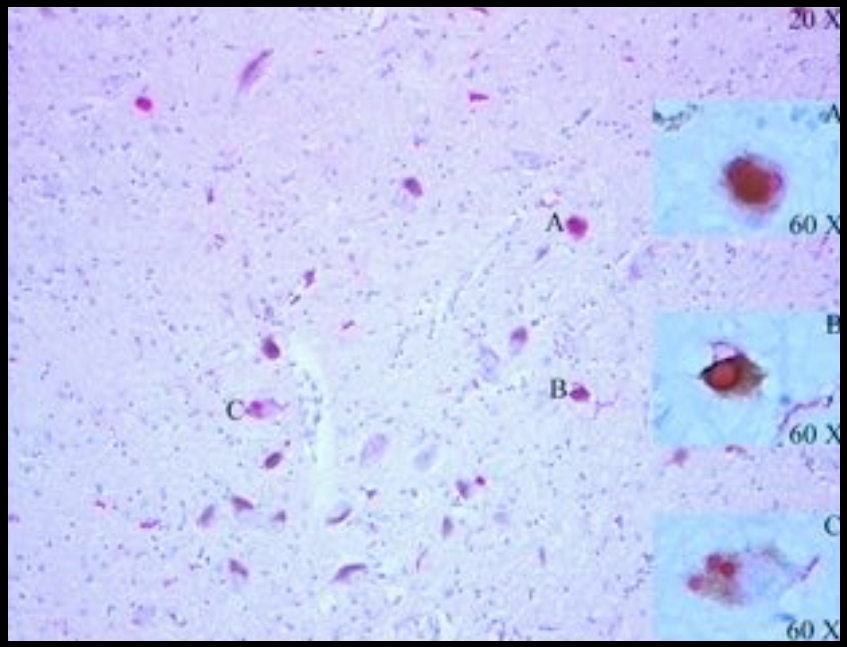
Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology

Models*	Parameter estimates for cognitive domain scores (p value)				
	Episodic memory	Working memory	Semantic memory	Perceptual speed	Visu al
1. One unit of AD pathology	−0.96	−0.36	−0.56	−0.56	–
	(<0.0001)	(0.0009)	(0.0005)	(<0.0001)	
2. One unit of AD pathology	−0.99	−0.37	−0.58	−0.61	–
	(<0.0001)	(0.0004)	(0.0002)	(<0.0001)	(<
Presence of macroscopic infarctions	−0.48	−0.25	−0.44	−0.80	–
	(0.02)	(0.08)	(0.04)	(<0.0001)	(<

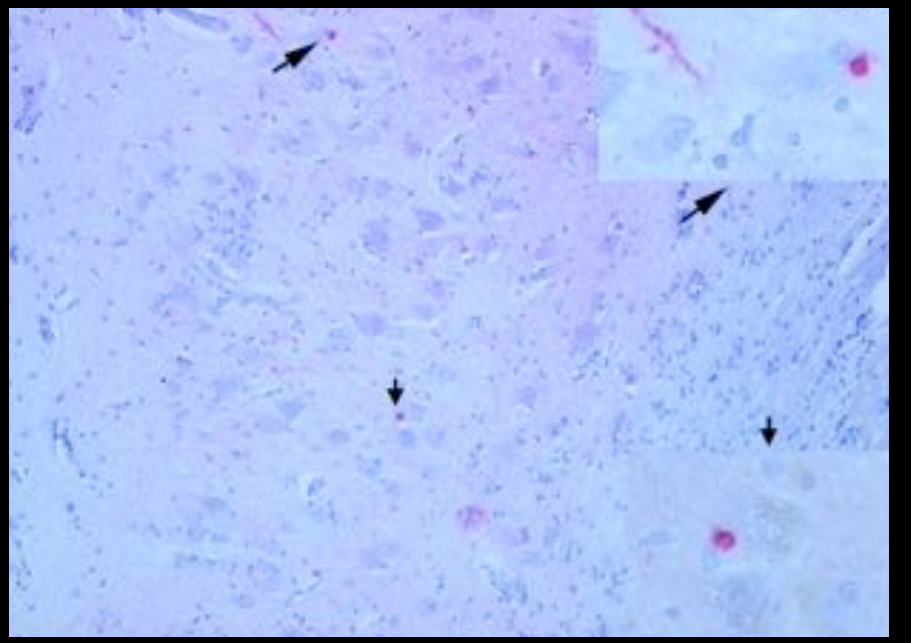
* Linear regression models control for age, sex, education.

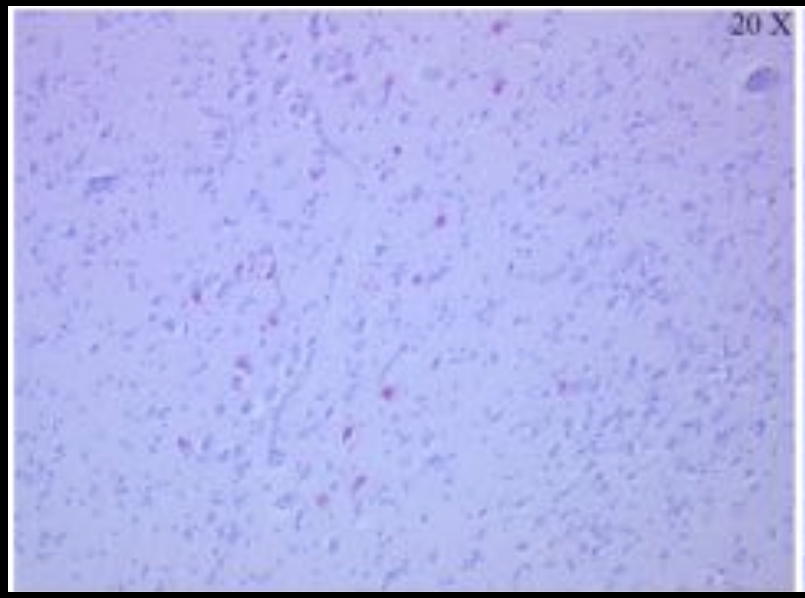
Schneider JA, et al. *Neurology* 2004;62:1148-1155.

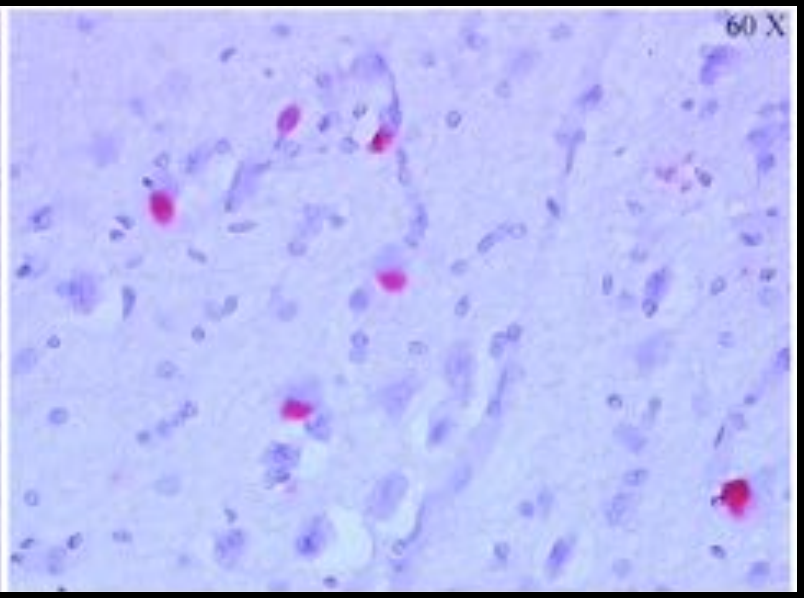
Alpha-Synuclein in substantia nigra



Alpha-Synuclein in hippocampus





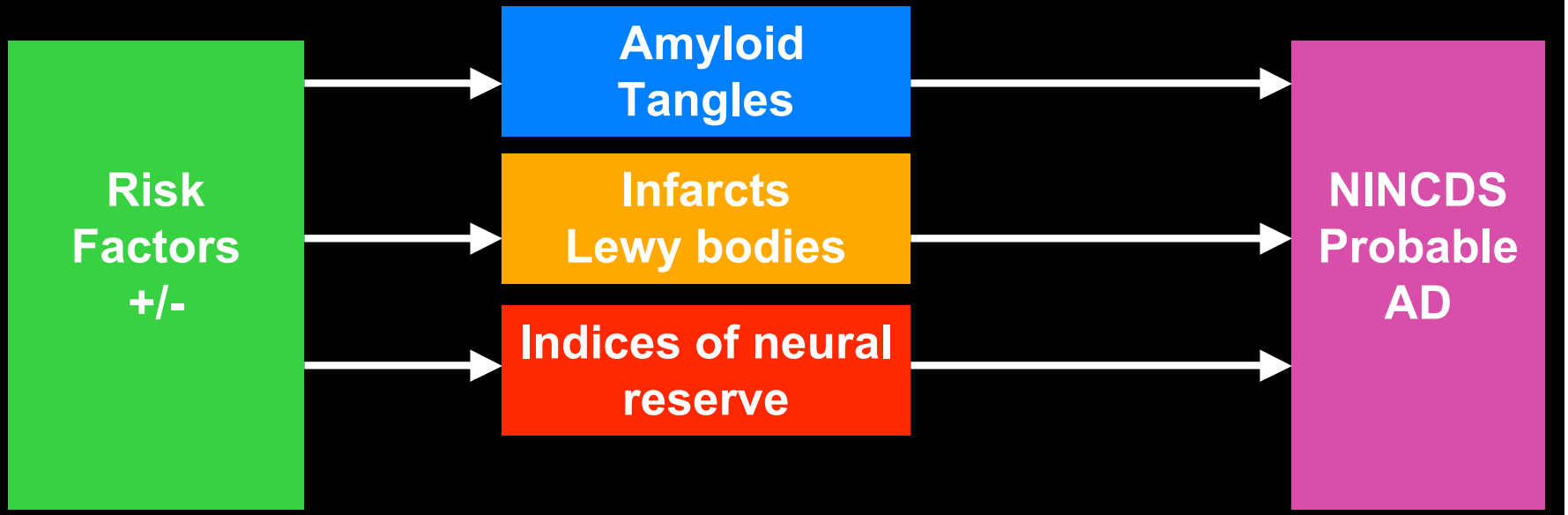


Alpha-Synu
in neocor

Objectives:

- Background to Religious Orders Study (ROS)
- ROS Study Design
  - Introduction to the Rush Memory and Aging Project for combined cohort analyses
- Distributions of neuropathology
- Relation of risk factors to:
  - Incident MCI and incident AD
  - Change in cognitive function
  - Neuropathology

- *There are no risk factors for AD*
- Factors lead to the accumulation of neuropathology and impair th structure and function of neural systems that subserve cognition
  - Some factors associated with amyloid and tangles
  - Others with CVD or LBD
  - Others with indices of neural reserve
  - Others are early signs of neuropathology

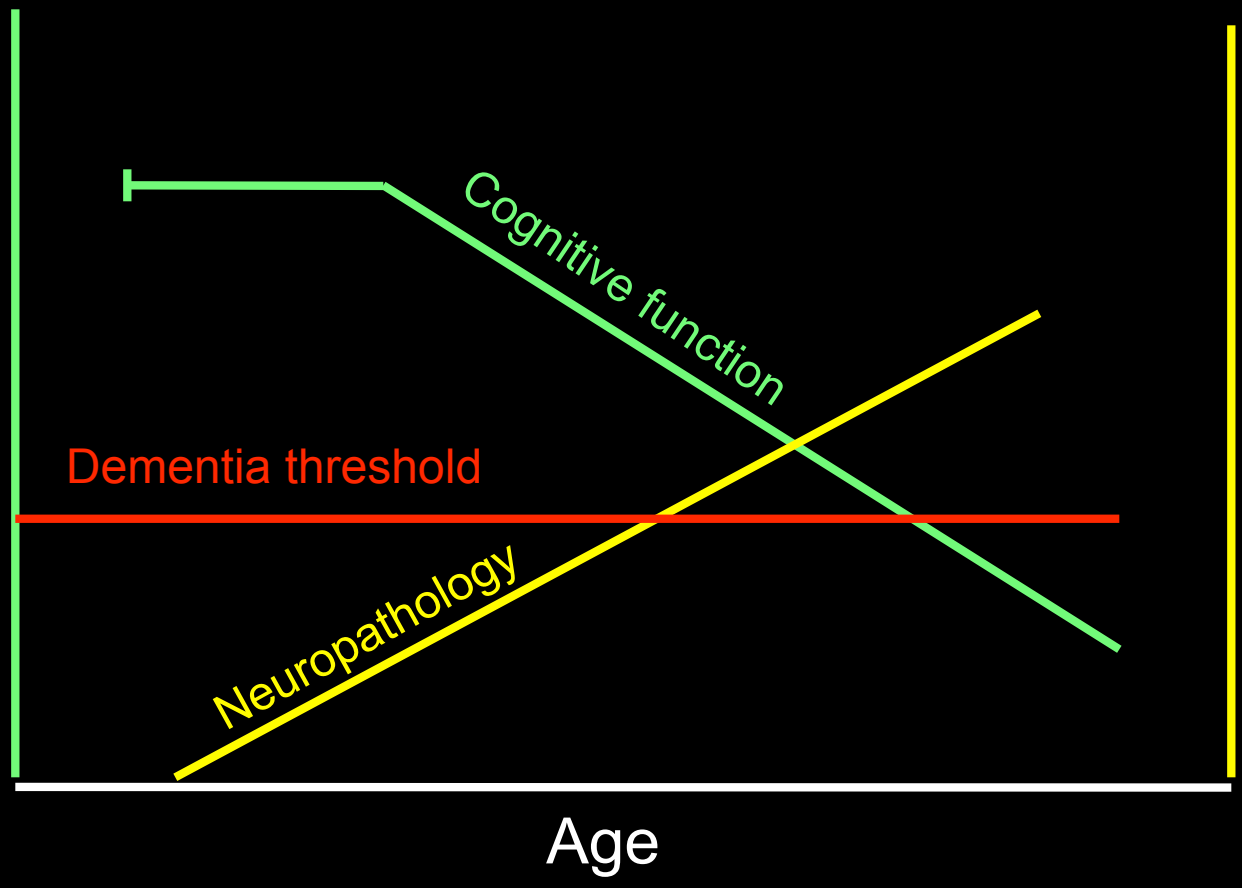


Clinical AD is a complex function of:

- Multiple genetic and environmental factors that lead to the deposition of amyloid and formation o neurofibrillary tangles

Clinical AD is a complex function of:

- Multiple genetic and environmental factors that lead to the deposition of amyloid and formation o neurofibrillary tangles
- Over time, the accumulation of AD pathology is accompanied by structural and functional chang in neural systems that subserve memory and oth cognitive abilities


Cognitive function
Dementia threshold
Neuropathology
Age

Concept of Neural Reserve:

- AD pathology accumulates within individual brai
  that differ in their capacity to withstand the
  deleterious effects that accompany these lesions

Concept of Neural Reserve:

- AD pathology accumulates within individual brai
  that differ in their capacity to withstand the
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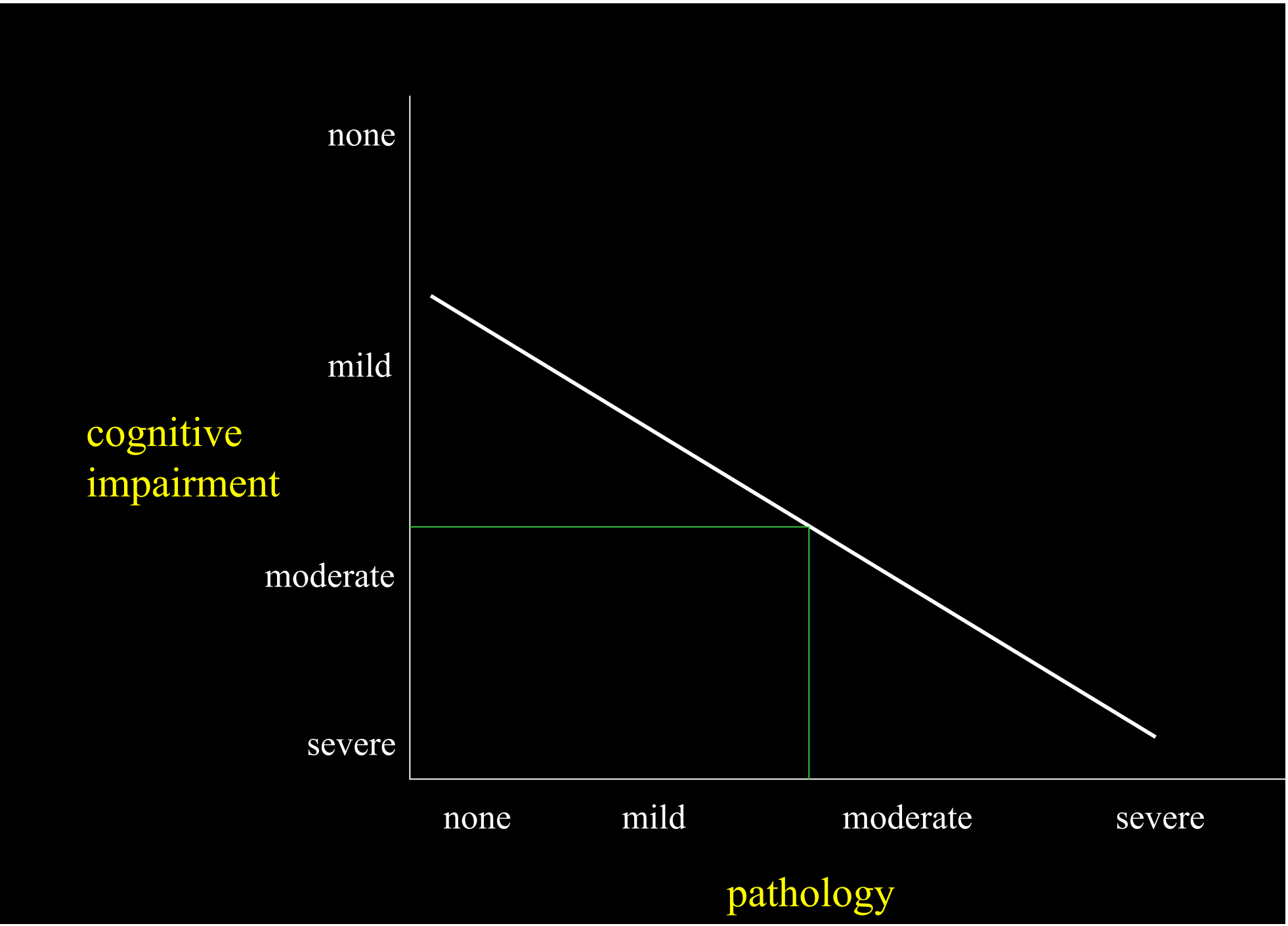
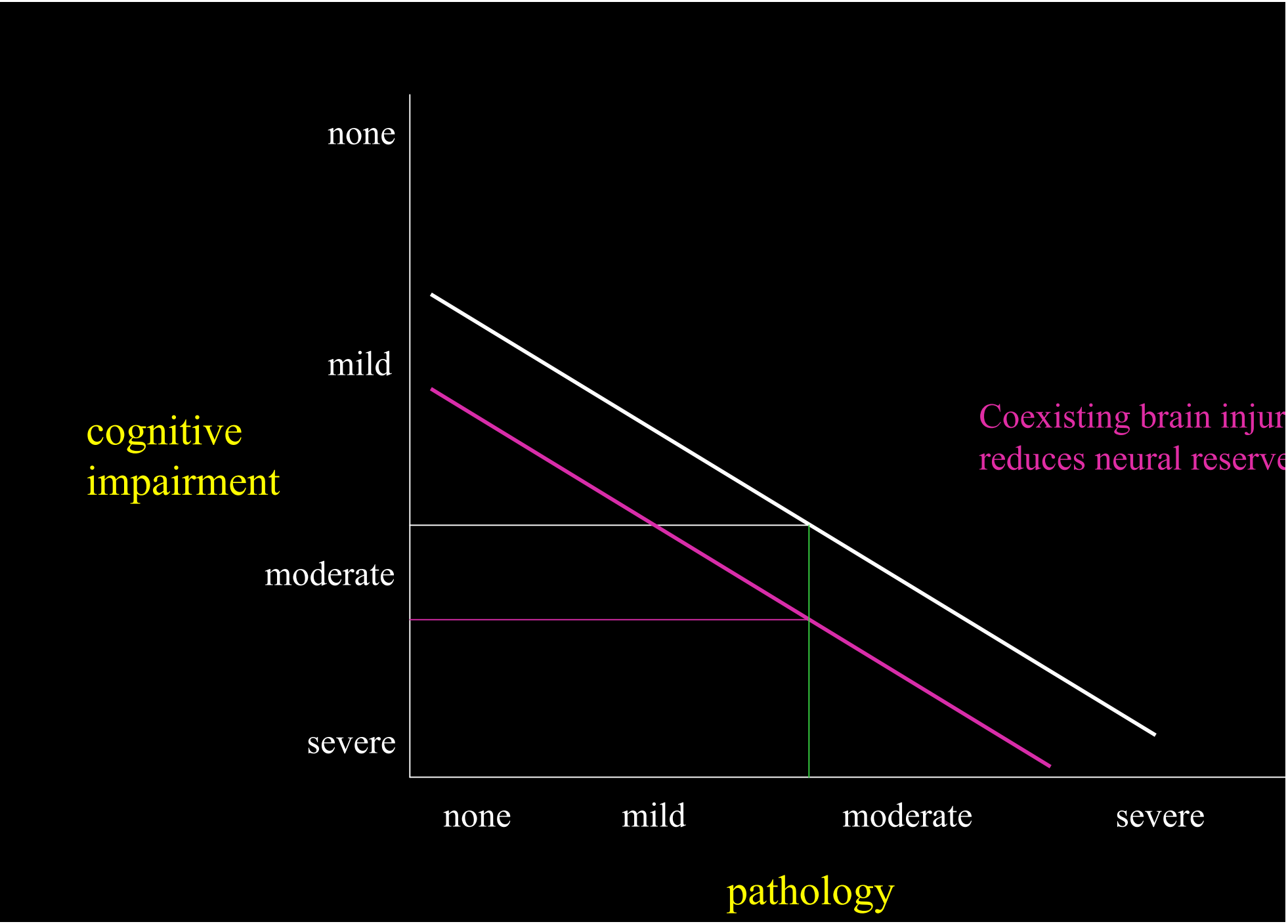
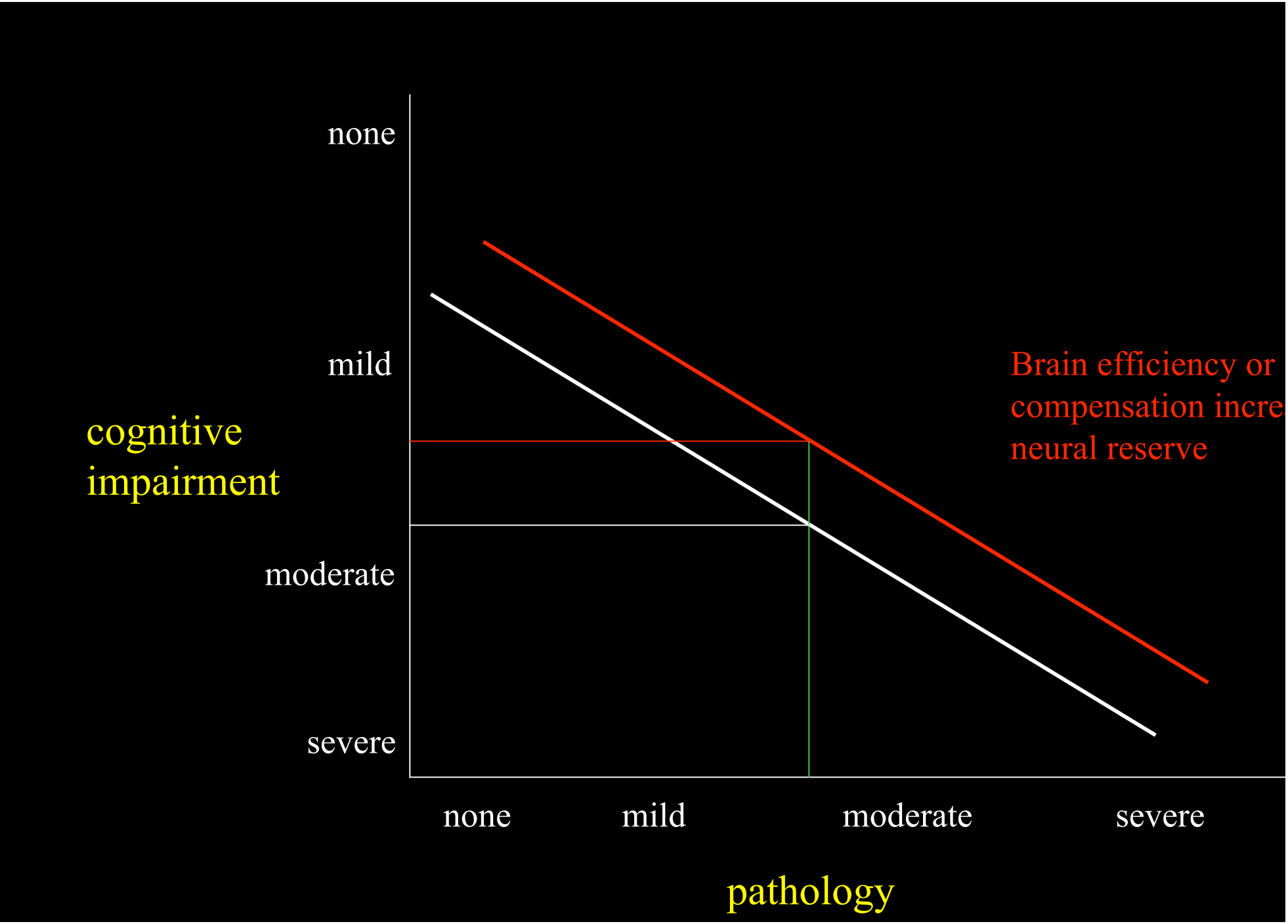
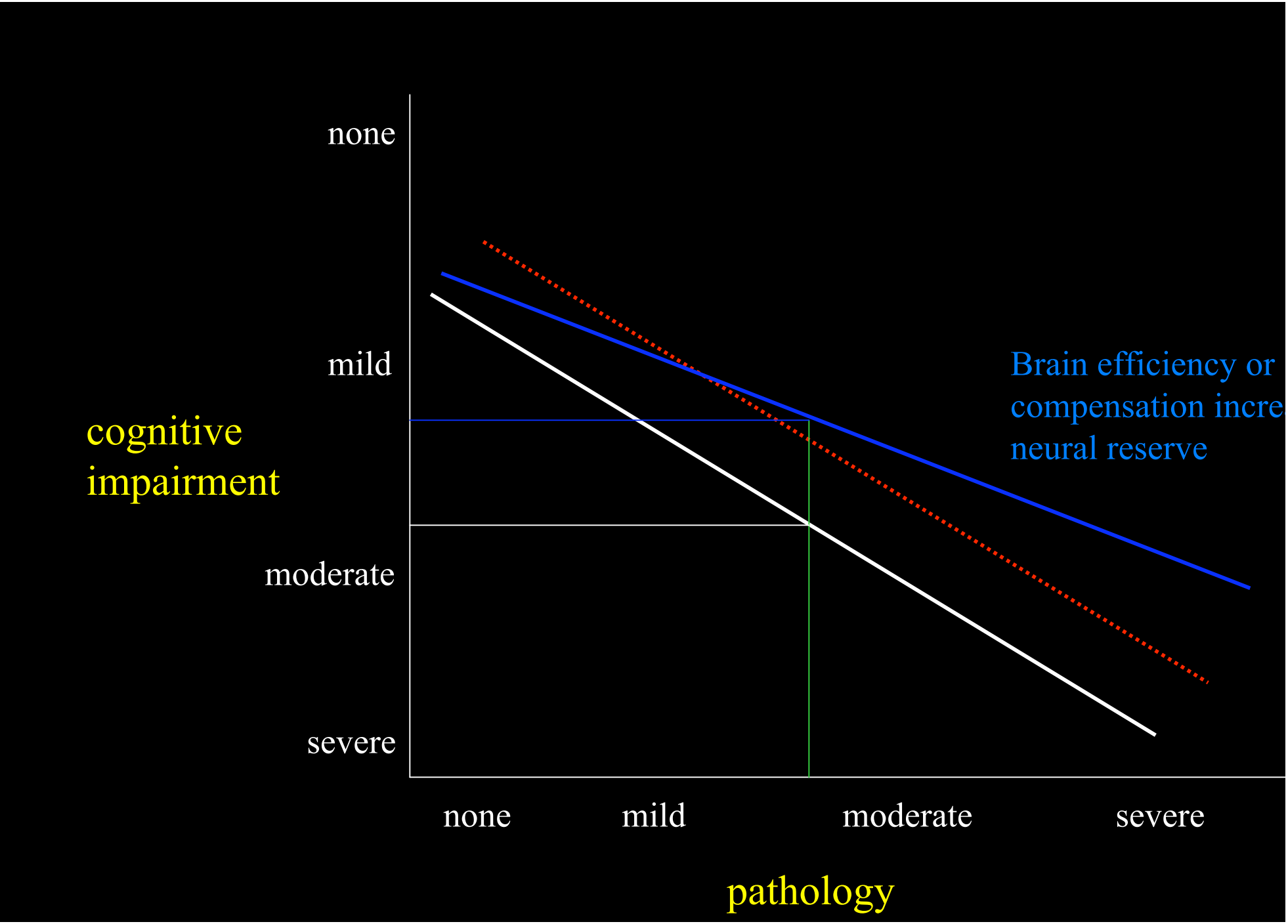
- Imperfect correspondence between amount of A
  pathology and level of cognition


none
mild
moderate
severe
cognitive impairment
none
mild
moderate
severe
pathology


none
mild
moderate
severe
cognitive impairment
Coexisting brain injur
reduces neural reserve
none
mild
moderate
severe
pathology


none
mild
moderate
severe
cognitive impairment
Brain efficiency or compensation incre
neural reserve
none
mild
moderate
severe
pathology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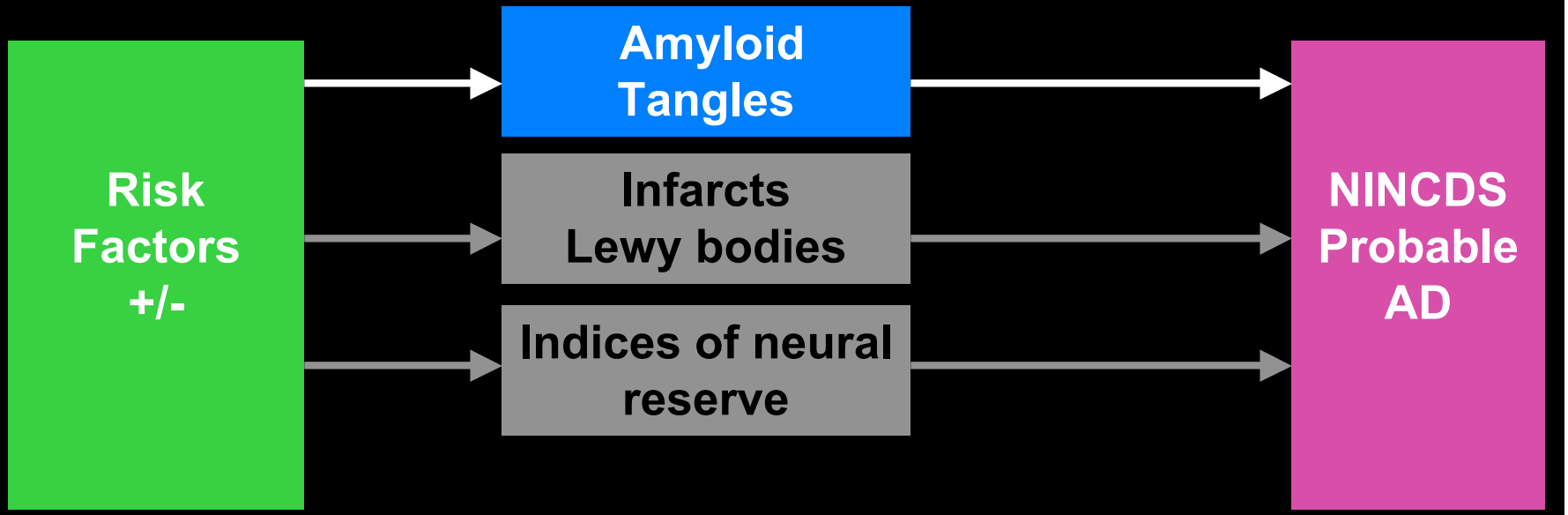


Apolipoprotein E ϵ4 allele, AD pathology, and the clinical expression of Alzheimer's disease

Pathologic indices	Terms	Model 1 Odds (95% CI)
Global pathology	ε4 allele	3.46 (1.44–8.33)
	Pathology	—

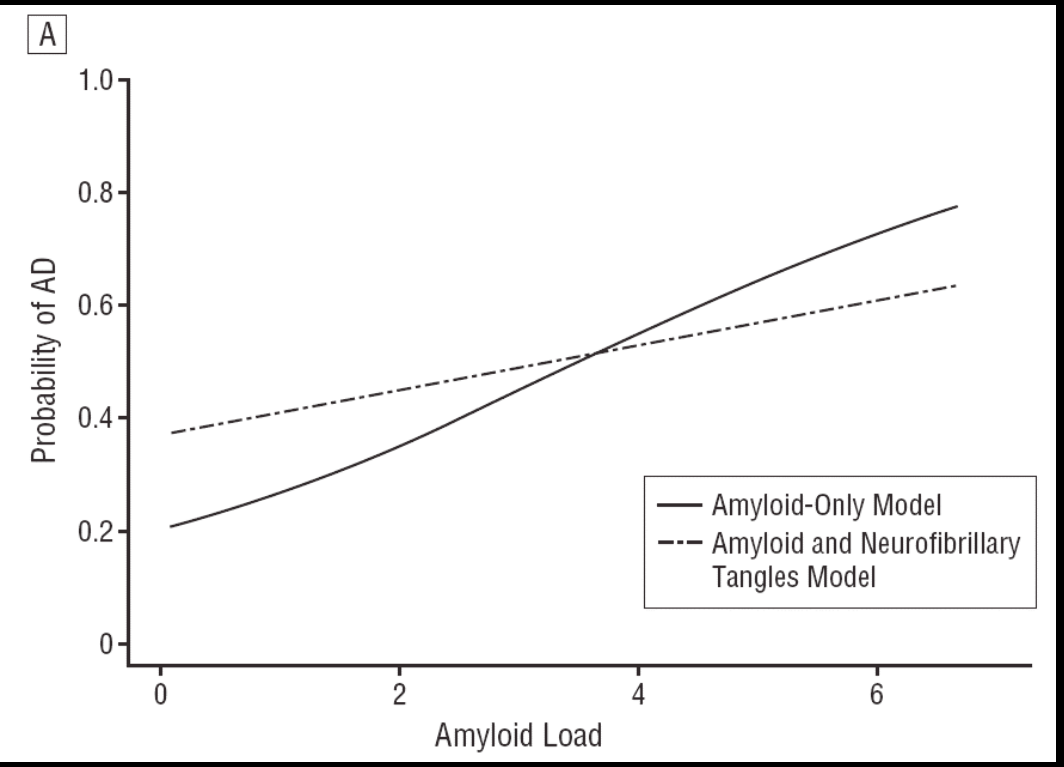
Bennett DA, et al. *Neurology* 2002;60:246-253

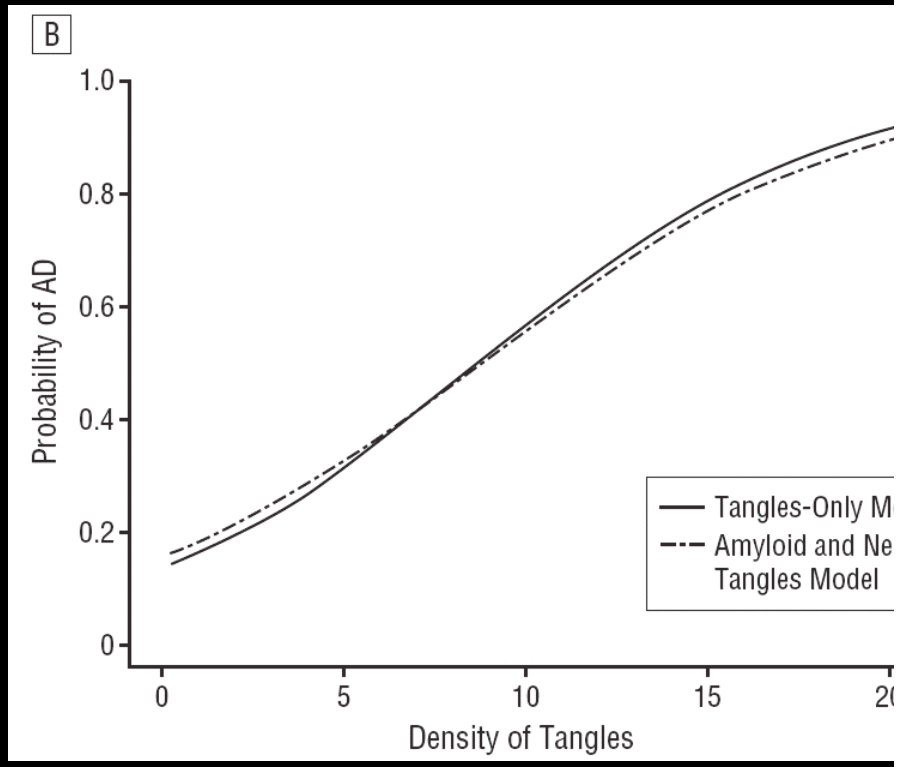
Apolipoprotein E ϵ4 allele, AD pathology, and the clinical expression of Alzheimer's disease

Pathologic indices	Terms	Model 1 Odds (95% CI)	Model 2 Od (95% CI)
Global pathology	ε4 allele	3.46 (1.44–8.33)	1.58 (0.56–4.
	Pathology	—	6.02 (2.59–13

Bennett DA, et al. *Neurology* 2002;60:246-253

Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function





Bennett DA, et al. *Arch Neurol* 61:378-384

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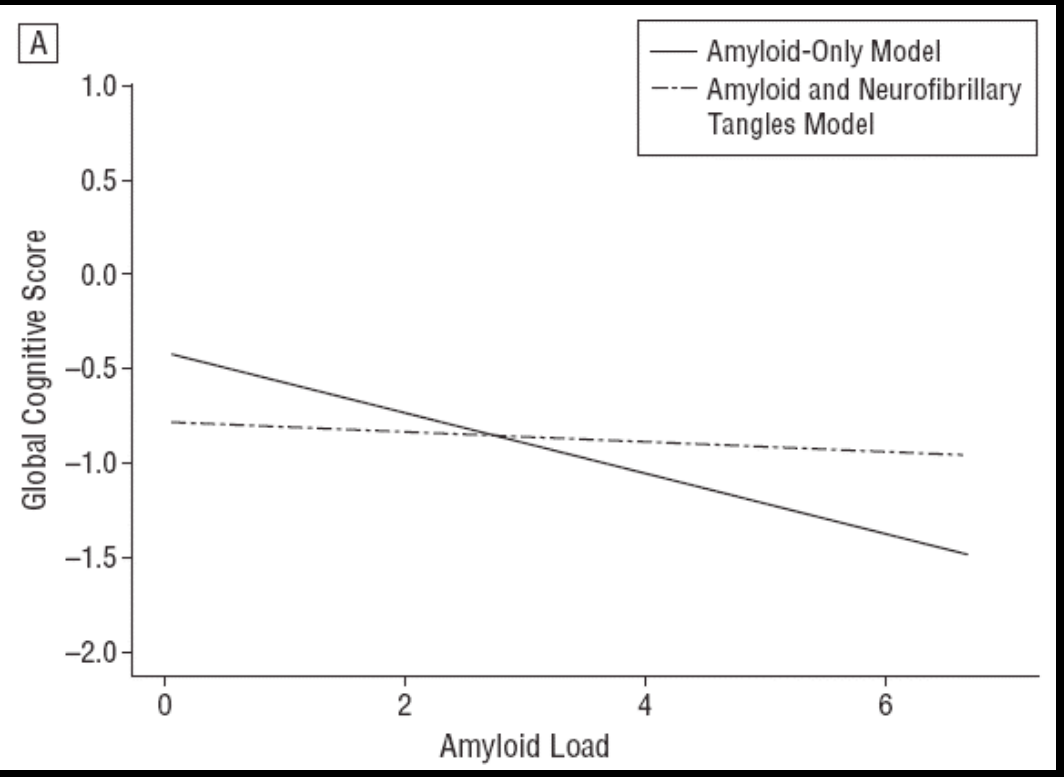
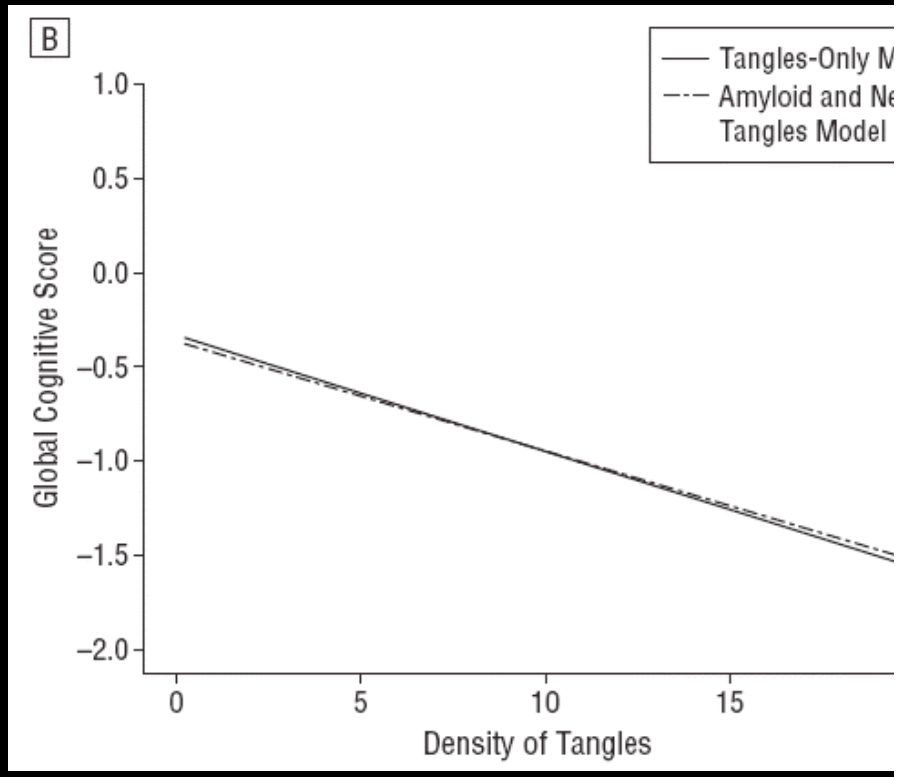
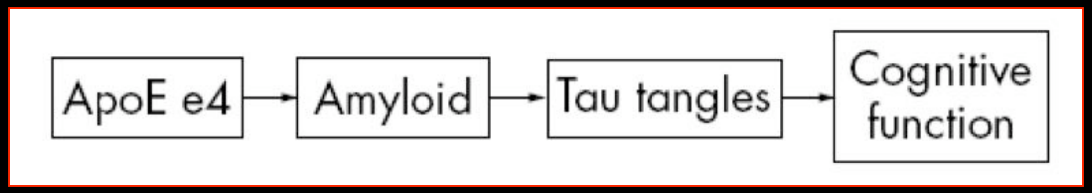




Bennett DA, et al. *Arch Neurol* 61:378-384

Amyloid mediates the association of apolipoprotein E e4 allele to cognitive function in older people



Outcome measure terms	Model 1 Estimate (SE)	p value	Model 2 Estimate (SE)	p value
GC				
e4 allele	−0.432 (0.210)	0.04	−0.176 (0.214)	0.41
Amyloid load	–	–	−0.145 (0.044)	0.001

Outcome measure terms	Model 1 Estimate (SE)	p value	Model 2 Estimate (SE)	p value
Tau tangles				
e4 allele	6.98 (2.21)	0.002	3.39 (2.13)	0.12
Amyloid load	–	–	2.04 (0.44)	<0.001

Bennett DA, et al. *JNNP* 2005;76:1194-1199.

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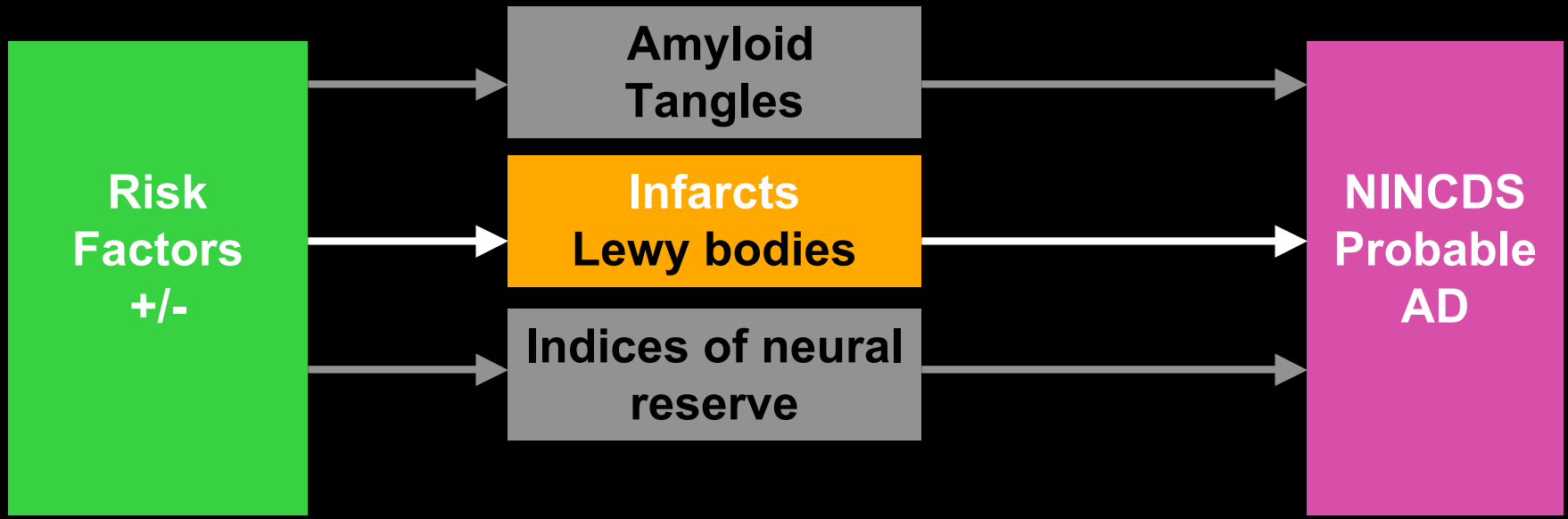
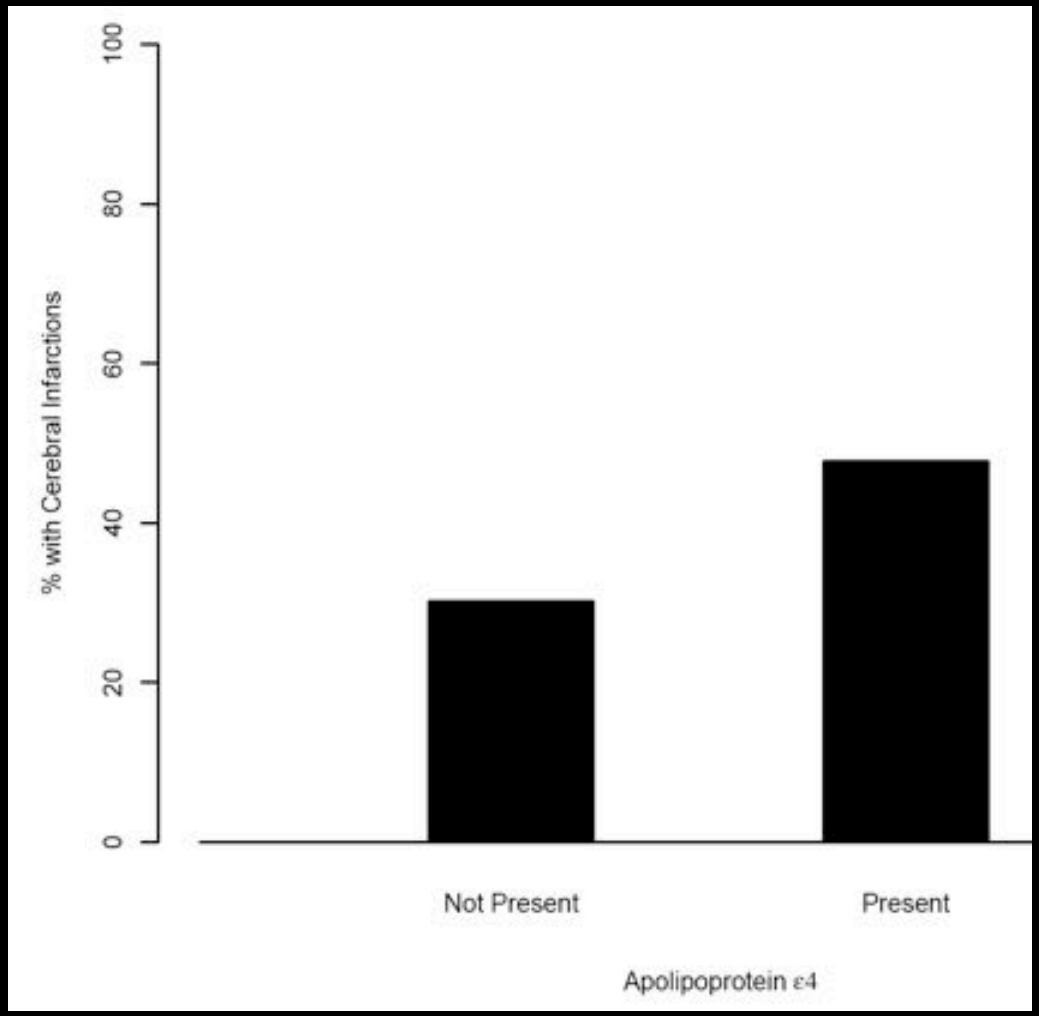


The Apolipoprotein E ϵ4 Allele Increases the Odds of Chronic Cerebral Infarction Detected at Autopsy in Older Persons

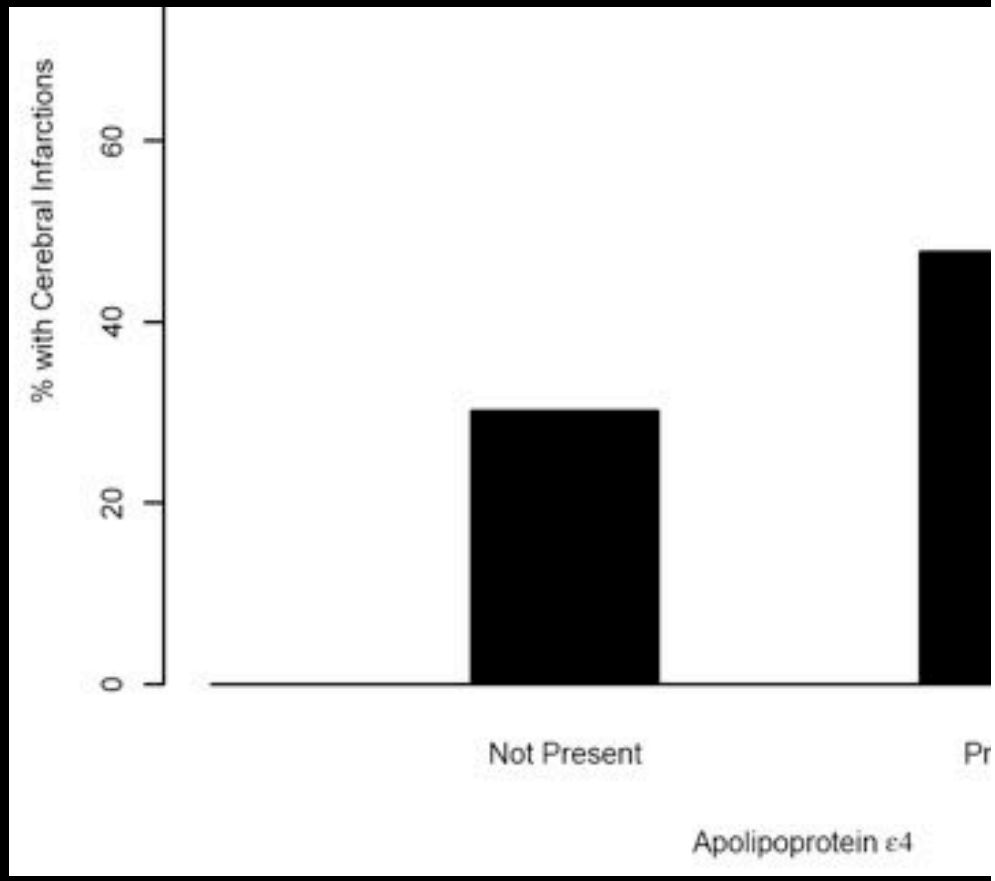


Outcomes*	Odds (95
Any cerebral infarction	2.3 (1
Subcortical infarction	2.3 (1
Cortical infarction	3.2 (1

Schneider JA, et al. *Stroke* 2005;36:954-959.

The Apolipoprotein E ε4 Allele Increases the Odds of Chronic Cerebral Infarction Detected at Autopsy in Older Persons

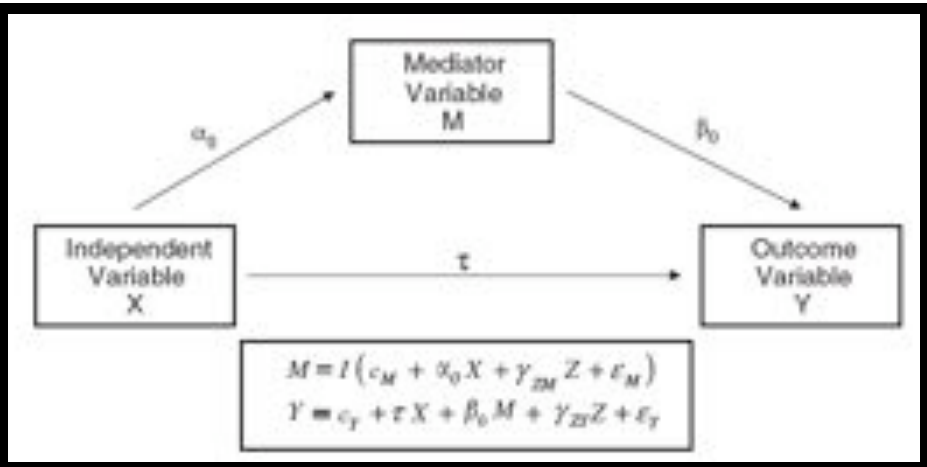
Outcomes*	Odds Ratios (95% CI)
Any cerebral infarction	2.3 (1.2–4.2)
Subcortical infarction	2.3 (1.2–4.5)
Cortical infarction	3.2 (1.3–7.7)
1 infarction	2.1 (1.0–4.6)
Multiple infarctions	2.5 (1.2–5.4)
Less than median volume	2.2 (1.0–4.7)
More than median volume	2.4 (1.1–5.1)



Schneider JA, et al. *Stroke* 2005;36:954-959.

Estimation of the mediation effect with a binary mediator‡

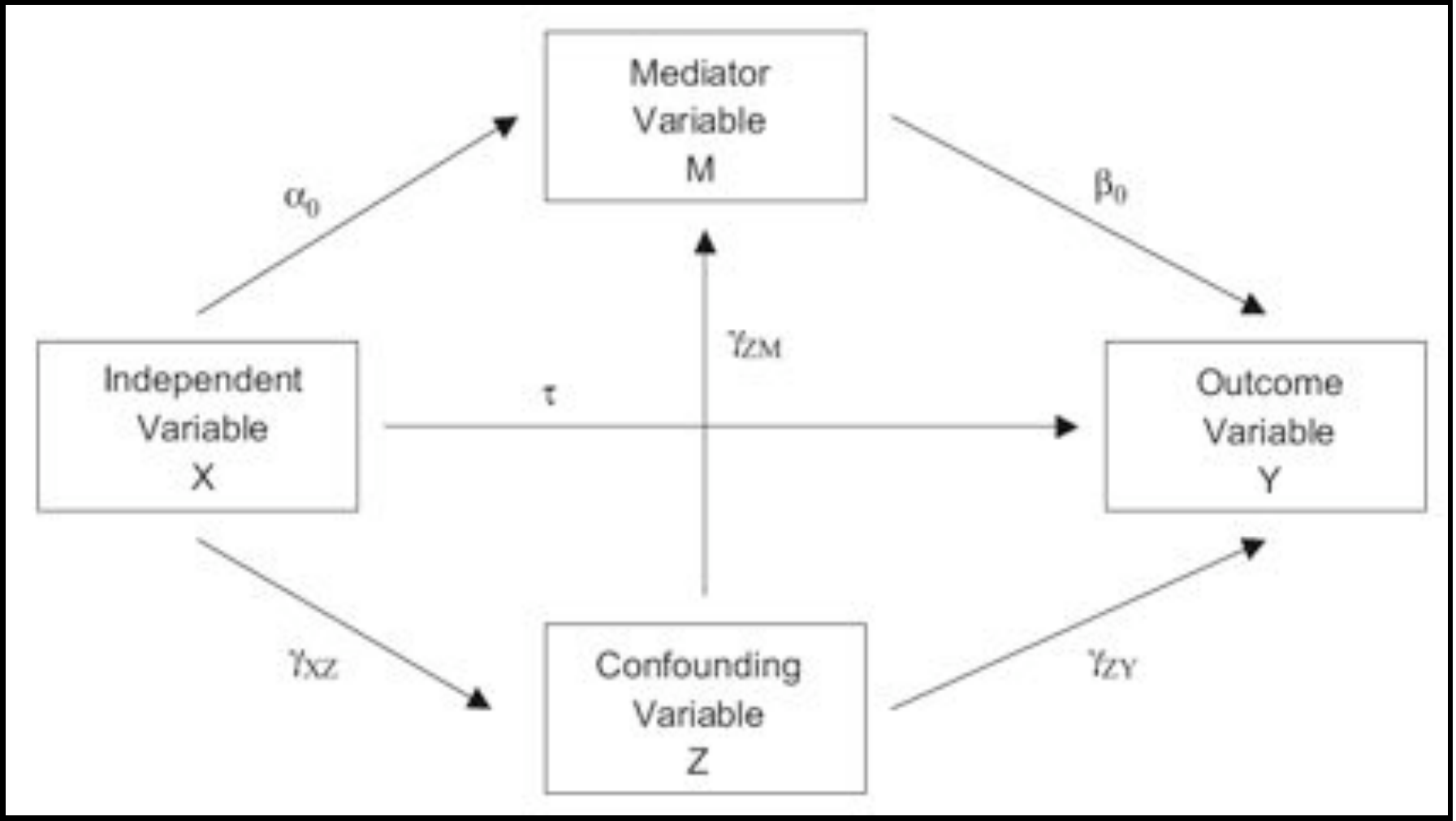
Path diagram for a mediation model with a binary mediator.



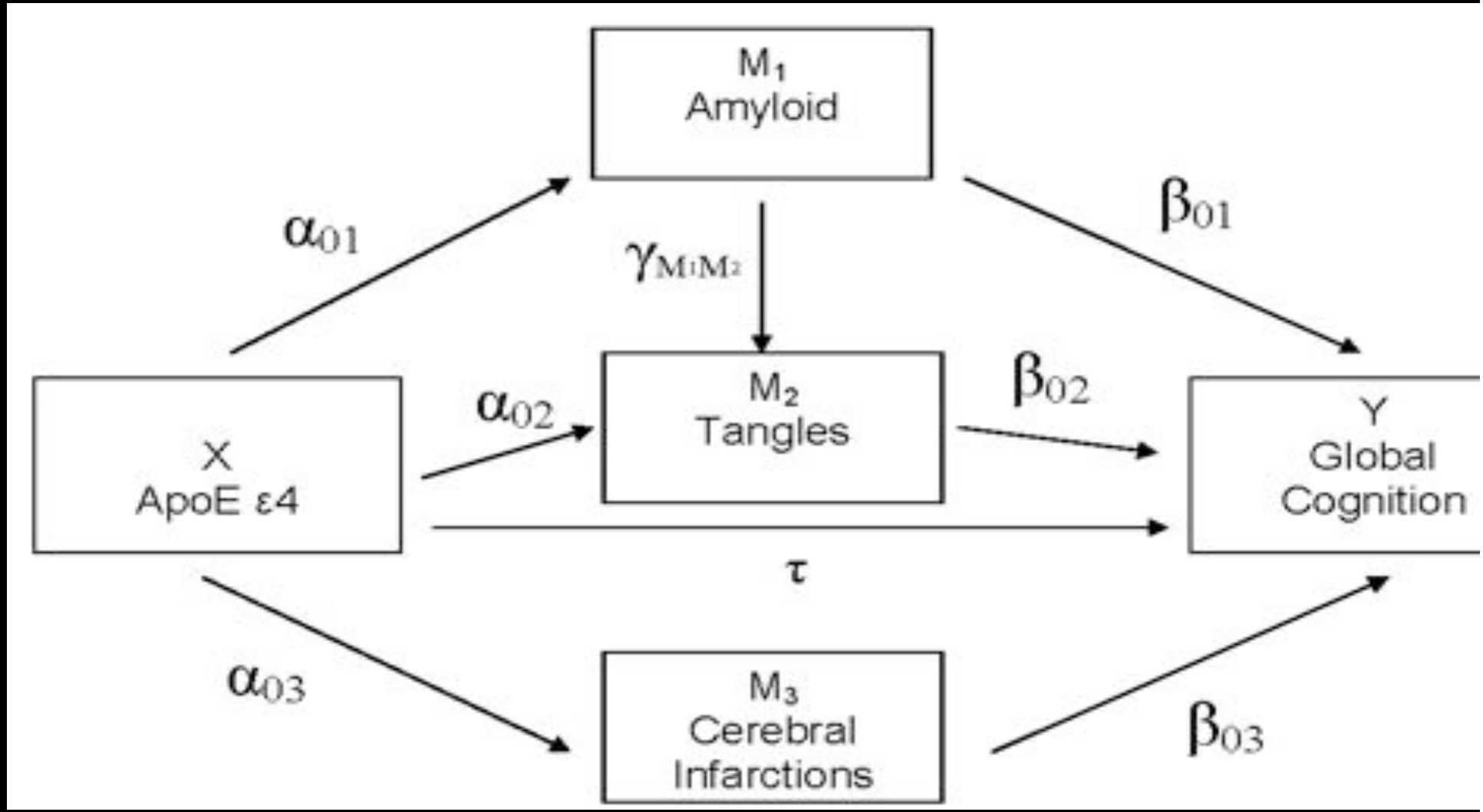
Dependent variable	Adjusted $\hat{\delta}_{AE}$ Logit	Adjusted $\hat{\delta}_{AE}$ Probit	Direct effect
Global cognition	−0.015 (−0.084, 0.046)	−0.015 (−0.084, 0.046)	−0.716 (−1.081, −0.388)
Episodic memory	−0.021 (−0.106, 0.050)	−0.022 (−0.106, 0.050)	−0.999 (−1.445, −0.573)
Semantic memory	−0.021 (−0.105, 0.050)	−0.021 (−0.106, 0.049)	−0.745 (−1.182, −0.362)
Working memory	−0.024 (−0.088, 0.029)	−0.025 (−0.089, 0.029)	−0.448 (−0.767, −0.175)
Perceptual speed	−0.065 (−0.152, −0.004)	−0.065 (−0.153, −0.004)	−0.570 (−0.939, −0.252)
Perceptual organization	−0.018 (−0.074, 0.032)	−0.018 (−0.074, 0.032)	−0.381 (−0.676, −0.081)

Li Y, et al. *Stat Med* 2007; 26:3398-414.

Confounding in the estimation of mediation effects



Li Y, et al. *Comp Stat Data Analysis* 2007;51:3173-3186.


M1
Amyloid
α01
γM1M2
β01
X
ApoE ε4
α02
M2
Tangles
β02
Y
Global
Cognition
τ
α03
M3
Cerebral
Infarctions
β03

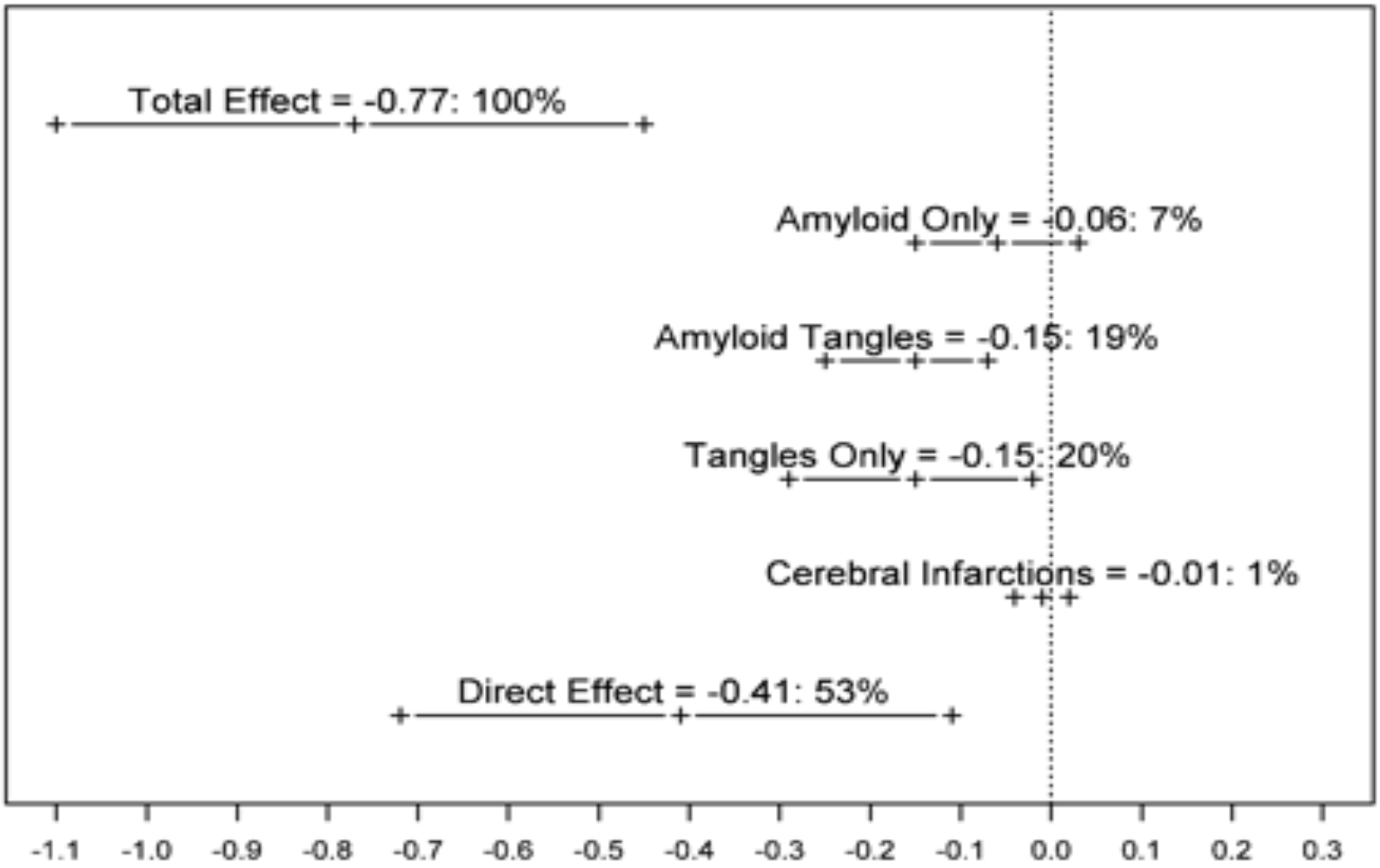
Estimation of the Mediation Effects through Multiple Pathways

Religious Order Study
Total = -0.77 (-1.10, -0.45)
Direct = -0.30 (-0.63, 0.02)
Mediation = -0.46 (-0.66, -0.29)

Memory and Aging Project
Total = -0.85 (-1.23, -0.43)
Direct = -0.29 (-0.72, 0.14)
Mediation = -0.56 (-0.85, -0.27)

Models control for age, sex, education, and cerebral infarctions

ApoE ε4 → Global Cognition

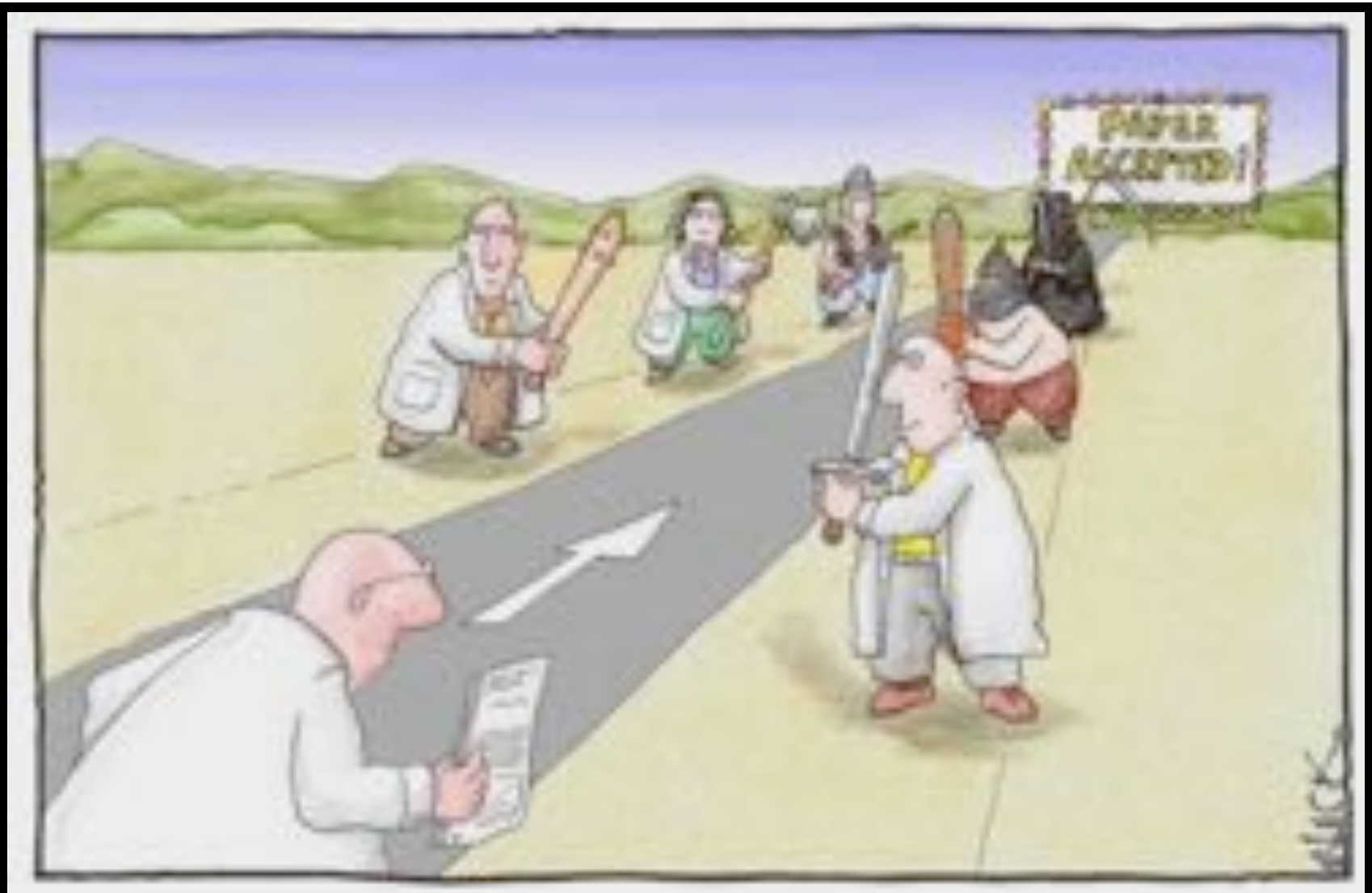


Anye2--> amyloid, tangles, amyloid & tangles --> DV

DV	TOTAL	DIRECT	MEDIATION	AMYLOID	TANGLES	AMYL _TANG
Globcog _last	-0.020 (-0.413, 0.357)	-0.128 (-0.498, 0.203)	0.109 (-0.068, 0.292)	0.016 (-0.036, 0.081)	0.002 (-0.144, 0.152)	**0.090** **(0.023, 0**

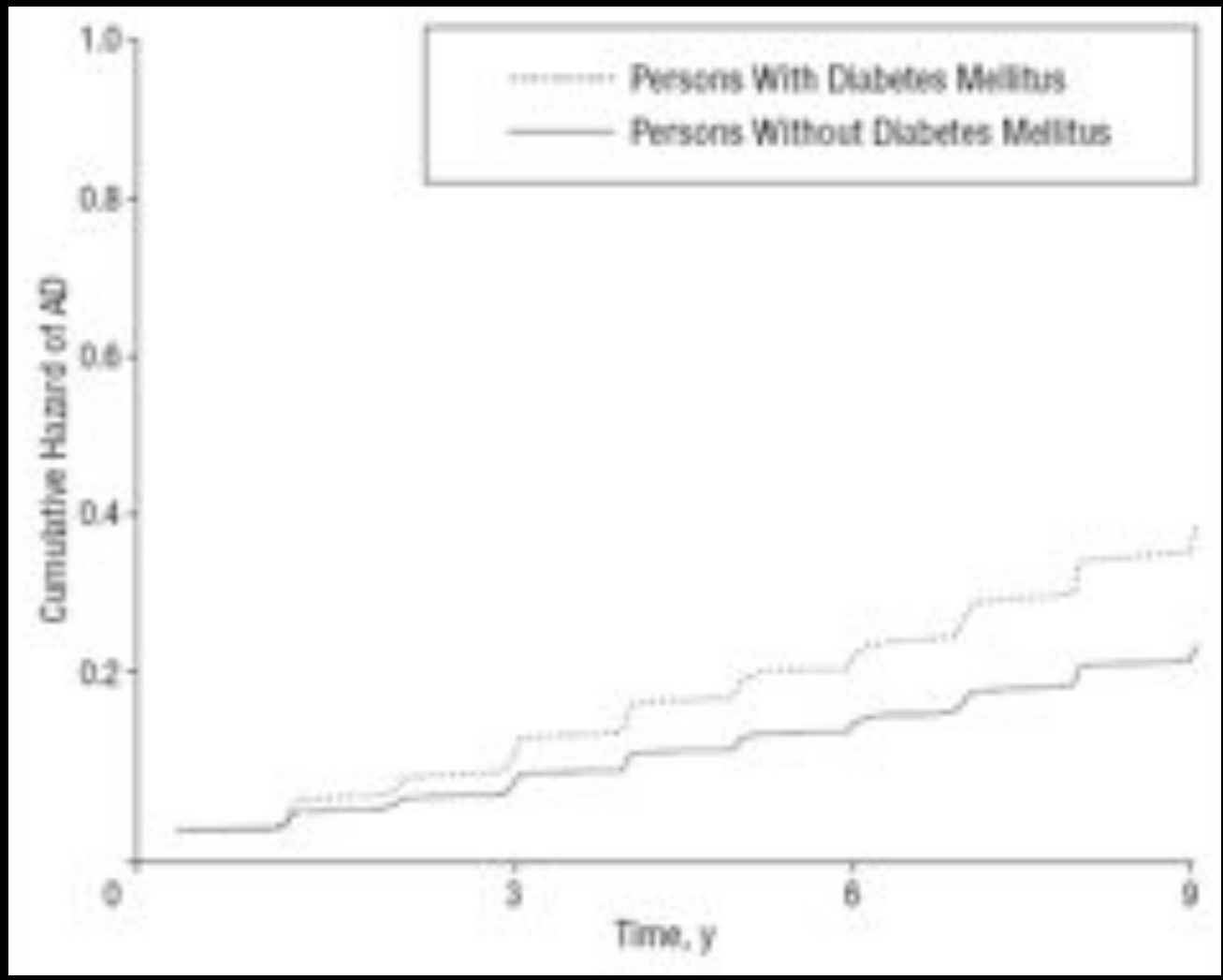
Anye2--> amyloid, tangles, amyloid & tangles --> DV

DV	TOTAL	DIRECT	MEDIATION	AMYLOID	TANGLES	AMYL _TANG
Globcog _last	-0.020 (-0.413, 0.357)	-0.128 (-0.498, 0.203)	0.109 (-0.068, 0.292)	0.016 (-0.036, 0.081)	0.002 (-0.144, 0.152)	**0.090** **(0.023, 0**
Cog_ep _last	0.106 (-0.387, 0.576)	-0.038 (-0.491, 0.390)	0.144 (-0.077, 0.381)	0.028 (-0.046, 0.124)	0.003 (-0.174, 0.191)	**0.113** **(0.030, 0**
Cog_se _last	-0.178 (-0.588, 0.210)	-0.263 (-0.657, 0.082)	0.085 (-0.093, 0.269)	-0.013 (-0.084, 0.054)	0.002 (-0.156, 0.160)	**0.096** **(0.026, 0**
Cog_ps _last	-0.108 (-0.537, 0.293)	-0.201 (-0.637, 0.193)	0.093 (-0.022, 0.241)	0.042 (-0.022, 0.143)	0.001 (-0.076, 0.094)	**0.050** **(0.012, 0**
Cog_po _last	-0.084 (-0.409, 0.227)	-0.139 (-0.463, 0.161)	0.054 (-0.037, 0.165)	0.009 (-0.043, 0.075)	0.001 (-0.069, 0.075)	**0.044** **(0.009, 0**
Cog_wo _last	-0.120 (-0.445, 0.182)	-0.181 (-0.506, 0.108)	0.061 (-0.062, 0.185)	-0.001 (-0.052, 0.054)	0.001 (-0.101, 0.101)	**0.060** **(0.015, 0**



Most scientists regarded the new streamlined peer-review process as 'quite an improvement.'

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function



Arvanitakis Z, et al. *Archives Neurology* 2004;61:661-666.

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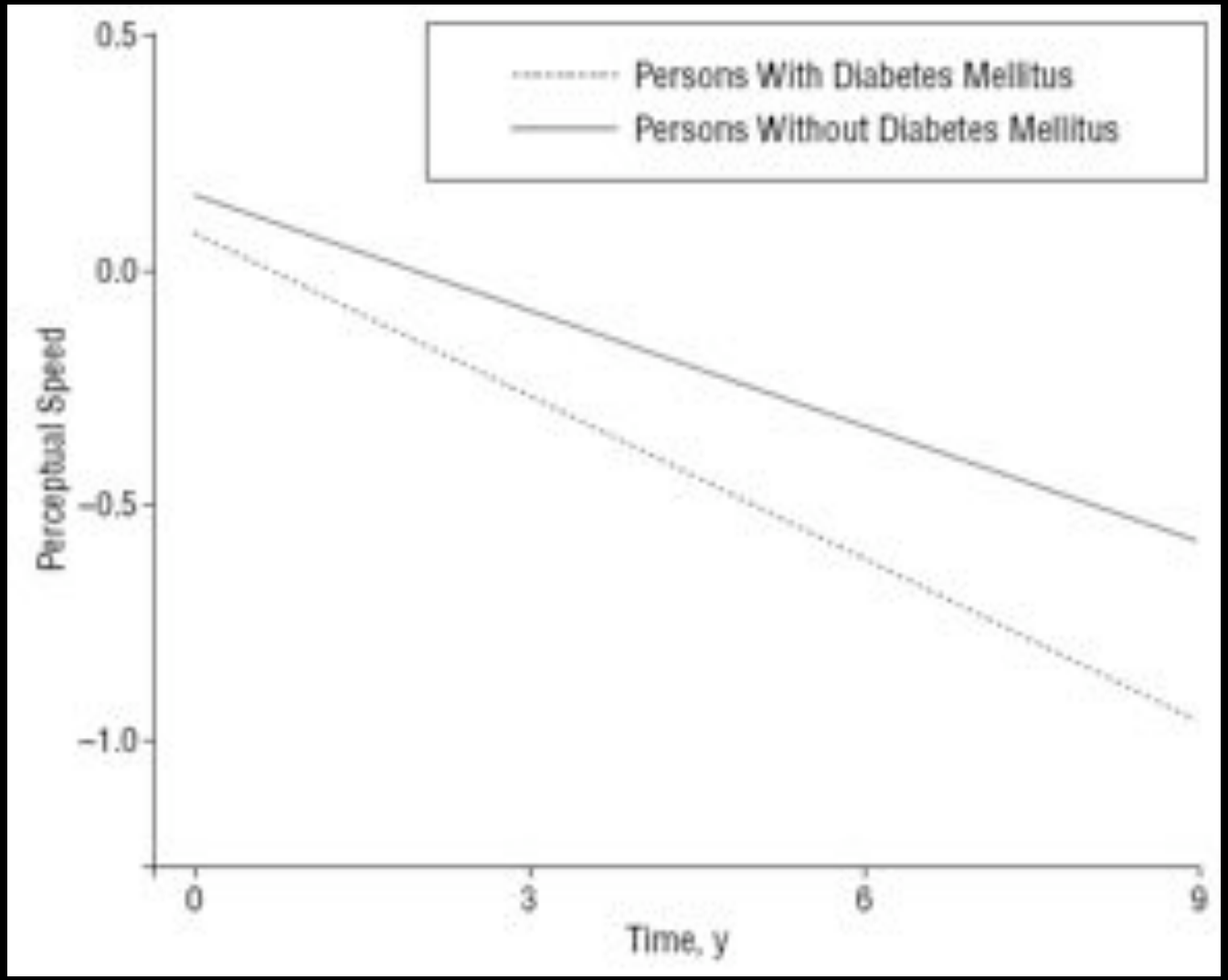

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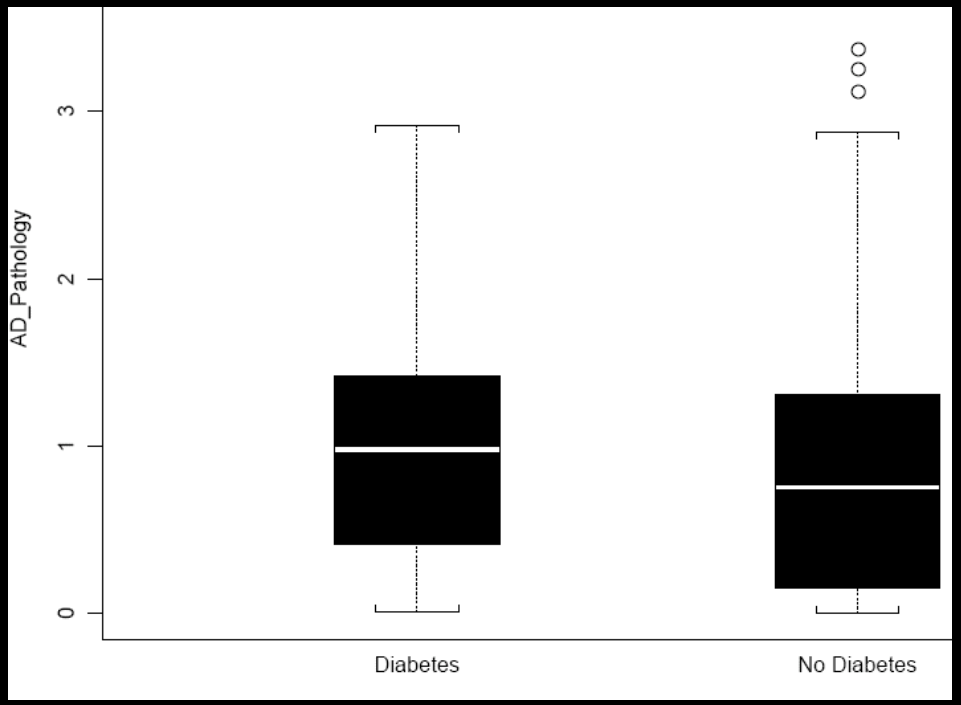
Diabetes is related to cerebral infarction but not to AD pathology in older persons



Pathologic marker	Variable estimate	Standard error
Overall level of AD pathology	0.01	0.12
Neuritic plaques	0.16	0.15
Diffuse plaques	–0.01	0.16
Neurofibrillary tangles	–0.13	0.13
Amyloid burden	–0.10	0.39
Tangle density	–0.61	1.45

Arvanitakis Z, et al. *Neurology* 2006;67:1960–1965.

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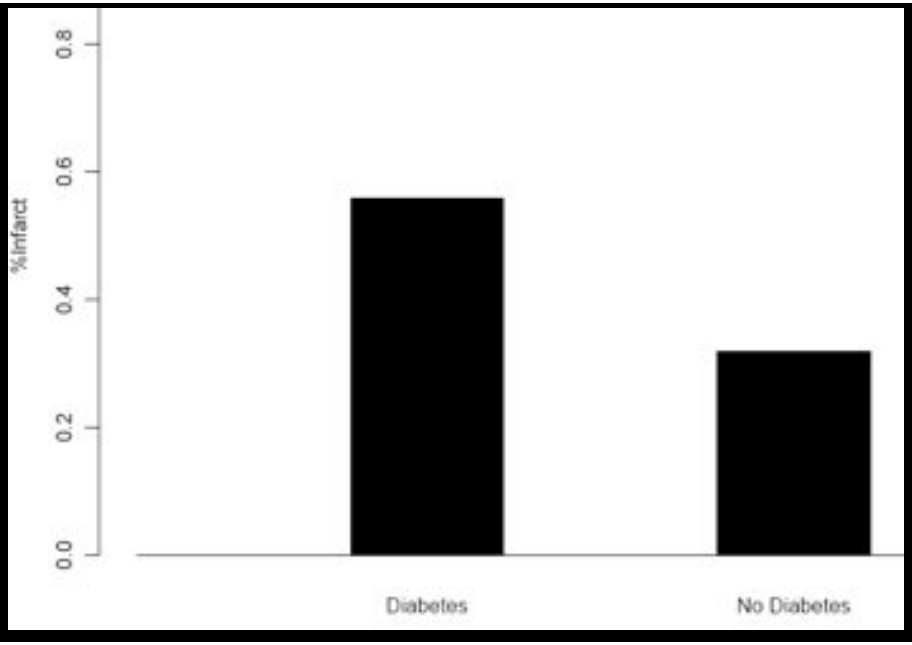

Pathologic marker	OR	95% CI
Cerebral infarction	2.47	1.16, 5.24
Cortical infarction	3.30	1.13, 9.63
Subcortical infarction	3.14	1.44, 6.83

Arvanitakis Z, et al. *Neurology* 2006;67:1960–1965.

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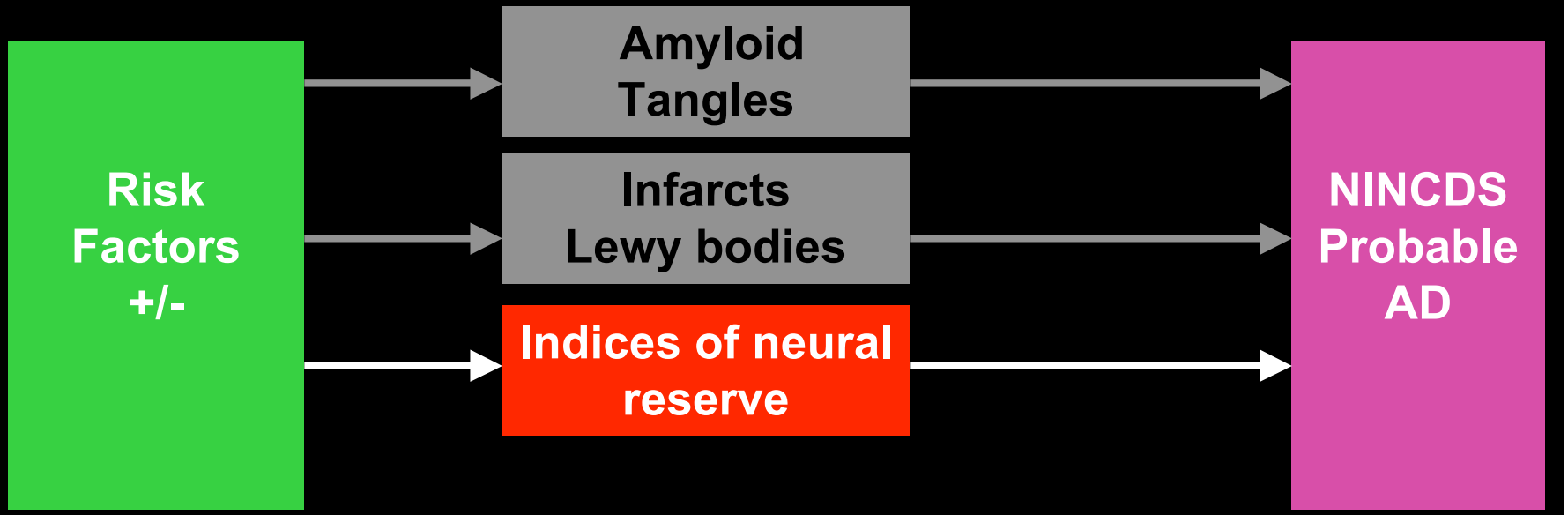
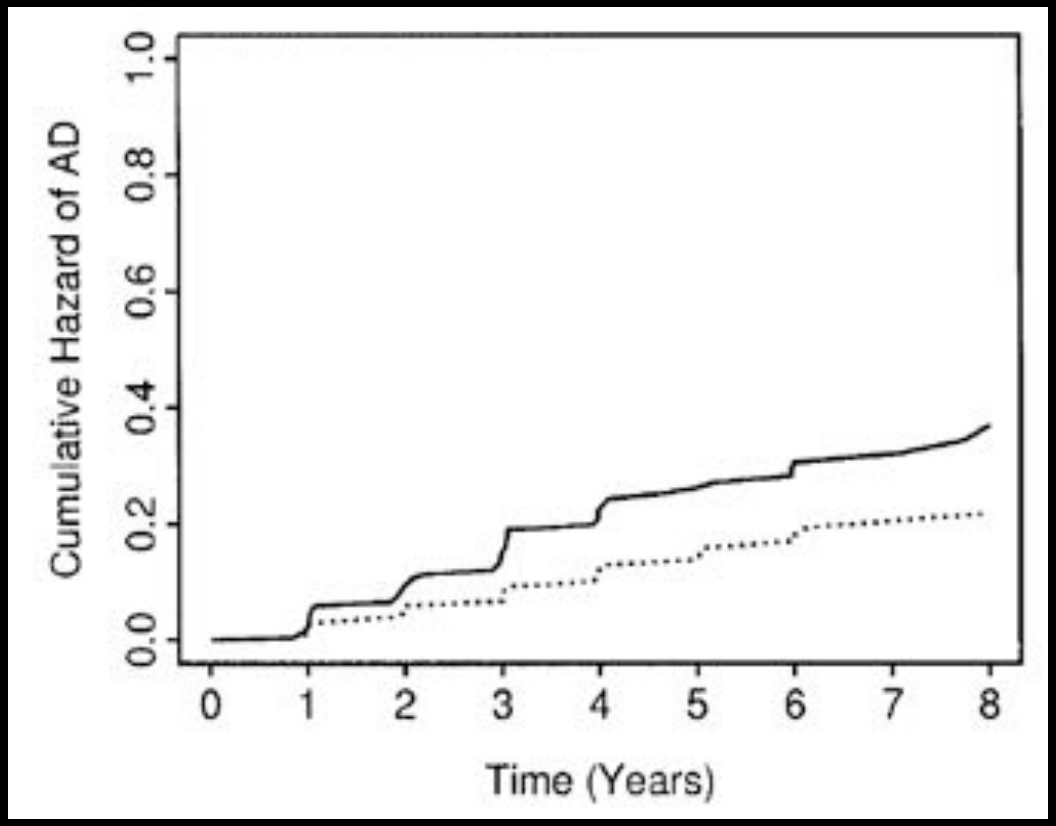


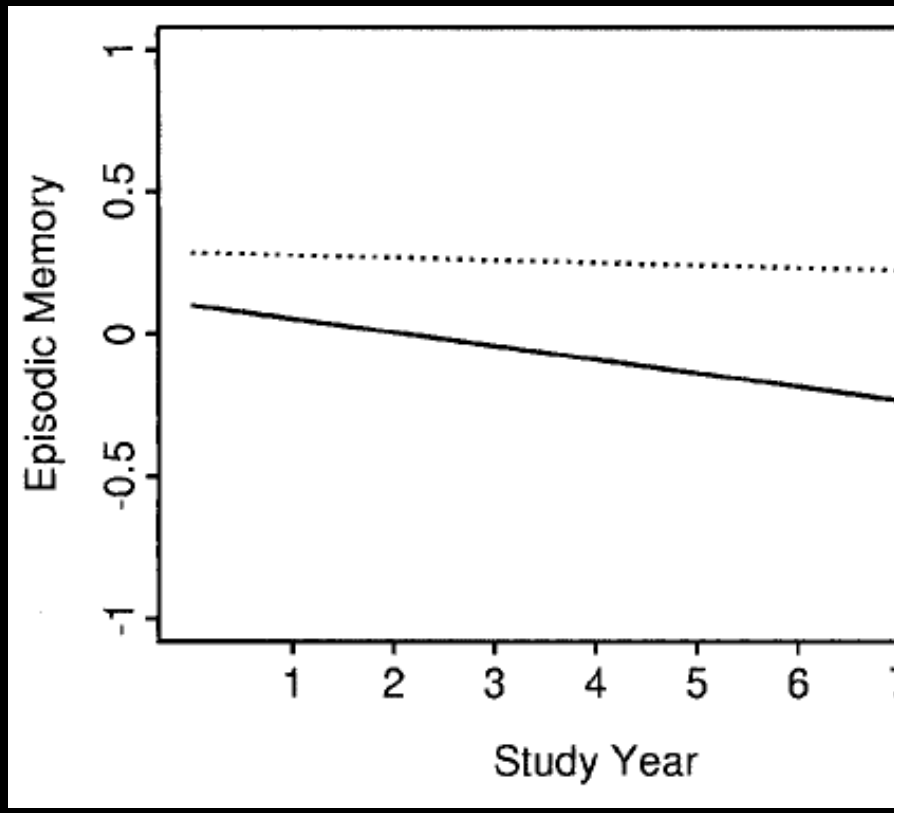
Selected Psychosocial and Experiential Facto

- Additive effects
  - Distress proneness
  - Depressive symptoms
- Interactive effects
  - Years of education
  - Conscientiousness

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

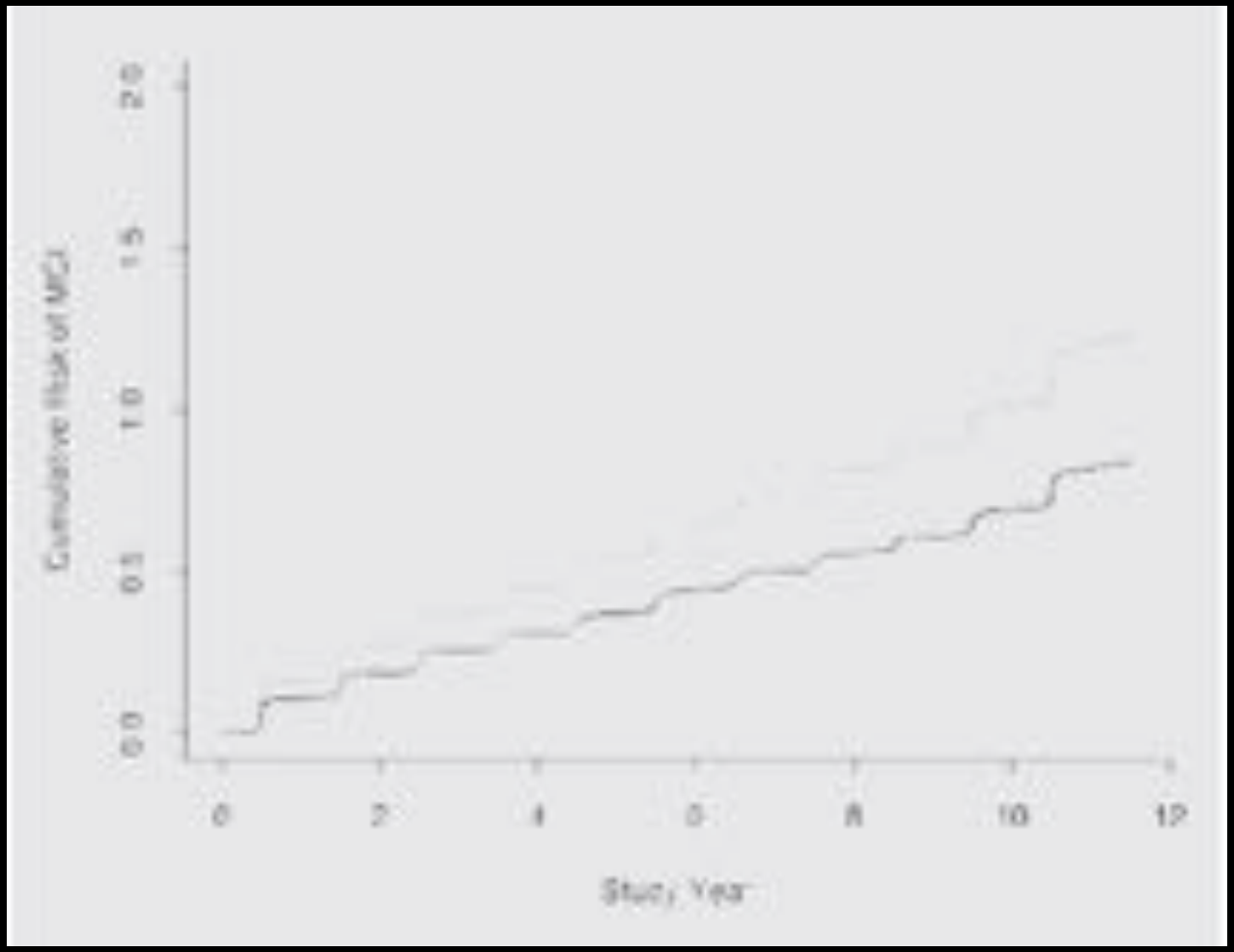
Neuroticism (NEO) refers to the disposition to experience psychological distress (
I am not a worrier; I often feel tense and jittery; I often get angry at the way peopl
treat me; I often feel helpless and want someone else to solve my problems).





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

Chronic distress and incidence of mild cognitive impairment



Wilson RS, et al. *Neurology* 2007;68:2085-92.

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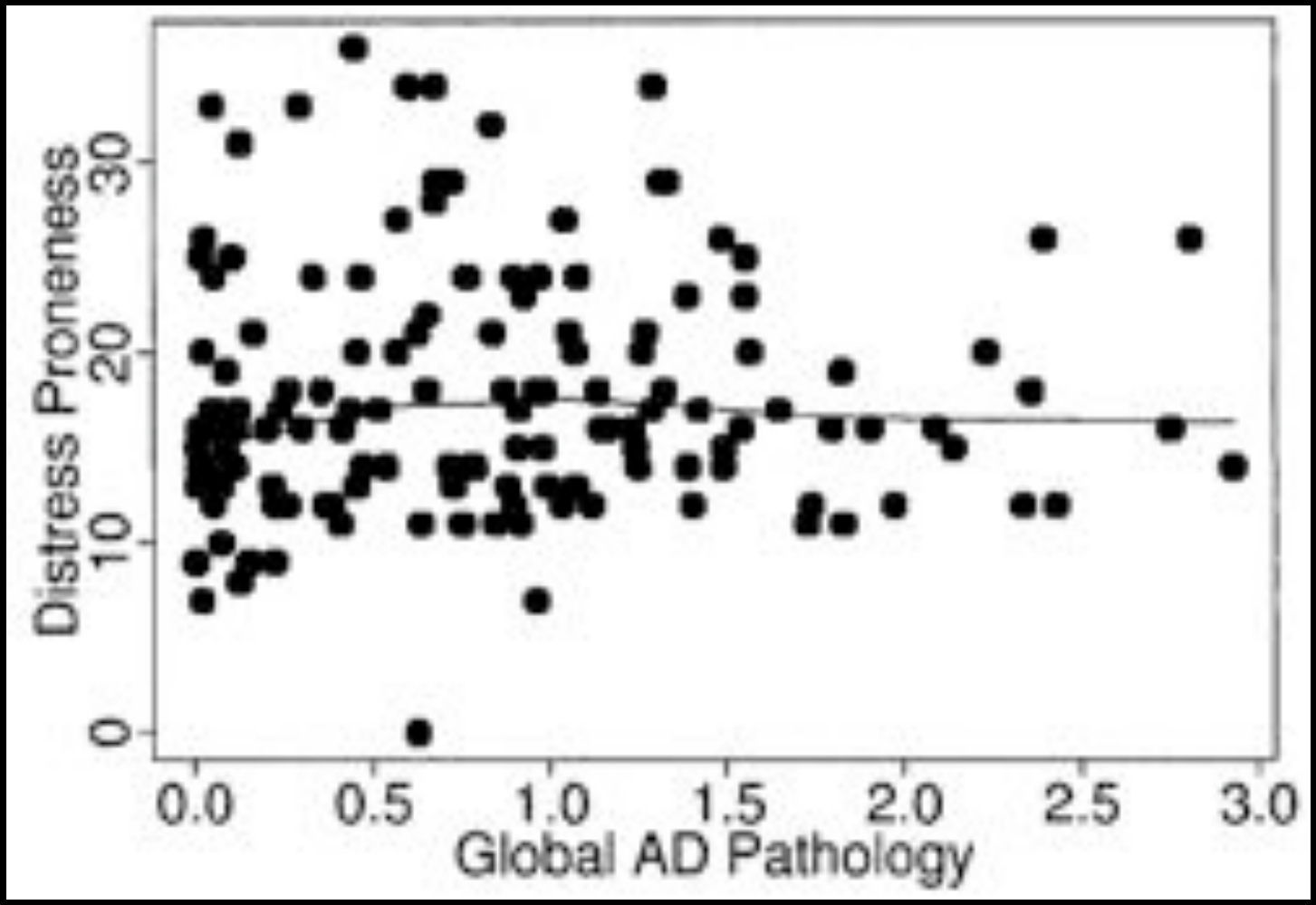


Wilson RS, et al. *Neurology* 2003;61:1479-1485.

Chronic Distress, Age-Related Neuropathology, and Late-Life Dementia

Model Term	Model A OR (95% CI)	Model B OR (95% CI)	Model C OR (95% CI)	Model D OR (95%
Chronic distress	1.53 (1.17–1.99)			
Amyloid		1.41 (1.20–1.66)		
Tangles			1.15 (1.09–1.22)	
Infarct				0.98 (0.49–1
Infarcts				2.20 (1.13–4

Model Term	Model E OR (95% CI)	Model F OR (95% CI)	Model G OR (95% CI)	Model H OR (95%
Chronic distress	1.64 (1.20–2.22)	1.79 (1.31–2.46)	1.53 (1.17–1.99)	1.71 (1.20–2
Amyloid	1.44 (1.21–1.70)			1.20 (0.97–1
Tangles		1.17 (1.10–1.23)		1.18 (1.09–1
Infarct			0.89 (0.43–1.83)	1.20 (0.44–3
Infarcts			2.34 (1.18–4.62)	2.65 (1.07–6

Wilson RS, et al. *Psychosomatic Med* 2007;69:47-53.

Chronic Distress, Age-Related Neuropathology, and Late-Life Dementia

Anxiety was assessed with a 20-item modified version of the Anxiety Trait Scale f the State-Trait Anxiety Inventory which queries about feelings of anxiety that are thought to be relatively stable over time (e.g., I feel nervous and restless.).

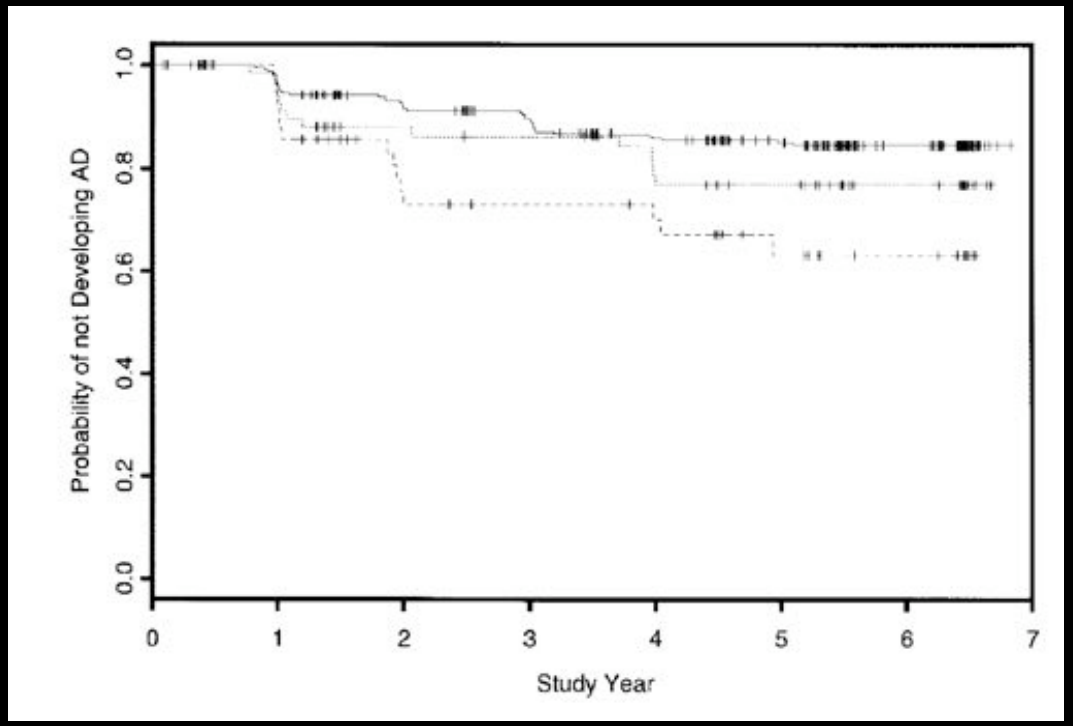
Cognitive Outcome	Trait Anxiety	
	Estimate (SE)	*p* Value
Episodic memory	−0.03 (0.02)	.189
Semantic memory	−0.05 (0.02)	.032
Working memory	−0.04 (0.02)	.006
Perceptual speed	−0.06 (0.02)	.003
Visuospatial ability	−0.07 (0.01)	<.001

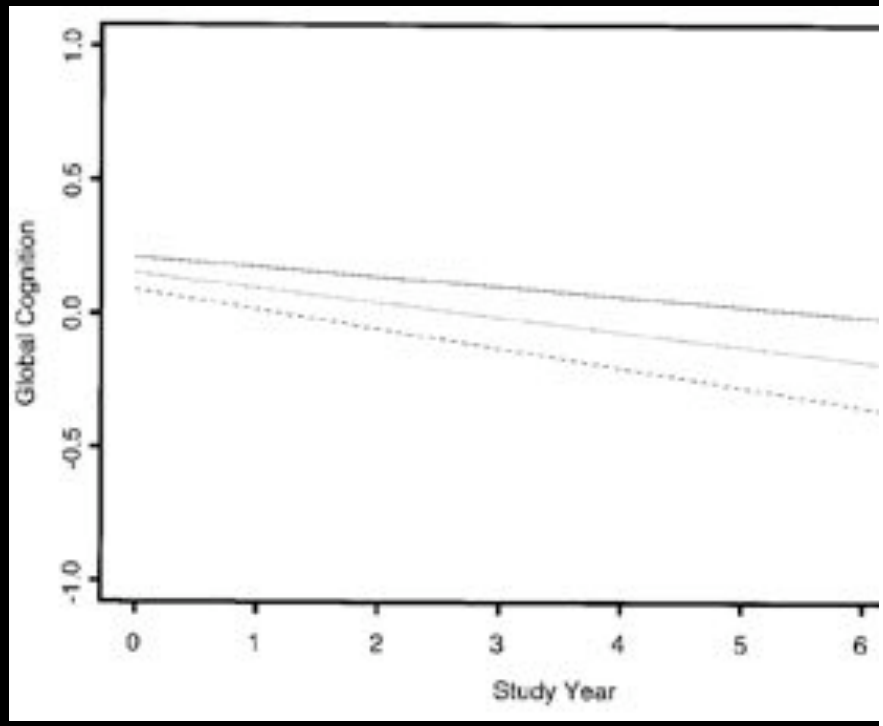
Separate linear regression models adjusted for age at death, gender, education, amyloid load, tangle density, cerebral infarction, and Lewy bodies.

Wilson RS, et al. *Psychosomatic Med* 2007;69:47-53.

Depressive symptoms, cognitive decline, and risk of AD in older persons

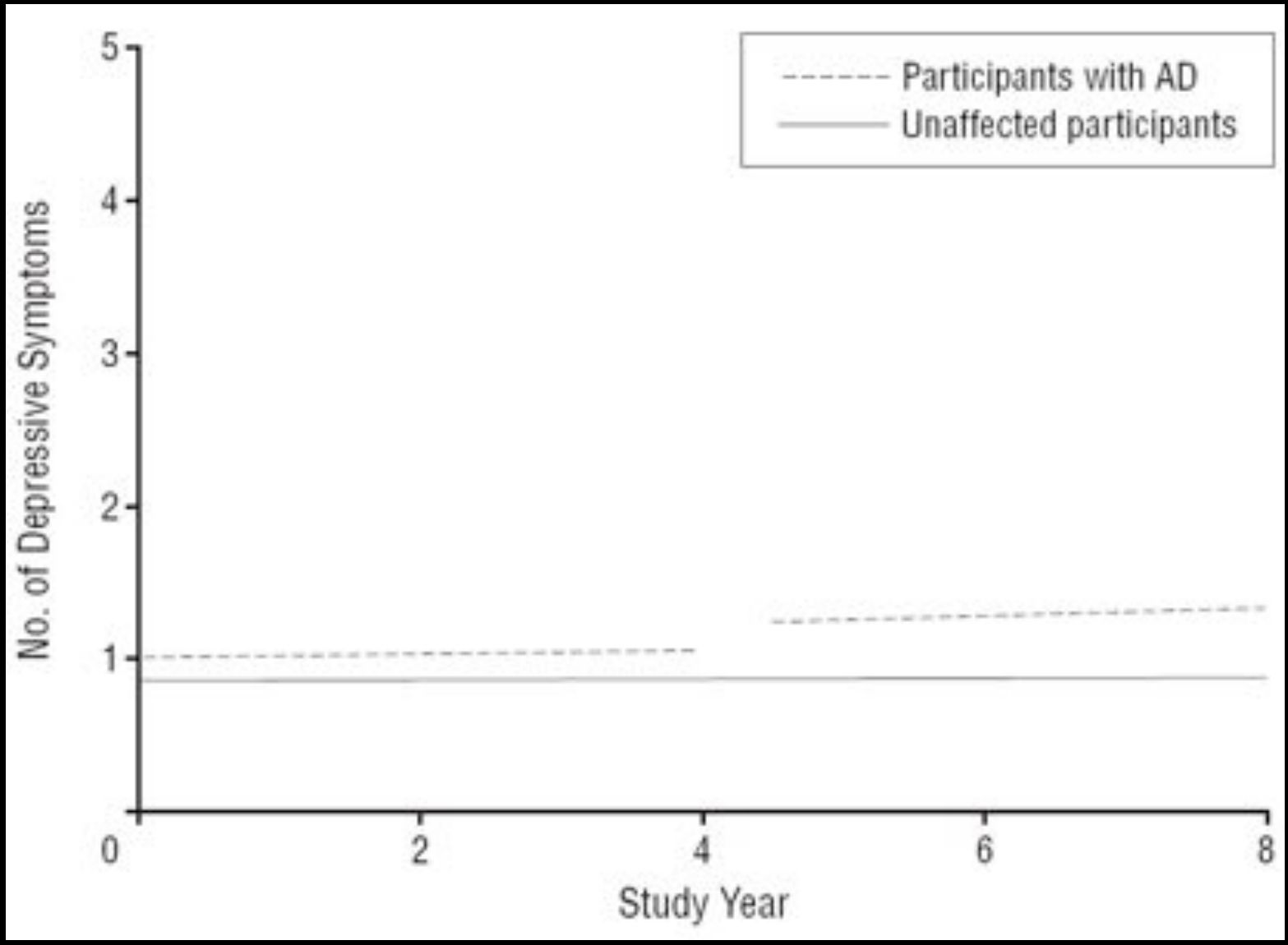
Depressive symptoms (CES-D) (e.g., I felt like everything was an effort, I felt depressed, I felt sad, I could not “get going”).





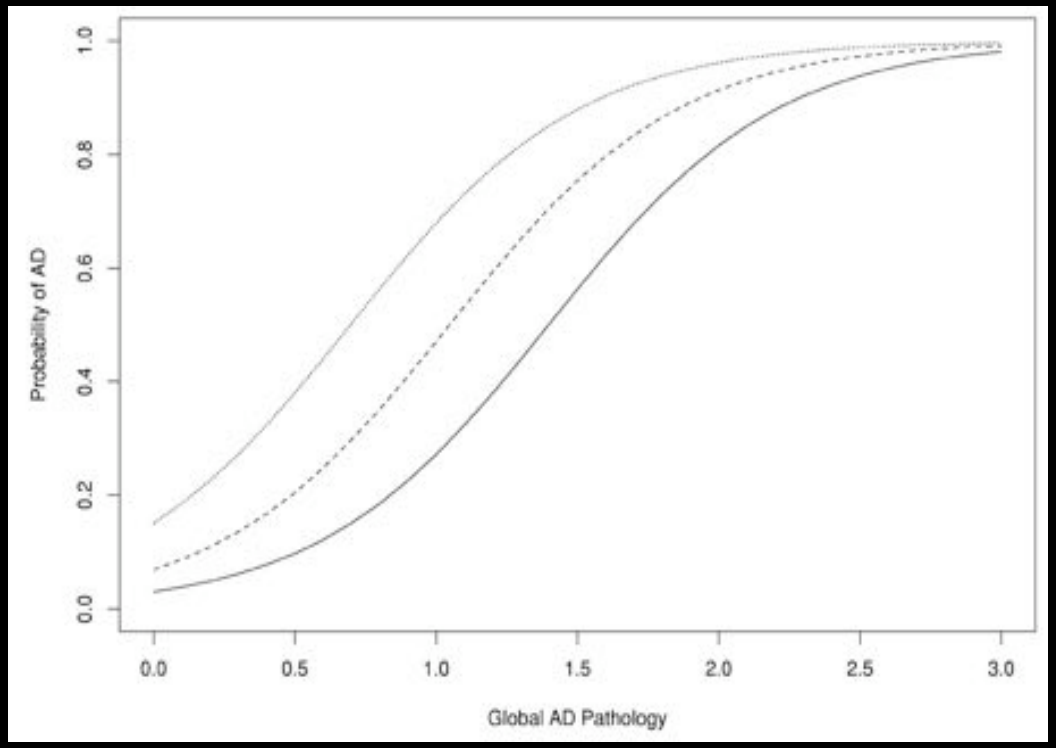
Wilson RS, et al. *Neurology* 2002;59:364-370.

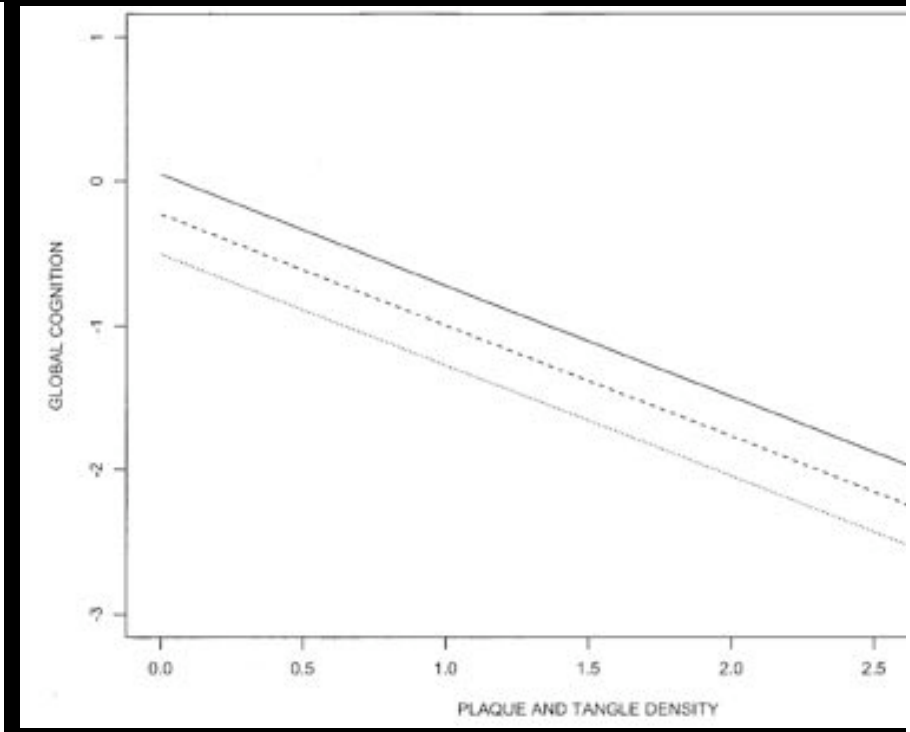
Change in Depressive Symptoms During the Prodromal Phase of Alzheimer Disease



Wilson RS, et al. *Arch Gen Psych* 2007;64:1204-12.

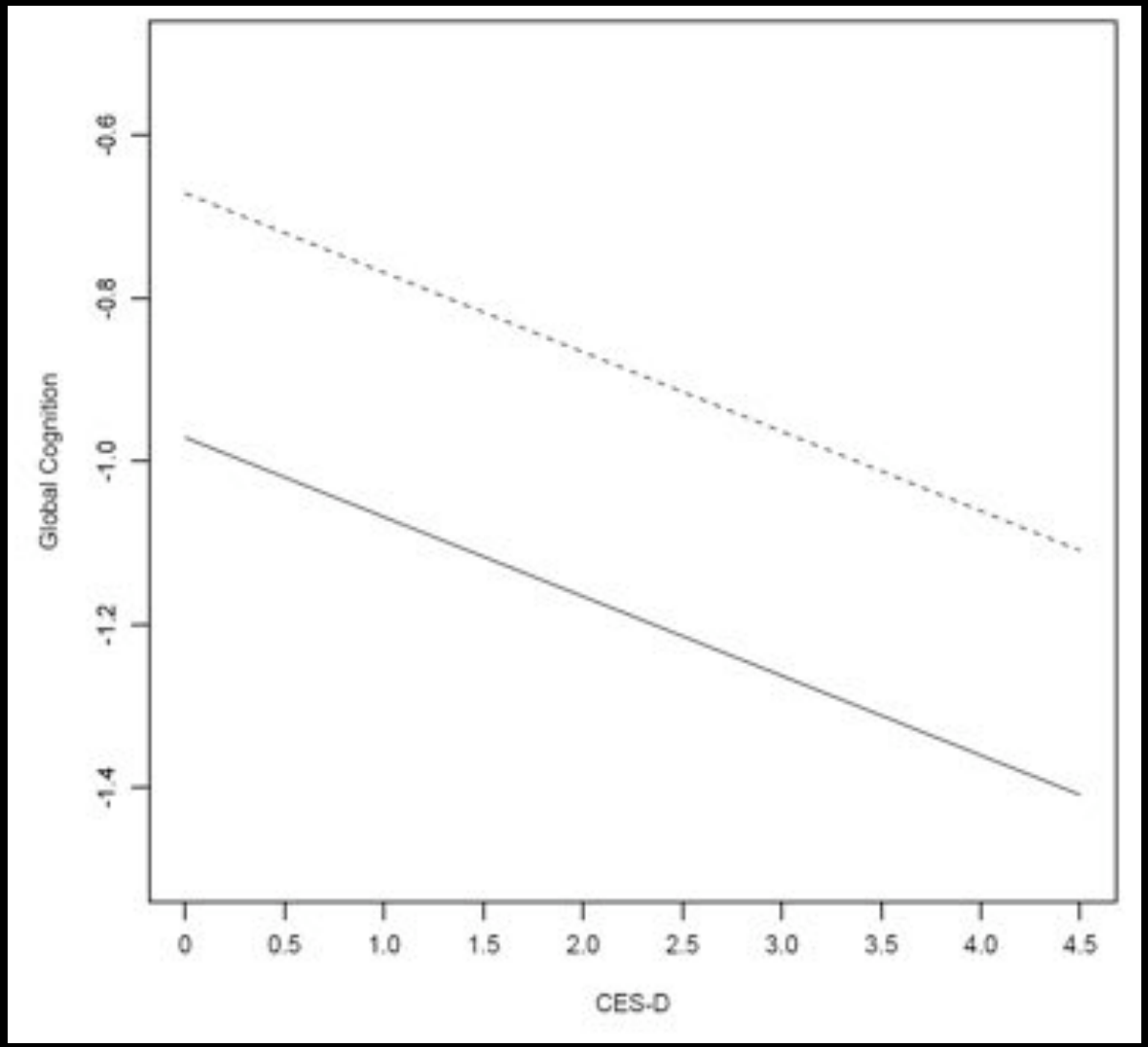
Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons





Wilson RS, et al. *Neurology* 2003;61:364-370.

Cerebral Infarctions and the Relationship of Depression Symptoms to Level of Cognitive Functioning in Older Persons



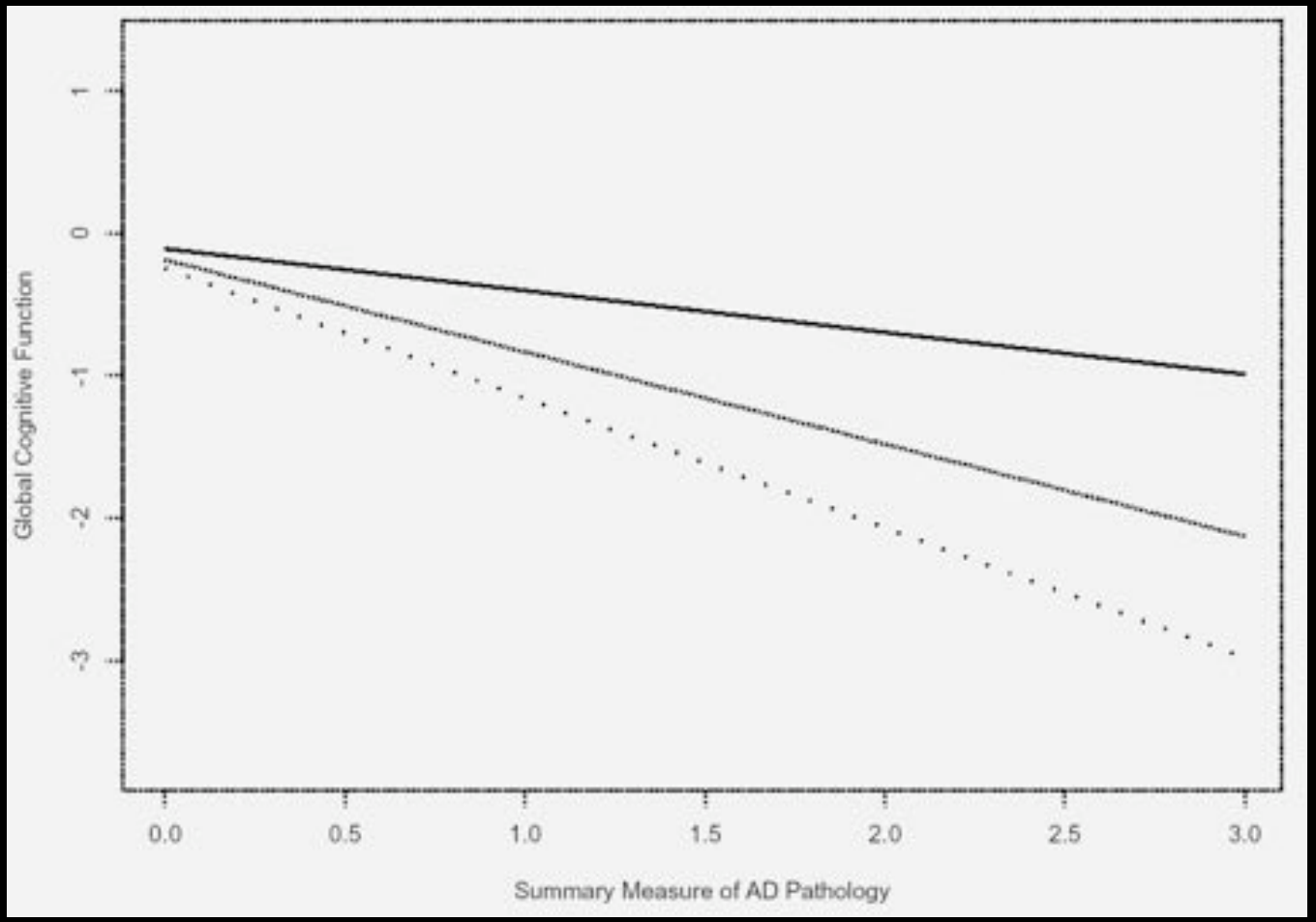
Bennett DA, et al. *Am J Geri Psych* 2004;12:211-219.

Selected Psychosocial and Experiential Facto

- Additive effects
  - Distress proneness
  - Depressive symptoms
- Interactive effects
  - Years of education
  - Conscientiousness

CME

Education modifies the relation of AD pathology to level of cognitive function in older persons



Bennett DA, et al. *Neurology* 2003;60:1909-1915.

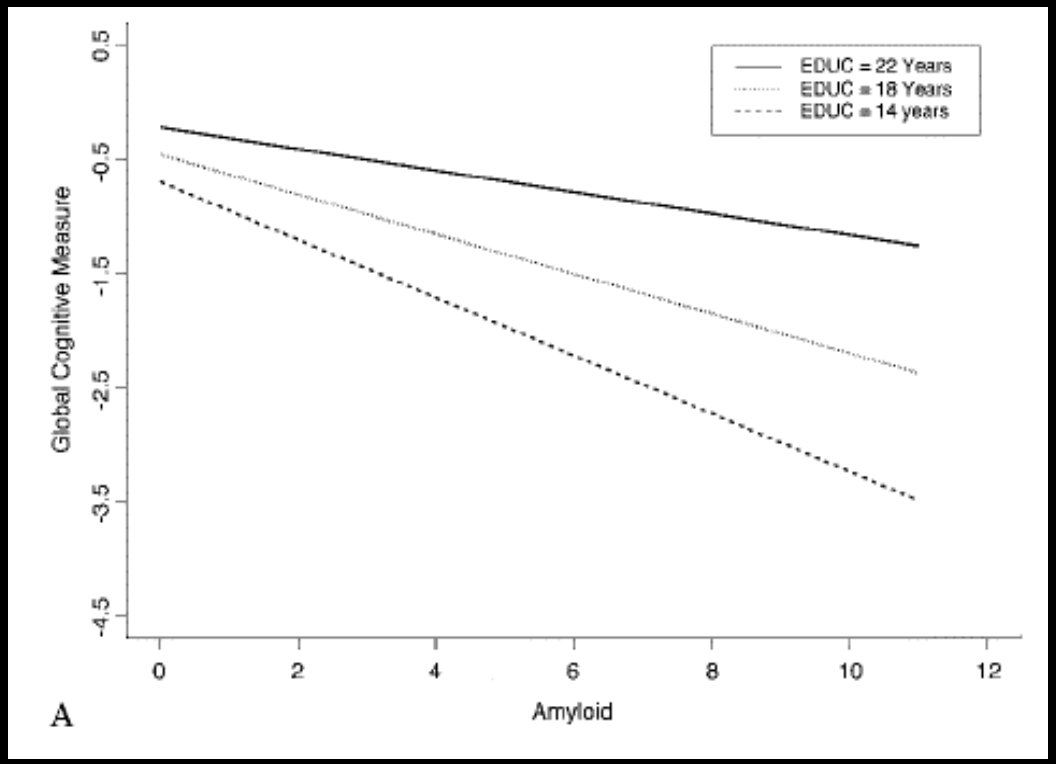
An example of the cognitive scores of two older women (scale: mean = 100, SD = 10, from baseline).

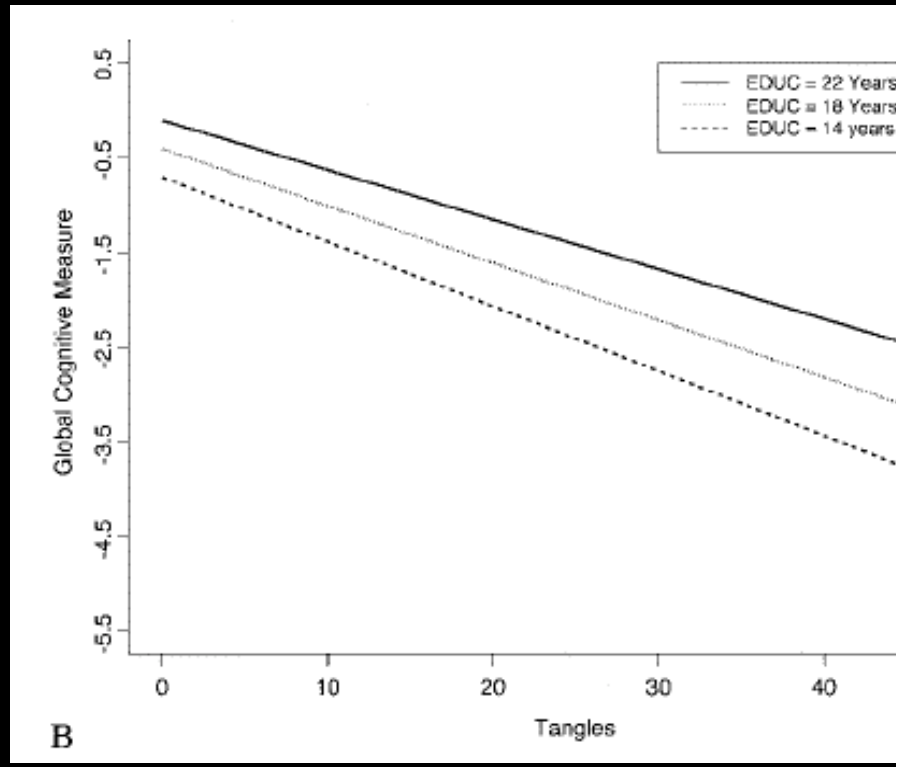
Education	plaques	score	plaques	score
18 years	0	98.1	18	96.2
15 years	0	96.8	18	82.0

Neuritic plaques have less effect on cognition as educational level increases

Bennett DA, et al. *Neurology* 2003;60:1909-1915.

Education modifies the association of amyloid but not tangles with cognitive function

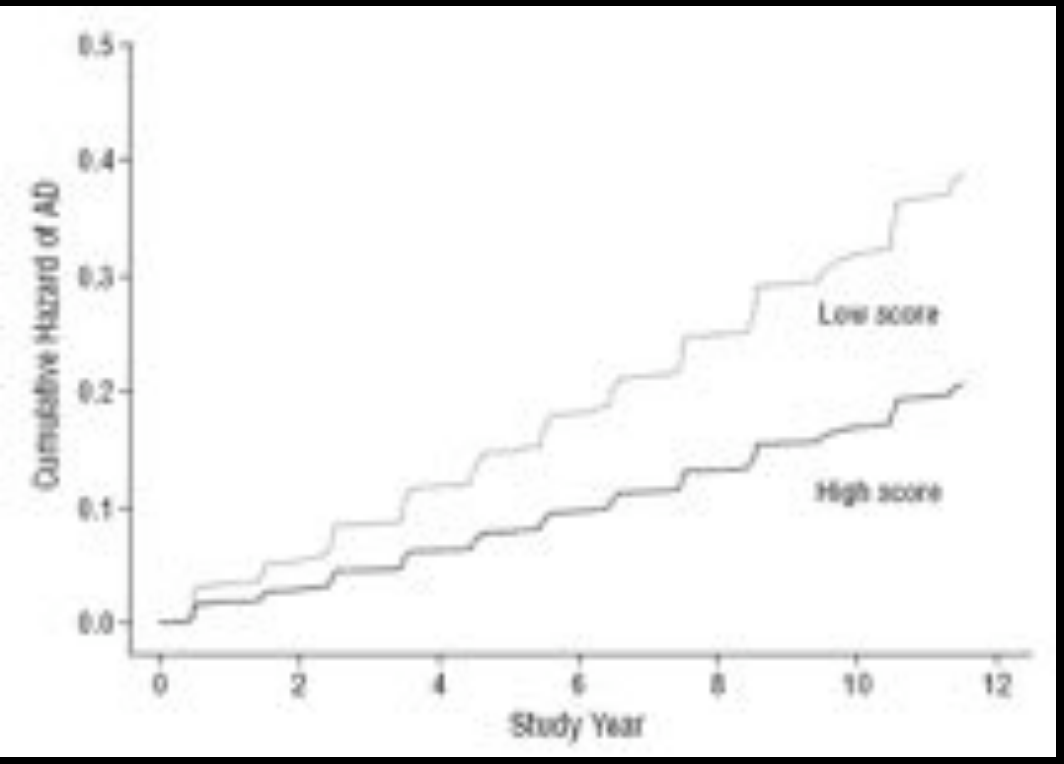


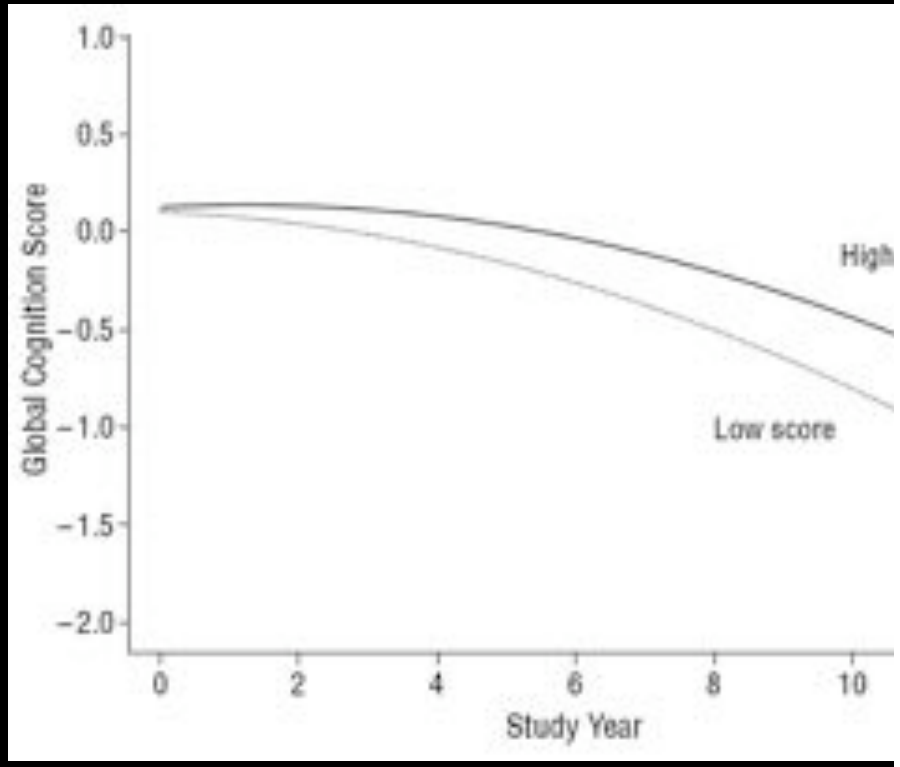


Bennett DA, et al. *Neurology* 2005;65:953-959.

Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment

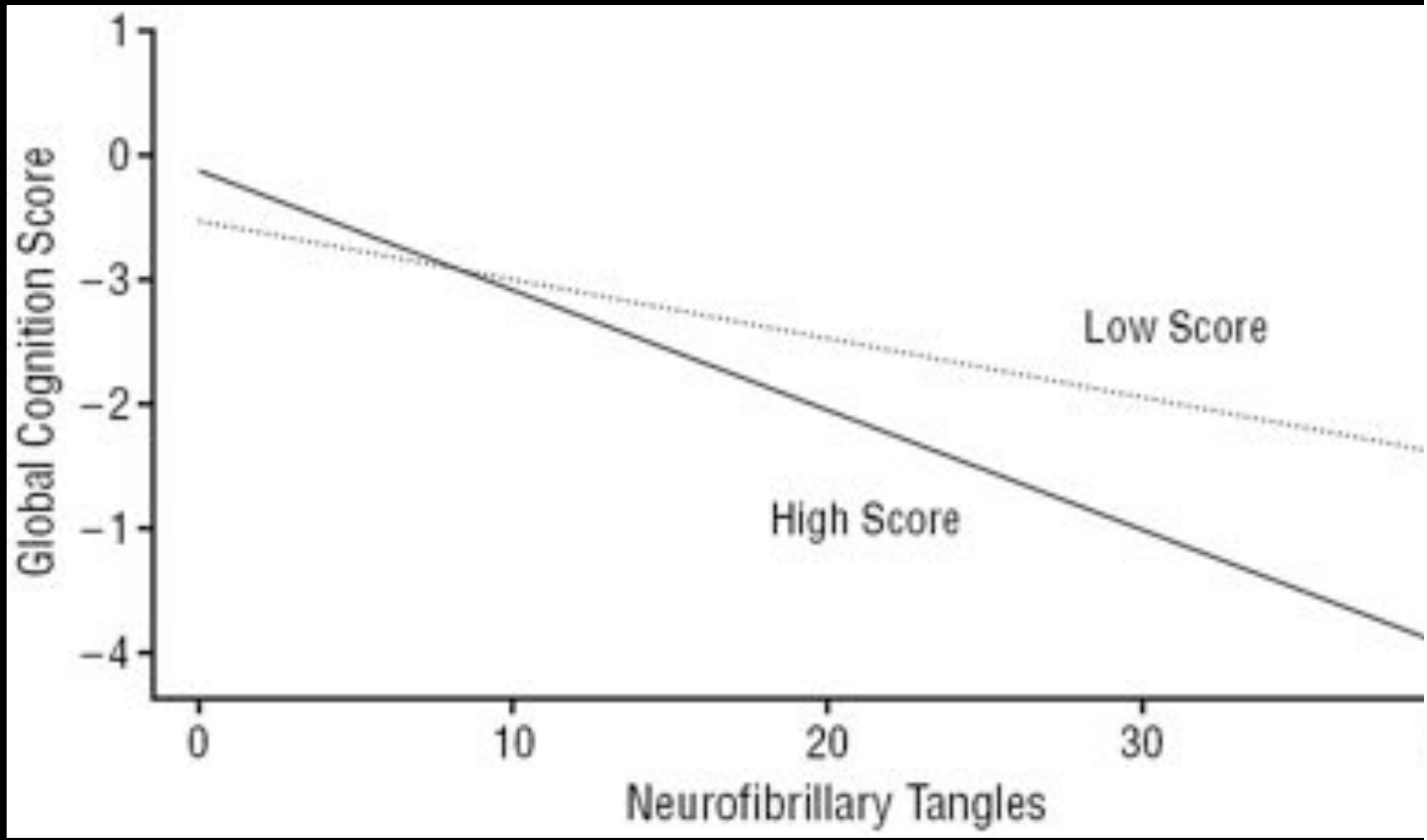
Conscientiousness (NEO) refers to a tendency to be self-disciplined, scrupulous, and purposeful (e.g., “I am a productive person who always gets the job done”).





Wilson RS, et al. *Arch Gen Psych* 2007;64:1204-12.

Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment



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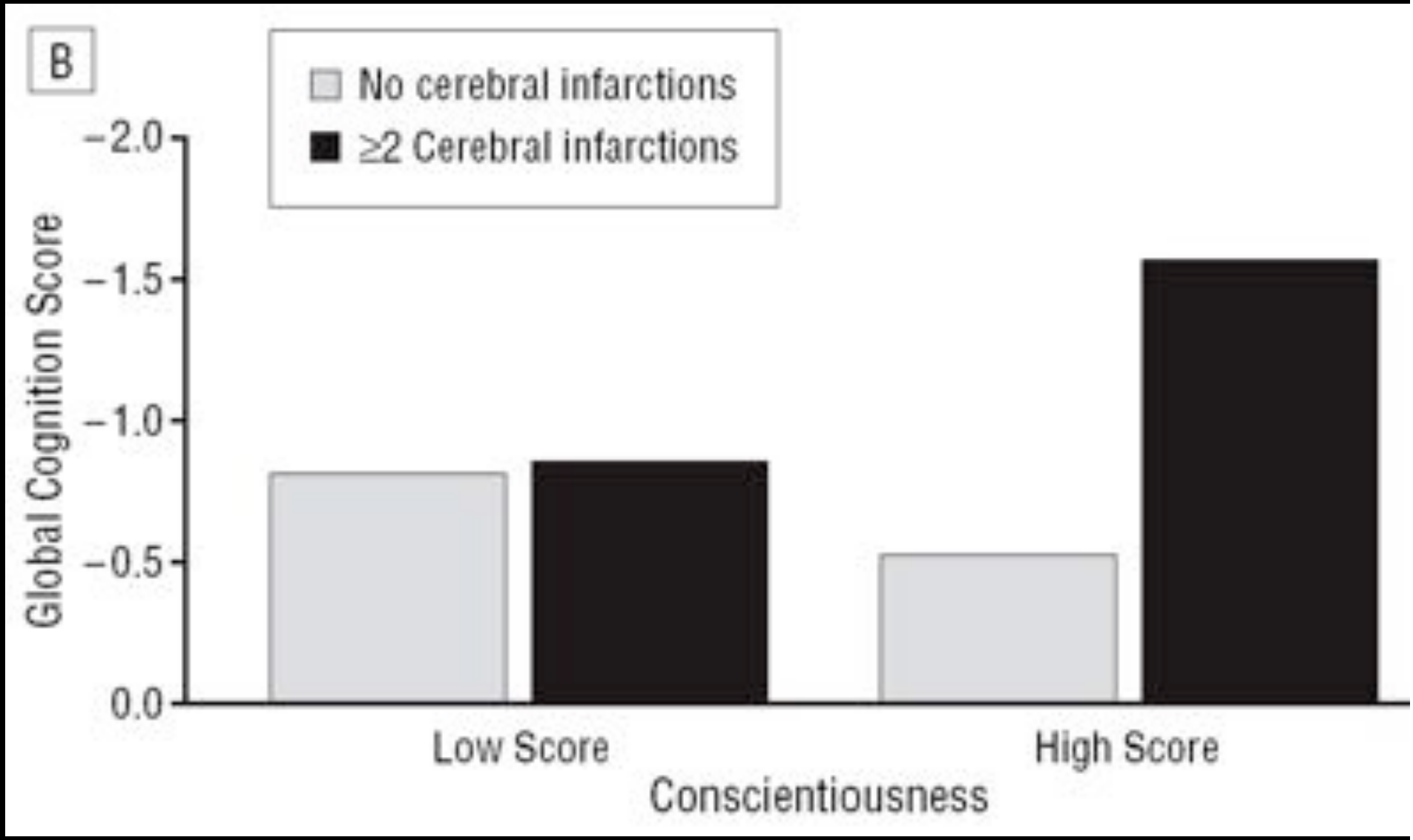
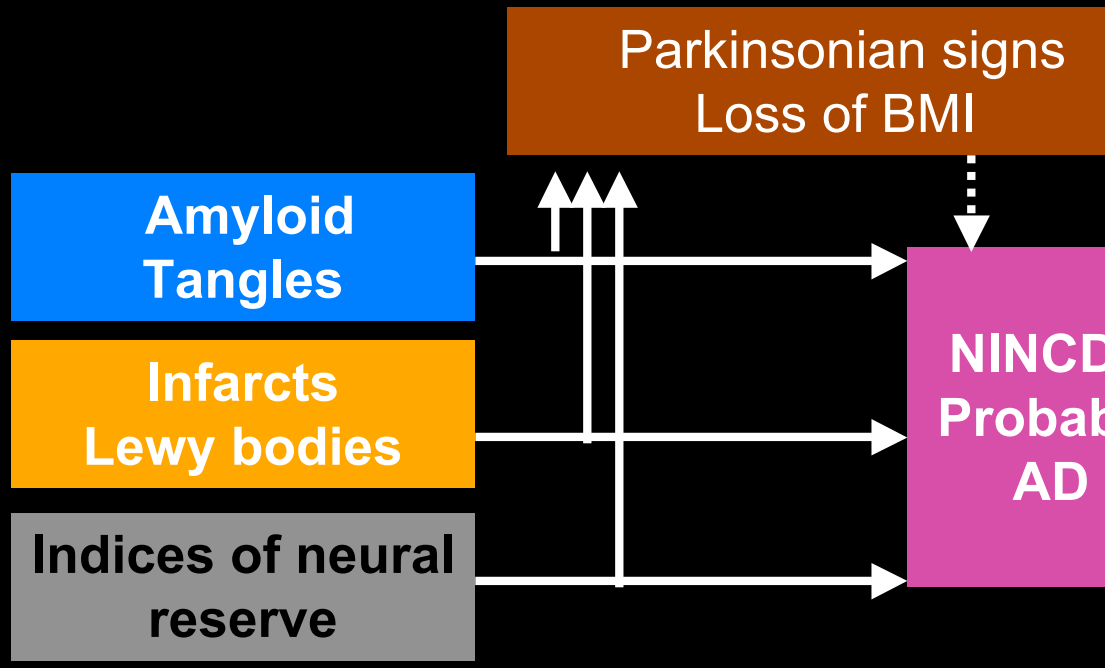
Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment

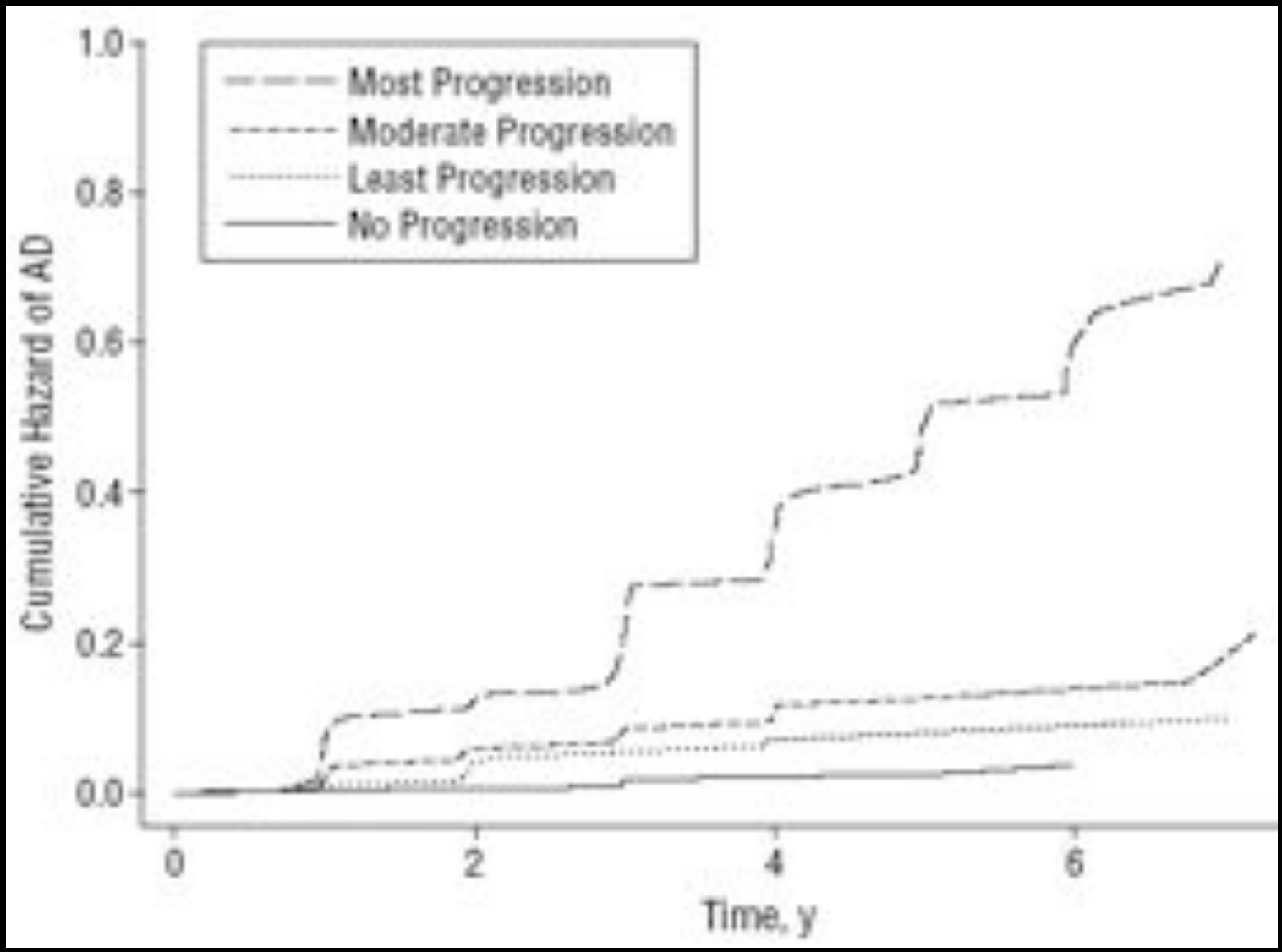


Wilson RS, et al. *Arch Gen Psych* 2007;64:1204-12.

- *There are no risk factors for AD*
- Factors lead to the accumulation of neuropathology and impair th structure and function of neural systems that subserve cognition
  - Some factors associated with amyloid and tangles
  - Others with CVD or LBD
  - Others with indices of neural reserve
  - Others are early signs of neuropathology



Parkinsonianlike Signs and Risk of Incident Alzheimer Disease in Older Persons

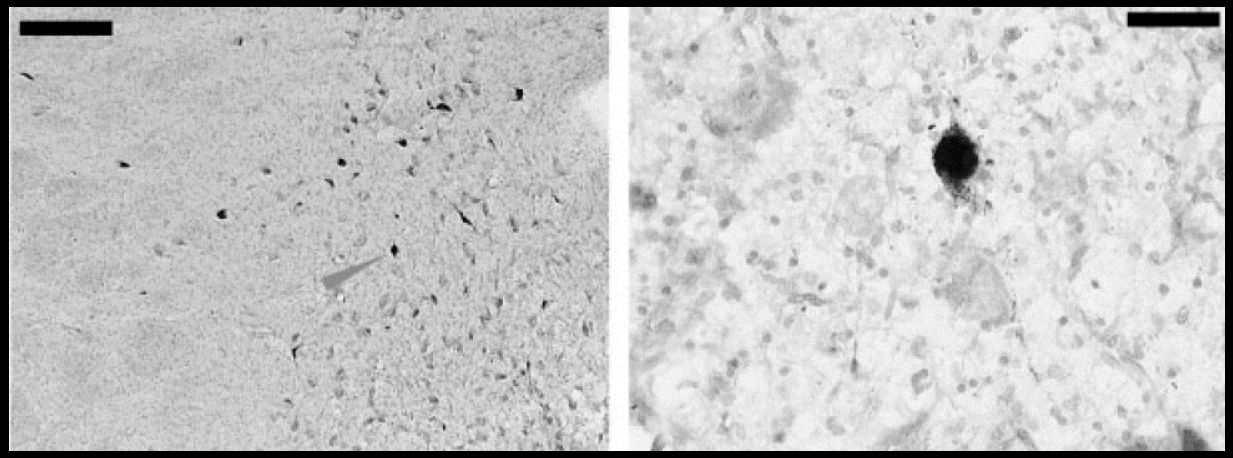


Wilson RS, et al. *Arch Neurol* 2003;60:539-44.

Substantia Nigra Tangles Are Related to Gait Impairment in Older Persons

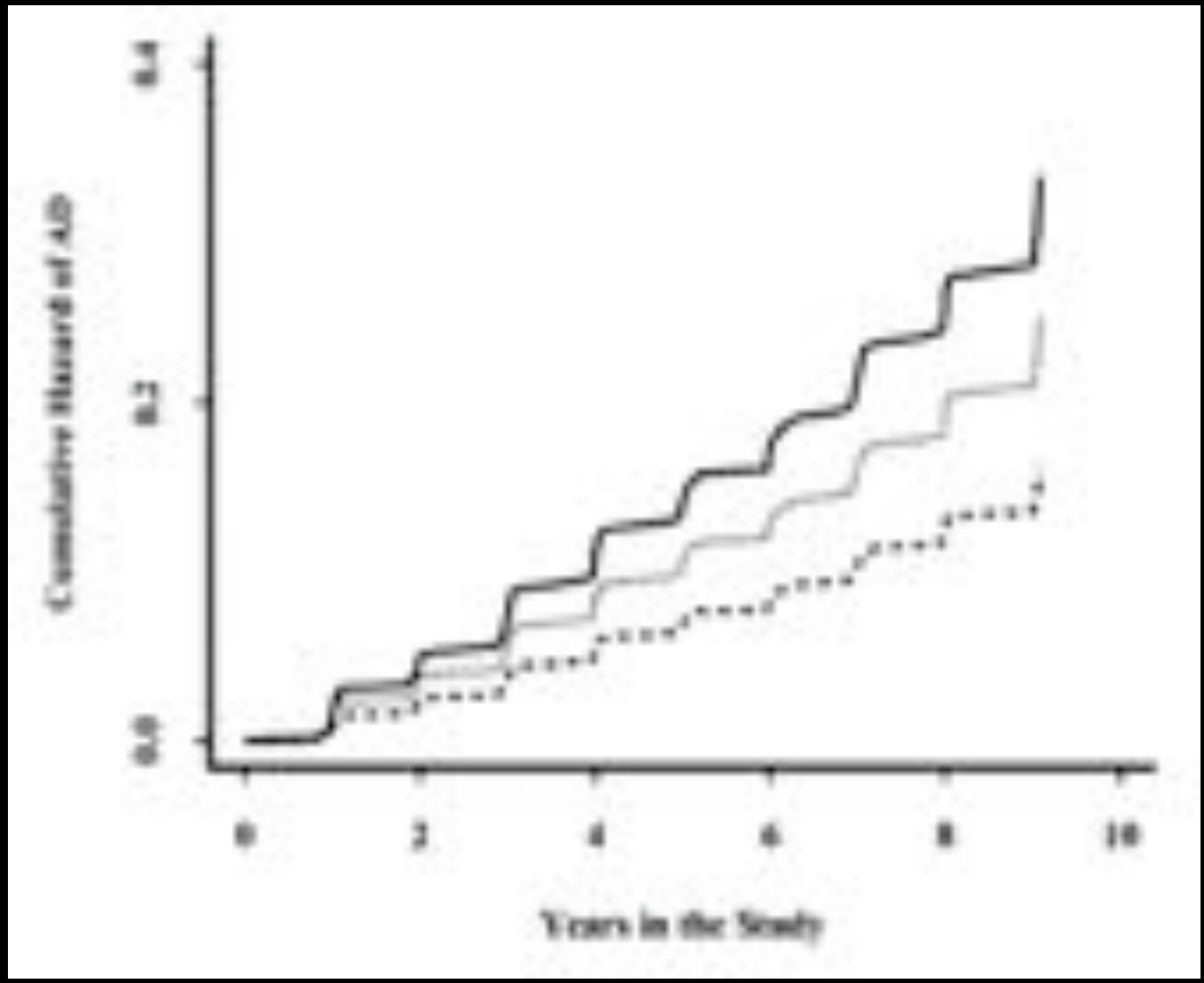
Variable	Gait Impairment
Age (yr)	0.39[a]
Male sex	−0.13
Dementia	0.45[a]
Braak score	0.22[c]
Cortical NFT density	0.32[b]
Amyloid %	0.15
Lewy bodies	0.17
Cerebral infarcts	0.18
Nigral neuronal loss	0.24[c]
Substantia nigra tangle count	0.30[b]

[a] $p < 0.001$; [b] $p < 0.01$; [c] $p < 0.05$.



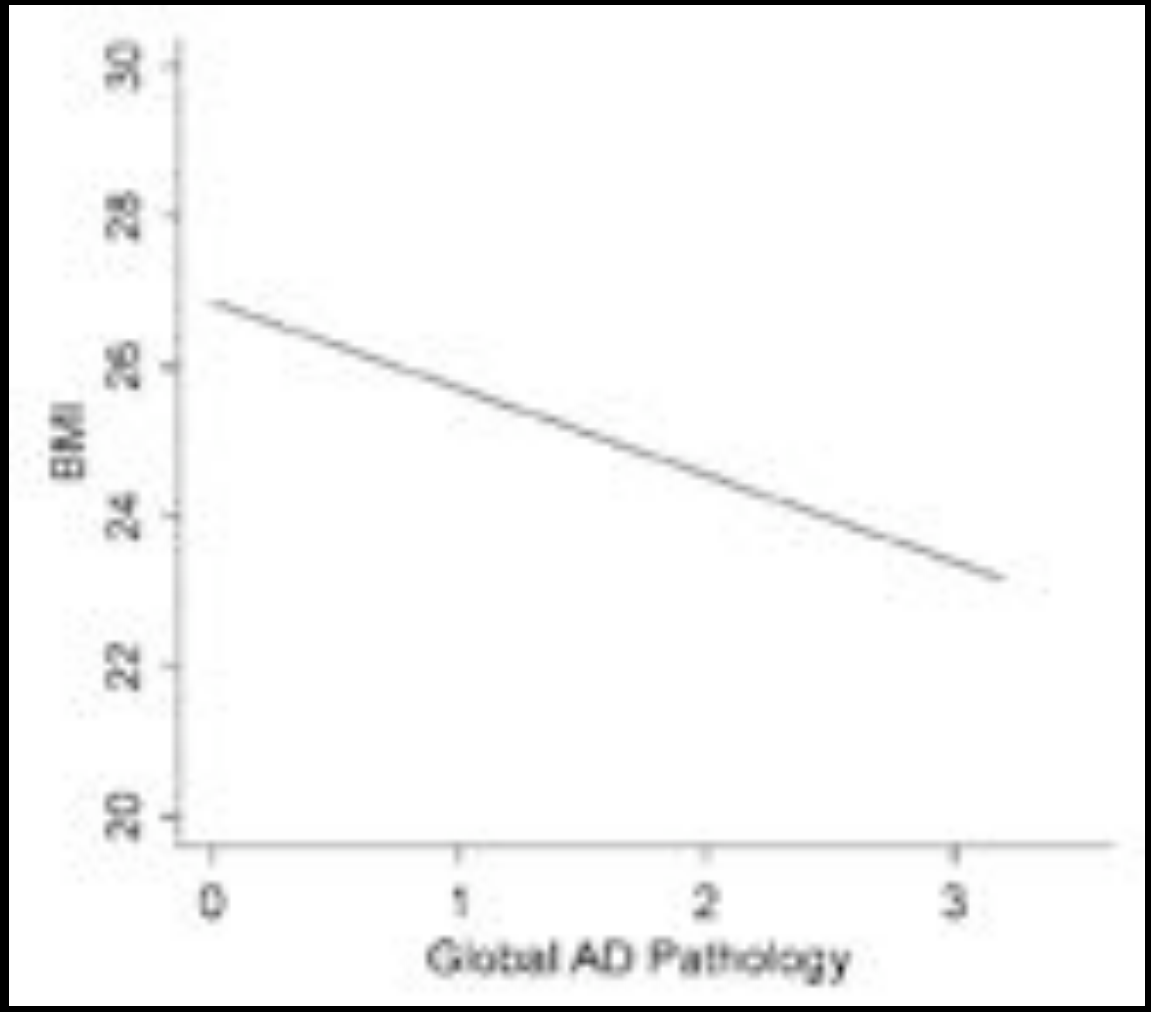
Schneider JA, et al. *Ann Neurol* 2006;59:166–73.

Change in body mass index and risk of incident Alzheimer disease

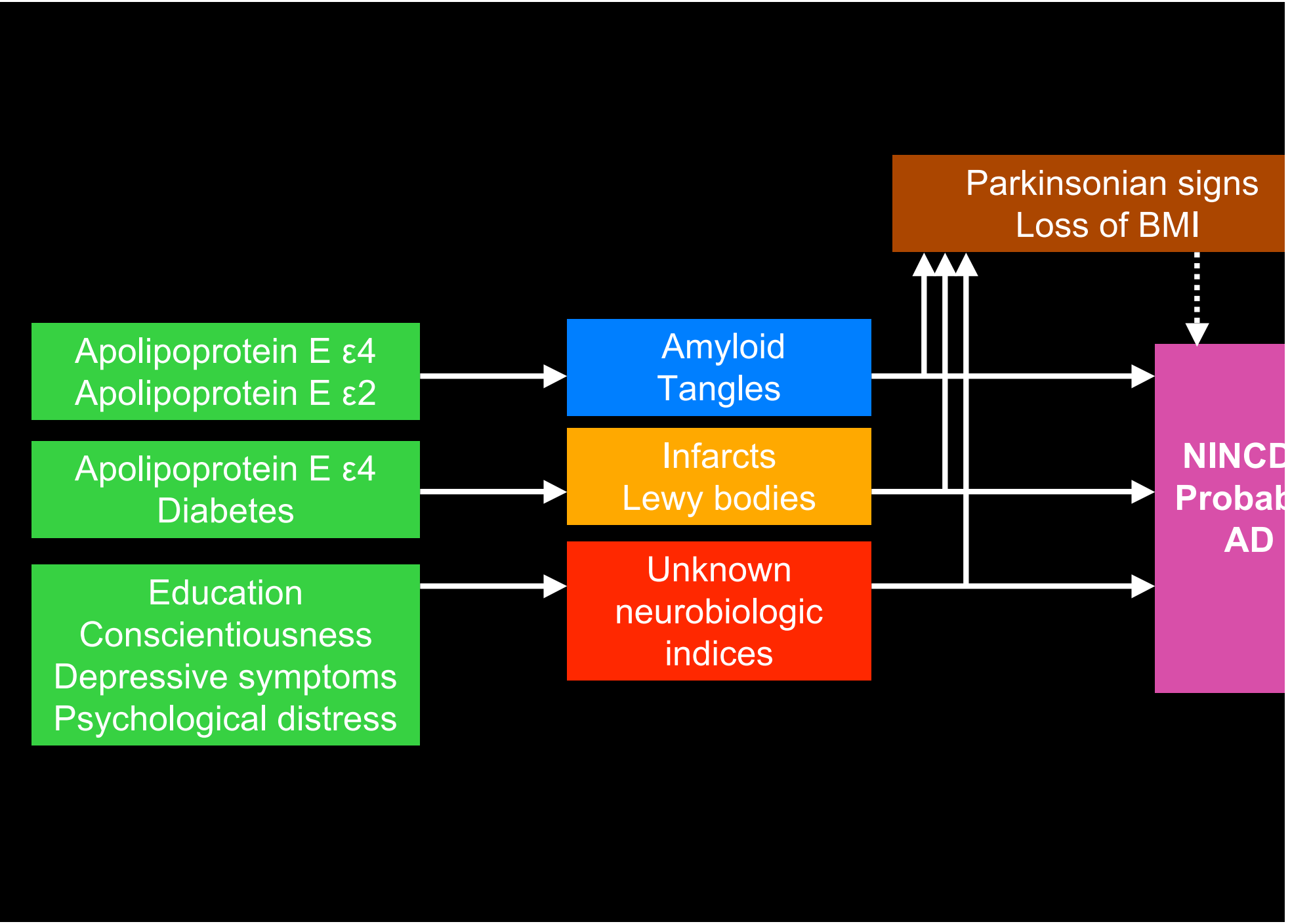


Buchman AS, et al. *Neurol* 2004;63:996–1001.

Body mass index in older persons is associated with Alzheimer disease pathology



Buchman AS, et al. *Neurol* 2006;67:1949–54.


Parkinsonian signs
Loss of BMI
Apolipoprotein E ε4
Apolipoprotein E ε2
Apolipoprotein E ε4
Diabetes
Education
Conscientiousness
Depressive symptoms
Psychological distress
Amyloid
Tangles
Infarcts
Lewy bodies
Unknown
neurobiologic
indices
NINCD
Probab
AD


JIM BORGMAN
WHAT A LONG STRANGE TRIP IT'S BEEN.
FREE ANGELA DAVIS
MAKE LOVE NOT WAR
WOODSTOCK
OUT OF NAM
HEY HEY LBJ!
BOOMERS
MCGOVERN
SOCIAL SECURITY