Clinical and Pathologic Complexities in Aging and Alzheimer's Disease

Julie A. Schneider MD MS

Professor,
Departments of Pathology and Neurological Sciences

Associate Director,
Neuropathology Core Leader, Rush Alzheimer's Disease Core Center
Rush University Medical Center

Disclosures

Scientific advisory boards

- Eli Lilly Inc
- Avid radiopharmaceuticals
- Genentech USA, Inc.,

Consultant

- Avid radiopharmaceuticals
- Navidea biopharmaceutcals

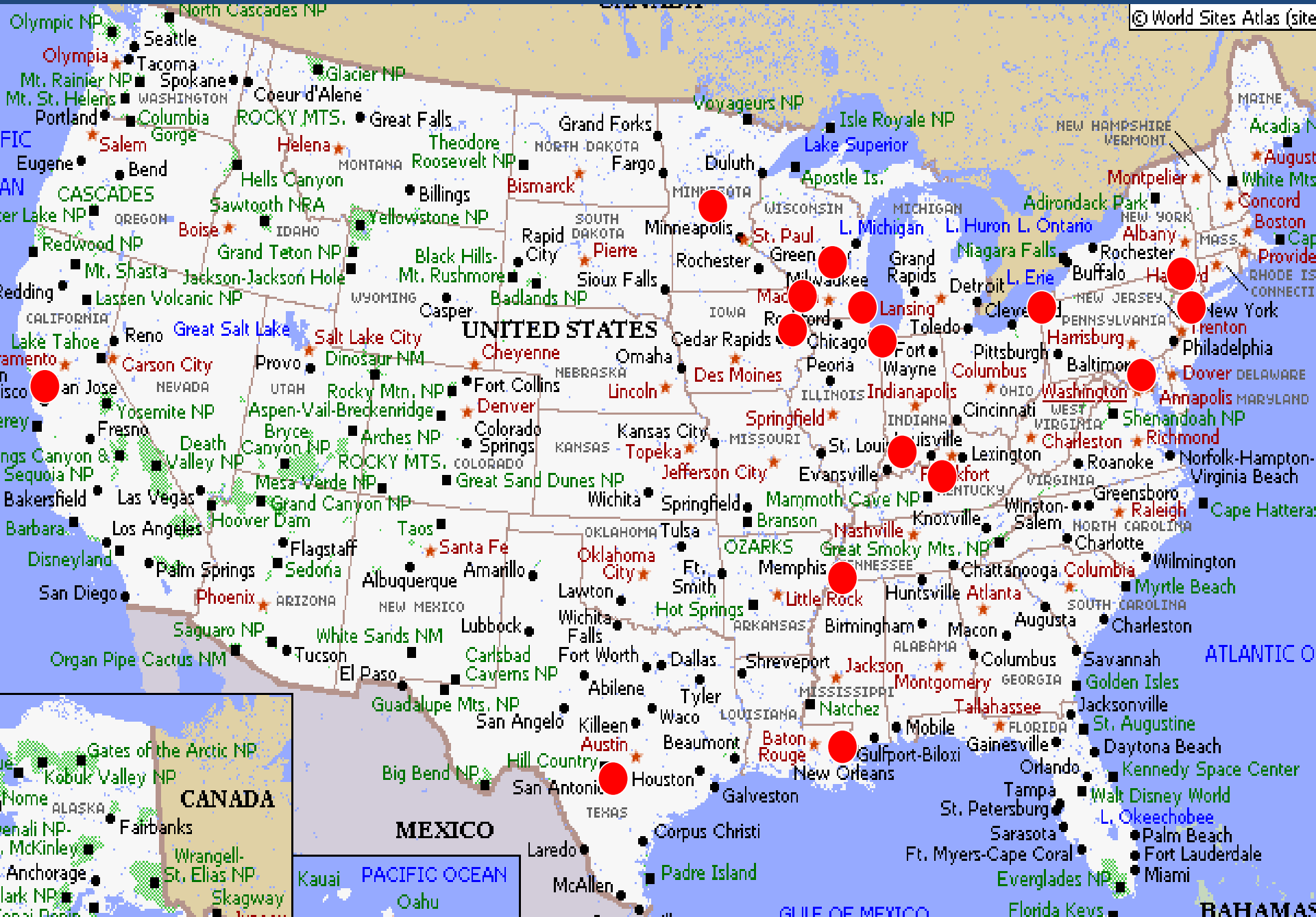
Clinical and Pathologic Complexities in Aging and Alzheimer's Disease

- The spectrum of pathologies in aging
- Concept of neural reserve - threshold of path to exhibit sxs
- Mixed pathology (AD plus another brain pathology)
  - Degenerative and Vascular pathologies
    - Macroinfarcts, large vessel atherosclerosis
    - SVD - microinfarcts, arteriolosclerosis, CAA
    - Lewy bodies, hippocampal sclerosis, TDP43
- Overlap of clinical phenotypes and the diagnosis AD dementia
- Implications for risk factors , public health, clinical trials

The Religious Orders Study

- Began in 1993
- Enrolls older persons without dementia, annual F/U
- Older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing, including a modified UPDRS
- All agreed to brain donation at the time of death
- ~
  - >90% follow-up rates
  - About 94% autopsy rate > 600 autopsies

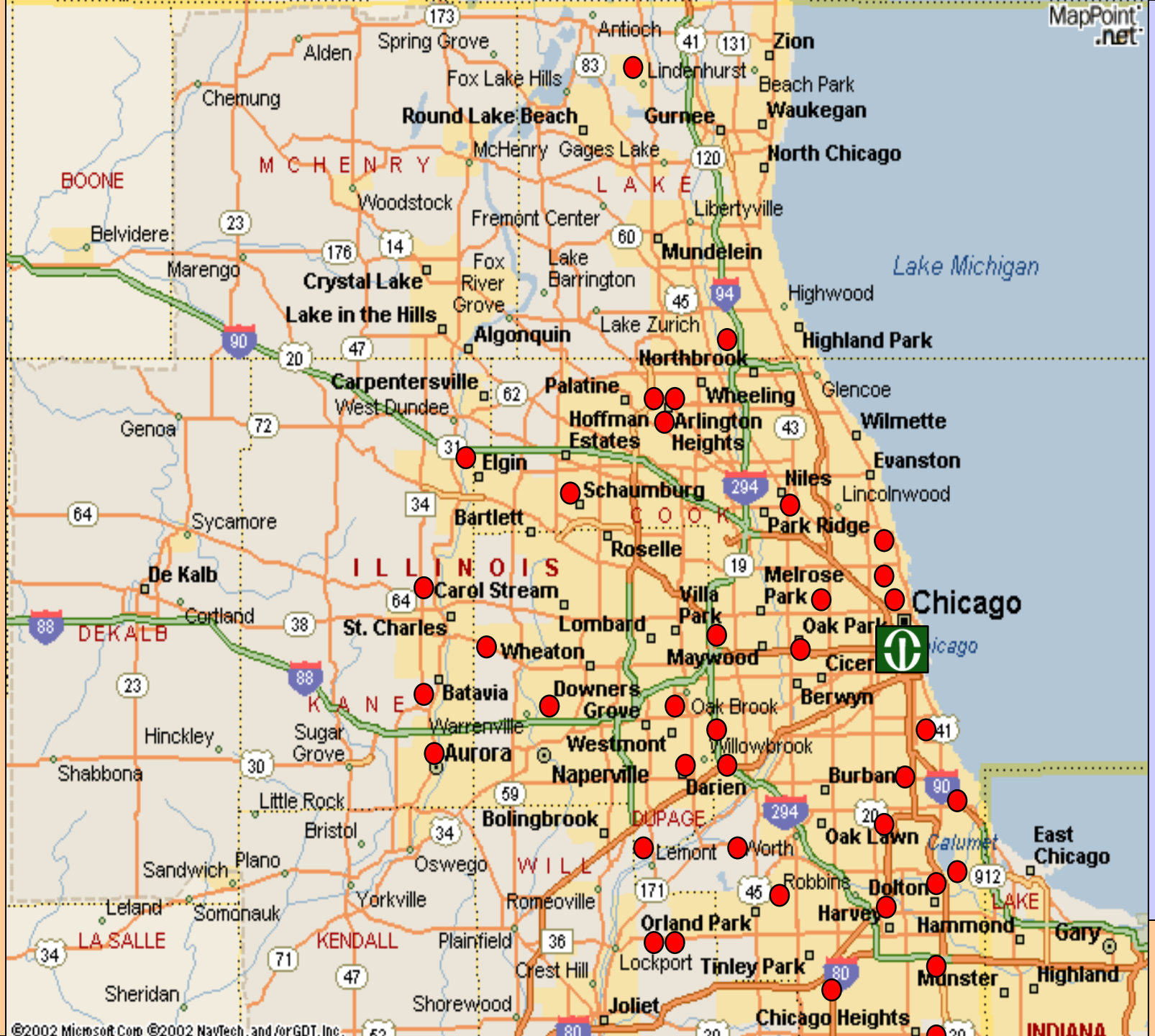
Religious Orders Study: Participating Sites



The Rush Memory and Aging Project

… because memories should last a lifetime

- Community based study with similar methodologies but lay population more reflective of general population - began in 1997
- Residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive/motor testing, blood draws
- All agreed to donate brain, spinal cord, muscle, nerve at the time of death
  F/U rates over 90%
- *Autopsy Rates 80%*
- *>500 autopsies*


MapPoint.net
Antioch
Zion
Lindenhurst
Beach Park
Waukegan
Spring Grove
Alden
Fox Lake Hills
Chemung
Round Lake Beach
Gurnee
North Chicago
McHenry
Gages Lake
M C H E N R Y
L A K E
BOONE
Woodstock
Libertyville
Fremont Center
Belvidere
Mundelein
Lake Michigan
Marengo
Crystal Lake
Fox River Grove
Lake Barrington
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
Carol Stream
Melrose Park
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
Darien
Burbank
Shabbona
Little Rock
Bolingbrook
D U P A G E
Oak Lawn
Calumet
East Chicago
Bristol
Lemont
Worth
Sandwich
Plano
Oswego
W I L L
Robbins
Dolton
LAKE
Yorkville
Romeoville
Harvey
Hammond
Gary
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Annual visits

- Interviews, Scales for depression, diet, decision making etc.
- Medical histories, Neurologic Exams, Neuropsych testing

- Clinical testing for cognition

- **Episodic Memory**: immediate and delayed recall Story A, WMS-R; immediate and delayed recall East Boston Story; Word List Memory, Recall and Recognition

- **Semantic Memory:** Verbal Fluency; Boston Naming; Vocabulary Test; National Adult Reading Test

- **Working Memory**: Digit Span forward/backward; Digit Ordering; Alpha Span

- **Perceptual Speed**: Symbol Digit Modalities Test; Number Comparison

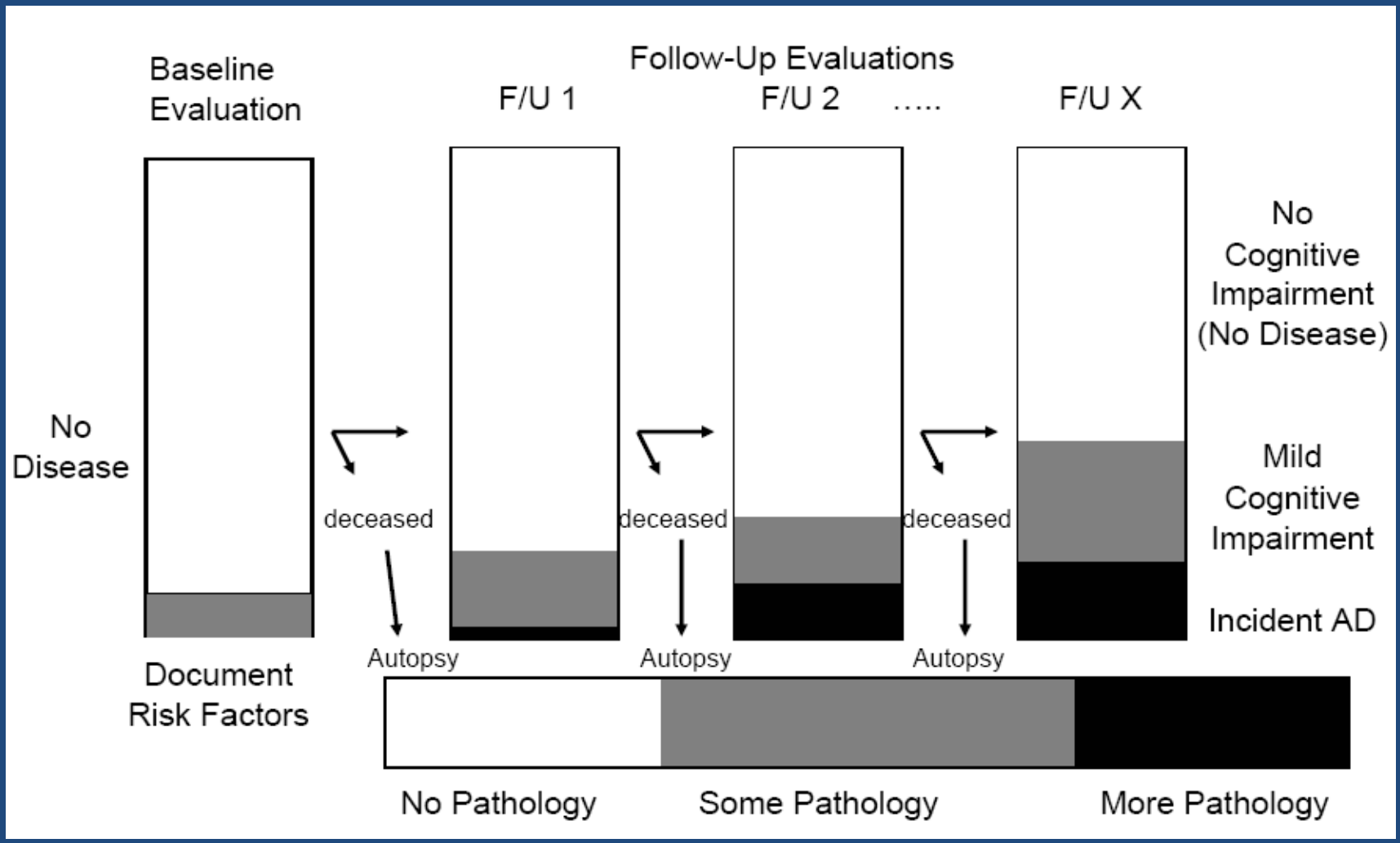
- **Visuospatial Ability**: Line Orientation; Progressive Matrices

Grouped to form a measure of overall cognitive function (global cognitive score)

Clinical diagnoses

- Neuropsychologist reviews neuropsychological test results
- Clinician with expertise in evaluation of older persons with and without dementia makes diagnostic classification of dementia and AD, according to current criteria
- At death, a board-certified neurologist with expertise in dementia reviews all clinical data (baseline and all annual follow-up data), blinded to postmortem data, and renders most likely clinical diagnosis proximate to death

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



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

Brain autopsies and AD Neuropathology

- Hemispheres cut into 1 cm slabs using a Plexiglas jig.
- Paraformaldehyde-fixed/paraffin-embedded/6µm sections

- **Pathologic Dx of AD** – using Bielschowsky/frontal, temporal, parietal, entorhinal, and hippocampal cx –

- Path diagnosis of AD present if intermediate/high likelihood AD by NIA– Reagan criteria (blinded to age/clinical/diagnostic data); at least moderate neocortical neuritic plaques and at least Braak III/IV

  - **Summary measure of AD pathology** using NP, DP, NFT counts from 5 regions and converting into standardized score

  - Molecularly specific amyloid load and tau tangle densities also performed

*AD pathology (NP and NFT) is moderately to strongly related to cognition/dementia; over 87% of those with clinical dx of probable AD have dx confirmed by pathology

Inter-individual variation in the expression of AD pathology

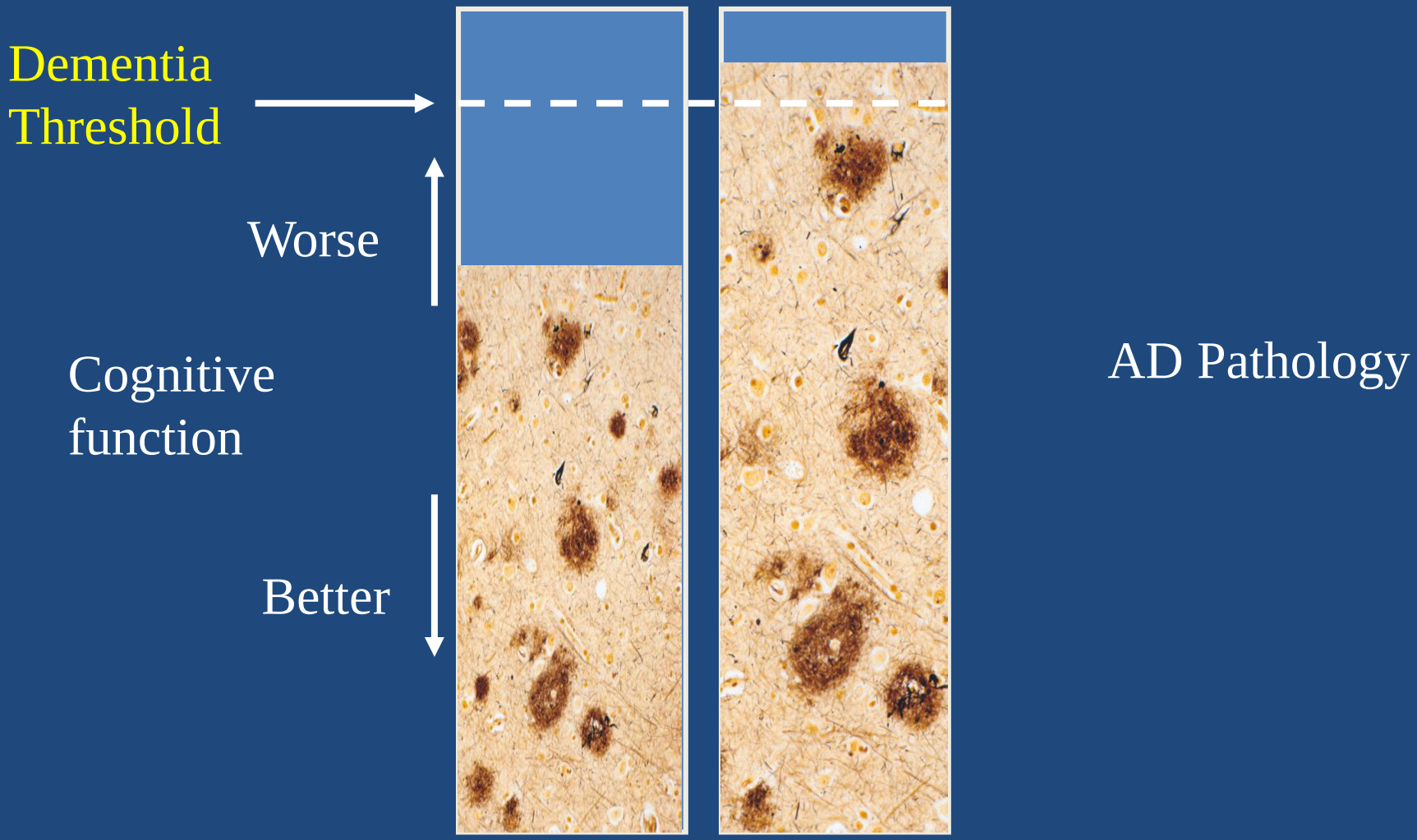
Normal Aging

- AD pathology also very common
- ~ 1/3 have sufficient path for pathologic dx of AD
- More subjective memory complaints and/or lower episodic memory than persons without the path diagnosis of AD

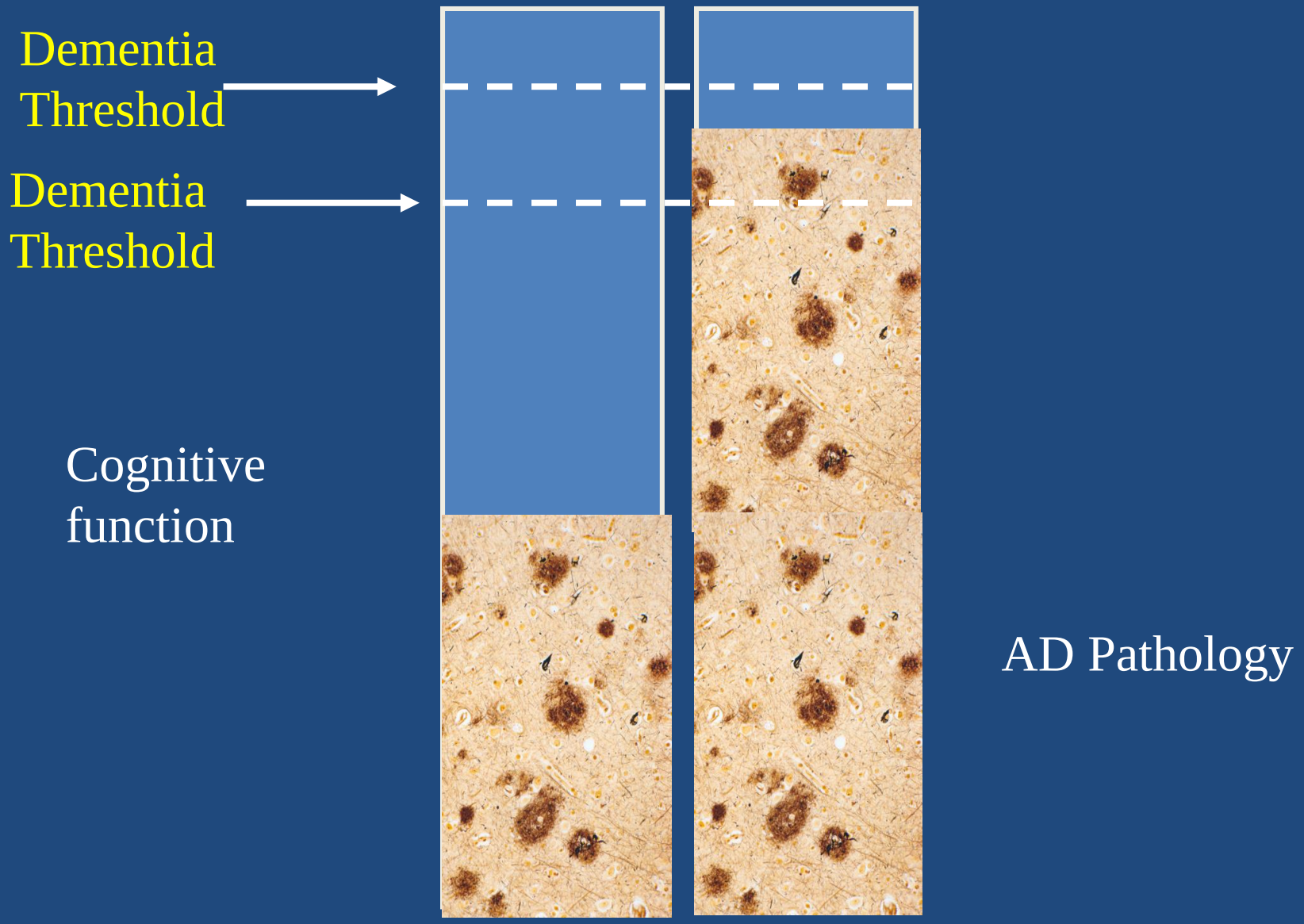
Mild Cognitive Impairment

- AD pathology is intermediate between normals and demented
- About ½ with sufficient pathology for a dx of AD but ~ 1/3 having no neocortical neuritic plaques; ~ 20% with Braak 1/2.

* Dementia and the accumulation of AD pathology and reserve



Dementia threshold and reserve

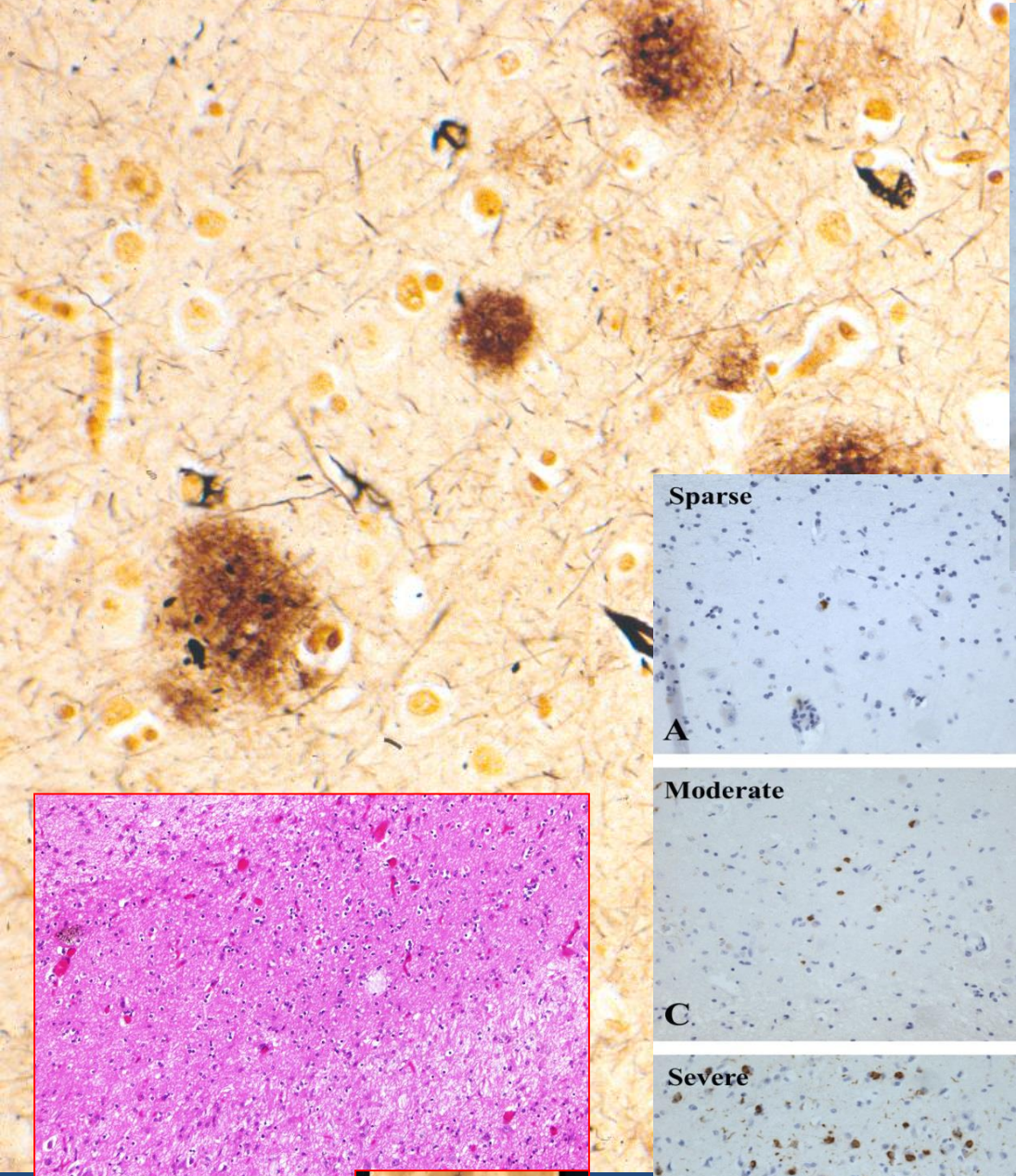


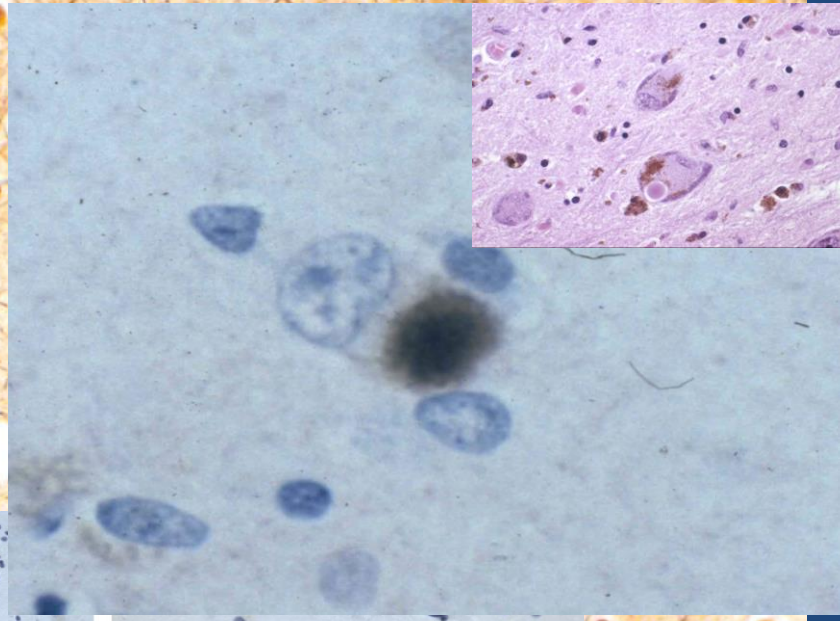
Neural Reserve

- 1/3 of older persons have sufficient AD pathology in brain to fulfill criteria for pathologic diagnosis of AD

- Those factors related to “reserve”
  - Education and Cognitive activities
  - Social, physical activity
  - Depression
  - Well-being/purpose in life
  - Diet
  - Genetic factors

  - Other age-related pathologies in the brain





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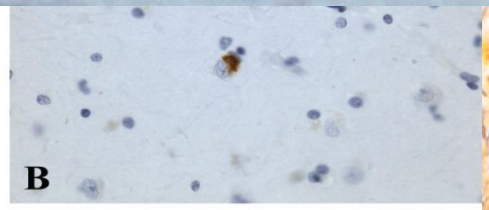
A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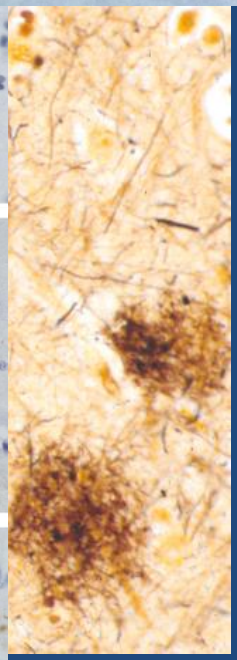
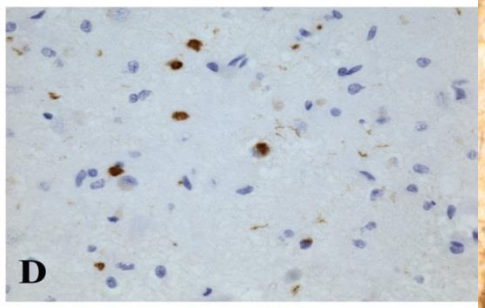


Moderate
C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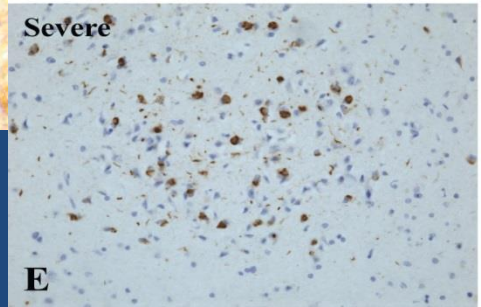
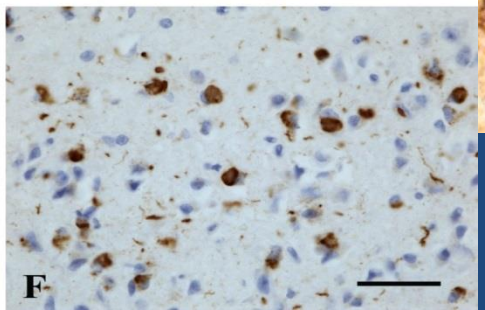

Severe
E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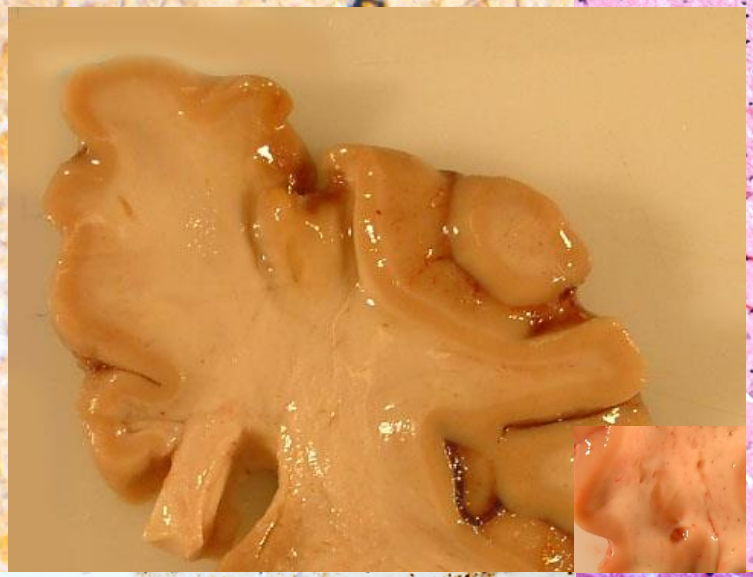
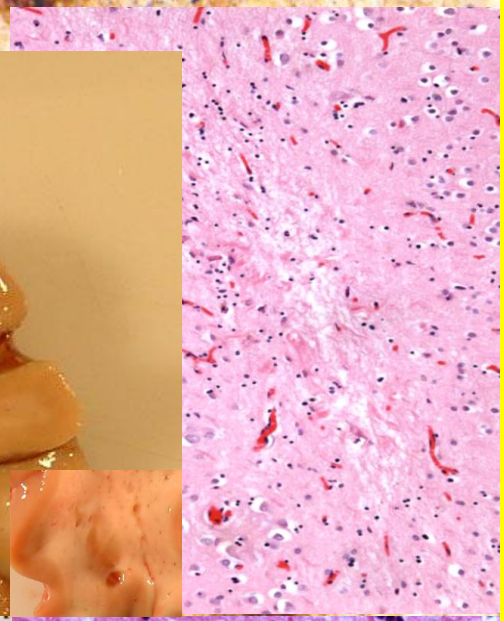
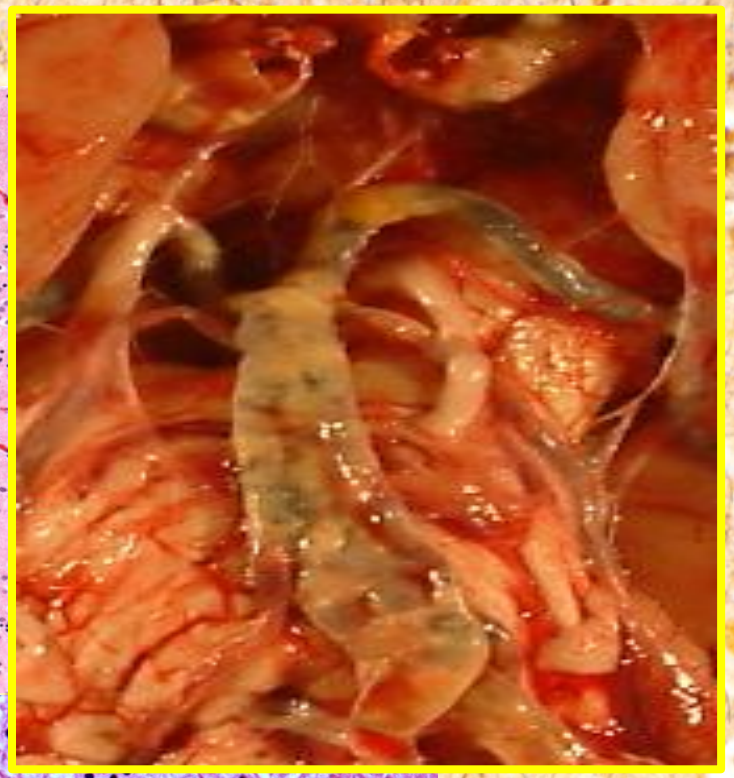
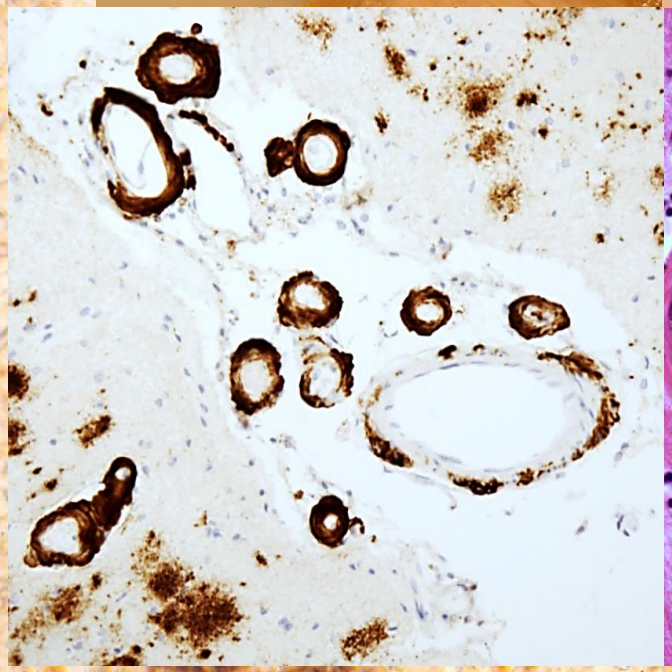
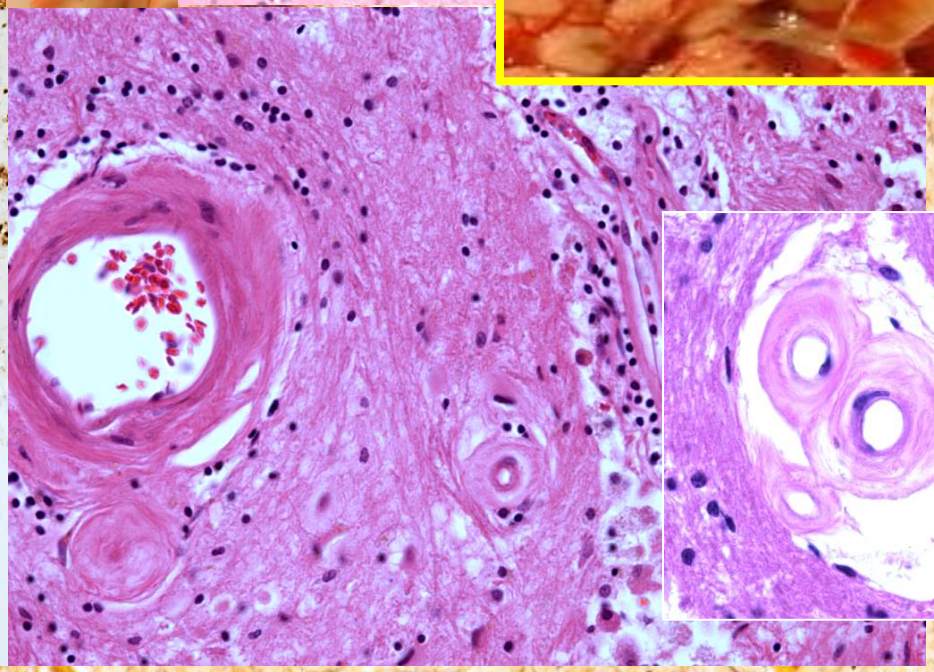










Pathologies that coexist with Alzheimer's disease pathology

Data from Rush Memory and Aging Project and Religious Orders Study - over 1100 community-dwelling older persons followed prospectively with high f/u, autopsy rates, cognitive function annually and proximate to death.

Pathologies in addition to AD in older persons

- Vascular (5)
  - gross infarcts
  - Microinfarcts
  - Atherosclerosis
  - Arteriolosclerosis
  - Cerebral amyloid angiopathy

- Neurodegenerative (3)
  - Lewy bodies
  - Hippocampal sclerosis
  - TDP-43

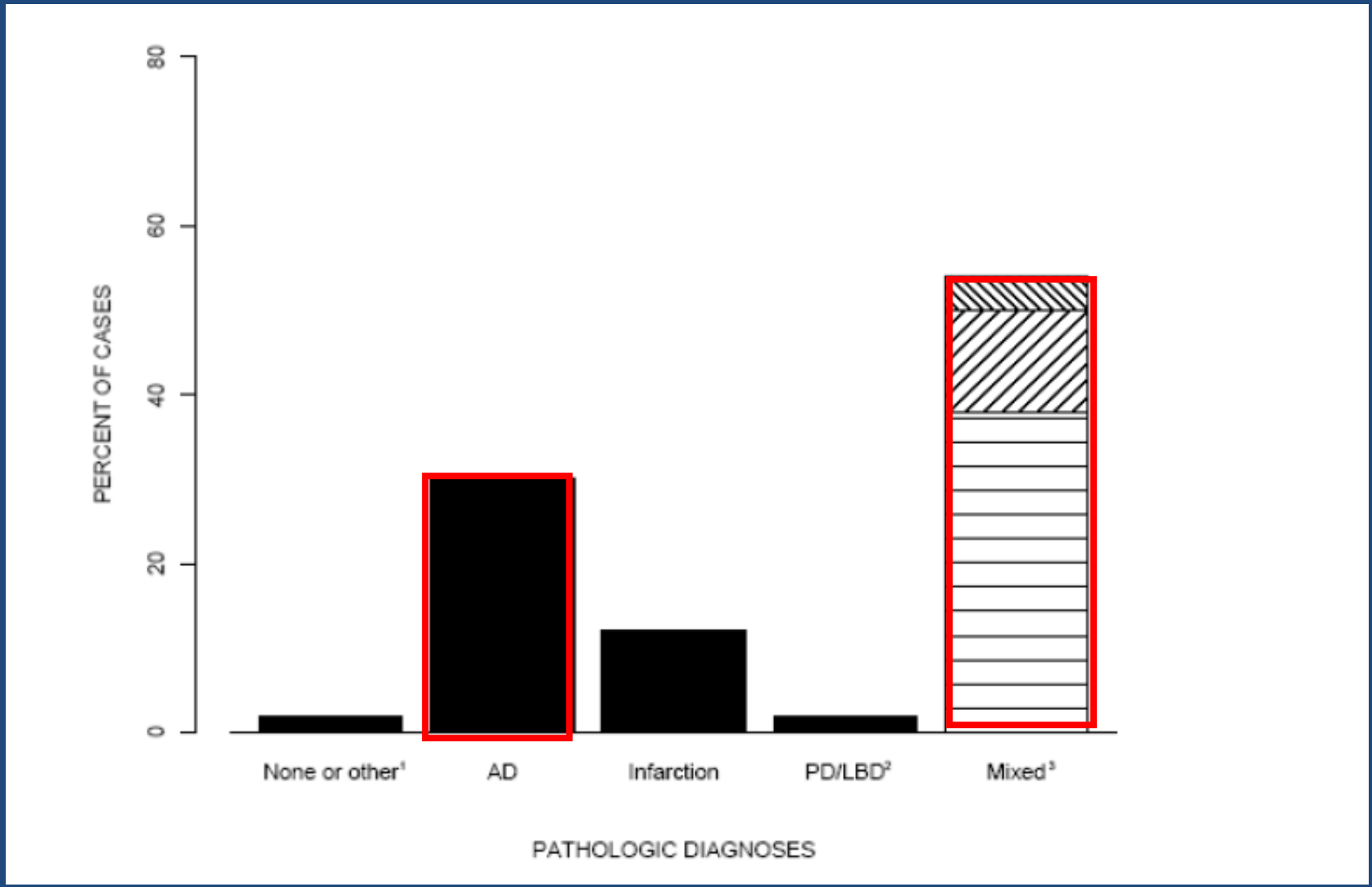
Frequency of different pathologies for dementia in older persons

1. Alzheimer's disease
2. Vascular
3. TDP-43 pathology
4. Lewy body
5. Hippocampal sclerosis

Mixed pathology in community-dwelling older subjects with dementia is more common than a single pathology

- 141 autopsies from the Memory and Aging Project –
  91 no dementia; 50 dementia
- Over 80% of cohort had chronic brain abn.
- Mixed pathologies more common than single in dementia
- Dementia; AD alone (n=15; 30%); AD + other path (n=25;50%)
  - AD + Cerebral infarcts (n=21) (42%)

Mixed brain pathologies in dementia – common in dementia



Rush Memory and Aging Project

Schneider JA et al. *Neurology* 2004;62:1148-1156.

Mixed brain pathologies in probable AD and MCI

- - 483 autopsied participants from the Religious Orders Study and the Rush Memory and Aging Project
  - probable AD,
  - MCI (amnestic and nonamnestic)
  - No cognitive impairment.
  - Excluded 41 persons with clinically possible AD and 14 with other dementias.
  - We documented the neuropathology of AD (National Institute on Aging-Reagan criteria), macroscopic cerebral infarcts, and neocortical Lewy body (LB) disease.

- 179 persons (average age, 86.9 years) with probable AD
  - 87.7% had pathologically confirmed AD
  - 45.8% had mixed pathologies,
    - most commonly AD with macroscopic infarcts (n = 54)
    - followed by AD with neocortical LB disease (n = 19)
    - and both (n = 8).

Mixed brain pathologies common in MCI and probable AD

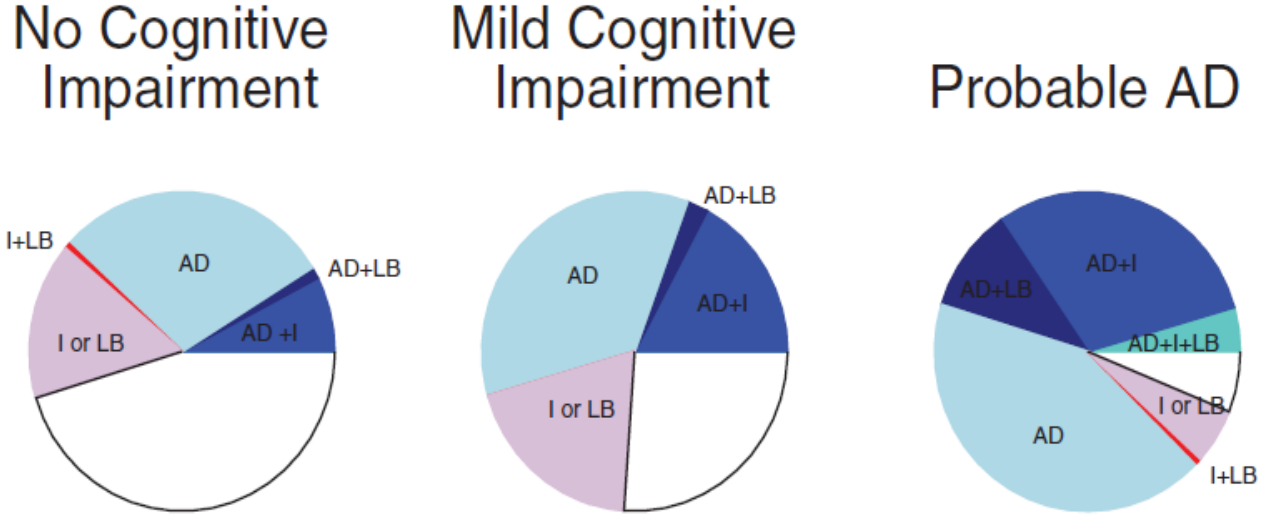


*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral infarcts (I); aqua = pathologic diagnosis of AD, I, and LB. (*Red shades*) I and/or LB (with no pathologic diagnosis of AD). Clockwise: pink = I or LB; red = I and LB. (*White*) No pathologic diagnosis of AD, no I, no LB.*

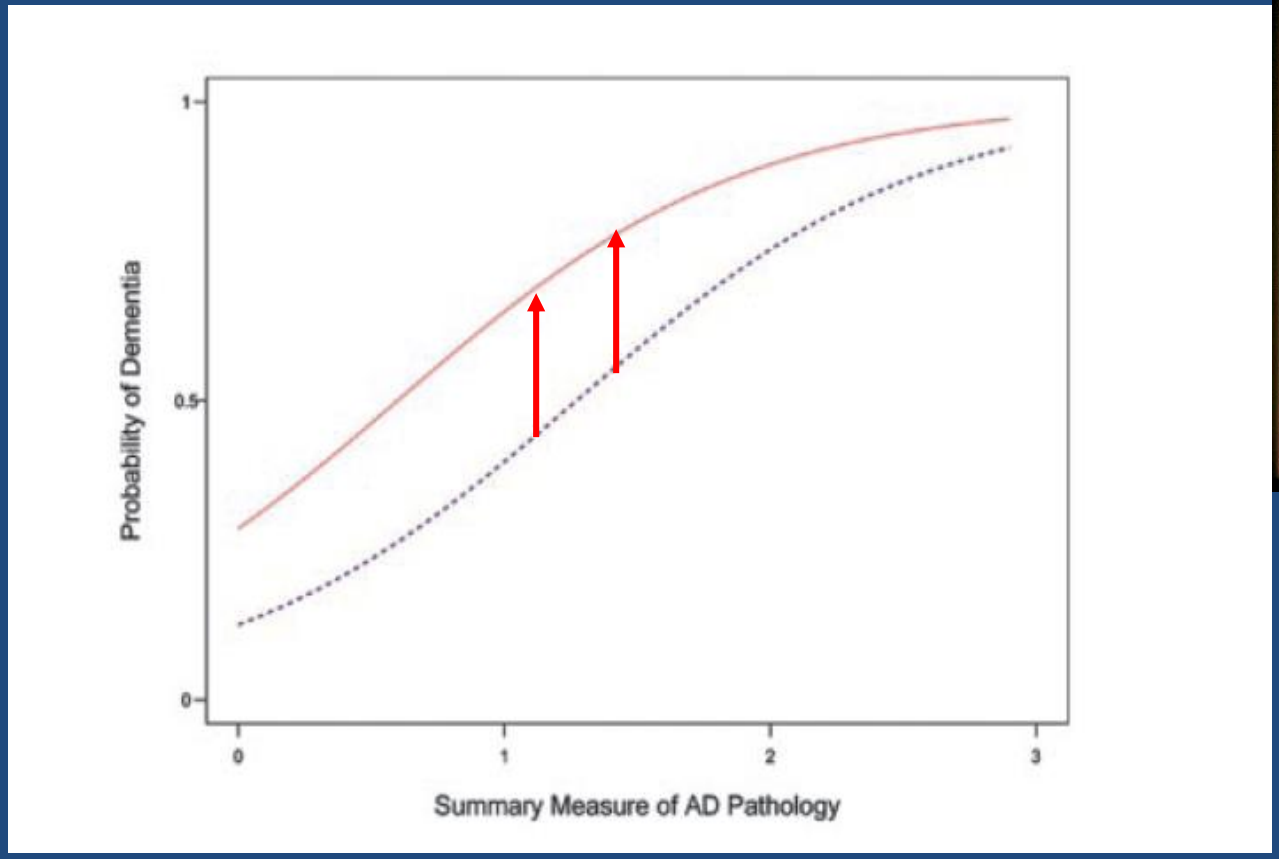
Schneider JA et al. *Ann Neurol* 2009;66:200–208.

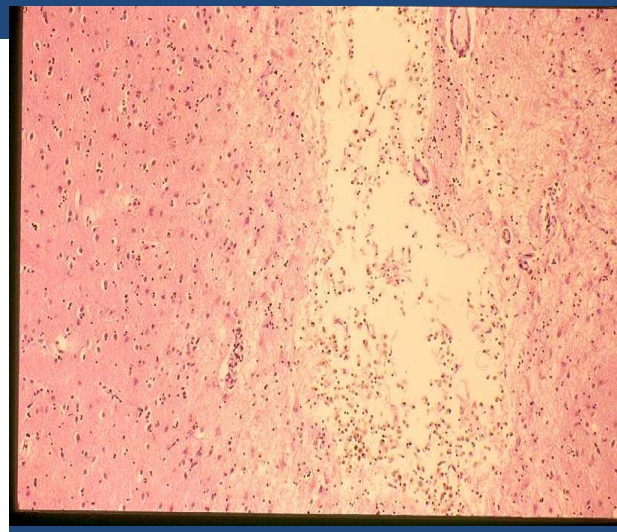
*** Estimates do not include vascular path other than gross infarcts**

**** Estimates do not include milder amounts of AD pathology**

Common – yes but are they bad for you??? YES!

Macroscopic infarcts increase odds dementia <u>at each level of AD pathology</u>
Worsens cognition/lowers threshold for dementia





Schneider JA et al.
Neurology
2004;62:1148-1156.

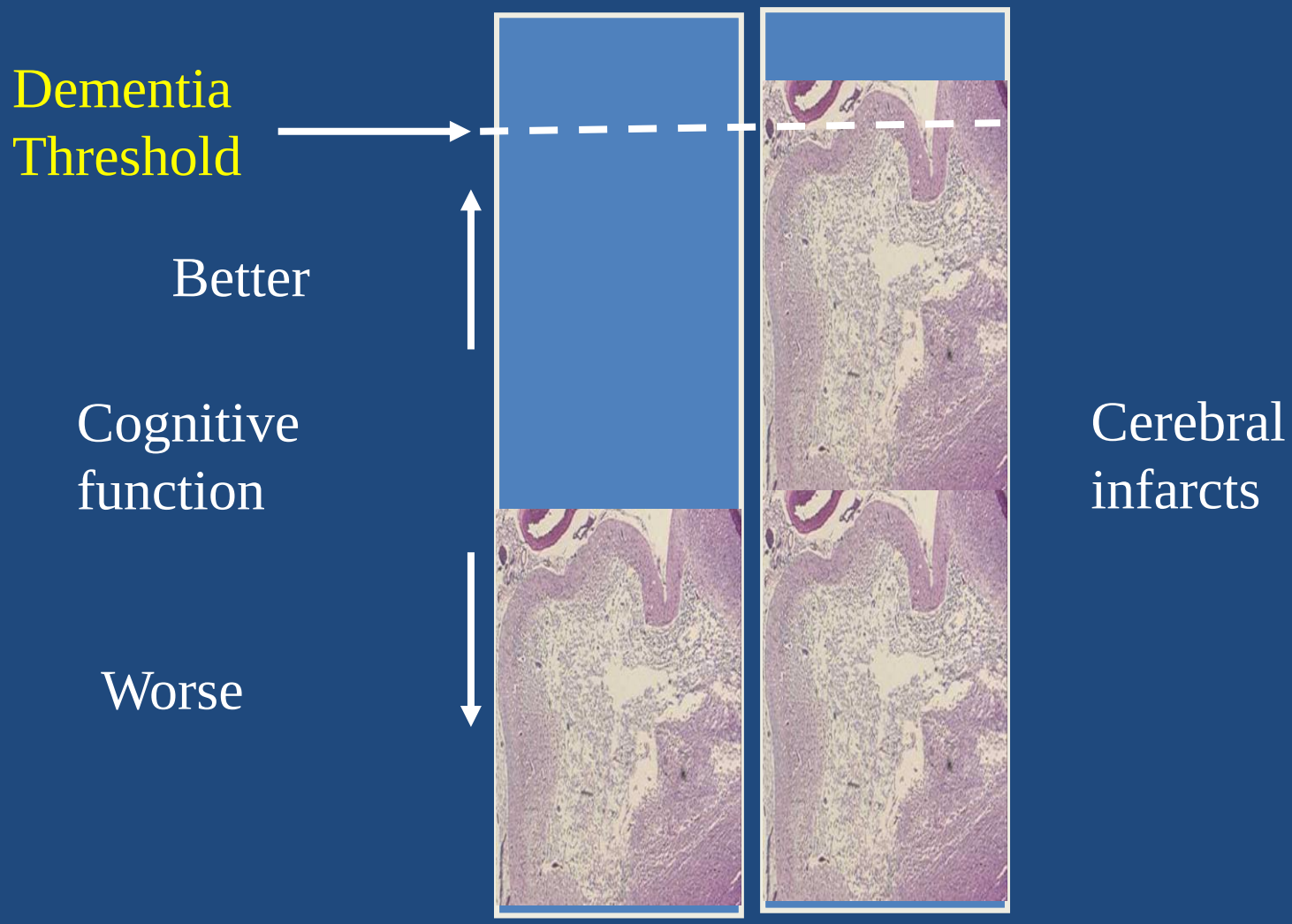
Cerebral infarcts affect Memory after controlling for AD path

Table 5 *AD pathology/macroscopic cerebral infarctions and cognitive domain scores*

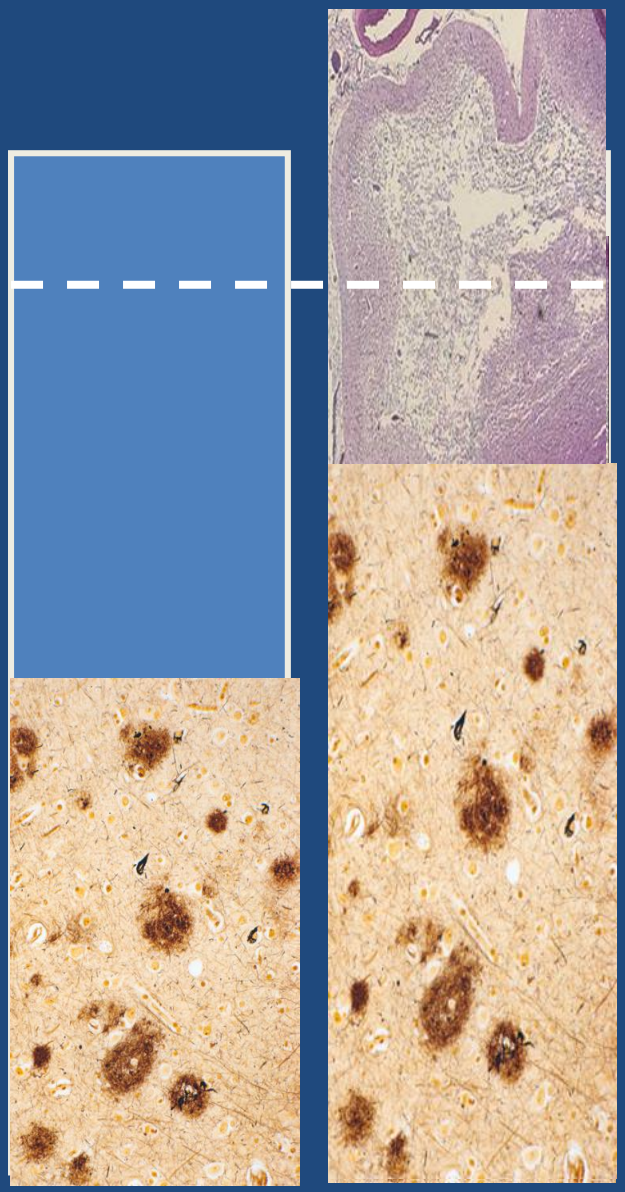
Models*	Parameter estimates for cognitive domain scores (p value)				
	Episodic memory	Working memory	Semantic memory	Perceptual speed	Visuospatial abilities
1. One unit of AD pathology	−0.96	−0.36	−0.56	−0.56	−0.29
	(<0.0001)	(0.0009)	(0.0005)	(<0.0001)	(0.009)
2. One unit of AD pathology	−0.99	−0.37	−0.58	−0.61	−0.31
	(<0.0001)	(0.0004)	(0.0002)	(<0.0001)	(<0.006)
Presence of macroscopic infarctions	−0.48	−0.25	−0.44	−0.80	−0.39
	(0.02)	(0.08)	(0.04)	(<0.0001)	(<0.01)

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

Schneider JA et al. *Neurology* 2004;62:1148-1156.


Dementia
Threshold
Better
Cognitive
function
Worse
Cerebral
infarcts

Dementia Threshold



Cognitive function

Cerebral infarction

AD Pathology

3BS.001

Tip of the iceberg….

- Microinfarcts
- Large vessel disease (Atherosclerosis)
- “Small vessel disease”
  - Arteriolosclerosis,
  - cerebral amyloid angiopathy
  - Atherosclerosis (small vessels)
  - White matter changes (partially)

More vascular pathology than just gross infarcts..

- **Chronic macroscopic infarcts** - slabs inspected for infarcts and other pathology; all suspected infarcts microscopically confirmed

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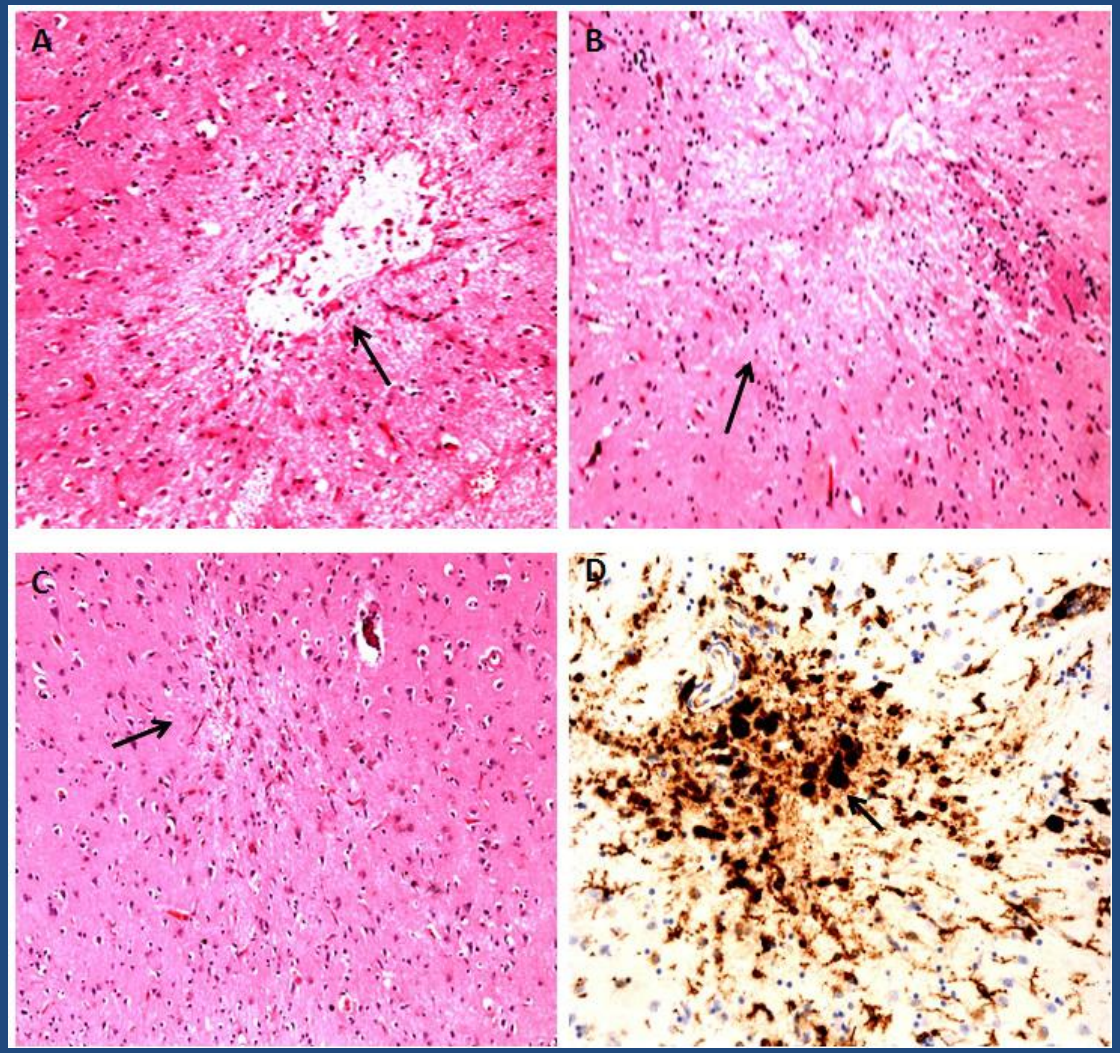
- Microscopic infarcts – examination of 6 cortical regions, 2 subcortical and 1 brainstem
- Lipohyalinosis/arteriolosclerosis – amorphous hyalinized thickening of arterioles; semiquant. none -severe)
- Amyloid angiopathy –anti-amyloid-β; semiquant scale
- Atherosclerosis – judged at circle of willis; semiquant scale

Microscopic infarcts – “invisible lesions”

- Infarcts that are too small to be seen by the naked eye on gross examination of the brain

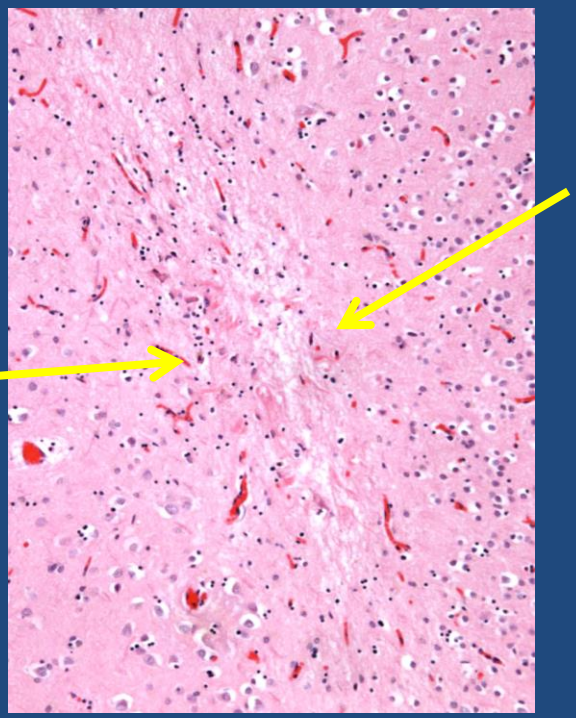


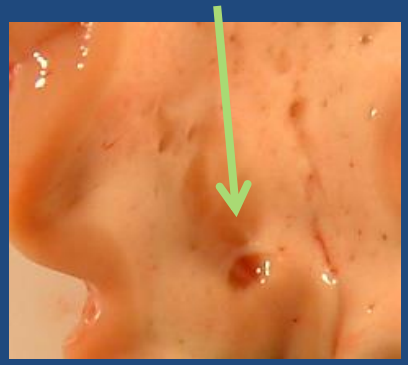
Smith E. et al. The invisible lesions. Lancet Neurology 2012

Pathology Nomenclature (differs from neuroimaging)

Not seen grossly → May be seen grossly

Microscopic infarcts Smallest diameter about 100um microns	1mm	2 mm	3 mm	GROSS INFARCTS >3 mm





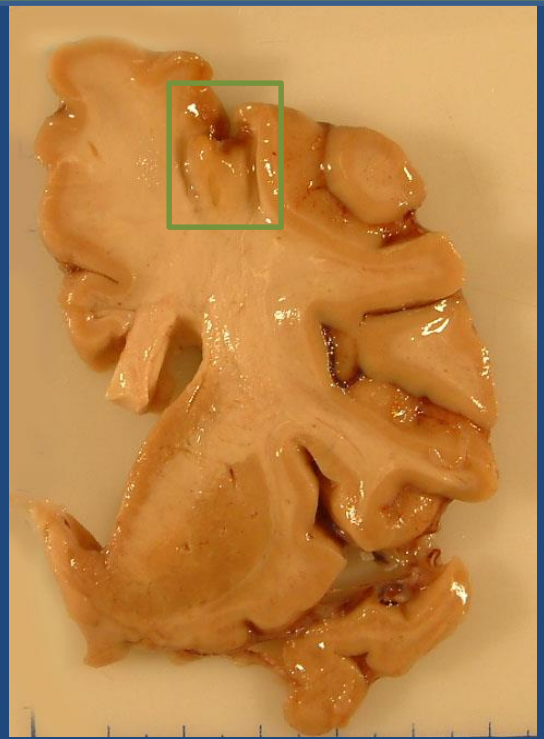


Table 1. Characteristics* of Subjects

	Dementia (n=192)	No Dementia (n=233)	OR (95% CI)†	Total n=425
Clinical				
Age at death, y	88.7 (6.5)	84.6 (6.8)	1.10 (1.06–1.13)	86.5 (7.0)
Male, n (%)	67 (35)	100 (43)	0.71 (0.48–1.06)	167 (39)
Education, y	17.7 (3.3)	18.2 (3.6)	0.96 (0.91–1.01)	18.0 (3.5)
Mini-Mental State Examination score	14.1 (8.6)	27.3 (3.0)	0.60 (0.53–0.66)	21.4 (9.0)
Pathological				
Microinfarct present, n (%)	70 (36.5)	59 (25.3)	1.69 (1.12–2.57)	129 (30.4)
N				
1, n	41	39	1.35 (0.83–2.20)	80
>1, n	29	20	1.89 (1.03–3.47)	49
Location				
Cortical, n	27	27	1.25 (0.71–2.21)	54
Subcortical, n	44	36	1.63 (0.997–2.65)	80
Brainstem/cerebellum, n	13	7	2.34 (0.92–6.0)	20
Macroscopic infarct present, n (%)	89 (46.4)	64 (27.5)	2.28 (1.52–3.42)	153 (36)
AD pathology score	1.0 (0.7)	0.5 (0.5)	4.11 (2.82–5.99)	0.7 (0.7)
Lewy bodies present, n (%)	54 (28.1)	33 (14.2)	2.37 (1.46–3.85)	87 (20.5)

*Mean (SD) unless otherwise indicated.
†Crude (unadjusted) OR for dementia and 95% CI.

Arvanitakis Z et al. Stroke 2011,42:722-727

Not only common but bad for you!

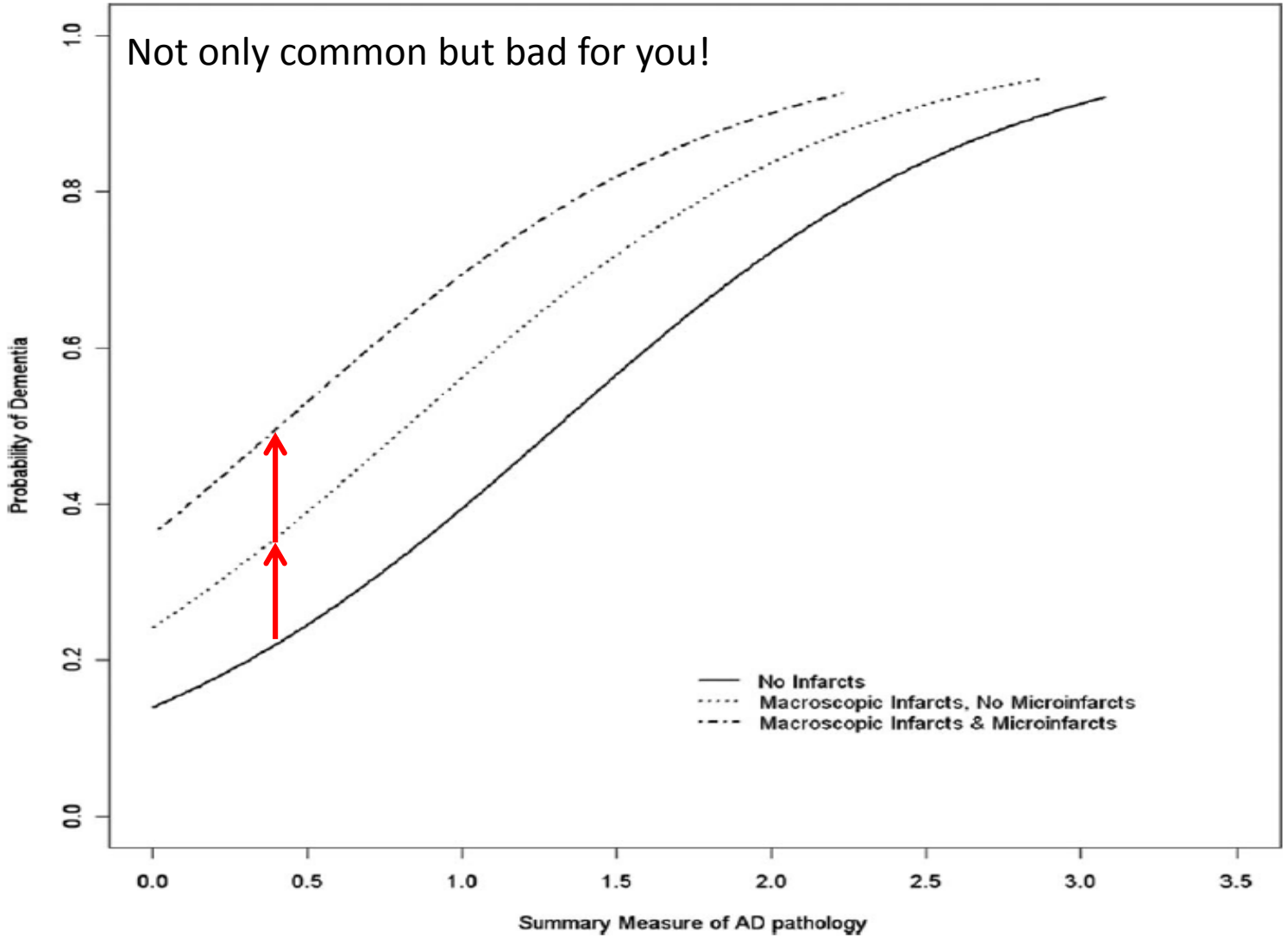


Figure 1. Probability of dementia by Alzheimer disease pathology showing additive effects of macroscopic infarcts and microinfarcts.

Arvanitakis Z et al. Stroke 2011,42:722-727

Number of microinfarcts

- **“Estimating Cerebral Microinfarct Burden From Autopsy Samples” (Westover et al.)**

  developed a simple mathematical method to estimate the total number of cerebral microinfarcts from counts obtained in the small amount of tissue routinely examined in brain autopsies.

“finding one cockroach in your kitchen means there are hundreds in your wall,”

# Microinfarcts	0	1	2	3	4	5	6	7	8	9
# Cases	475	111	42	11	7	1	0	0	0	1
% Cases	73.30	17.13	6.48	1.70	1.08	0.15	0.0	0	0	0.15
MLE	0	409	819	1228	1638	2048	2457	2867	3277	3686

How about Vessel pathology?

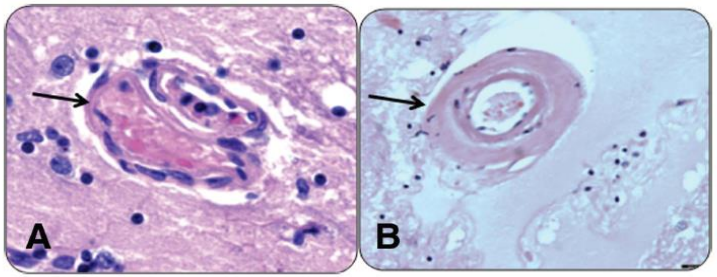
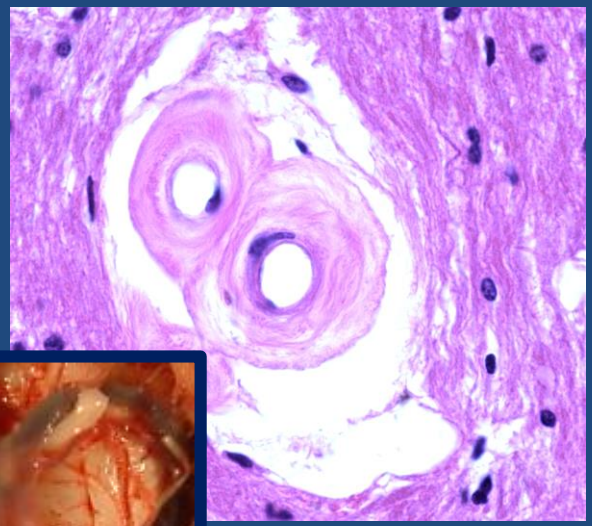
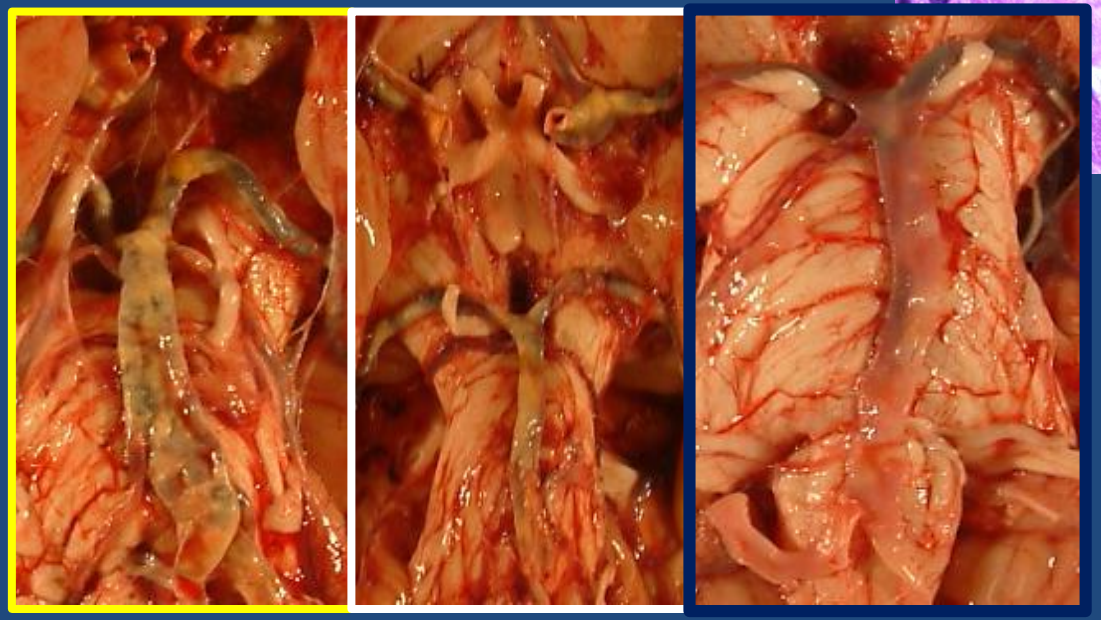


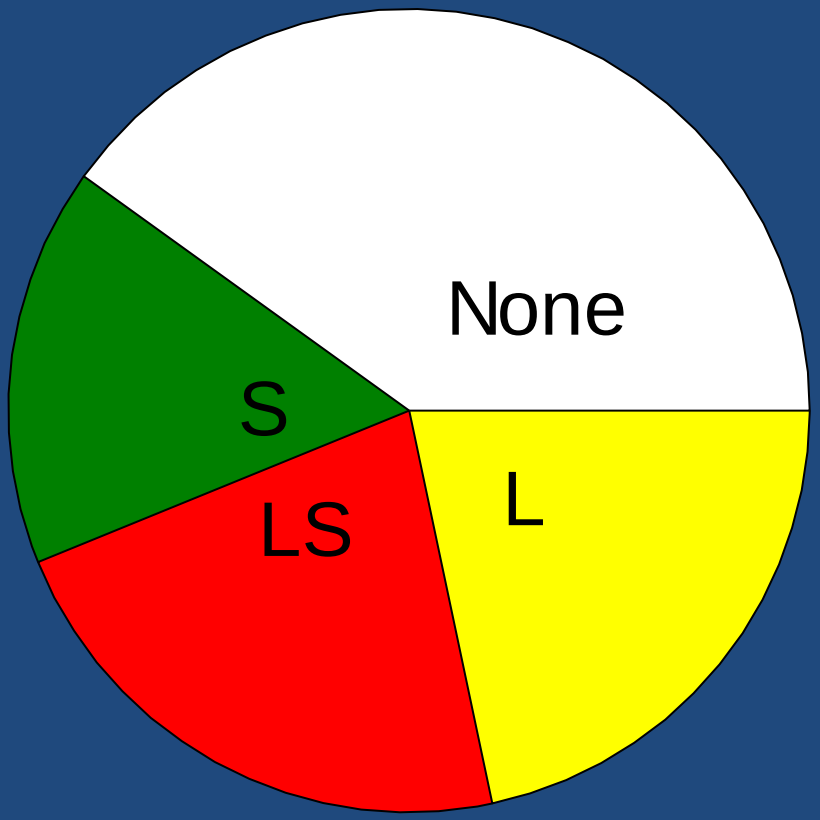
Figure 2. Arteriolosclerosis. The spectrum of small vessel changes in cases of arteriolosclerosis. On the left (**A**), an hematoxylin and eosin stain of a normal vessel (arrow). On the right (**B**) is an example of severe arteriolosclerosis (arrow).





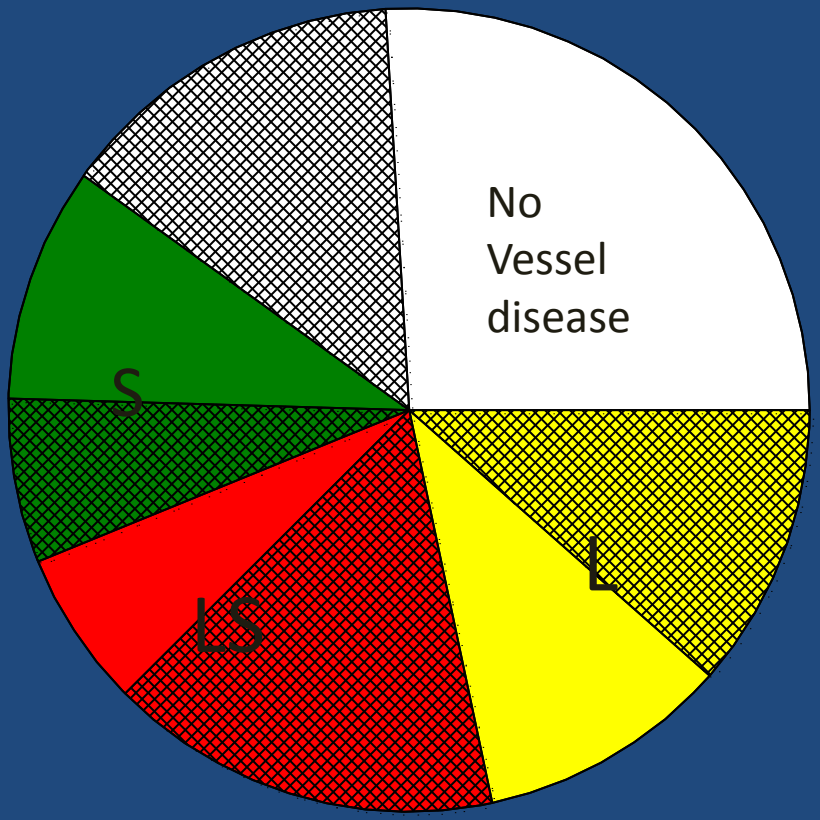
Number of subjects	1, 125
DEMOGRAPHIC	
Age at death, years (SD)	88.2 (6.7)
Female, n (%)	727 (65%)
NEUROPATHOLOGIC	
Gross infarct present, n (%)	396 (35%)
Cortical, n (%)	139 (12%)
Subcortical, n (%)	314 (28%)
Microinfarct present, n (%)	322 (29%)
Cortical, n (%)	181 (16%)
Subcortical, n (%)	175 (16%)
Any chronic infarct present, n (%)	545 (48%)
Vessel pathology**	
Atherosclerosis, n (%)	452 (41%)
Arteriosclerosis, n (%)	400 (36%)

Vessel Disease



Vessel Disease, with Infarctions

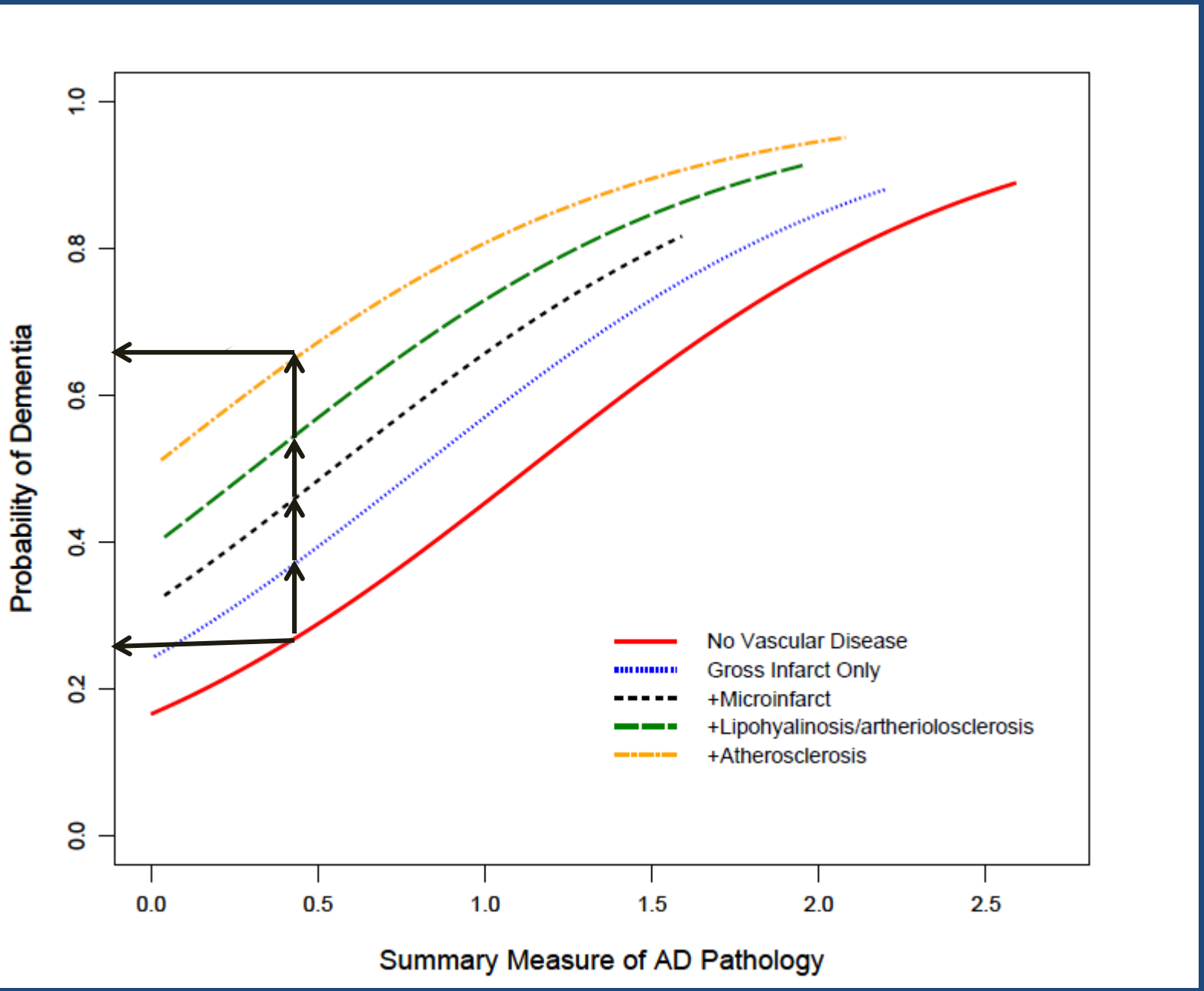
Cross hatches are infarctions



Vascular brain injury/vessel disease and Dementia

Odds of Dementia
(Single model - logistic regression accounting for age, sex, edu, AD & LB pathology)

– **Macroscopic**	**1.60 (1.13- 2.27)**	**p=0.008**
– **Microscopic**	**1.44 (1.01-2.06)**	**p=0.04**
– **Arteriolosclerosis**	**1.19 (1.00-1.40)**	**p=0.04**
– **Atherosclerosis**	**1.24 (1.01-1.53)**	**p=0.04**


Probability of Dementia
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
2.5
Summary Measure of AD Pathology
No Vascular Disease
Gross Infarct Only
+Microinfarct
+Lipohyalinosis/artheriolosclerosis
+Atherosclerosis

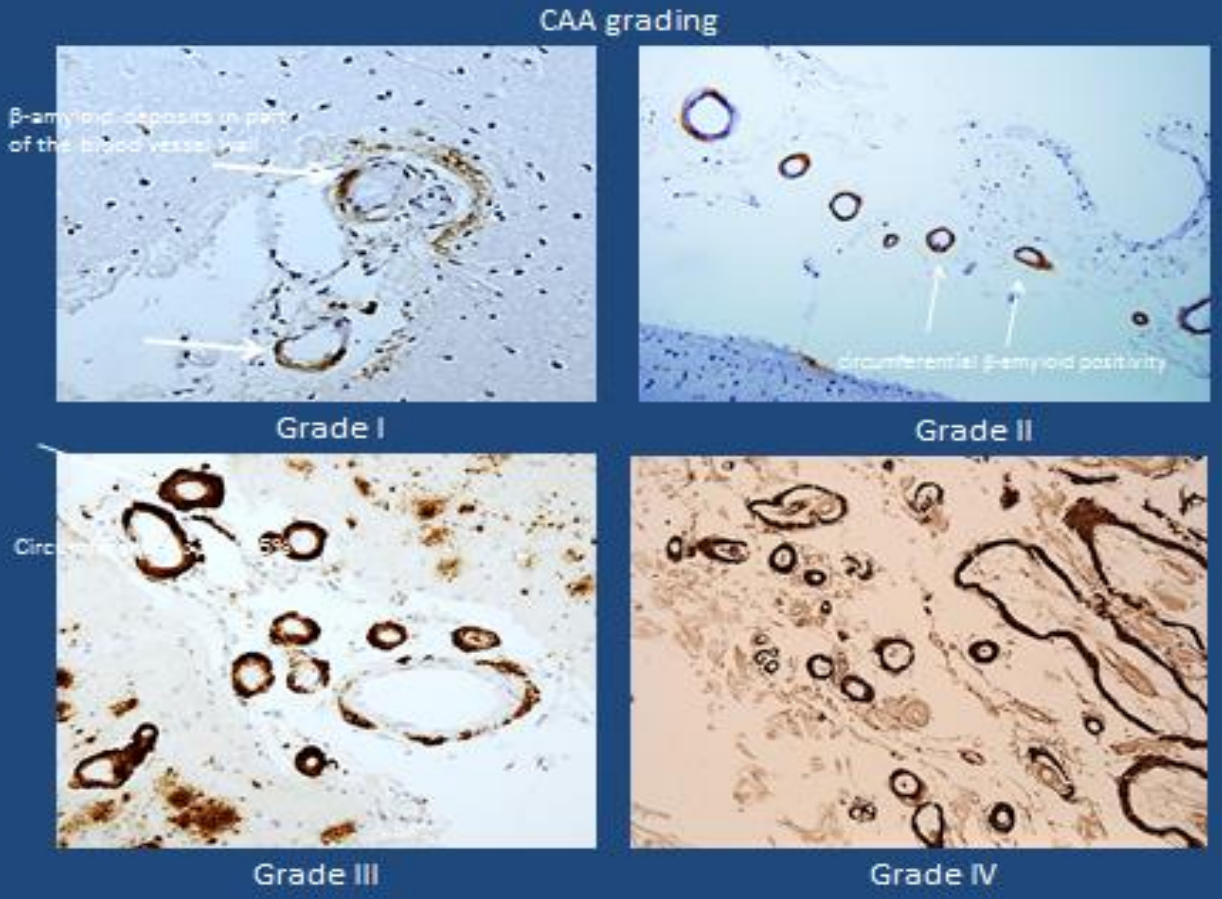
Likelihood of clinical diagnosis of Alzheimer's disease

- Logistic regression controlling for age, sex, education, AD path, Lewy bodies, macro and micro infarcts. Vessel disease is ordinal, 4 levels.

- Macroscopic infarcts OR = 1.6 (p=0.005)
- Microinfarcts OR = 1.4 (p=0.04)

- Atherosclerosis OR= 1.3 (p=.02)
- Arteriolosclerosis OR= 1.3 (p=0.038)

- Cerebral Amyloid Angiopathy, n (%) 379 (35%)

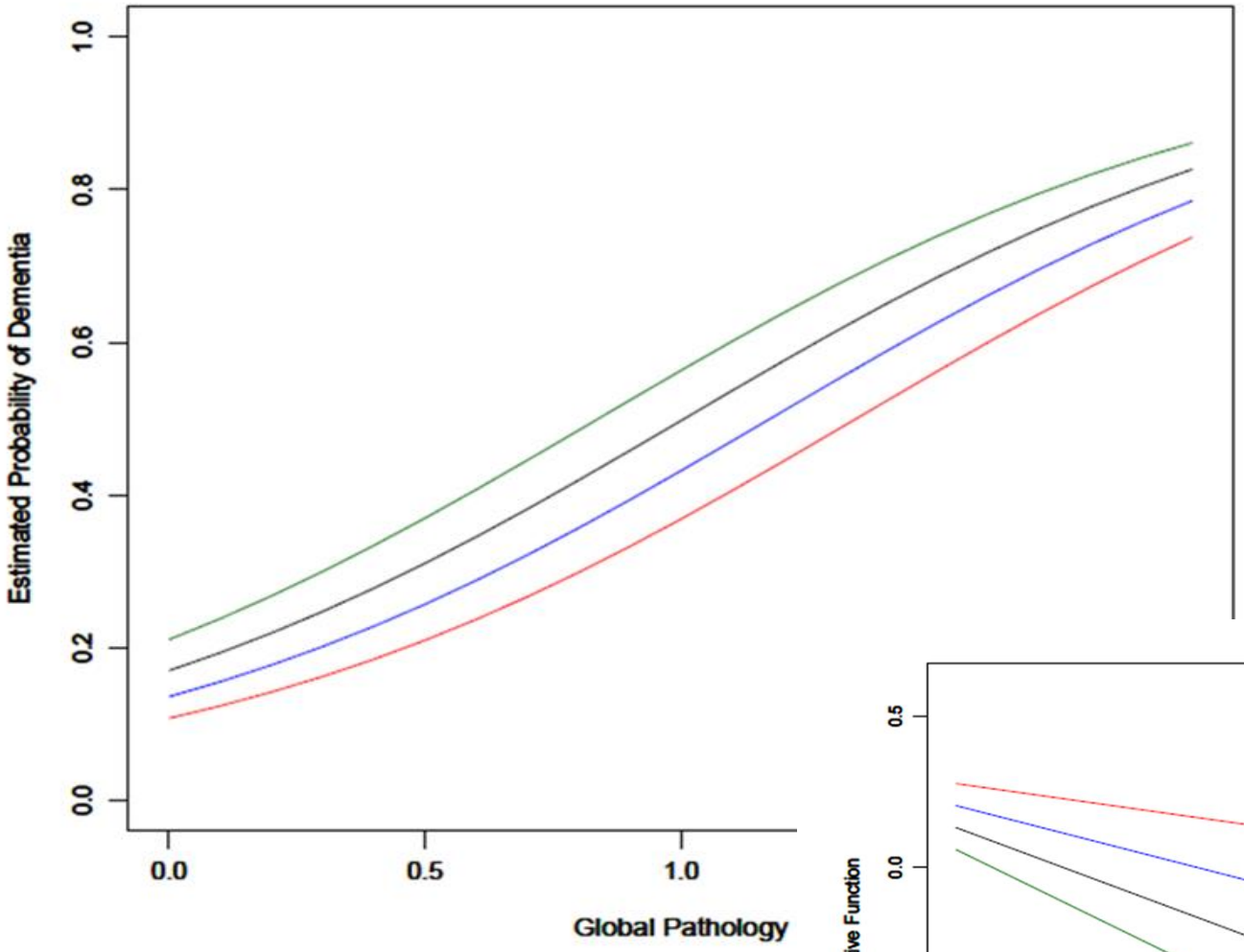


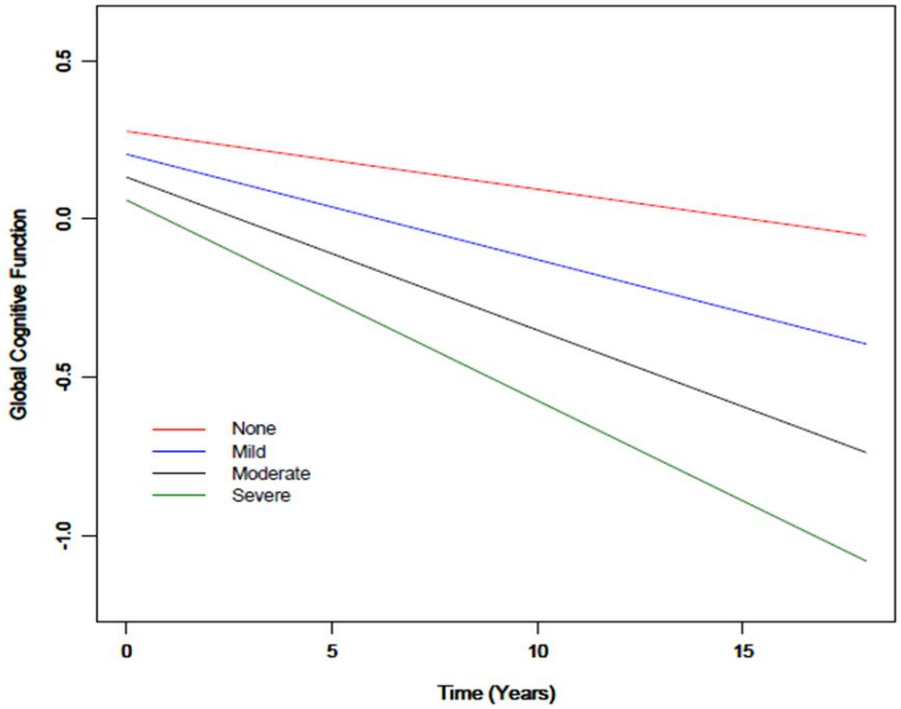
CAA

DEMENTIA

AND

COGNITIVE DECLINE





Boyle et al. submitted

Association of CAA with decline in 5 specific cognitive systems

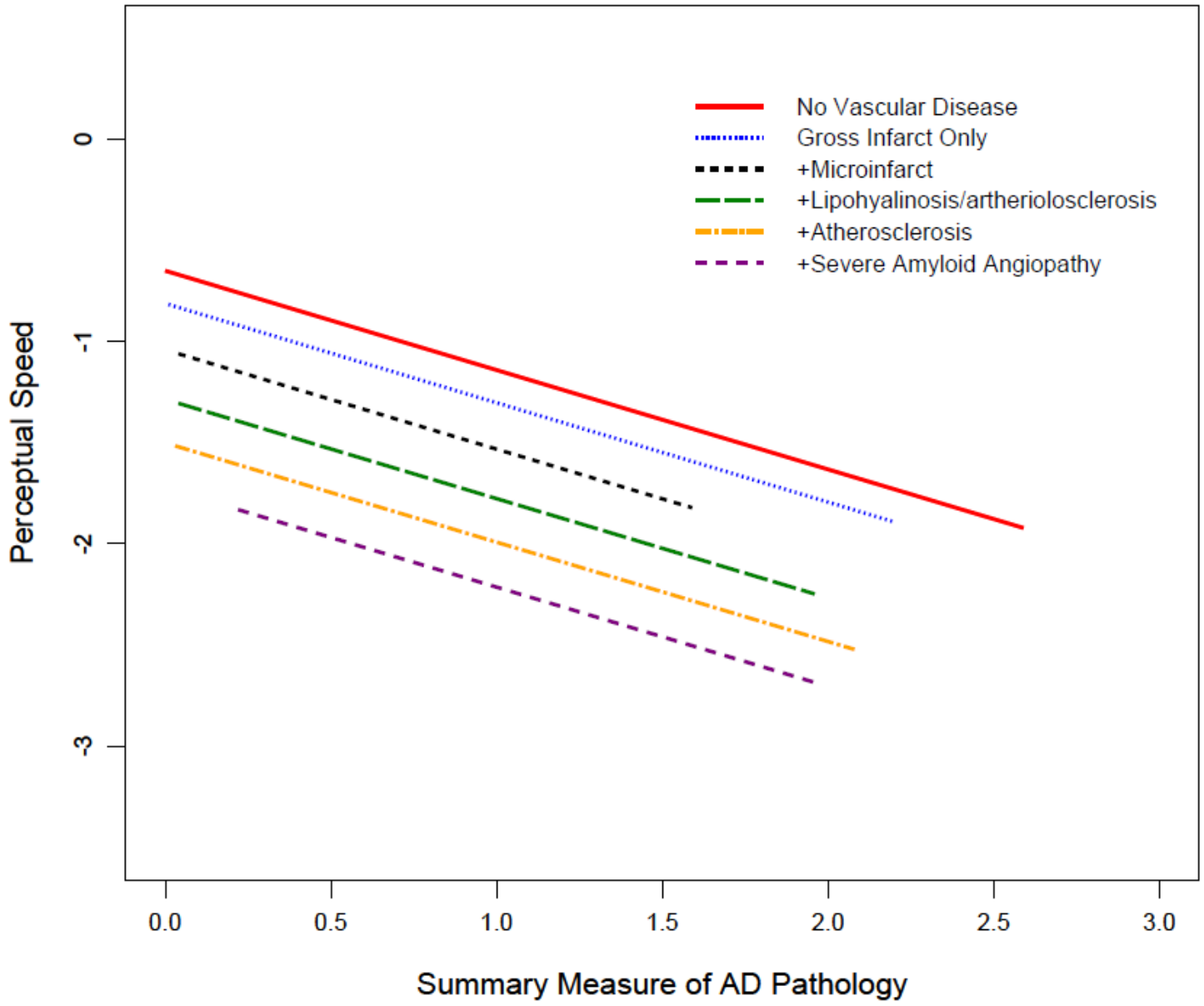
	Episodic Memory beta (SE), p	Perceptual Speed beta (SE), p	Visuospatial abilities beta (SE), p	Working Memory beta (SE), p	Semantic Memory beta (SE), p
Age at death	-.0008 (.0007), 0.290	.0008 (.0007), 0.264	.0007 (.0006), 0.195	-.0002 (.0006), 0.772	.0002 (.0008), 0.837
Male Sex	0.015 (0.010), 0.132	0.018 (0.010), 0.053	0.016 (0.008), 0.033	0.001 (0.008), 0.862	-0.003 (0.011), 0.760
Education	0.0006 (0.001), 0.635	0.001 (0.001), 0.244	-0.00007 (0.001), 0.982	0.001 (0.001), 0.155	0.0006 (0.001), 0.656
AD	-0.115 (0.010), <.0001	-0.076 (0.010), <.0001	-0.050 (0.008), <.0001	-0.072 (0.008), <.0001	-0.117 (0.011), .0001
Macroscopic infarcts	-0.026 (0.006), <.0001	-0.018 (0.006), 0.002	-0.016 (0.005), 0.001	-0.023 (0.005), <.0001	-0.016 (0.007), 0.016
Microinfarcts	-0.001 (0.007), 0.944	-0.008 (0.007), 0.247	-0.001 (0.005), 0.792	-0.003 (0.005), 0.629	-0.007 (0.008), 0.343
Lewy Bodies	-0.037 (0.011), 0.0005	-0.051 (0.010), <.0001	-0.027 (0.008), 0.001	-0.029 (0.008), 0.0005	-0.053 (0.012), <.0001
CAA	**-0.014 (0.004), 0.001**	**-0.011 (0.004), 0.014**	**-0.006 (0.004), 0.105**	**-0.007 (0.004), 0.062**	**-0.022 (0.005), <.0001**

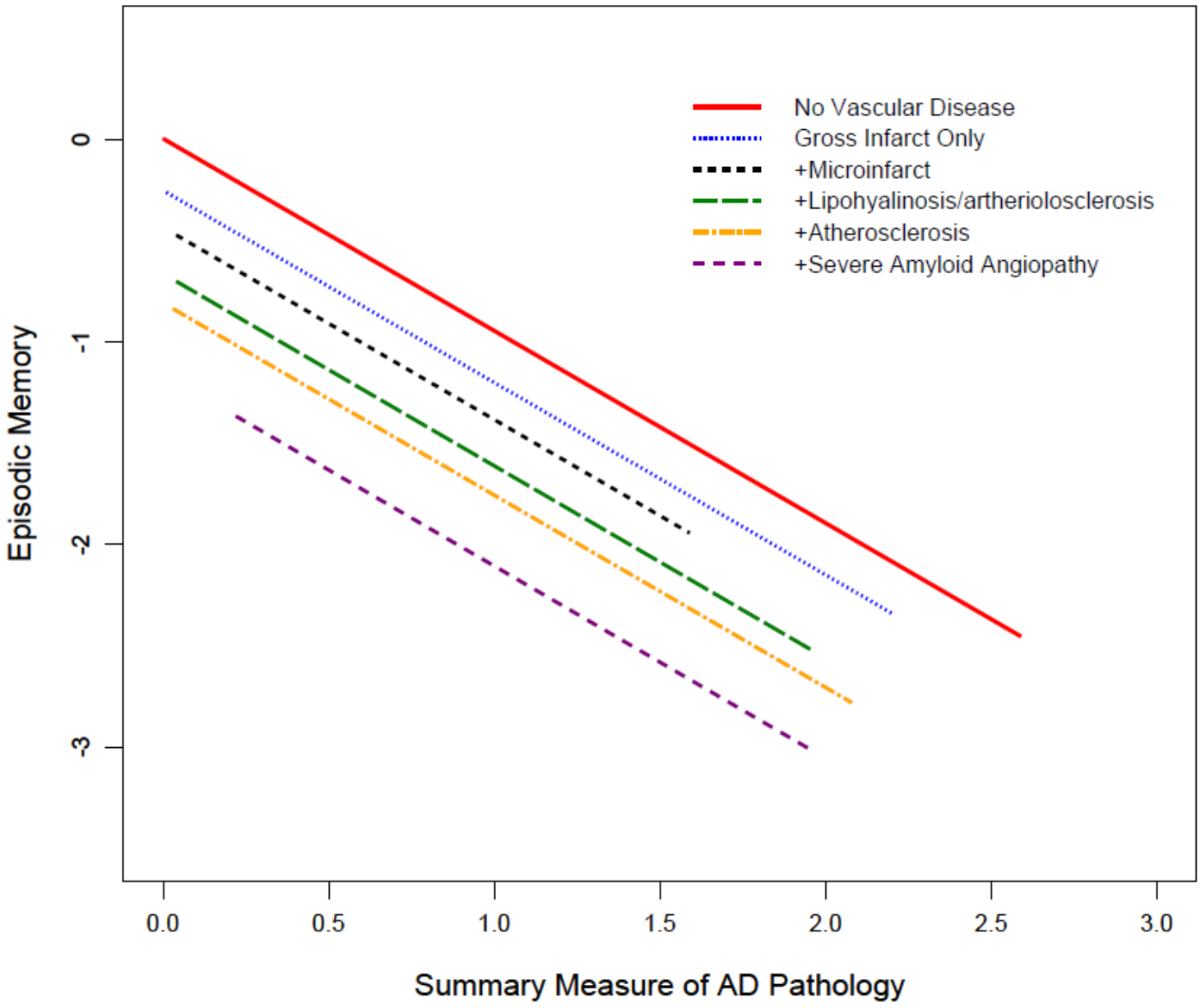
Table 3. Relation of Microinfarcts to Global Cognition and 5 Cognitive Systems*

Cognitive Outcome	Estimate (SE), *P*
Global cognition	−0.287 (0.113), 0.012
Episodic memory	−0.279 (0.138), 0.044
Semantic memory	−0.391 (0.130), 0.003
Working memory	−0.146 (0.099), 0.139
Perceptual speed	−0.400 (0.117), <0.001
Visuospatial abilities	−0.153 (0.098), 0.119

*Each model adjusted for age at death, sex, education, macroscopic infarcts, Alzheimer disease pathology, and Lewy bodies.

Arvanitakis Z et al. *Ann Neurol* 2011;69(2):320-327


No Vascular Disease
Gross Infarct Only
+Microinfarct
+Lipohyalinosis/artheriolosclerosis
+Atherosclerosis
+Severe Amyloid Angiopathy
Perceptual Speed
0
-1
-2
-3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Summary Measure of AD Pathology

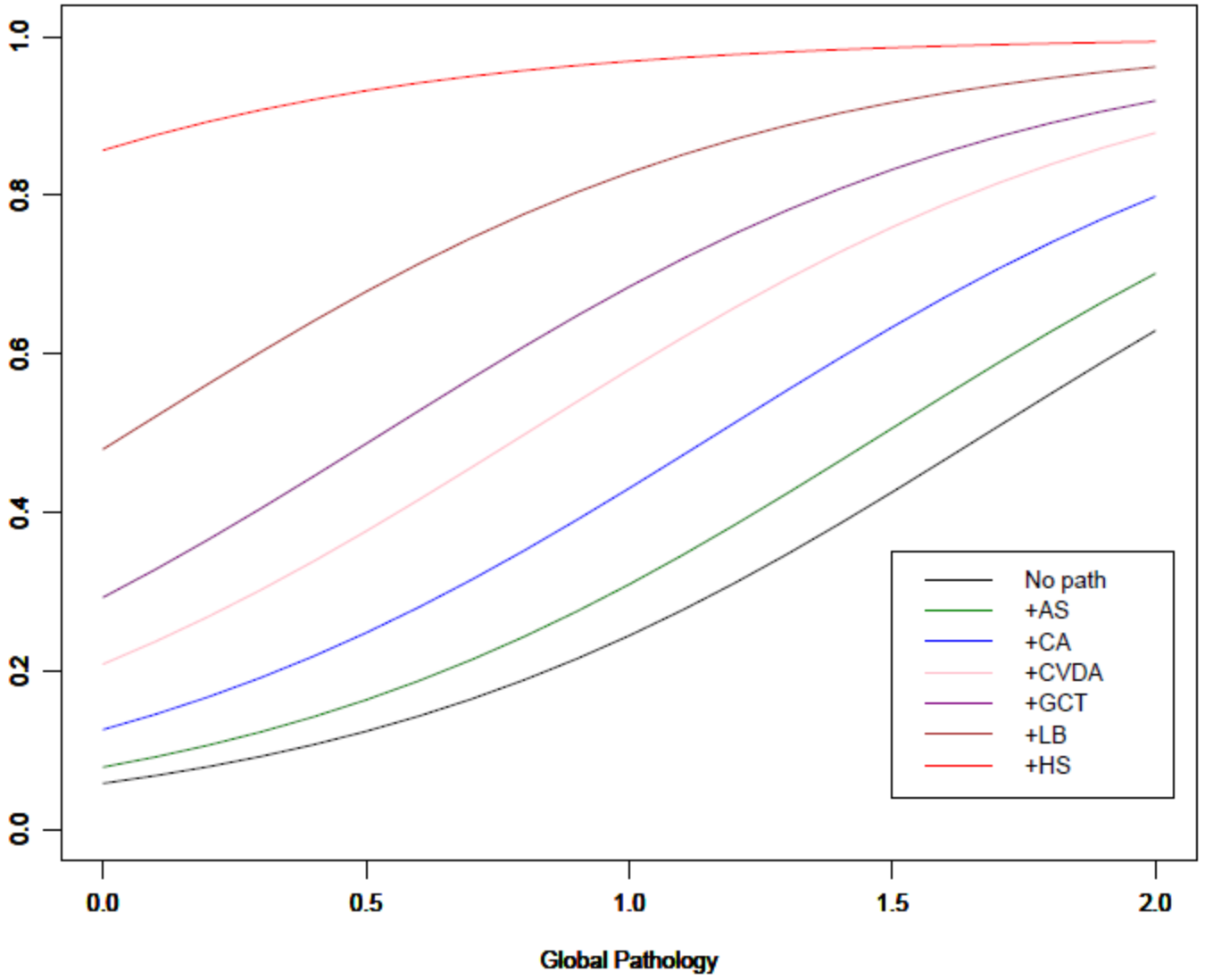

No Vascular Disease
Gross Infarct Only
+Microinfarct
+Lipohyalinosis/artheriolosclerosis
+Atherosclerosis
+Severe Amyloid Angiopathy
Episodic Memory
0
-1
-2
-3
0.0
0.5
1.0
1.5
2.0
2.5
3.0
Summary Measure of AD Pathology

Not everything is vascular!
Role for other pathologies in cognitive impairment in aging

- Lewy bodies - Neocortical Lewy bodies increase odds of dementia and effect all cognitive domains
- TDP-43 – very common proteinopathy associated with aging, lowers episodic memory, MCI, and increases odds of dementia.
- Hippocampal sclerosis - very common in the oldest old and increases odds of MCI and dementia
- Mesial temporal lobe NFT and memory in late life – PART (primary age related tauopathy)

Add the effect of Lewy bodies and Hippocampal sclerosis….

Probability Of Clinical Diagnosis Of AD



Hippocampal Sclerosis

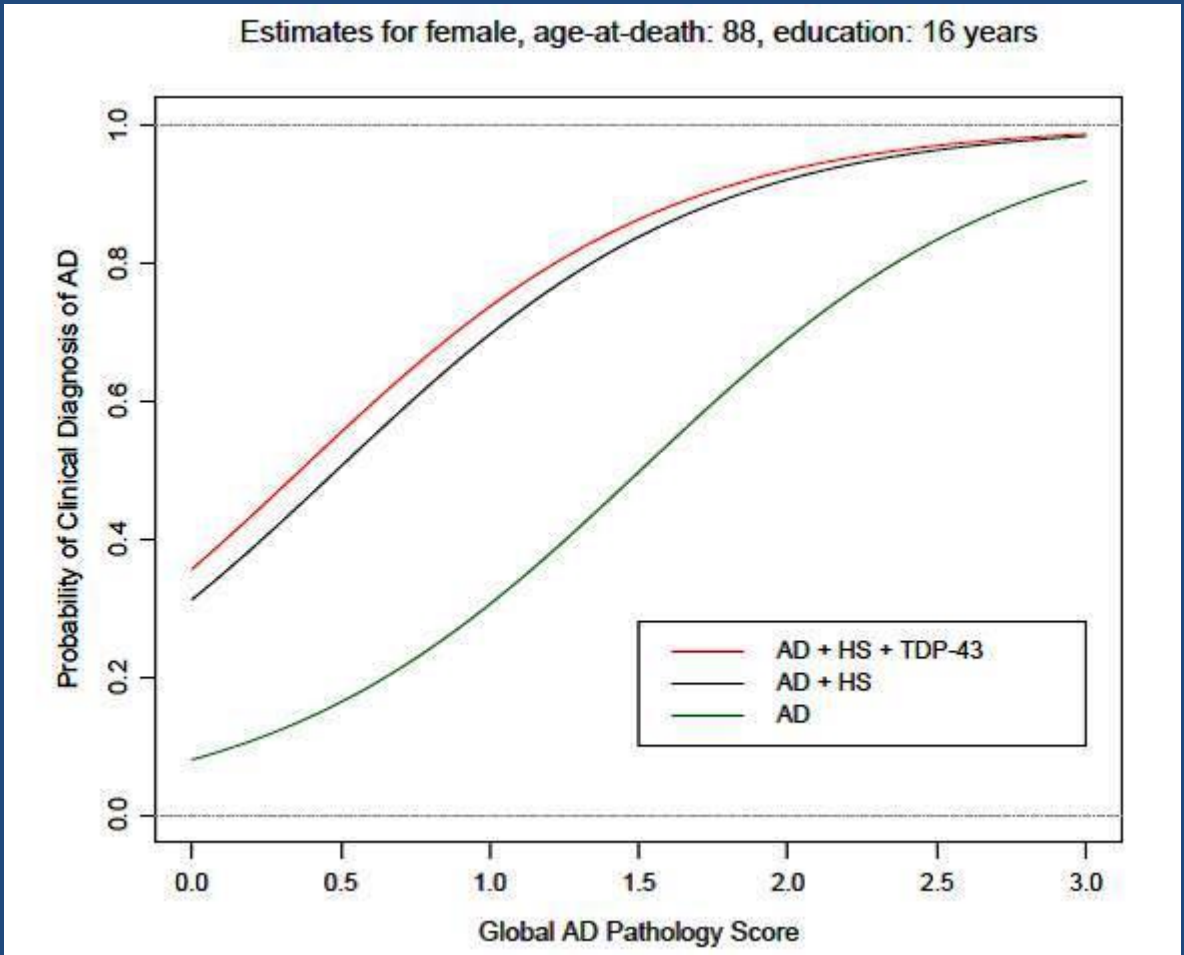
- Less than 10% of cohort
- But strongly related to age (about 15-18% of those over 90 y/o)

- About 87% have TDP-43 pathology

- HS+TDP independently related to multiple domains of impairment and probable AD

- TDP alone with separate independent effect on episodic memory

Nag S, et al. Ann Neurol. 2015 Feb 23.
doi: 10.1002/ana.24388.



Nag S, et al. Ann Neurol. 2015 Feb 23. doi: 10.1002/ana.24388

TDP-43 and aging

Very common abnormal protein deposit in aging

Approximately 50% of cohort (amygdala, Hippocampus/entorhinal cortex, inferior temporal and frontal)

Related to AD path diagnosis and HS diagnosis but also seen in those without AD or HS path dx.

Independently related to loss of episodic memory and increases odds of clinical AD

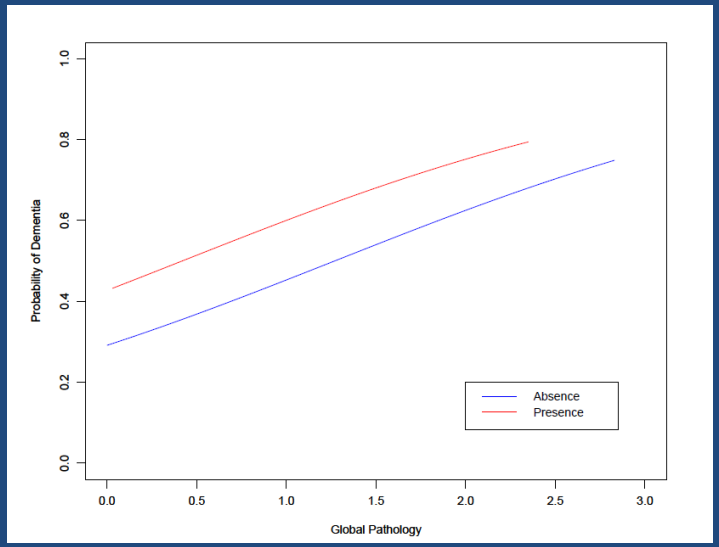
Original Investigation

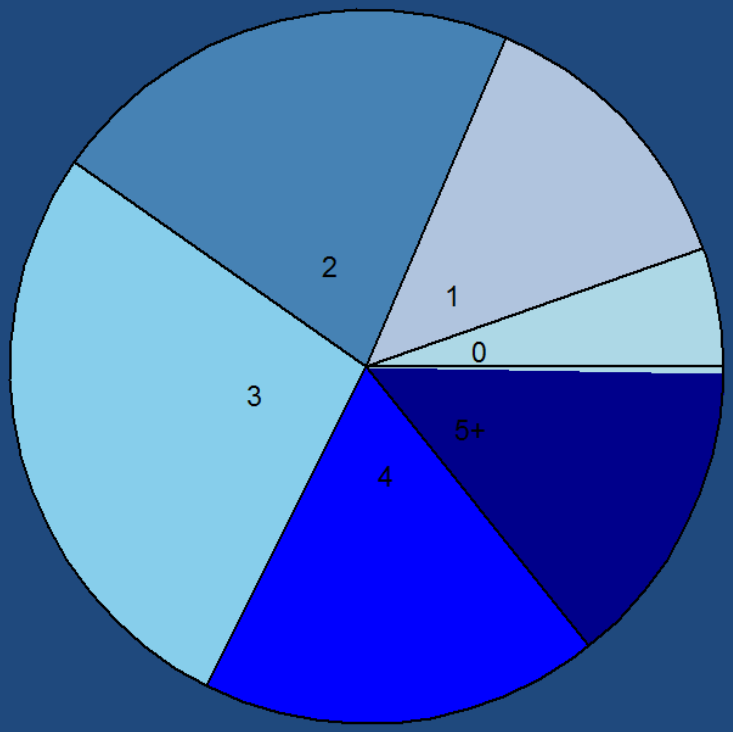
TDP-43 Pathology, Cognitive Decline, and Dementia in Old Age

Robert S. Wilson, PhD; Lei Yu, PhD; John Q. Trojanowski, MD, PhD; Er-Yun Chen, MD; Patricia A. Boyle, PhD; David A. Bennett, MD; Julie A. Schneider, MD

JAMA Neurol. 2013 Nov 1;70(11):1418-24.

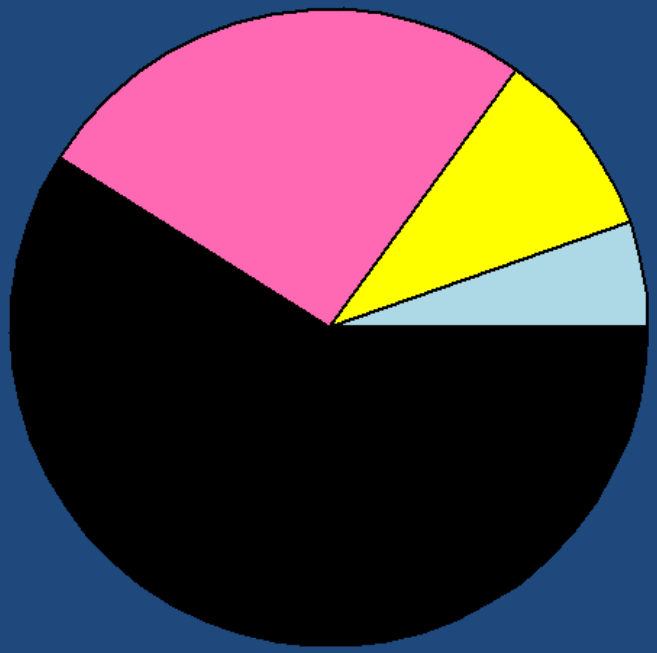
Effect similar to that of tangles in mixed effect models on decline





Number of mixed pathologies in persons with pathologic diagnosis of AD - over half have 3 or more

Neurodegenerative (yellow) and vascular (pink) or both (black) pathologies in persons with pathologic diagnosis of AD - over half have both ND and vascular



Implications (prob AD)

1. **Clinical trials: implementation / interpretation**
   - **For instance, reconsider the exclusion of coexistent vascular disease and risk factors in AD clinical trials?**
   - **Also consider drug mechanisms – potentially vascular or other mechanisms.**

2. **Epidemiologic studies:** One should be cautious making inferences – can not assume that risk factors for clinical AD are risks factors for AD pathology

3. **Public health:** vascular health likely to be extraordinarily important in the prevention of dementia, eg. life style, BP, blood glucose, likely large impact on primary prevention of clinical AD; data from the oldest-old

•

NEITHER DIABETES OR BLOOD PRESSURE RELATED TO PLAQUES OR TANGLES…

- Diabetes (any diagnosis during study period)
  - Shown to increase risk of AD in the Religious Orders Study
  - Dx of diabetes increased odds of gross infarcts– 2.6 - fold increase in odds of gross (p=0.0002)
    - 2- fold increase odds of subcortical micro (p=0.006)
    - 60% increase of each level of lipohyalinosis (p = 0.007)
- High Blood pressure
  - Dx of hypertension – (38.3%)
  - Direct measures of systolic and diastolic blood pressures
  - Increase odds of infarcts, controlling for age, sex, education
    - Ave systolic not diastolic BP increased odds of infarcts
      - » Per 10 mmHg increase – 15% increase odds of gross (p=0.01)
      - » Per 10 mmHg increase - 18% increase odds of micro (p=0.04)

Pathology and dementia in the oldest old

(age 90+ vs. <90)

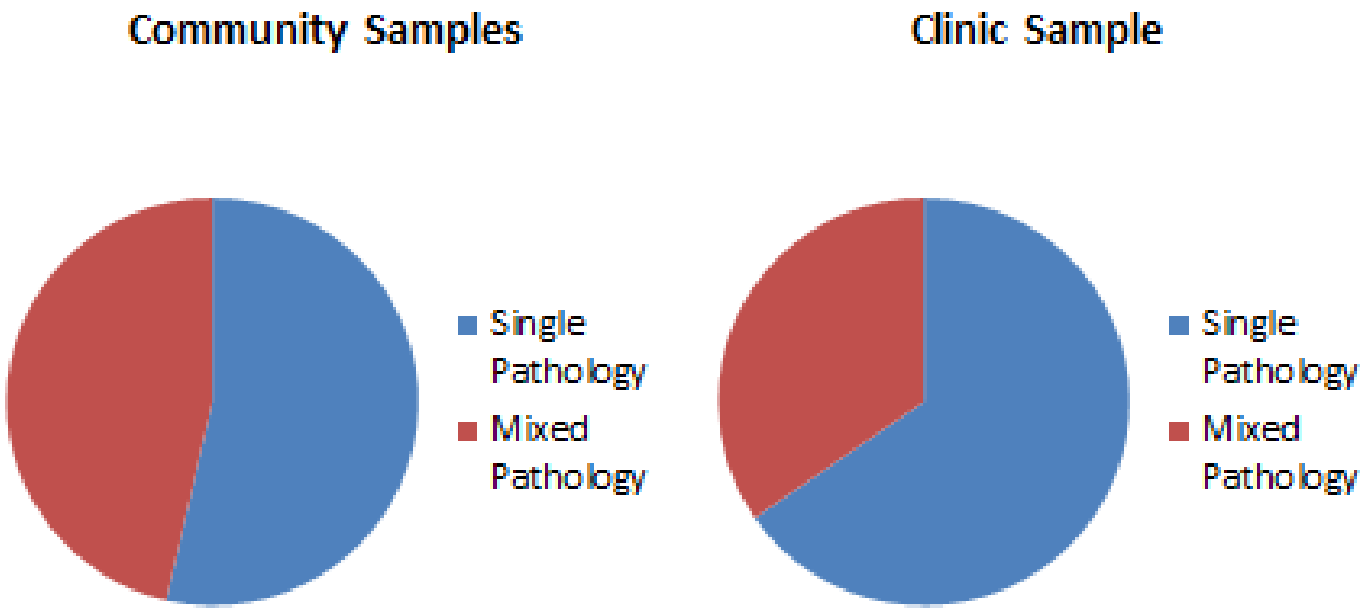
James BD et al., JAMA. 2012 May 2;307(17):1798-800.

Characteristic	Total (n=804)	Age 65-89 (n=503)	Age 90 + (n = 301)	P value
Age at death, yrs(SD)	87.7 (6.7)	83.8 (4.8)	94.3 (3.3)	<0.001
Female, no. (%)	508 (63.2%)	290 (57.7%)	218 (72.4%)	<0.001
Education, years (SD)	16.5 (3.7)	16.7 (3.8)	16.2 (3.4)	0.05
Dementia[a], no. (%)	304 (37.8%)	143 (28.4%)	161 (53.5%)	<0.001
AD[c]	493 (61.3%)	279 (55.5%)	214 (71.1%)	< 0.001
Infarcts[d]	272 (33.8%)	147 (29.2%)	125 (41.5%)	< 0.001
Single pathologies	374 (46.5%)	238 (47.3%)	136 (45.2%)	0.56
AD (no infarcts/LB)	271 (33.7%)	167 (33.2%)	104 (34.6%)	0.70
Infarcts (no AD/LB)	88 (11.0%)	59 (11.7%)	29 (9.6%)	0.36
Mixed pathologies	225 (28.0%)	113 (22.5%)	112 (37.2%)	<0.001
AD + LB	41 (5.1%)	25 (5.0%)	16 (5.3%)	0.83
AD + Infarcts	162 (20.2%	79 (15.7%)	83 (27.6%)	<0.001
AD + LB + Infarct	19 (2.4%)	8 (1.6%)	11 (3.7%)	0.06

Other special populations

- Clinic vs. Community…

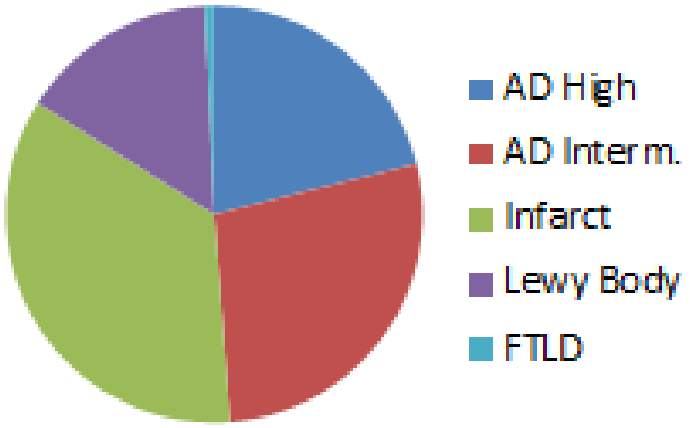
Single vs. Mixed Neuropathology (all clinical dementias)



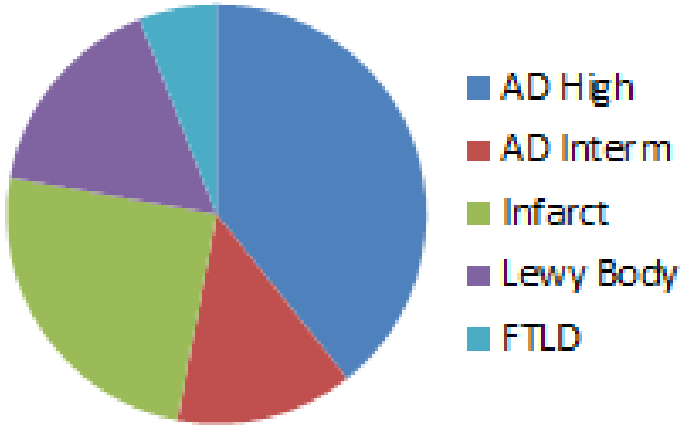
Schneider JA et al., J. Alz. Disease 2009

Neuropathological Diagnoses in all individuals with clinical dementia

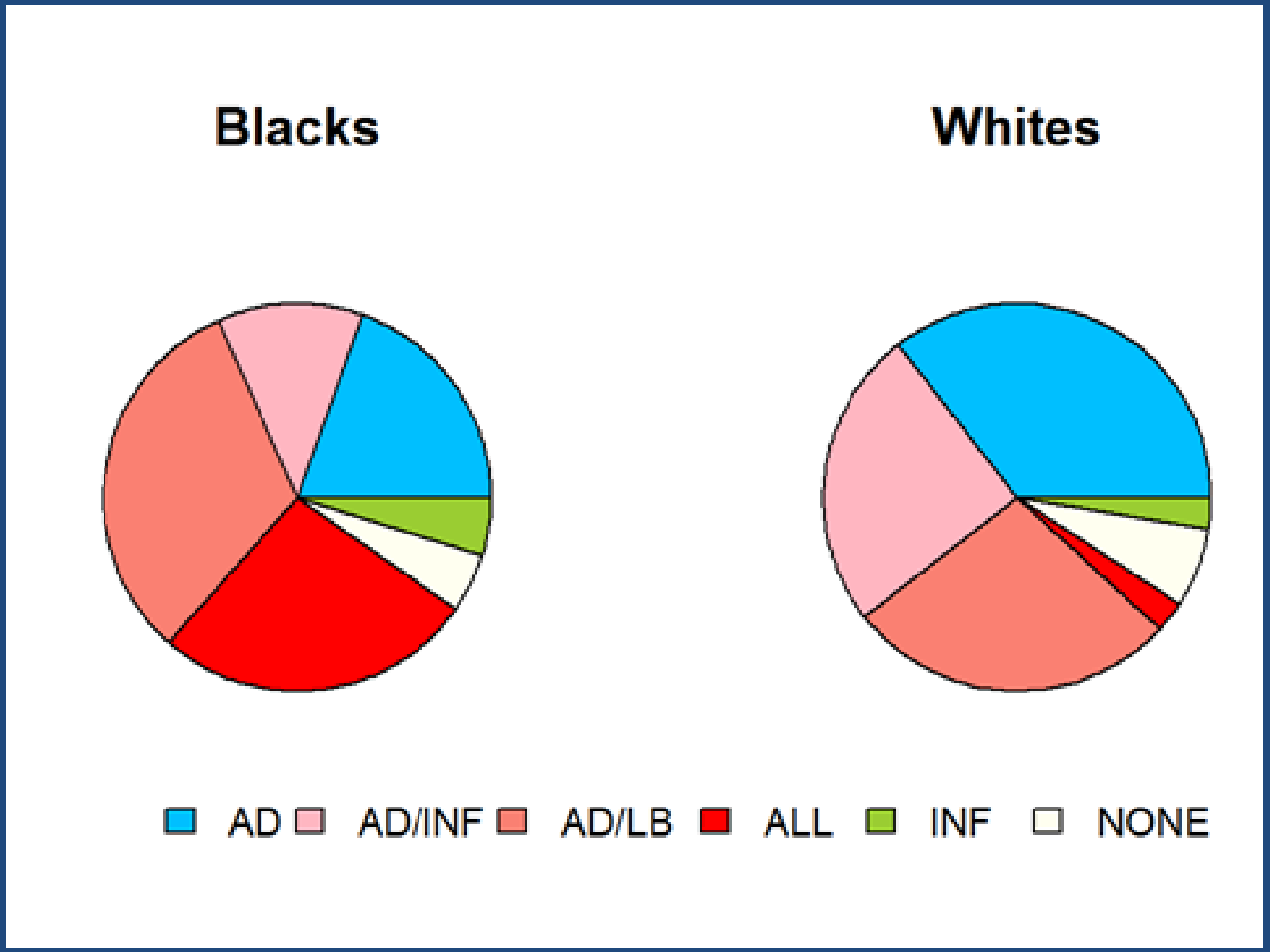
Community Samples



Clinic Sample



Schneider JA et al., J. Alz. Disease 2009



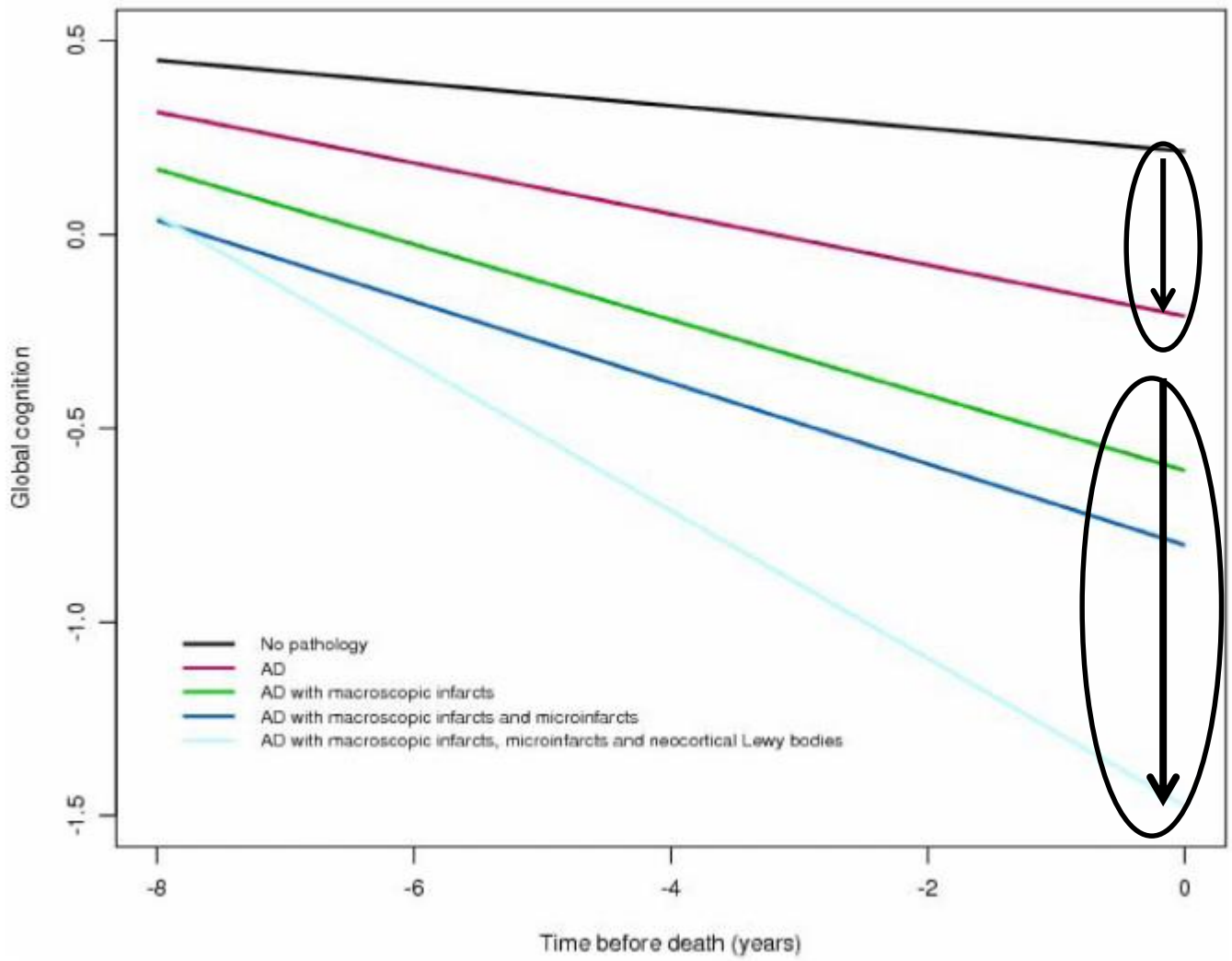
Barnes LL et al. Neurology 2015 in press.

- **Implications for Clinical and Prevention trials in the community: power, timing, and targets/biomarkers**

1. Power

- AD is only one among multiple pathologies that is related to the trajectory of decline in older persons
- In clinical trials will need greater numbers (increased power) to see effect from an agent targeting just one of the myriad of pathologies that is related to decline…
- Or have accepted biomarker…

Power



Boyle PA, et al., Ann Neurol. 2013 Sep;74(3):478-89.

2. Timing

- As everyone knows going earlier in disease, when amyloid and/or tangles may not have reached critical threshold, is likely important…
  - However, using change point modelling, data suggests that trajectory of decline in this early time period is much less steep (pre-terminal decline)
  - And depending on the cohort characteristics (too healthy) the change point may be late…

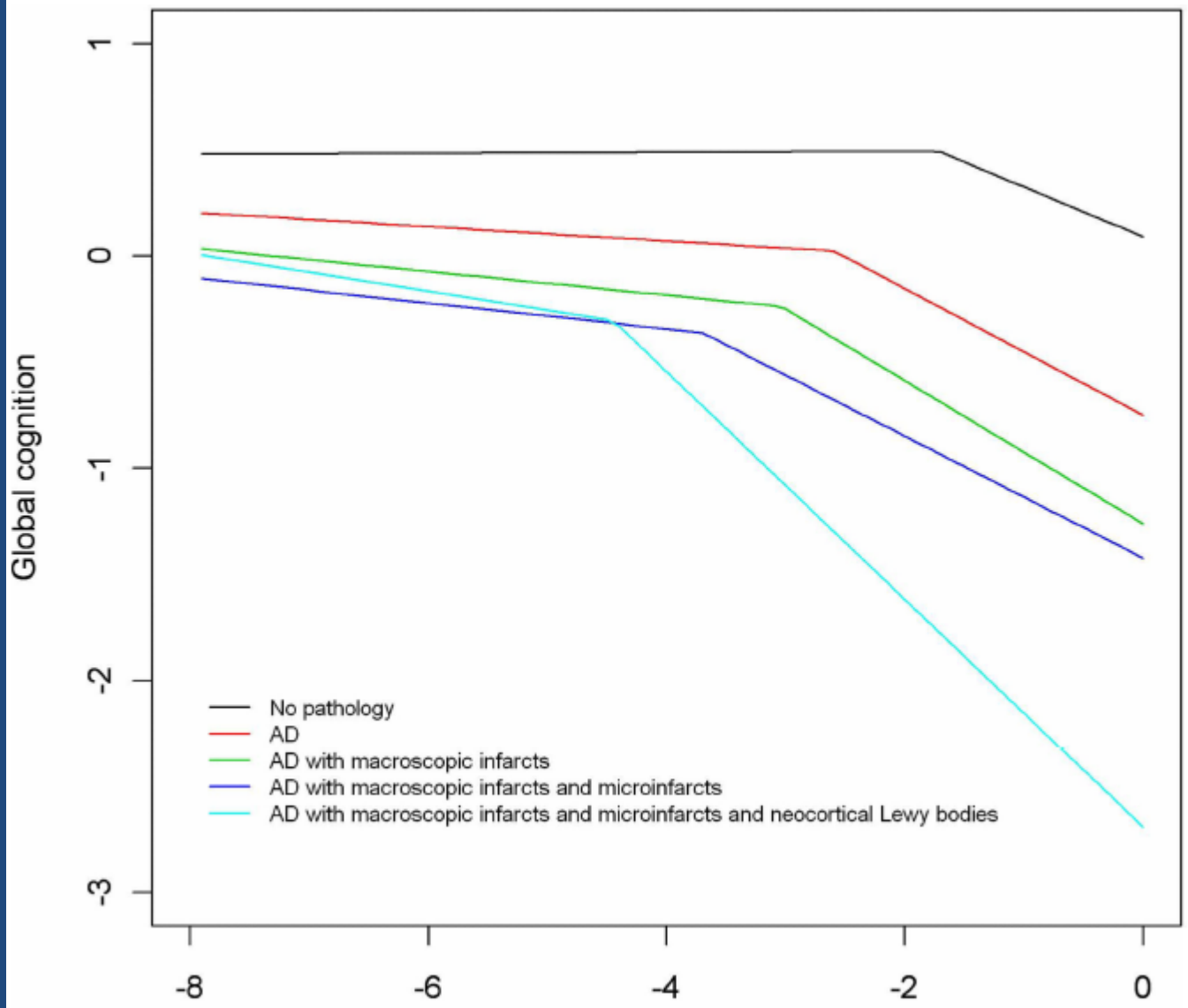
1. Preterminal slope relatively shallow

2. Change point earlier with mixed pathologies

3. Infarcts appear to effect change point (earlier) but not slope

4. Lewy bodies effect change point and slope of change

Figure 4.
Contributions of combinations of the pathologic indices to rates of preterminal and terminal cognitive decline, respectively (model derived slopes).



Boyle PA, et al., Ann Neurol. 2013 Sep;74(3):478-89.

Timing

- Targeting early disease when slope of decline is less steep again may need more power to see effect

- **Suggest need to target those individuals close to the change point; eg. target at risk individuals

  eg. apoE , subjective memory complaints

  Need to be aware that mixed pathologies lead to earlier change point (vascular/Lewy bodies) and may effect slope (Lewy bodies)

Targets

- Alzheimer's disease pathology is just one of a myriad of pathologies involved in decline in persons with "clinical AD"

- Consider targeting known non-AD pathologies and drug discovery for other up or down stream targets…

TARGETS

Does not include atherosclerosis, arteriolosclerosis, CAA, TDP, HS…

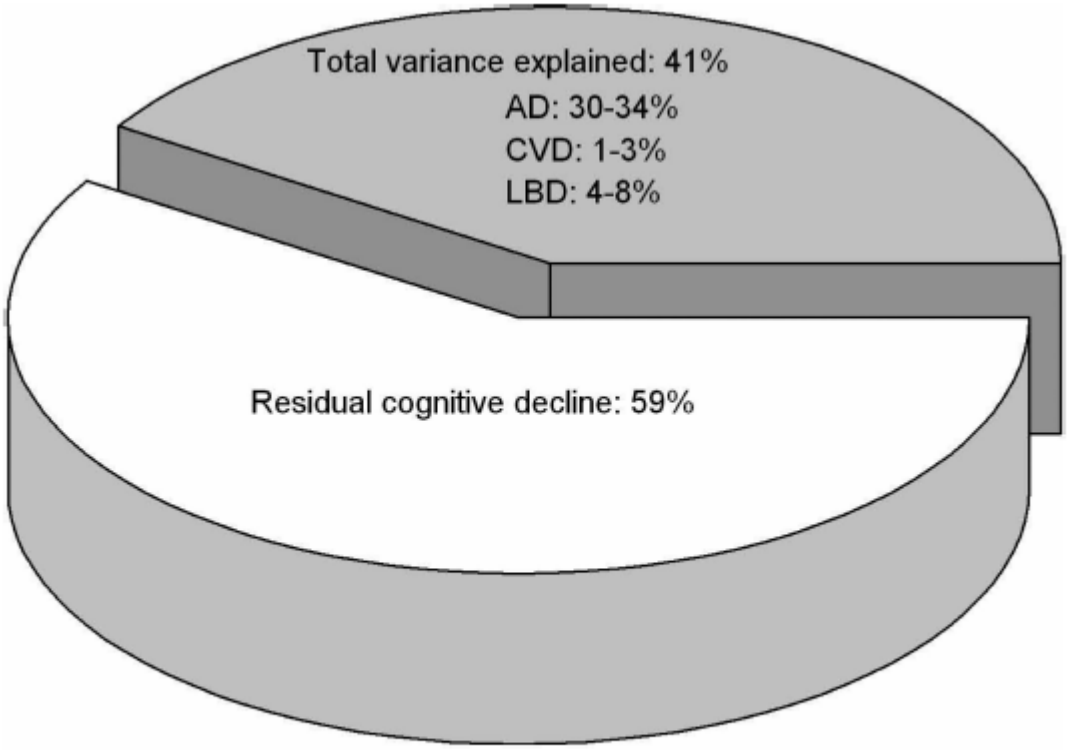


Figure 3.
Variation in cognitive decline explained by the pathologic indices (grey) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models.

Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, Bennett DA. Ann Neurol. 2013 Sep;74(3):478-89.

Conclusions

- Mixed pathologies very common in those with Clinical AD (and dementia overall).
- Neurodegenerative and vascular, often multiple
- Add to likelihood of dementia, clinical AD, and trajectory of cognitive decline

- Implications for Clinical/Prevention Trials:
  - Power – mixed pathologies explain a lot of decline so when targeting individual path need increased power to see effect
  - Timing - in preclinical state need to target at risk individuals if using cognition as outcome otherwise trajectory of change may be too shallow BUT mixed pathologies confound…
  - Targets - expand drug targets to nonAD and common mechanisms

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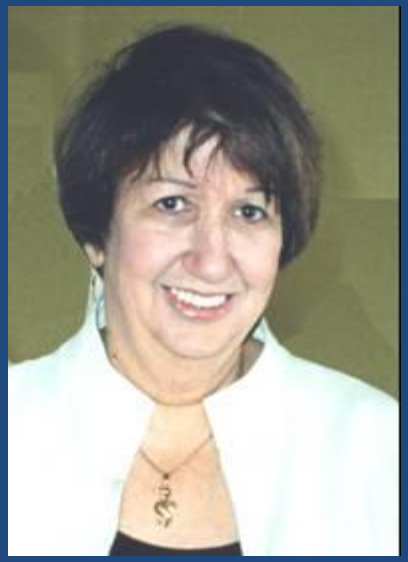
- Robert C. Borwell Endowment Fund

- Study Participants
- Religious Orders Study
- Rush Memory and Aging Project

Suzanne S. Mirra MD

Professor Emeritus, Dept. of Pathology
SUNY Downstate Medical Center




Stu's Views
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"I'm stumped.
We'll have to wait for
the autopsy."