Pathology of Cognitive Decline and Dementia in Aging and Alzheimer's Disease

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Disclosures

Scientific advisory boards

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Consultant

- Avid radiopharmaceuticals
- Navidea biopharmaceutcals

Pathologic basis of cognitive decline in aging

- Alzheimer's pathology and concept of neural reserve - threshold of path to exhibit sxs
- Spectrum of pathologies and mixed pathologies in aging (AD plus)
  - Degenerative and Vascular pathologies
    - Macroinfarcts, large vessel atherosclerosis
    - SVD - microinfarcts, arteriolosclerosis, CAA
    - Lewy bodies, hippocampal sclerosis, TDP43
- Overlap of clinical phenotypes and the dx 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%*
- *>600 autopsies*


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

- Overall over 3060 enrolled/1429 died/1232 autopsies

- 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

Z-scored and grouped to form a 5 domains measures and
a measure of overall cognitive function (global cognitive score)

Clinical diagnoses

- Annually, neuropsychologist reviews neuropsychological test results and gives impression regarding level of impairment;
- And expert Clinician makes diagnostic classification of dementia and AD, according to current criteria
- At death, a board-certified neurologist reviews all years of clinical data, blinded to postmortem data, and renders most likely clinical diagnosis proximate to death (ave.interval about 6 months)

Brain autopsies and AD Neuropathology

- One Hemisphere cut into 1 cm slabs using Plexiglas jig; paraformaldehyde-fixed/paraffin-embedded/6 or 20 µm sections
- Multiple variables for dx, stage and burden of of AD pathology –
- For dx use silver stains; frontal, temporal, parietal, entorhinal, and hippo cx –NFT and NP counted and now Thal amyloid stage.
- Modified NIA– Reagan criteria; path dx of AD if intermed or high "likelihood" AD (blind to age, clinical dx); at least moderate neocortical neuritic plaques (CERAP NP score) and at least Braak III/IV
- New NIA-AA path dx in over 300 – excellent agreement with NIA-Reagan - includes CERAD NP score, Braak, and Thal amyloid stage.
- Summary measure of AD pathology using NP, DP, NFT counts from 5 regions and converting into standardized score
- Amyloid load and tau tangle densities via immunohistochemistry also performed in 8 regions across

AD pathology – heterogeneity and neural reserve.

Path criteria shows excellent agreement with clinical dx of AD and AD pathology (NP and NFT) is moderately to strongly related to cognition/dementia;

Inter-individual variation in the expression of AD pathology

"Normal" Aging

- AD pathology very common ; ~ 1/3 brain sufficient path for path 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 heterogenous group.

Neural Reserve

About 1/3 of older persons have sufficient AD path in brain to fulfill criteria for pathologic dx 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

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.

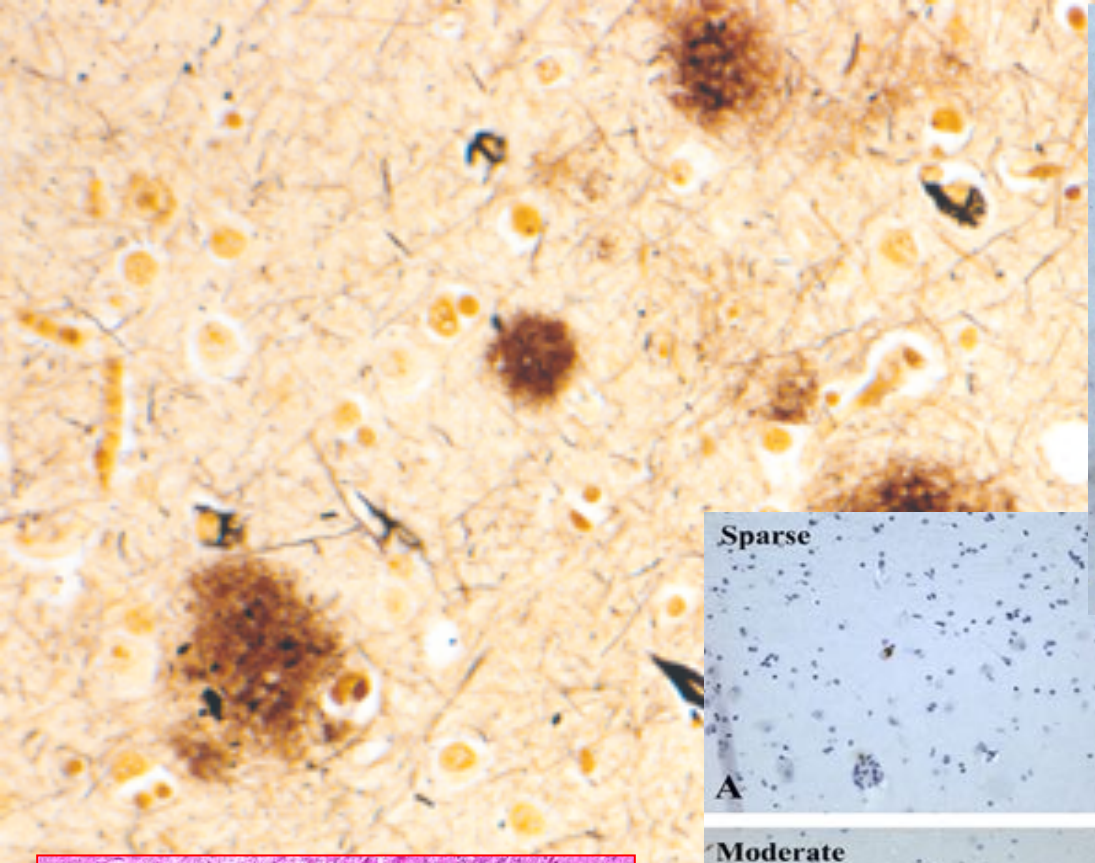
Pathologies in addition to AD in older persons

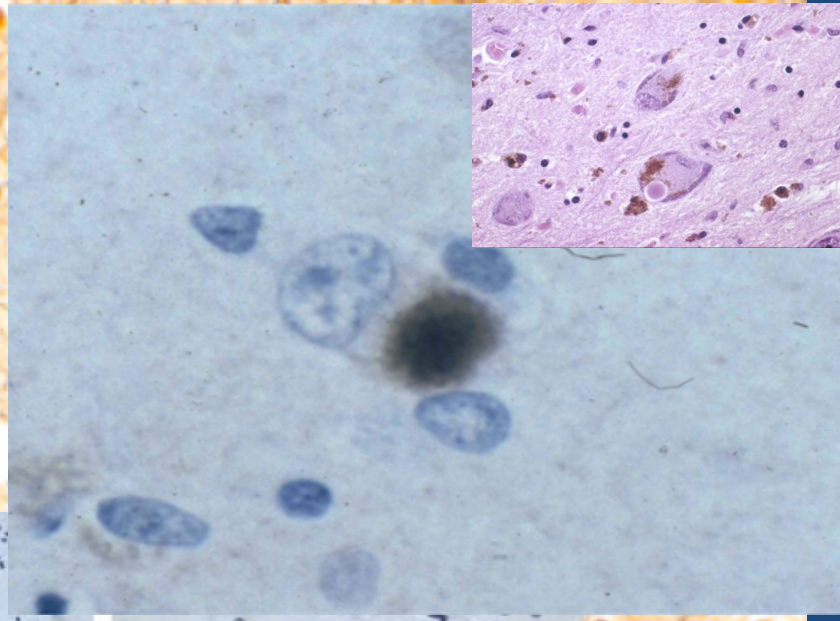
- Vascular (5)
  - gross infarcts
  - Microinfarcts
  - Atherosclerosis
  - Arteriolosclerosis
  - Cerebral amyloid angiopathy

- 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





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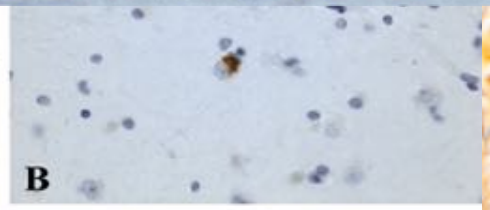
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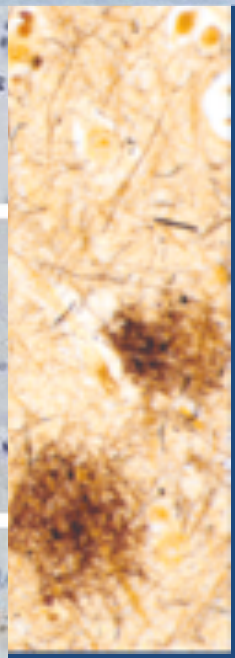

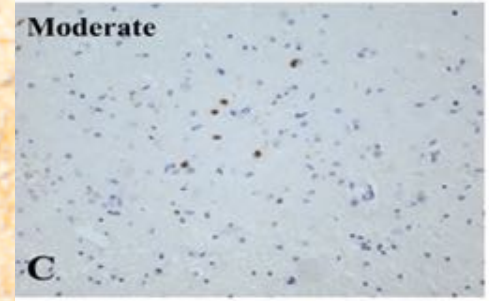
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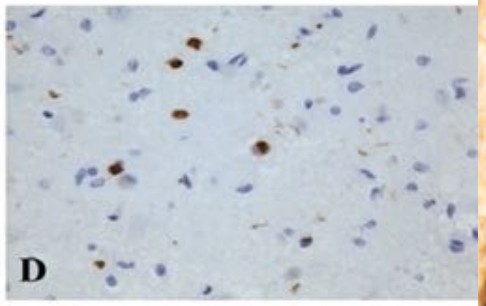
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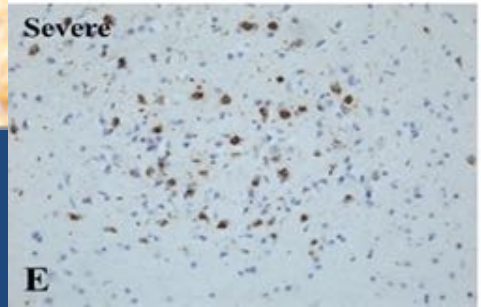
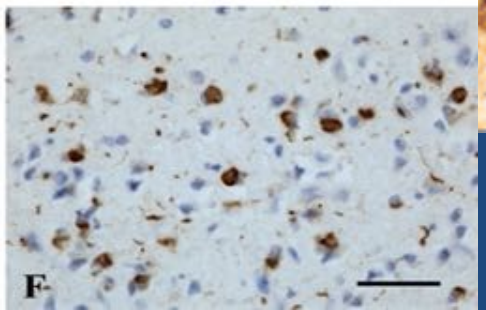

Severe
E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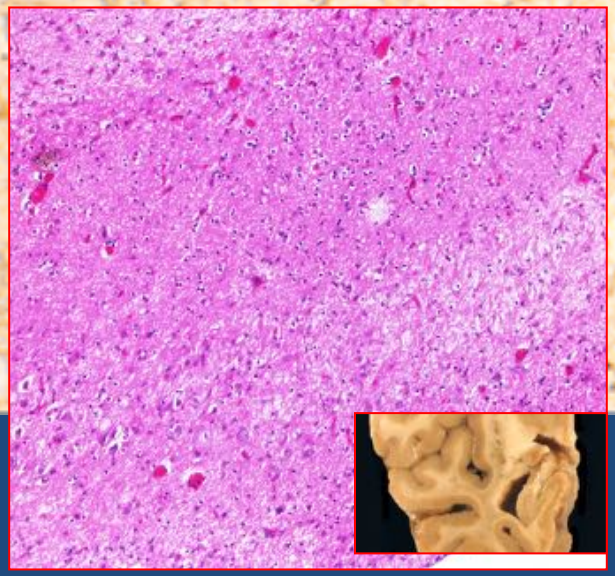
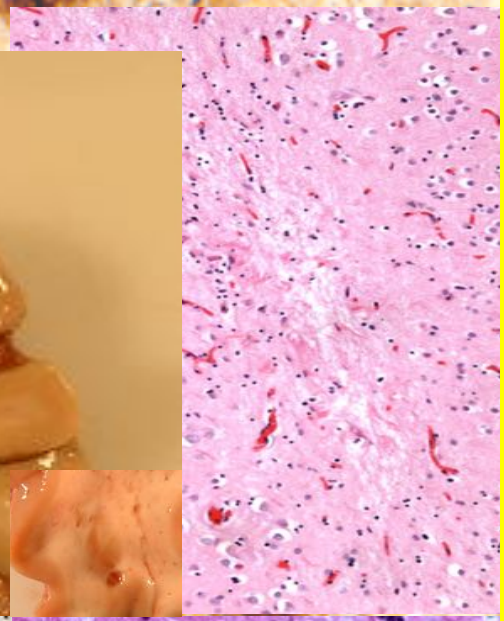
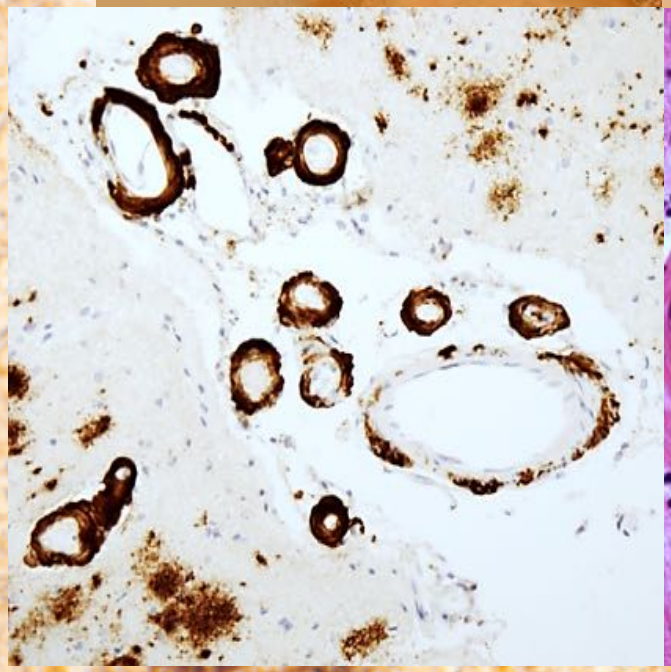
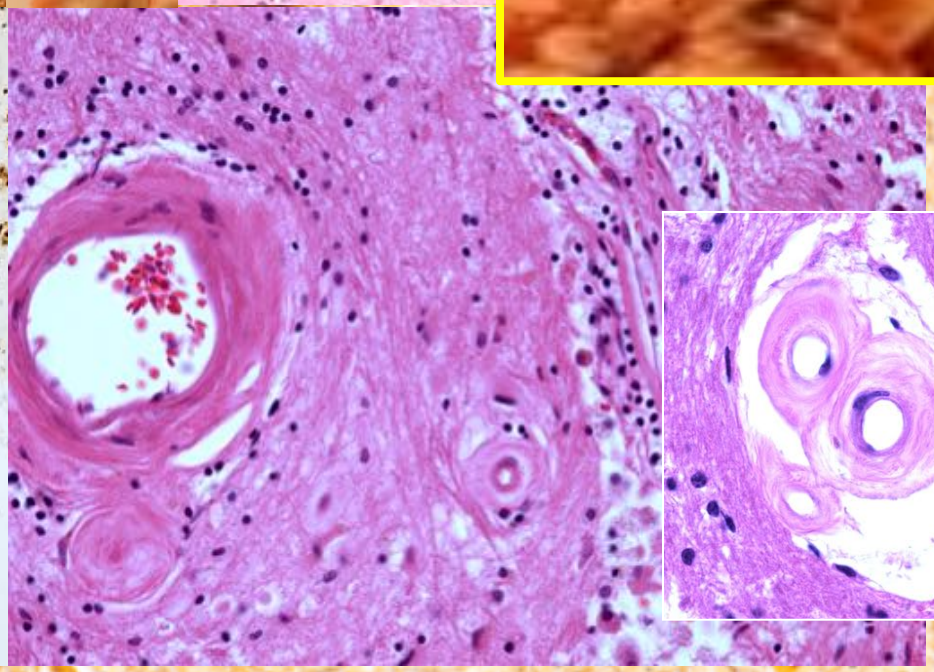




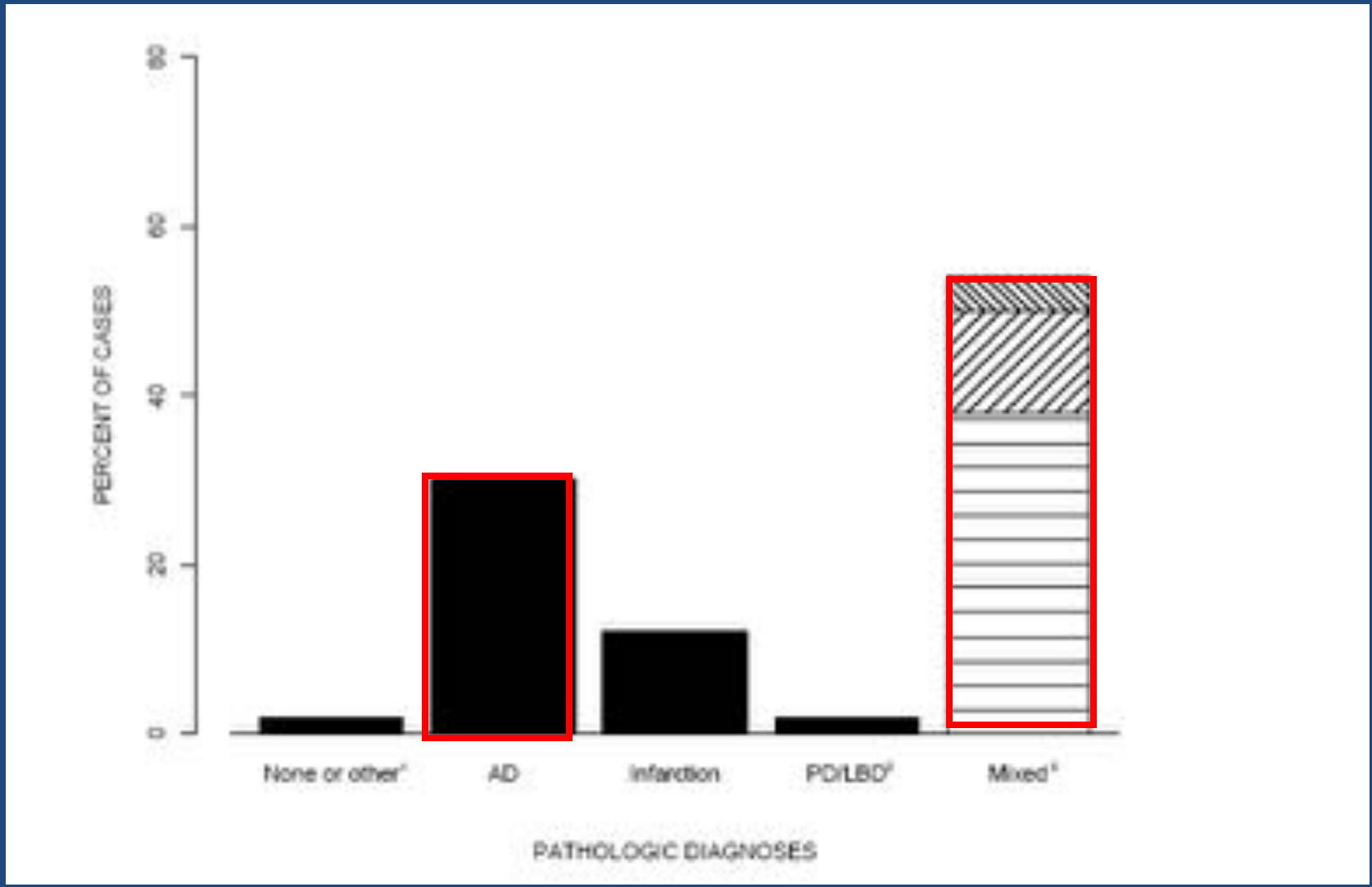




Mixed pathology in community-dwelling older subjects with dementia is more common than a single pathology

- 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

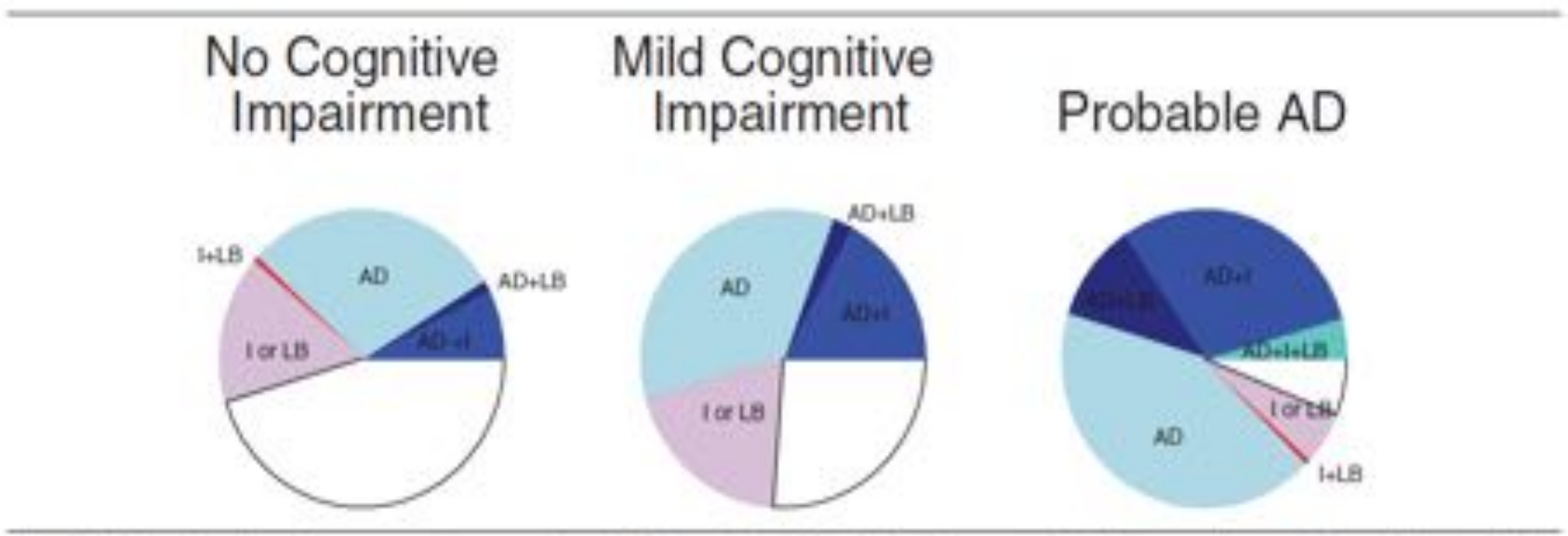


*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral 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.*

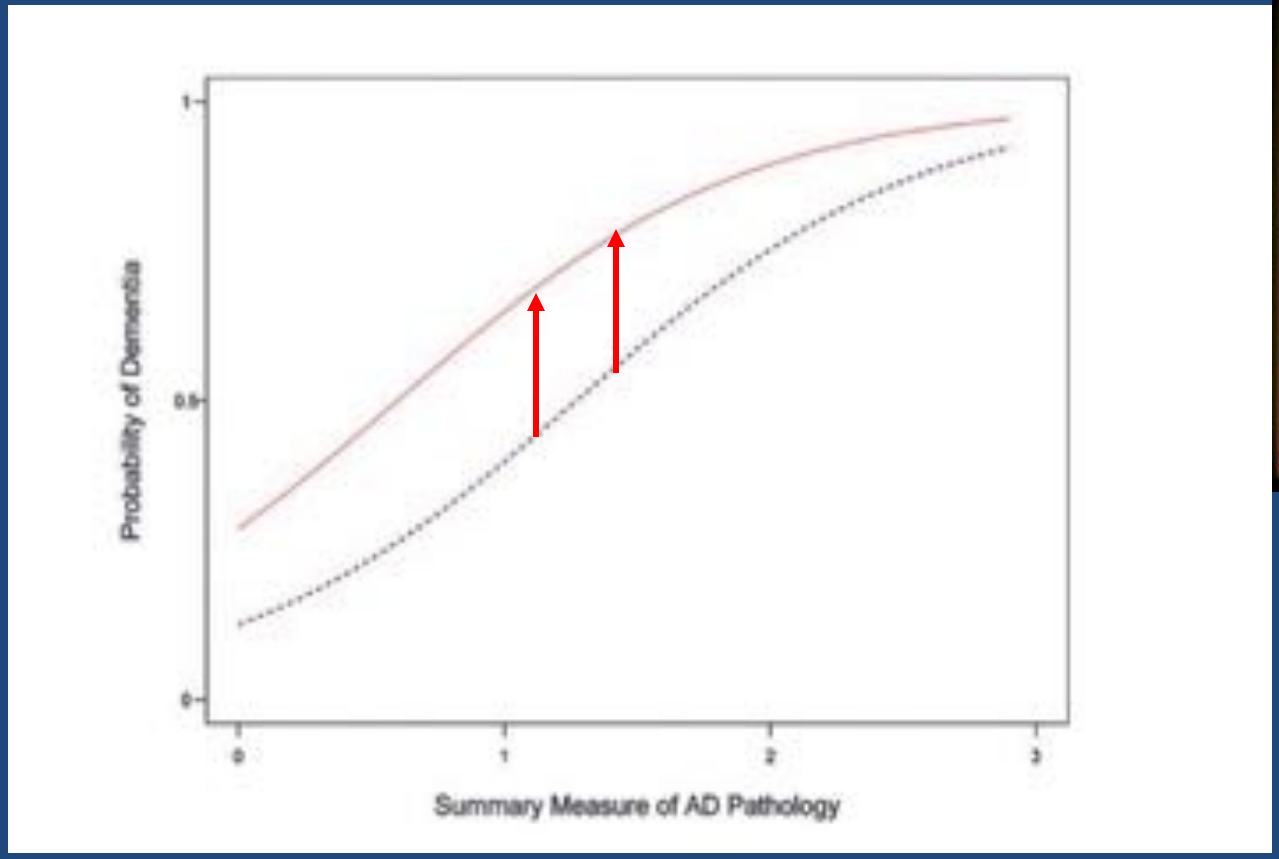
Schneider JA et al. *Ann Neurol* 2009;66:200–208.

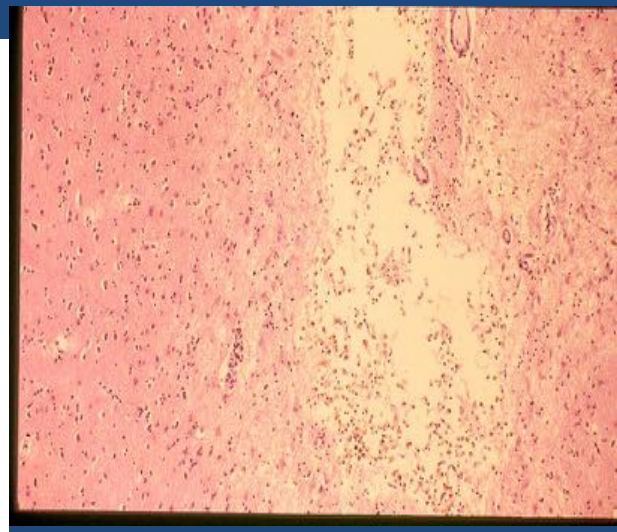
*** Estimates do not include vascular path other than gross infarcts**

**** 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 3 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.

Tip of the iceberg….in vascular brain pathology

- 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. Blocks are 1cm thick so can missed because within slab or not visibile

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- Microscopic infarcts – examination of 6-7 cortical regions, 2 subcortical and 1 brainstem (number is skewed; often analyze as 2 or 3 level)

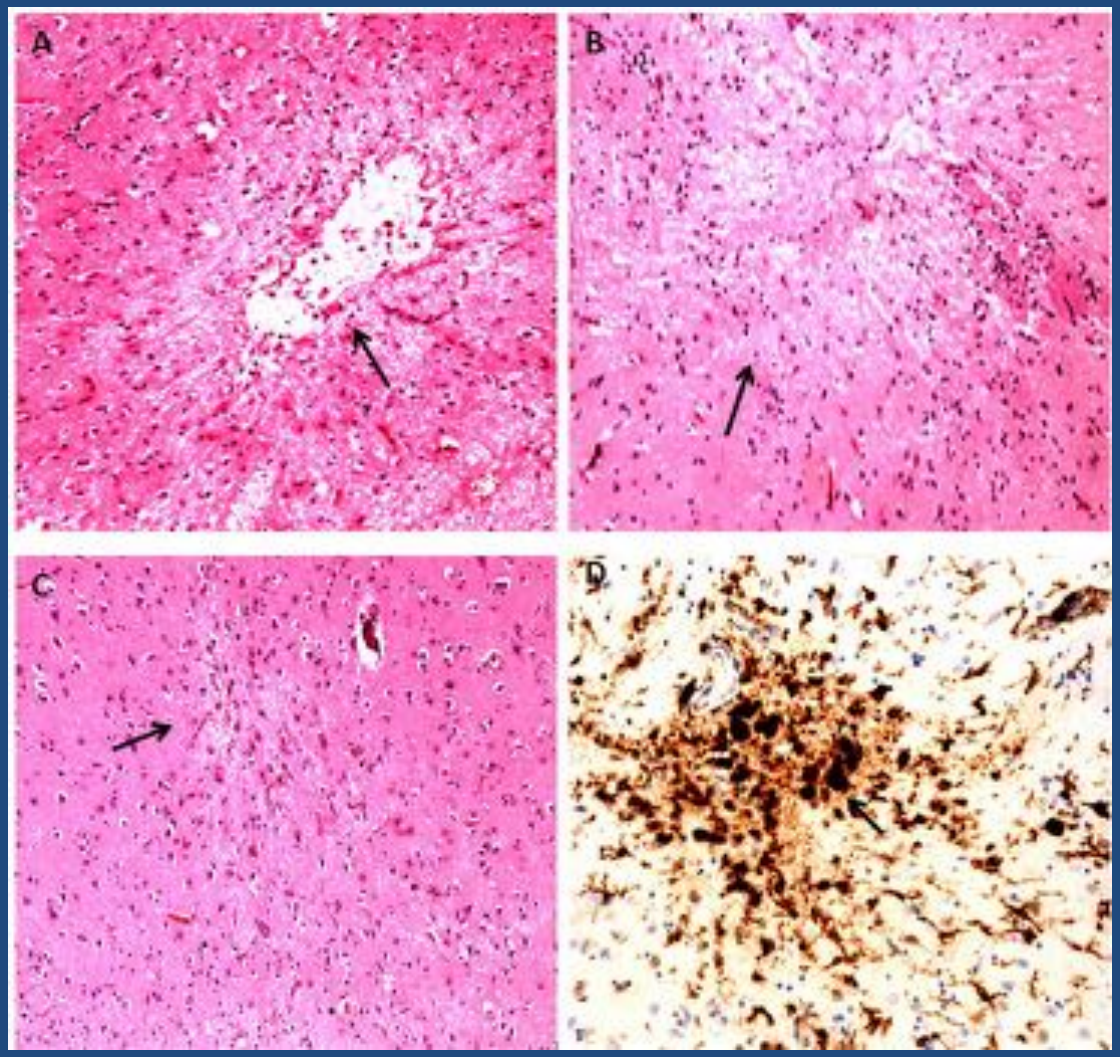
- Lipohyalinosis/arteriolosclerosis – amorphous hyalinized thickening of arterioles; semiquant. none -severe). Semiquantiative (0-6)

- Amyloid angiopathy –anti-amyloid-β; semiquant scores (0-4) are averaged into continuous measure; also have mild, moderate, severe

- Atherosclerosis – judged at circle of willis; semiquant scale (0-6)

Microscopic infarcts – “invisible lesions”

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

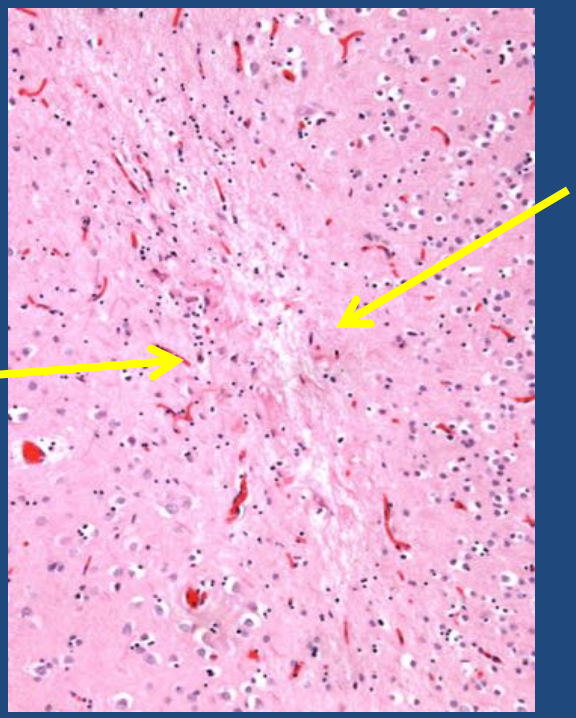


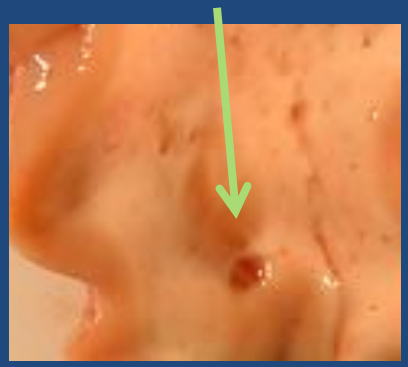
Smith E. et al. The invisible lesions. Lancet Neurology 2012

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





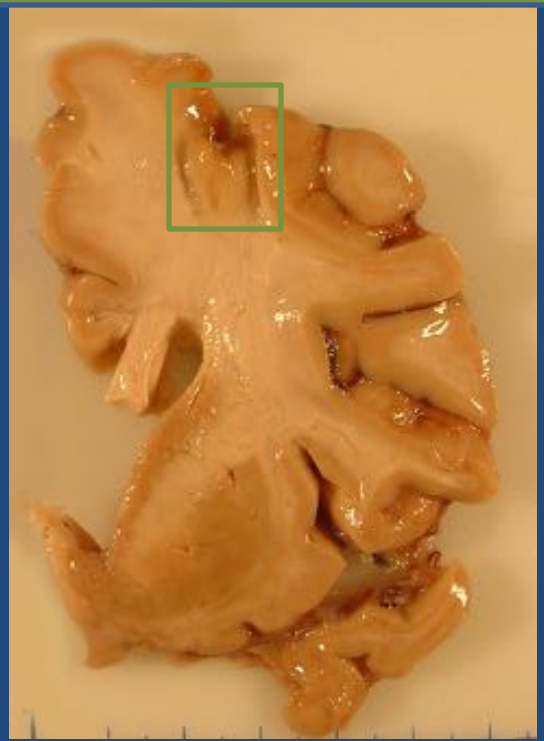


Table 1. Characteristics* of Subjects

	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 (0.53–0.68)	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!

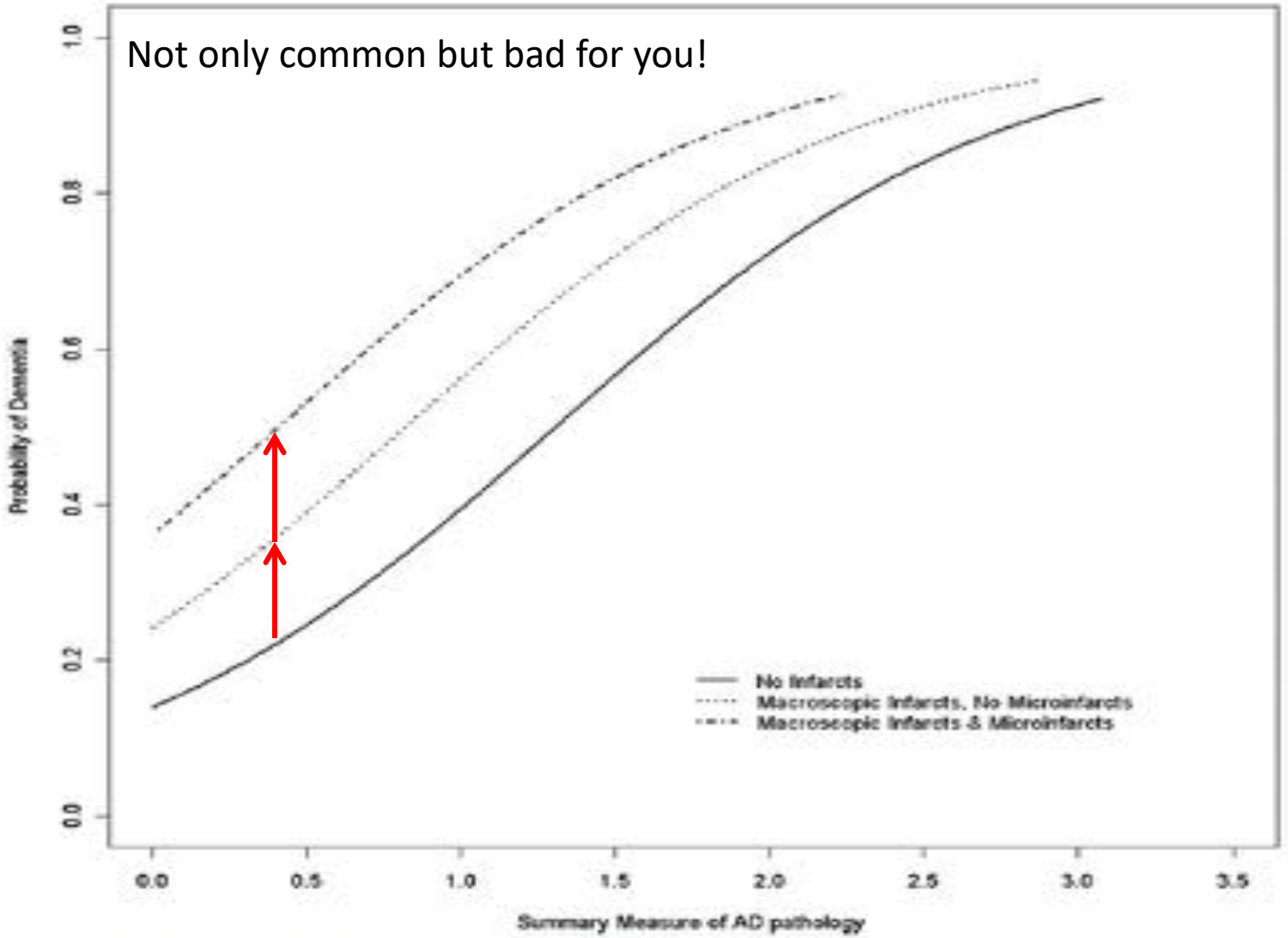


Figure 1. Probability of dementia by Alzheimer disease pathology showing additive effects of macroscopic infarcts and microinfarcts.

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

How about Vessel pathology?

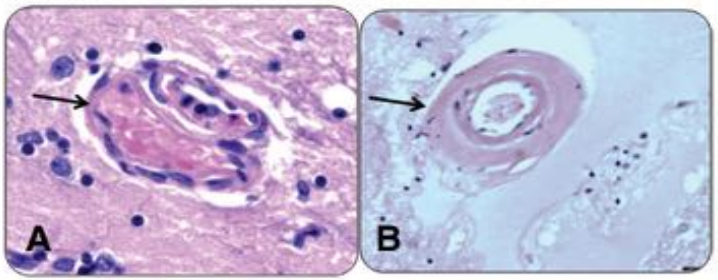
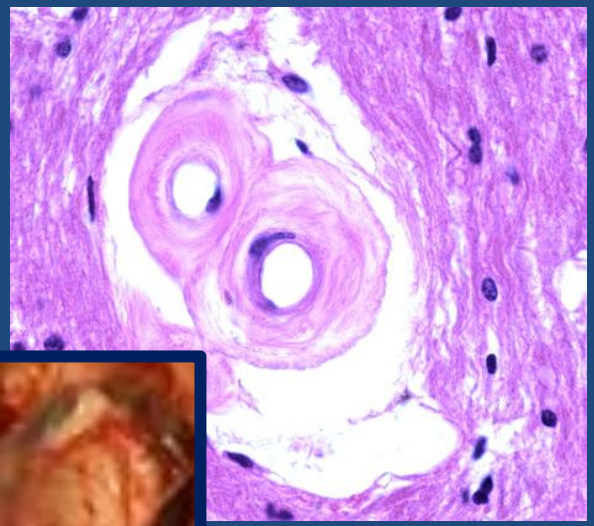
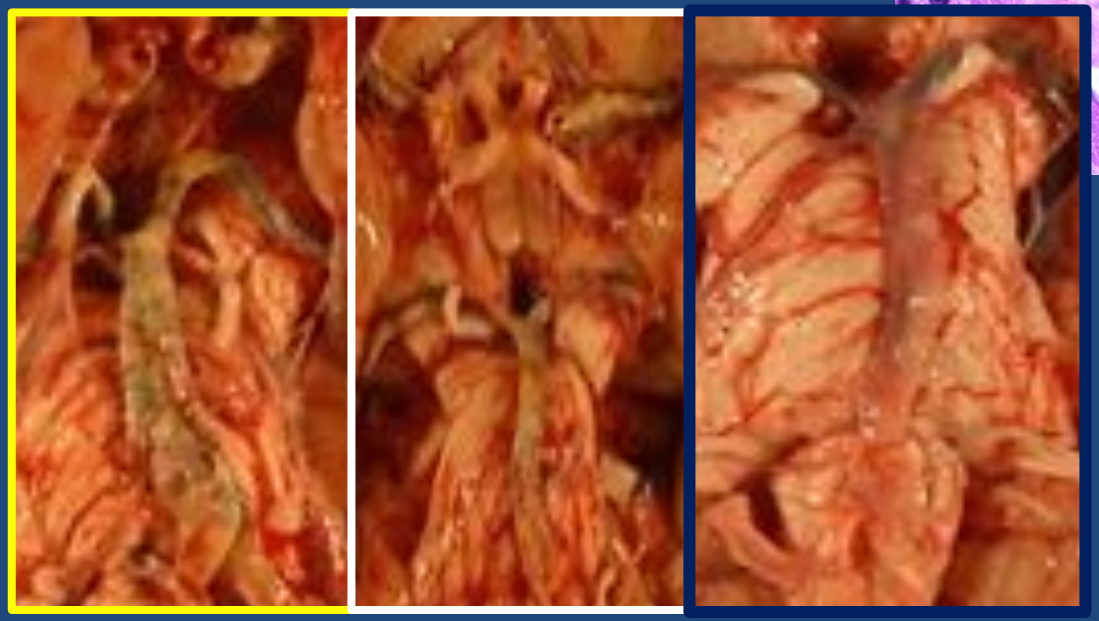


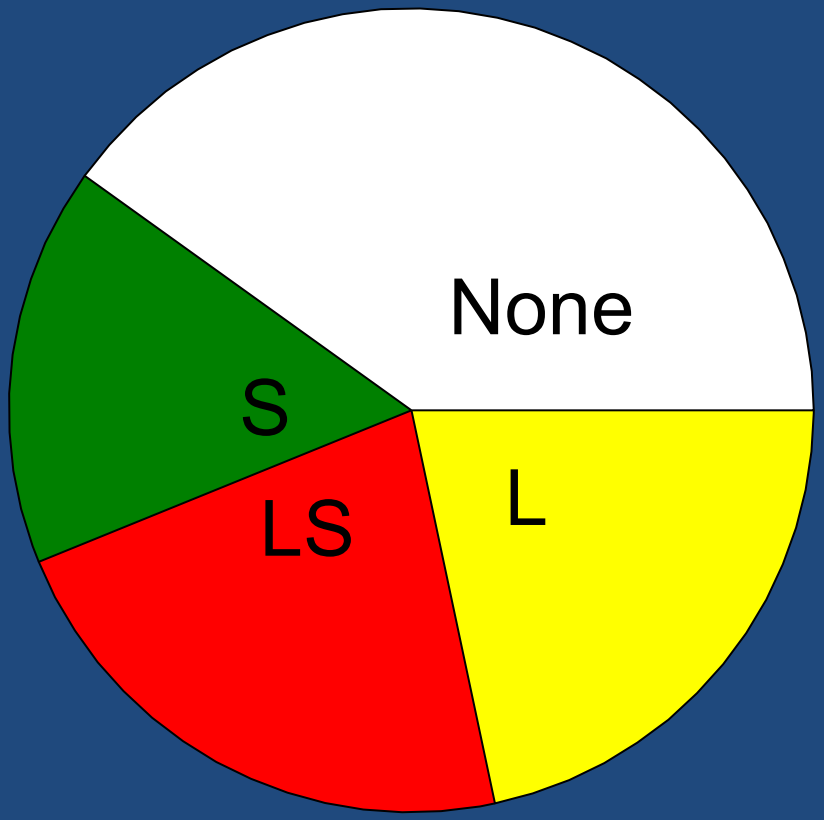
Figure 2. Arteriolosclerosis. The spectrum of small vessel changes in cases of arteriolosclerosis. On the left (**A**), an hematoxylin and eosin stain of a normal vessel (arrow). On the right (**B**) is an example of severe arteriolosclerosis (arrow).





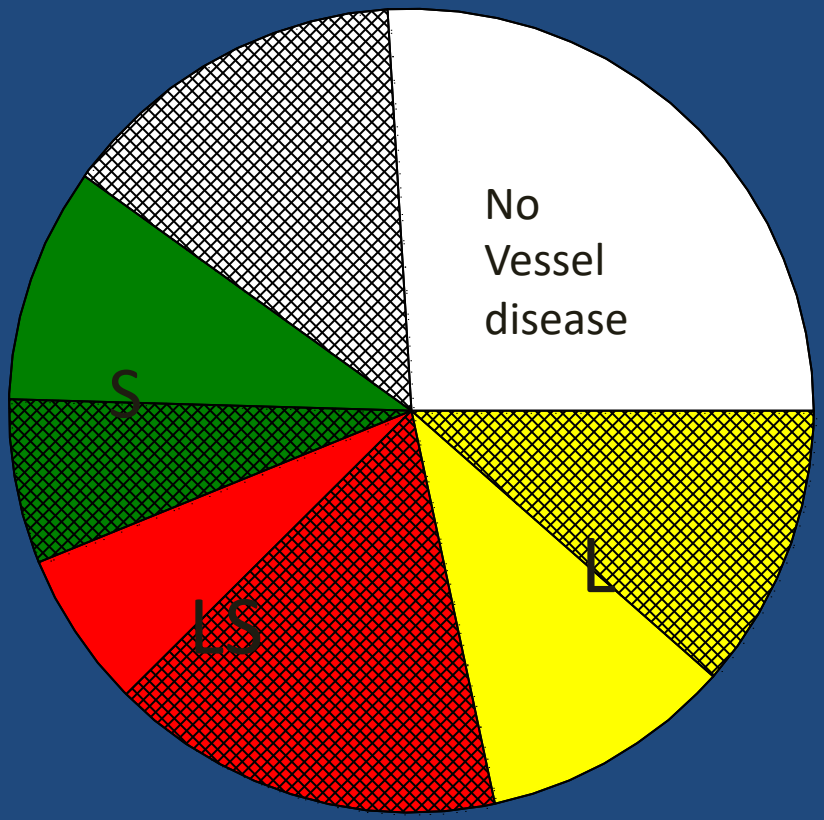
Number of subjects	1, 125
DEMOGRAPHIC	
Age at death, years (SD)	88.2 (6.7)
Female, n (%)	727 (65%)
NEUROPATHOLOGIC	
Gross infarct present, n (%)	396 (35%)
Cortical, n (%)	139 (12%)
Subcortical, n (%)	314 (28%)
Microinfarct present, n (%)	322 (29%)
Cortical, n (%)	181 (16%)
Subcortical, n (%)	175 (16%)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

Vessel Disease



Vessel Disease, with Infarctions

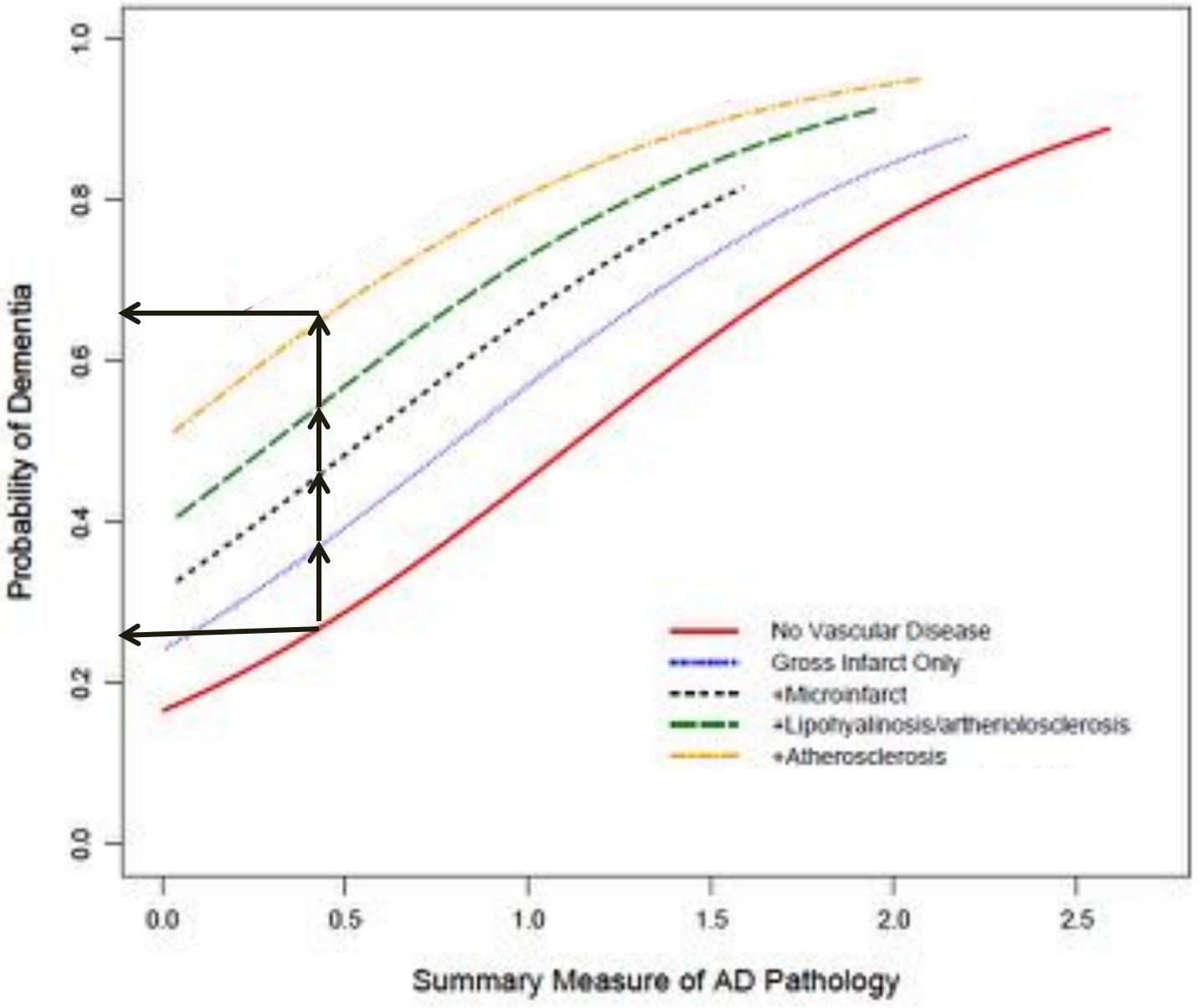
Cross hatches are infarctions



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/arteriolosclerosis
+Atherosclerosis

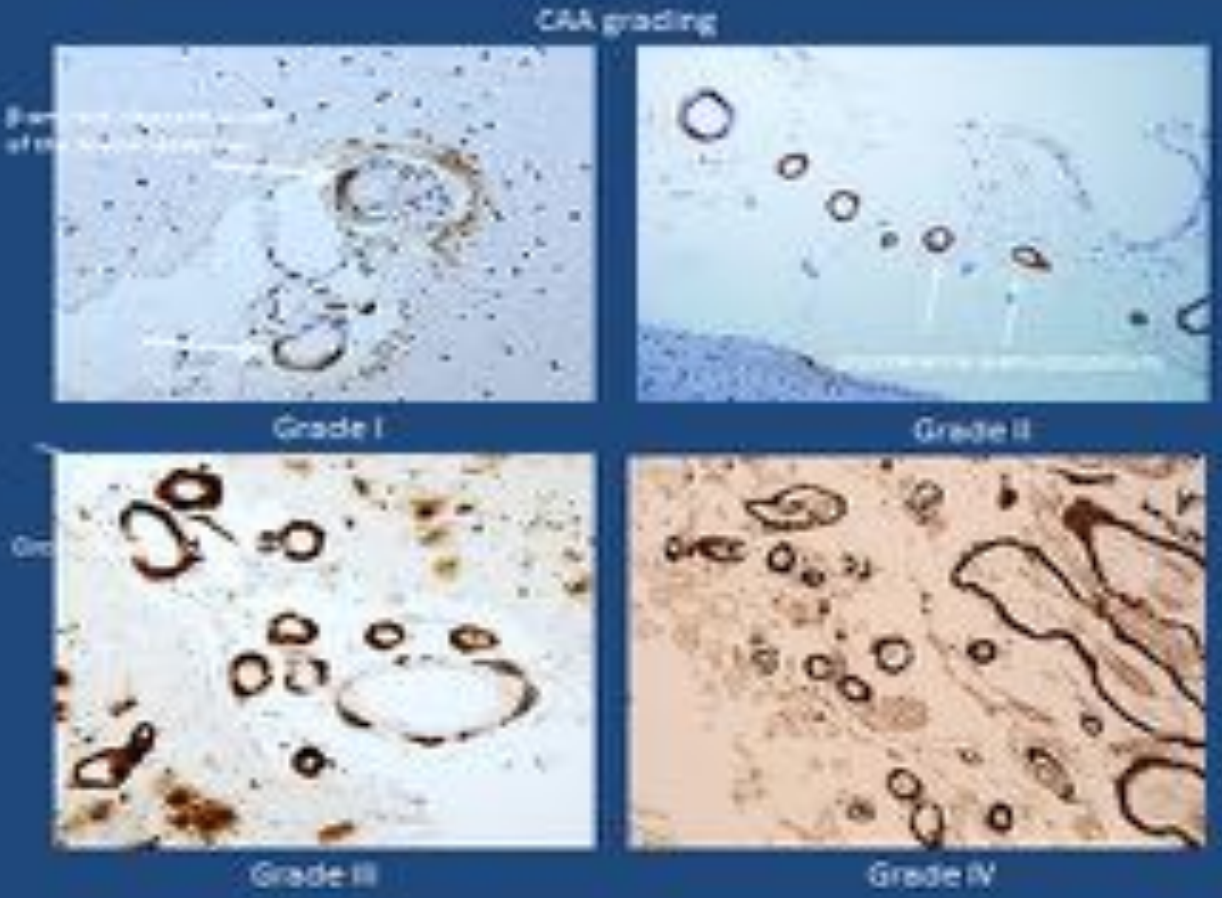
Likelihood of clinical diagnosis of Alzheimer's disease

- 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%)

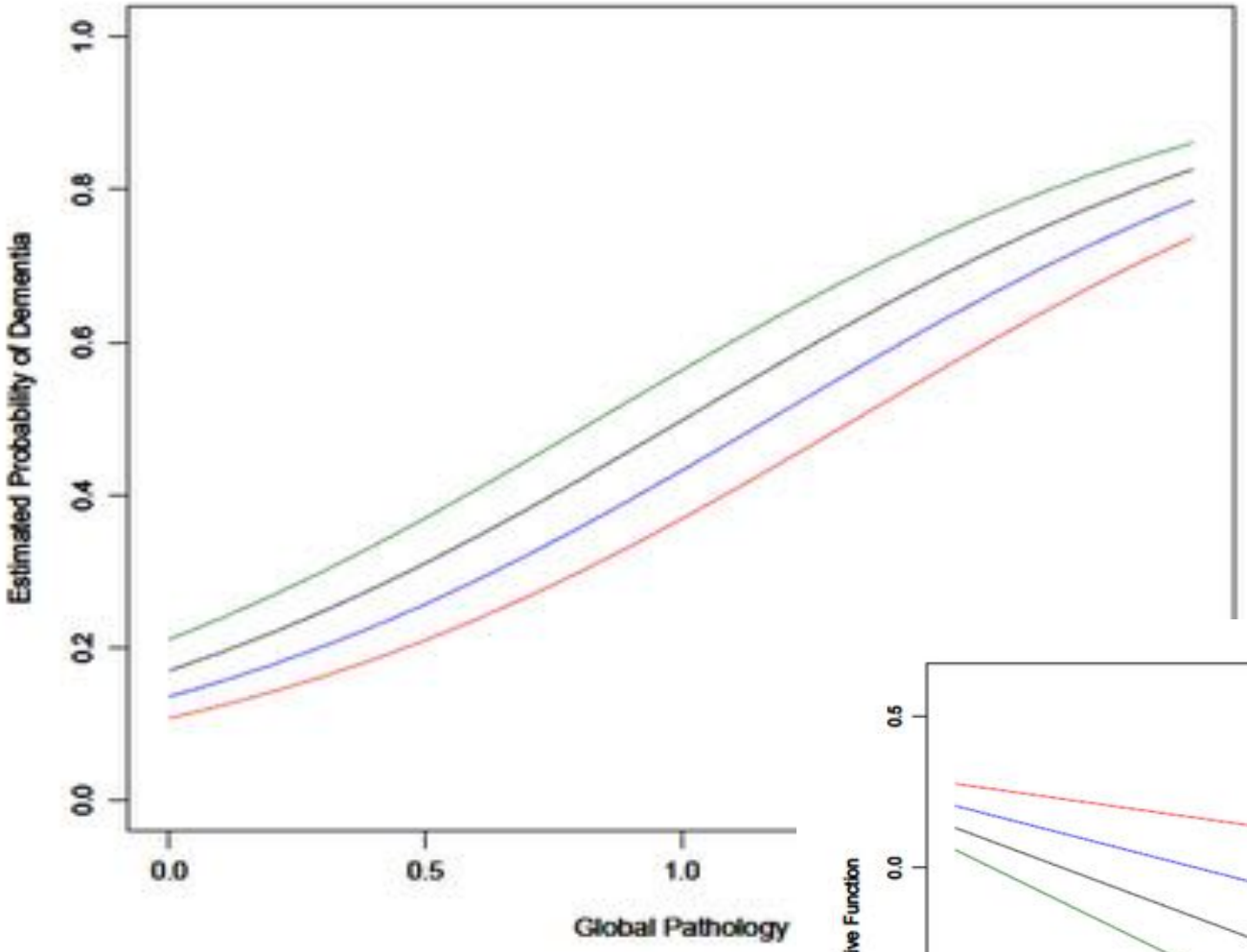


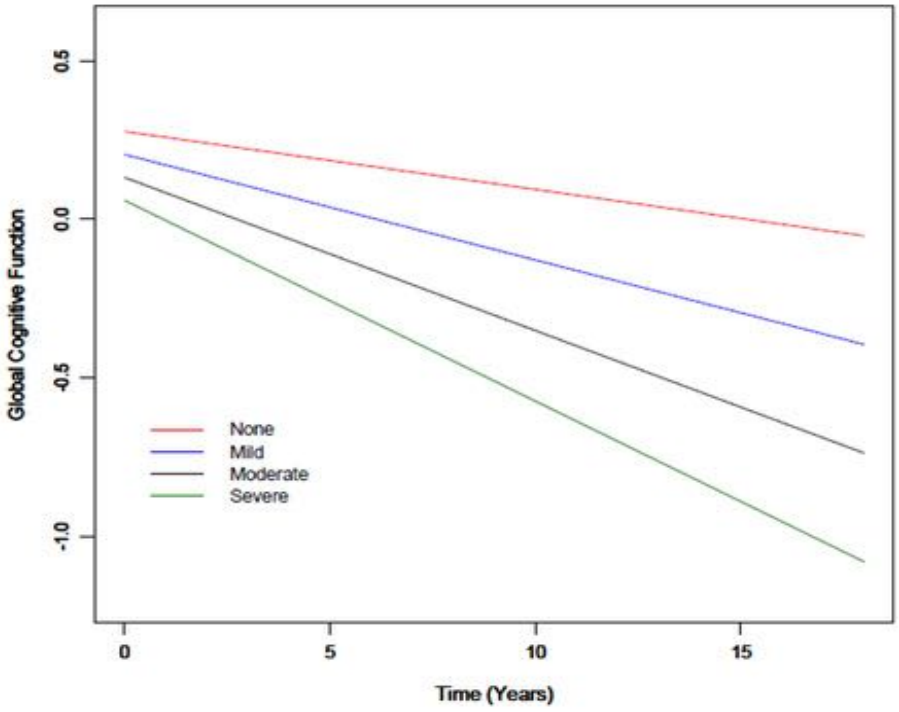
CAA

DEMENTIA

AND

COGNITIVE DECLINE





Boyle et al. Cerebral amyloid angiopathy and cognitive outcomes. Neurology 2015. in press.

Association of CAA with decline in 5 specific cognitive systems

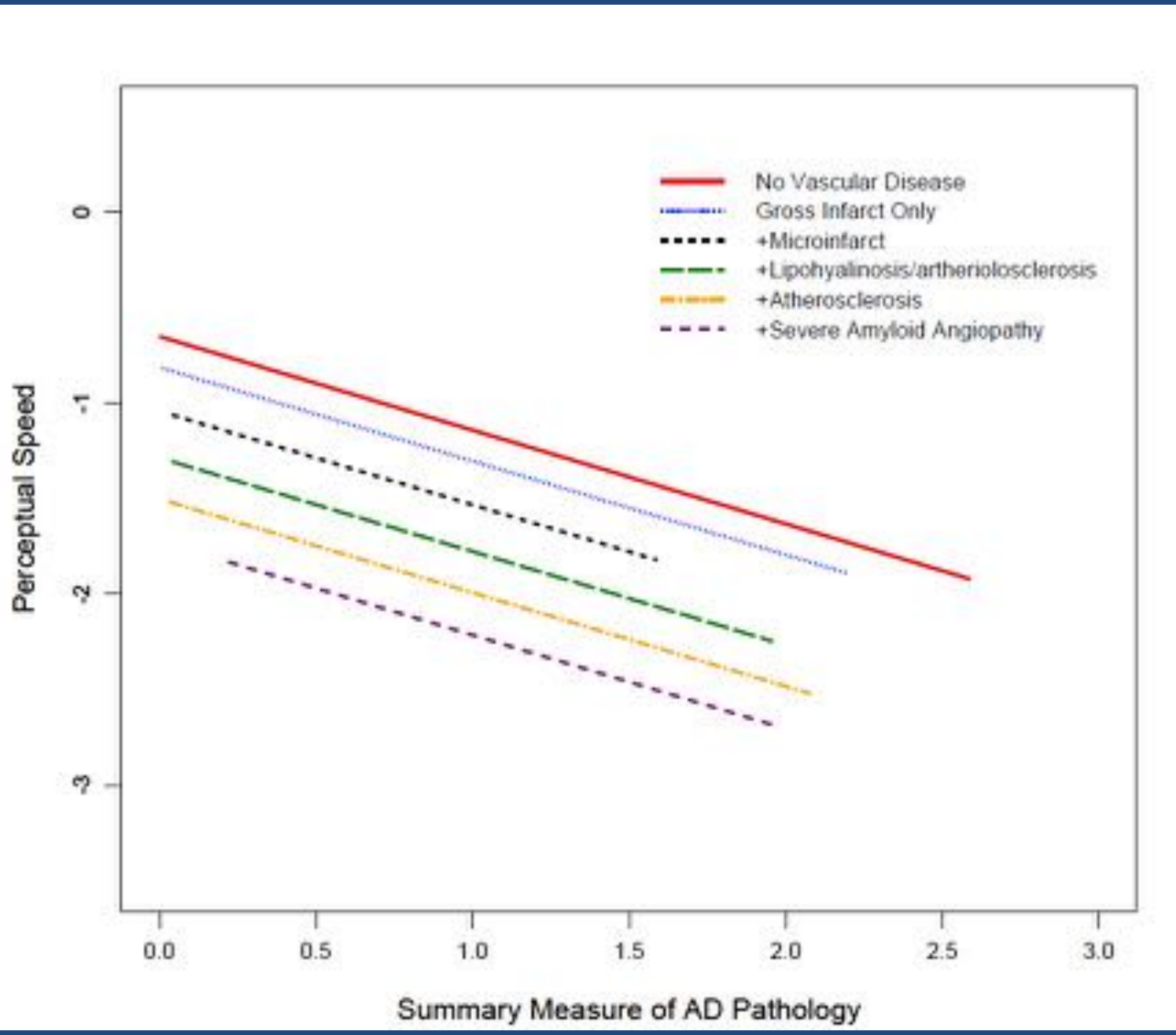
	Episodic Memory beta (SE), p	Perceptual Speed beta (SE), p	Visuospatial abilities beta (SE), p	Working Memory beta (SE), p	Semantic Memory beta (SE), p
Age at death	-.0008 (.0007), 0.290	.0008 (.0007), 0.264	.0007 (.0006), 0.195	-.0002 (.0006), 0.772	.0002 (.0008), 0.837
Male Sex	0.015 (0.010), 0.132	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**

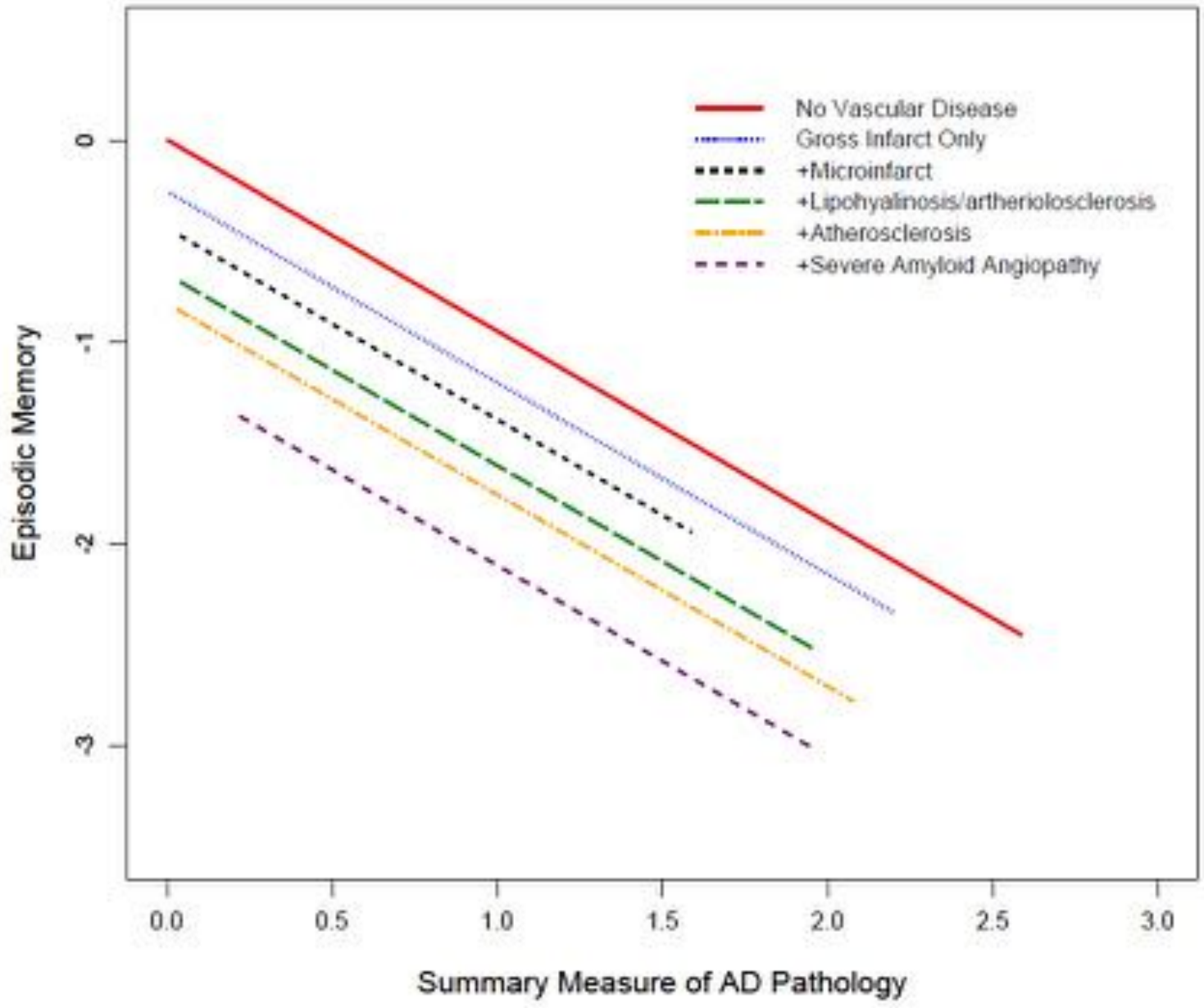
Table 3. Relation of Microinfarcts to Global Cognition and 5 Cognitive Systems*

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/arteriolosclerosis
+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

Role for other pathologies in cognitive impairment in aging

- Lewy bodies - Neocortical Lewy bodies increase odds of dementia and effect all cognitive domains

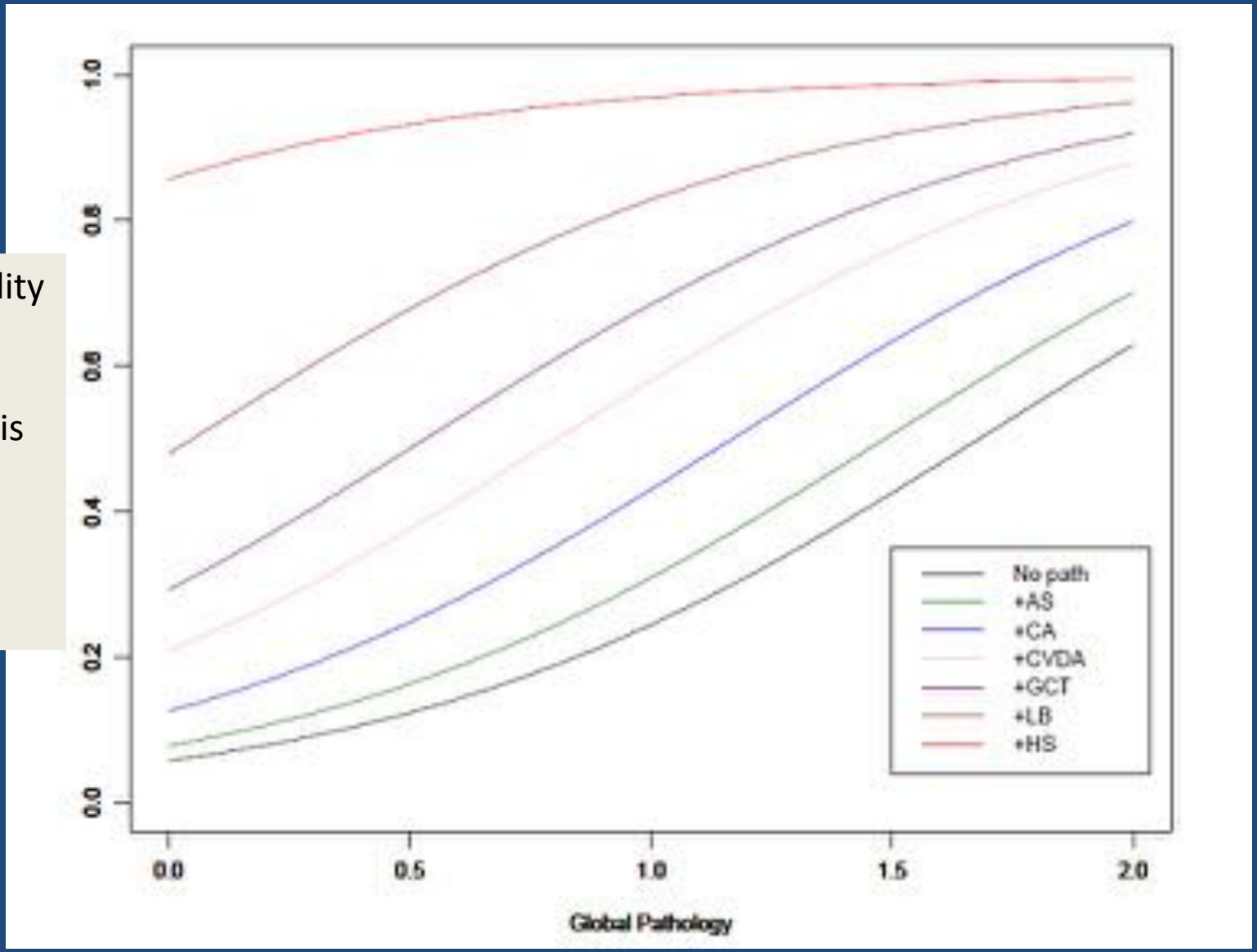
- TDP-43 – very common proteinopathy associated with aging, lowers episodic memory, MCI, and increases odds of dementia.

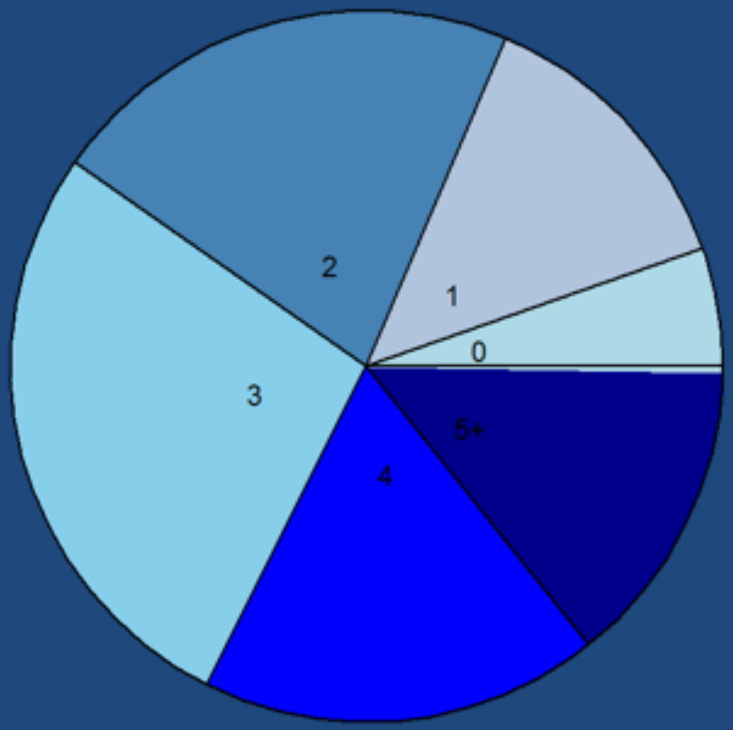
- Hippocampal sclerosis - very common in the oldest old and increases odds of MCI and dementia

- Mesial temporal lobe NFT and memory in late life – PART (primary age related tauopathy)

Add the effect of Lewy bodies and Hippocampal sclerosis….

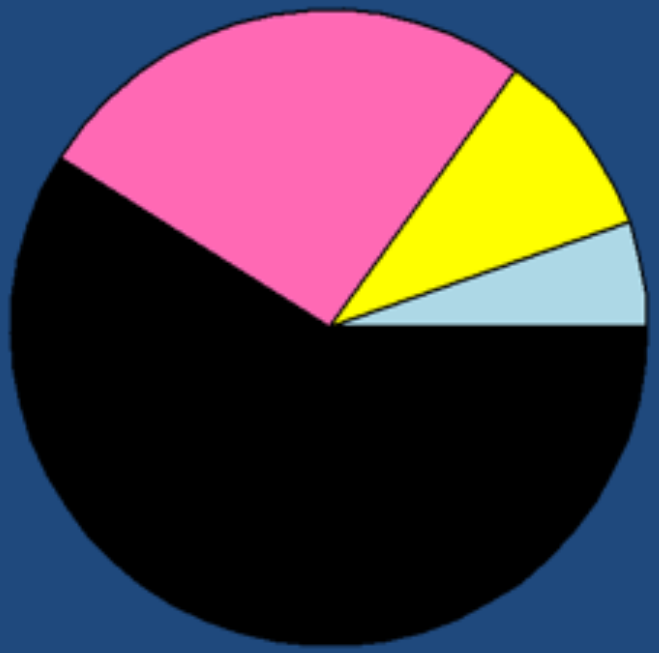
Probability Of Clinical Diagnosis Of AD





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



TDP-43 and aging

~ 50% of cohort (amygdala, Hippocampus/entorhinal cortex, midtemp and frontal)

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

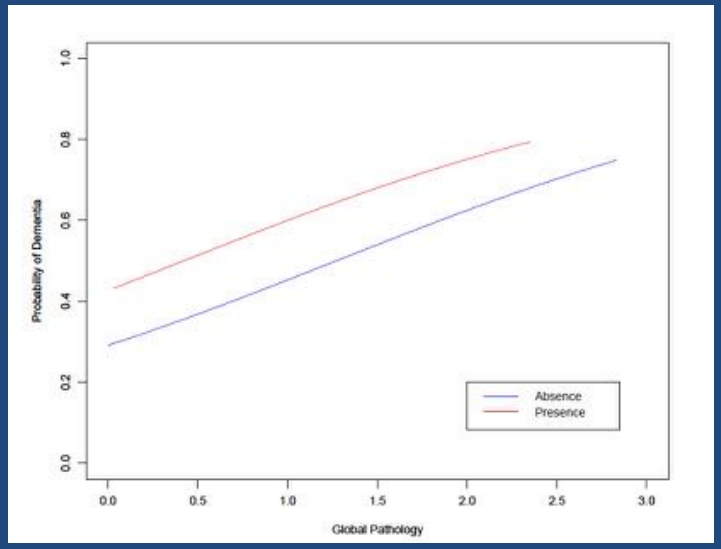
Independently related to loss of episodic memory and increases odds of clinical AD

Original Investigation

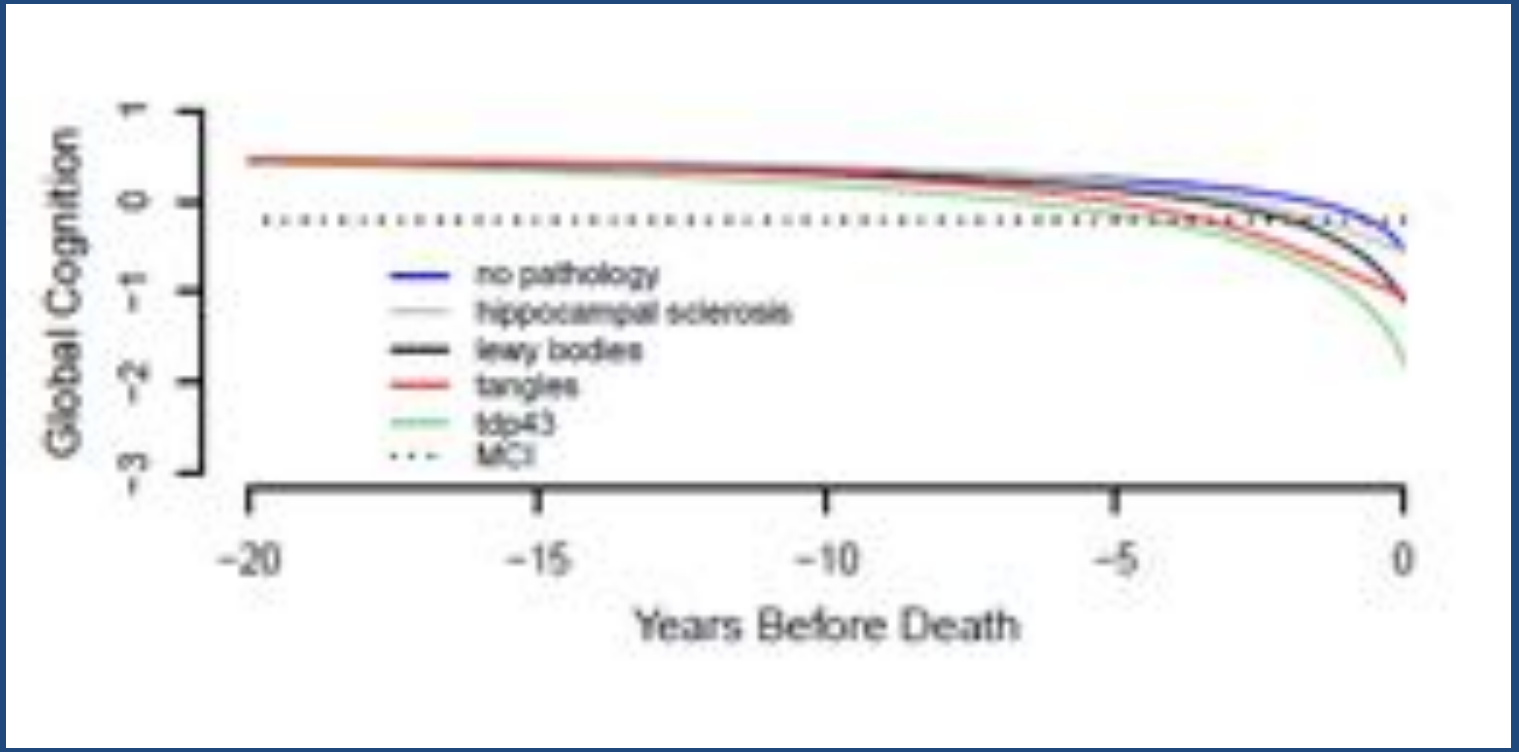
TDP-43 Pathology, Cognitive Decline, and Dementia in Old Age

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

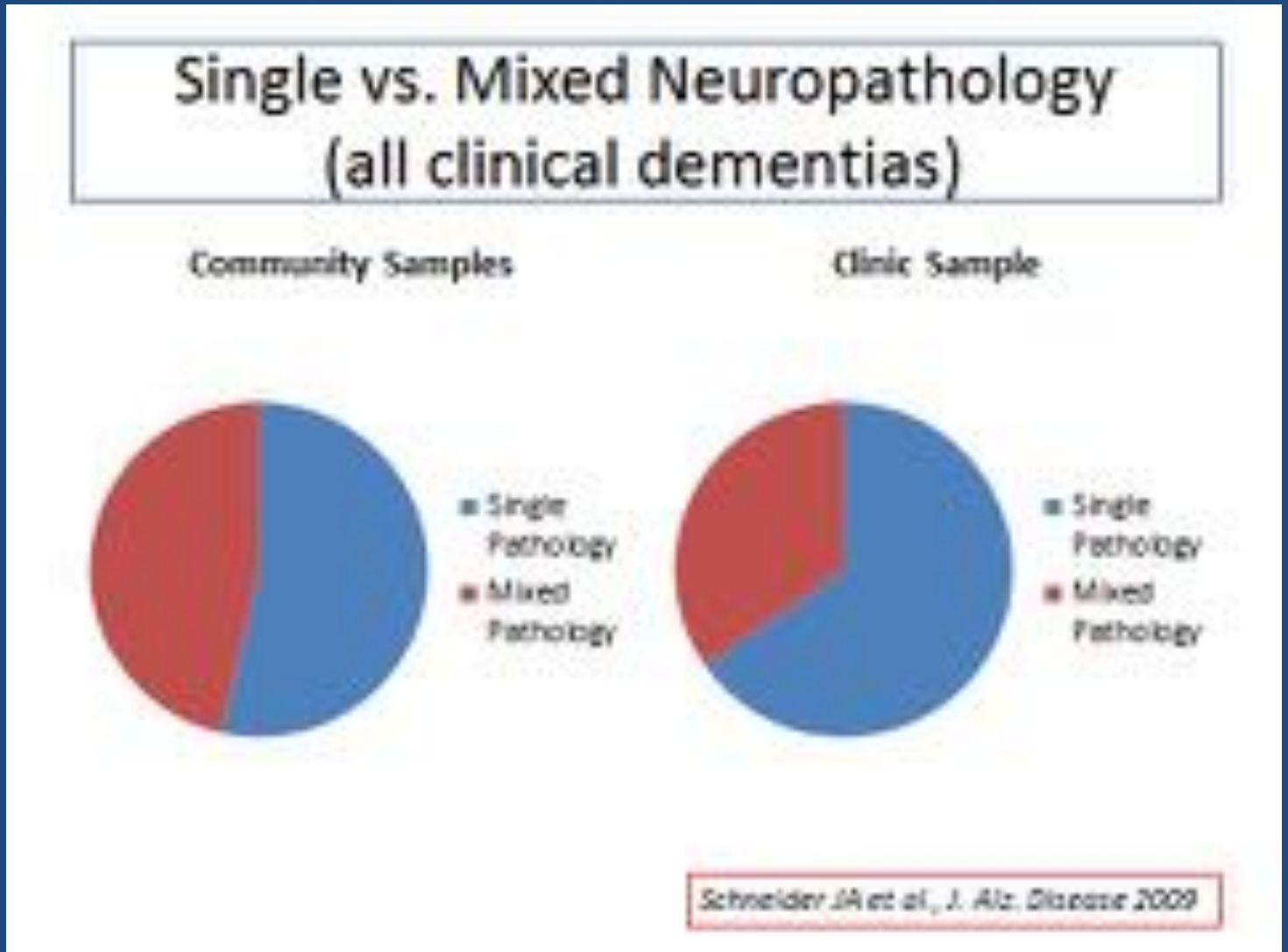
JAMA Neurol. 2013 Nov 1;70(11):1418-24.

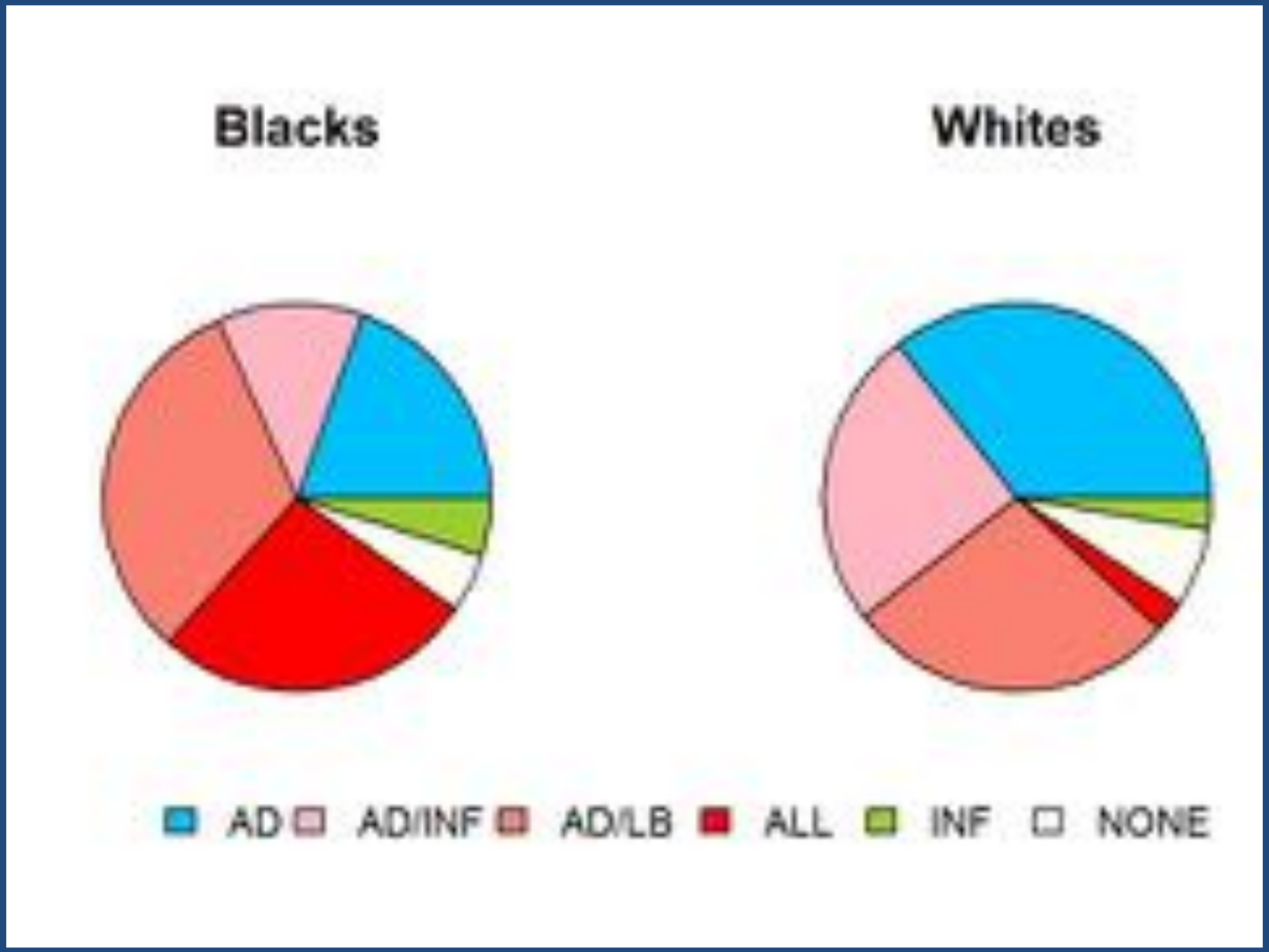


Effect similar to that of tangles in mixed effect models on decline


Global Cognition
1
0
−1
−2
−3
no pathology
hippocampal sclerosis
lewy bodies
tangles
tdp43
MCI
−20
−15
−10
−5
0
Years Before Death

Other special populations and cohort characteristics





Barnes LL et al. Neurology 2015 in press.

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

Implications

1. **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

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. **Clinical trials: implementation / interpretation**

NEITHER DIABETES OR BLOOD PRESSURE RELATED TO PLAQUES OR TANGLES…

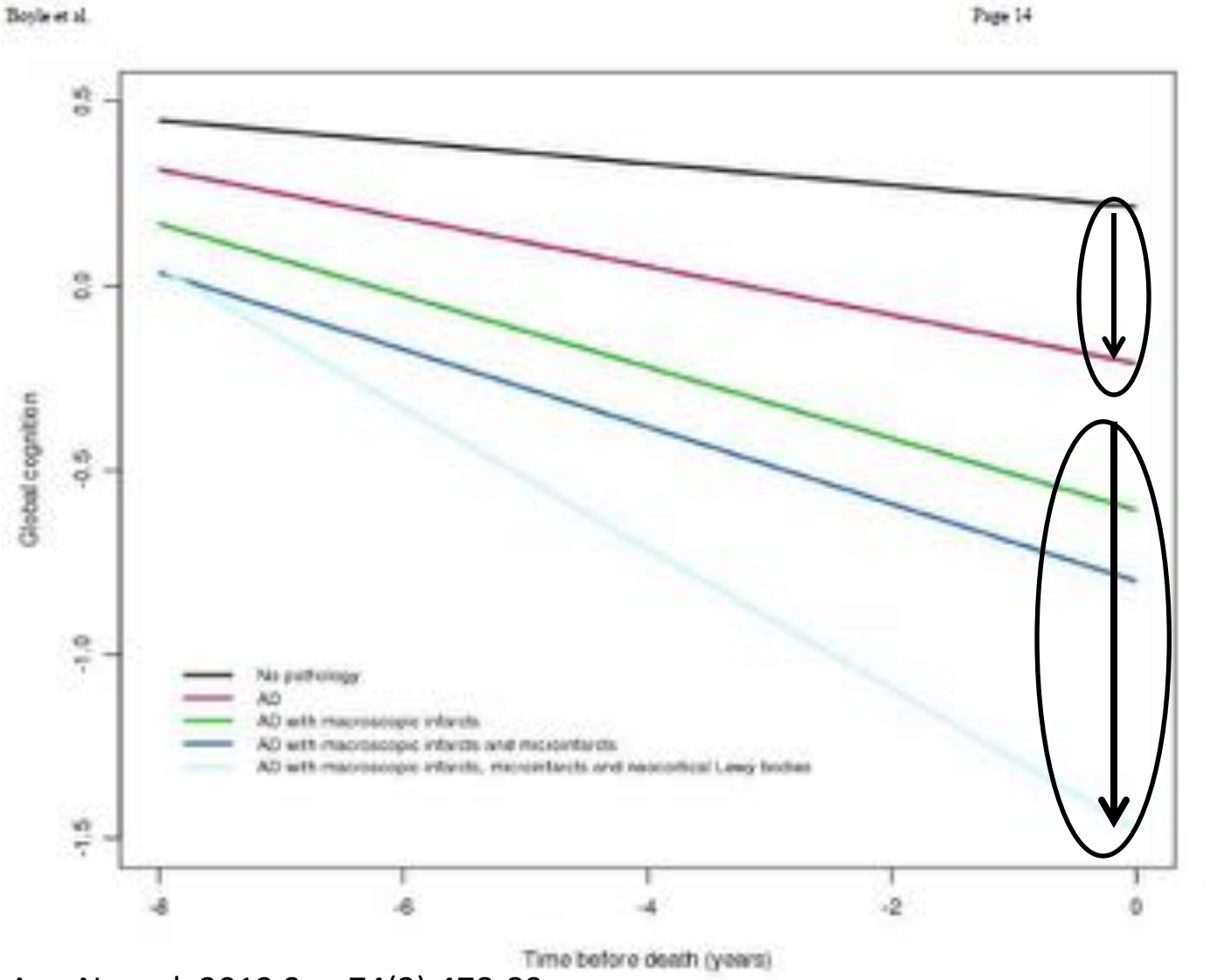
- Diabetes (any diagnosis during study period)
  - Shown to increase risk of AD in the Religious Orders Study
  - Dx of diabetes increased odds of gross infarcts– 2.6 - fold increase in odds of gross (p=0.0002)
    - 2- fold increase odds of subcortical micro (p=0.006)
    - 60% increase of each level 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)

- **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…
- Current Biomarkers helpful but not sufficient - to change problem of many of the mixed pathologies…

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…

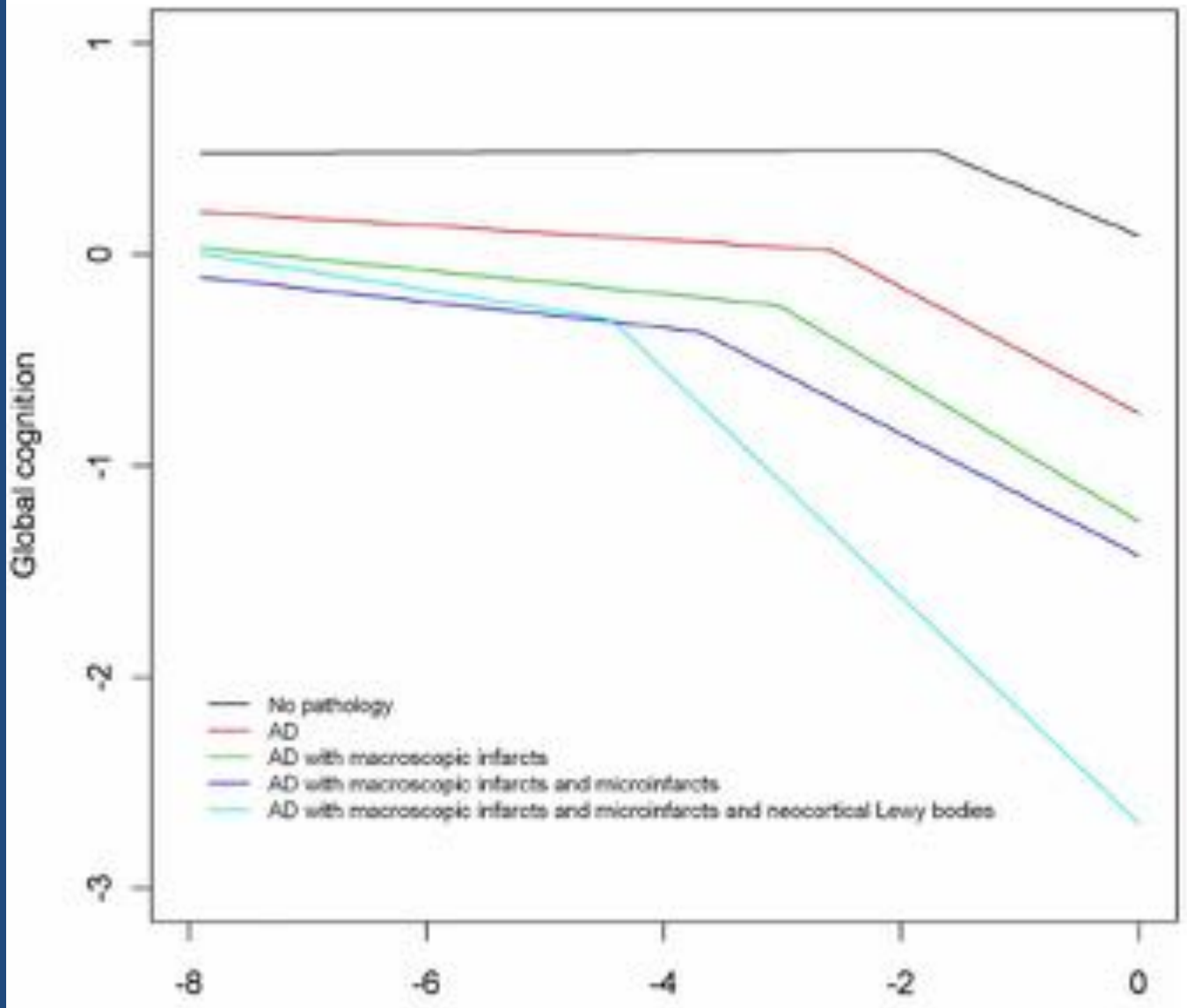
1. Preterminal slope shallow

2. Change pt early 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…

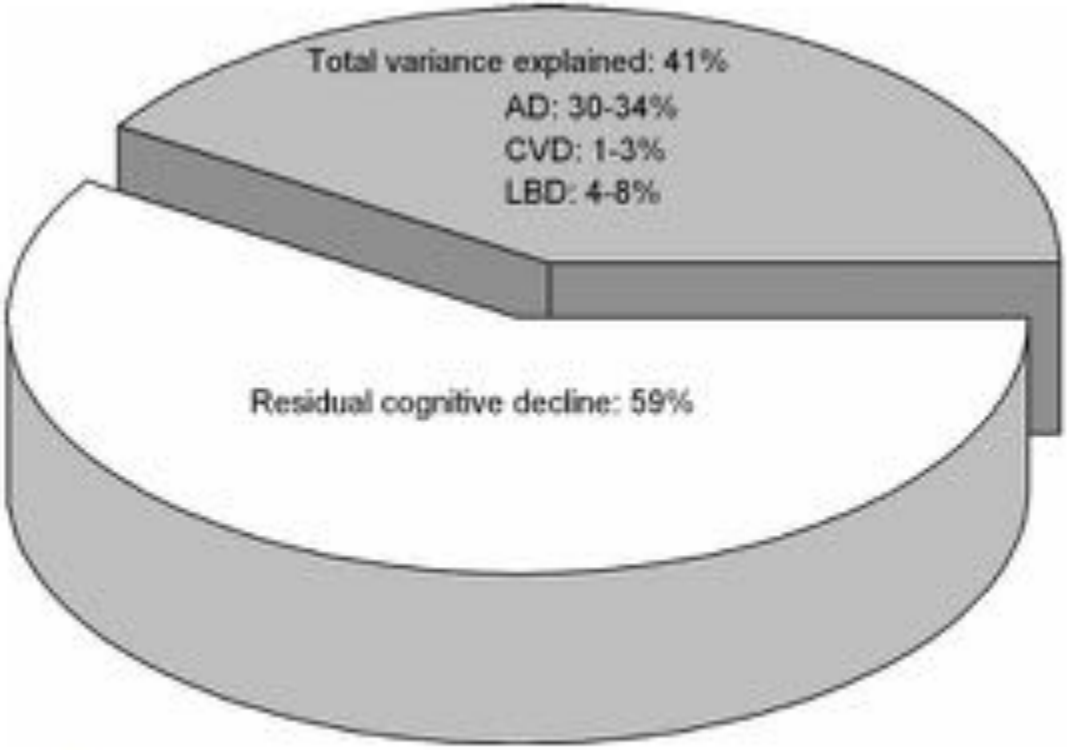


Figure 3.
Variation in cognitive decline explained by the pathologic indices (grey) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models.

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 Clinical AD (dementia overall).
- Neurodegenerative and vascular, often multiple
- Add to likelihood of dementia, clinical AD, trajectory/pattern 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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- Study Participants
- Religious Orders Study
- Rush Memory and Aging Project


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