Diagnostic Complexities in Current Clinical and Morphological Criteria for Alzheimer's Disease

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Disclosures

Consultant

- Avid radiopharmaceuticals
- Navidea biopharmaceutcals

Neither relevant for current talk

Diagnostic Complexities in Current Clinical and Morphological Criteria for Alzheimer's Disease

- Spectrum of pathologies accumulate in the aging brain

- Neural reserve – diverse pathologies decrease reserve

- Complex mix of pathologies expands beyond cerebral infarcts and LB
  - Vascular – vessel disease
  - Degenerative – TDP and HS
  - Primary Age Related Tauopathy
  - Complex Mix of Genetic factors (eg. apoE and TMEM106)

- Overlap of clinical phenotypes
  - Episodic memory - primary domain of AD pathology, TDP-43 pathology, primary age related tauopathy
  - Also affected by HS/LB/vascular pathologies

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 > 660 autopsies

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%*
- *>650 autopsies*

- **Overall over 3160 enrolled/1520 died/1313 autopsies**

- **Annual visits: Interviews, Scales for depression, diet, decision making etc., Medical histories, Neurologic Exams, Neuropsych testing, Annual Clinical diagnoses of AD and other dementias (and final dx)**

- **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

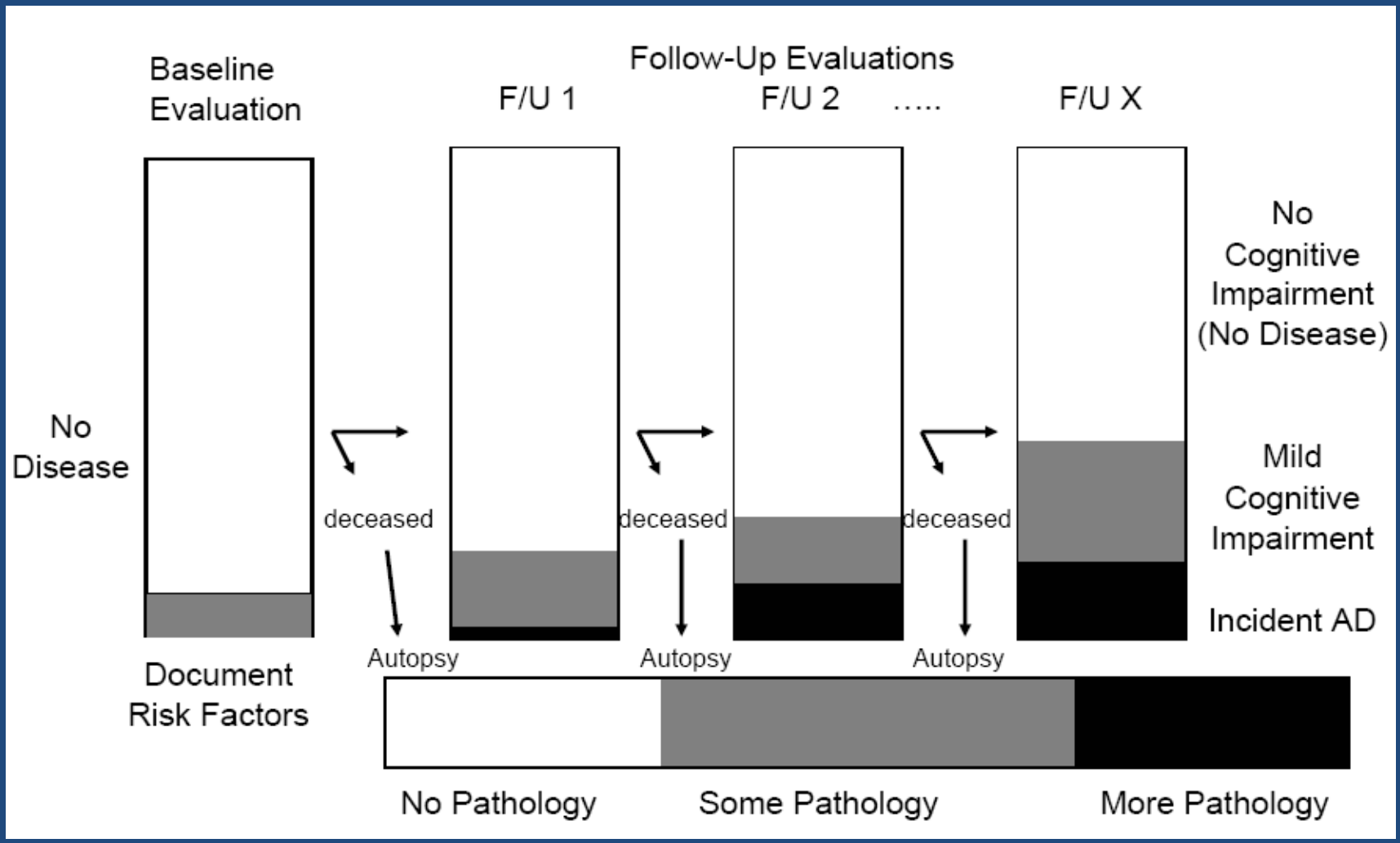
  Working Memory: Digit Span forward/backward; Digit Ordering; Alpha Span

  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)

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.
- Slabs from 1 hemisphere imaged, then fixed – other frozen

- Paraformaldehyde-fixed/paraffin-embedded/6µm sections

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

- Path diagnosis of AD
  - Modified NIA – Reagan (CERAD and Braak)
  - New NIA-AA criteria

- **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

Important notes about AD pathology

1. Moderately to strongly related to cognition/dementia; about 87% of those with clinical dx of AD dementia have dx confirmed by pathology

2. Inter-individual variation in the expression of AD pathology

3. Normal Aging

   - 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

4. Mild Cognitive Impairment

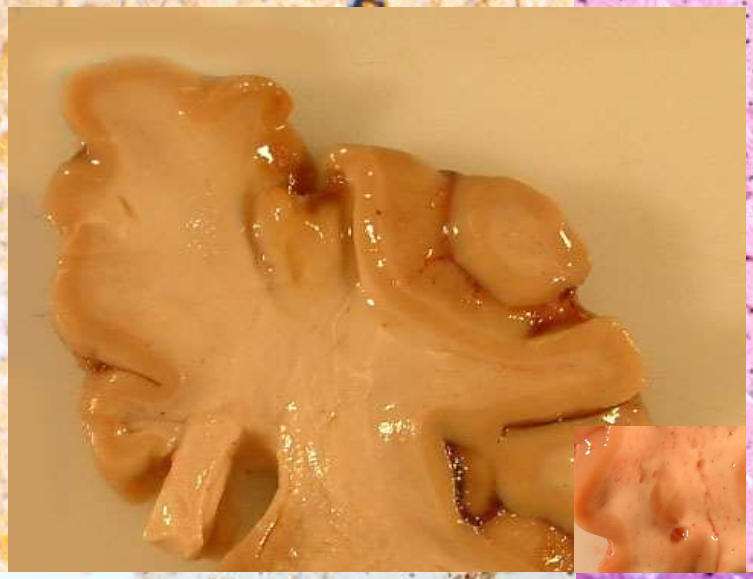
   - AD pathology is intermediate between normals and demented
   - About ½ with sufficient pathology for a dx of AD but ~ 1/3 having no neocortical neuritic plaques; ~ 20% with Braak 1/2.

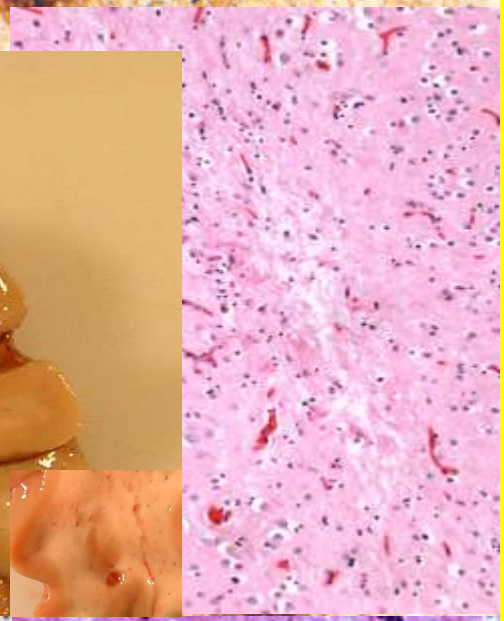
Neural Reserve

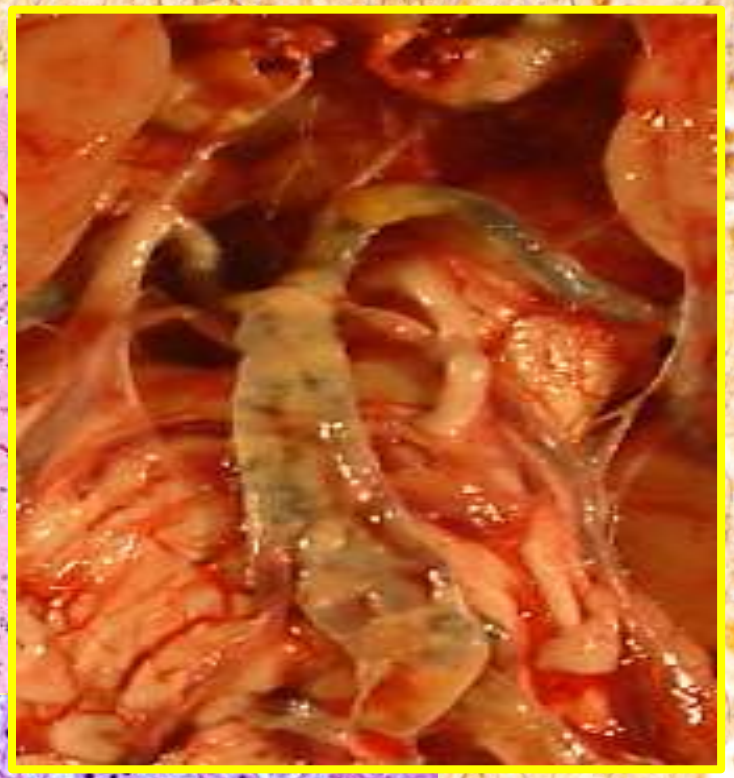
- 1/3 of older persons have sufficient AD pathology in brain to fulfill criteria for pathologic diagnosis of AD

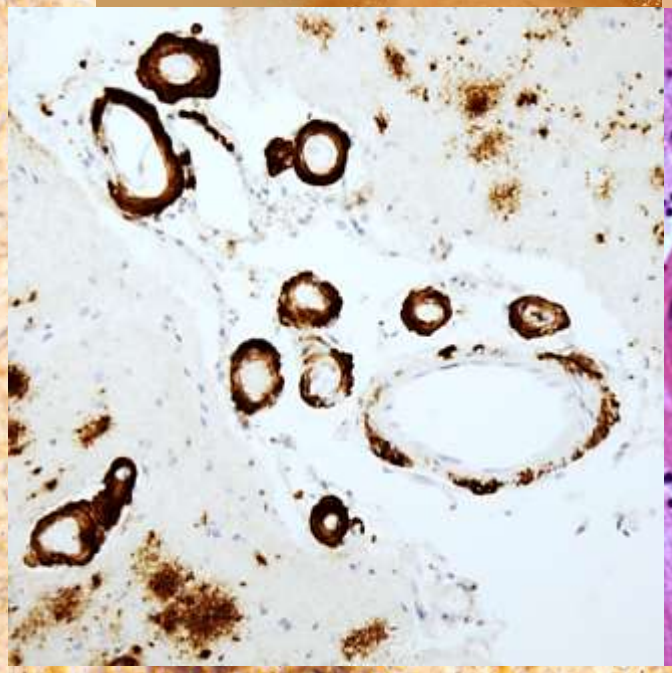
- Those factors related to “reserve”
  - Education and Cognitive activities
  - Social, physical activity
  - Depression
  - Well-being/purpose in life
  - Diet
  - Genetic factors

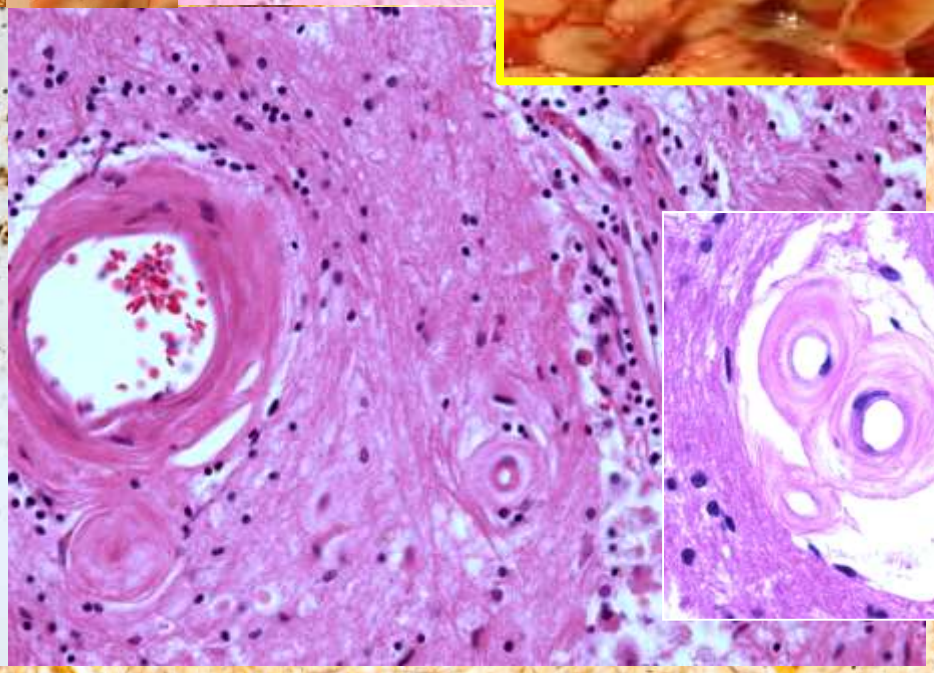
  - Other age-related pathologies in the brain

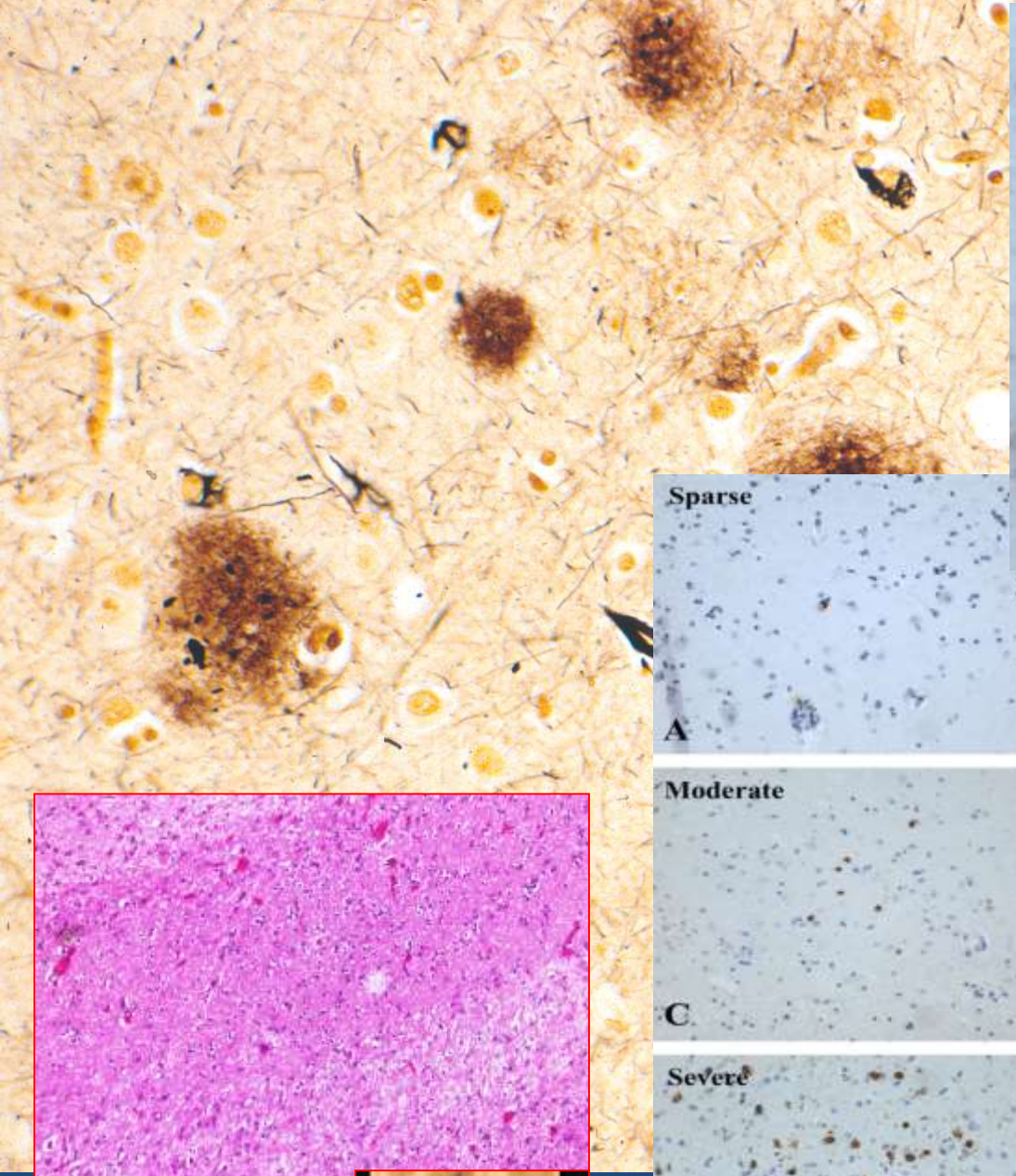


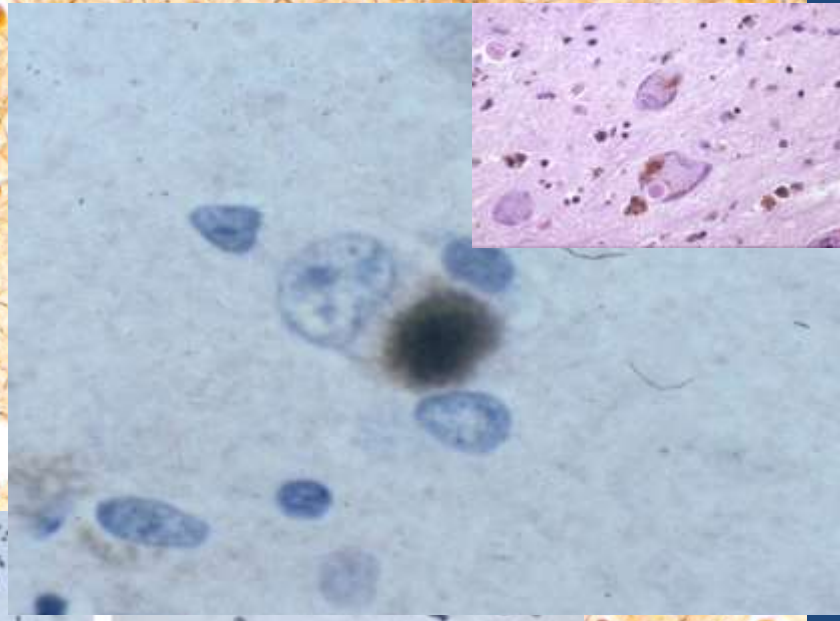








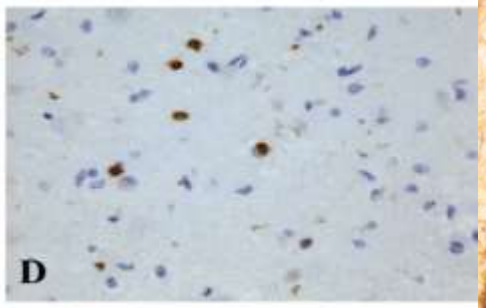


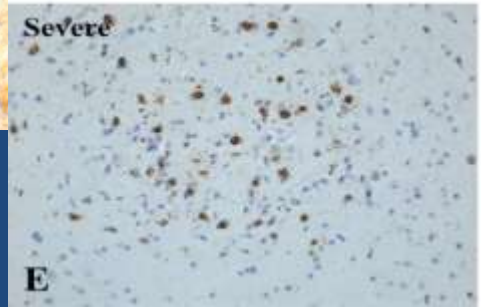


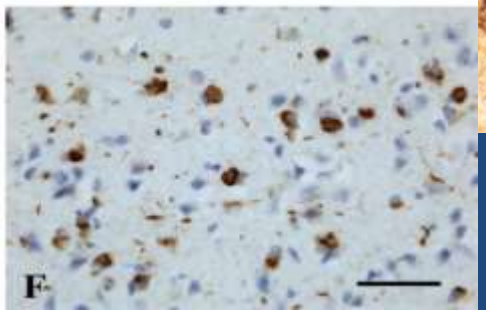
Sparse
A


B

Moderate
C


D


Severe
E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Brain pathologies associated with cognitive impairment in older persons

Alzheimer's disease pathology (amyloid/and tangles)

Vascular (infarcts/vessel disease)

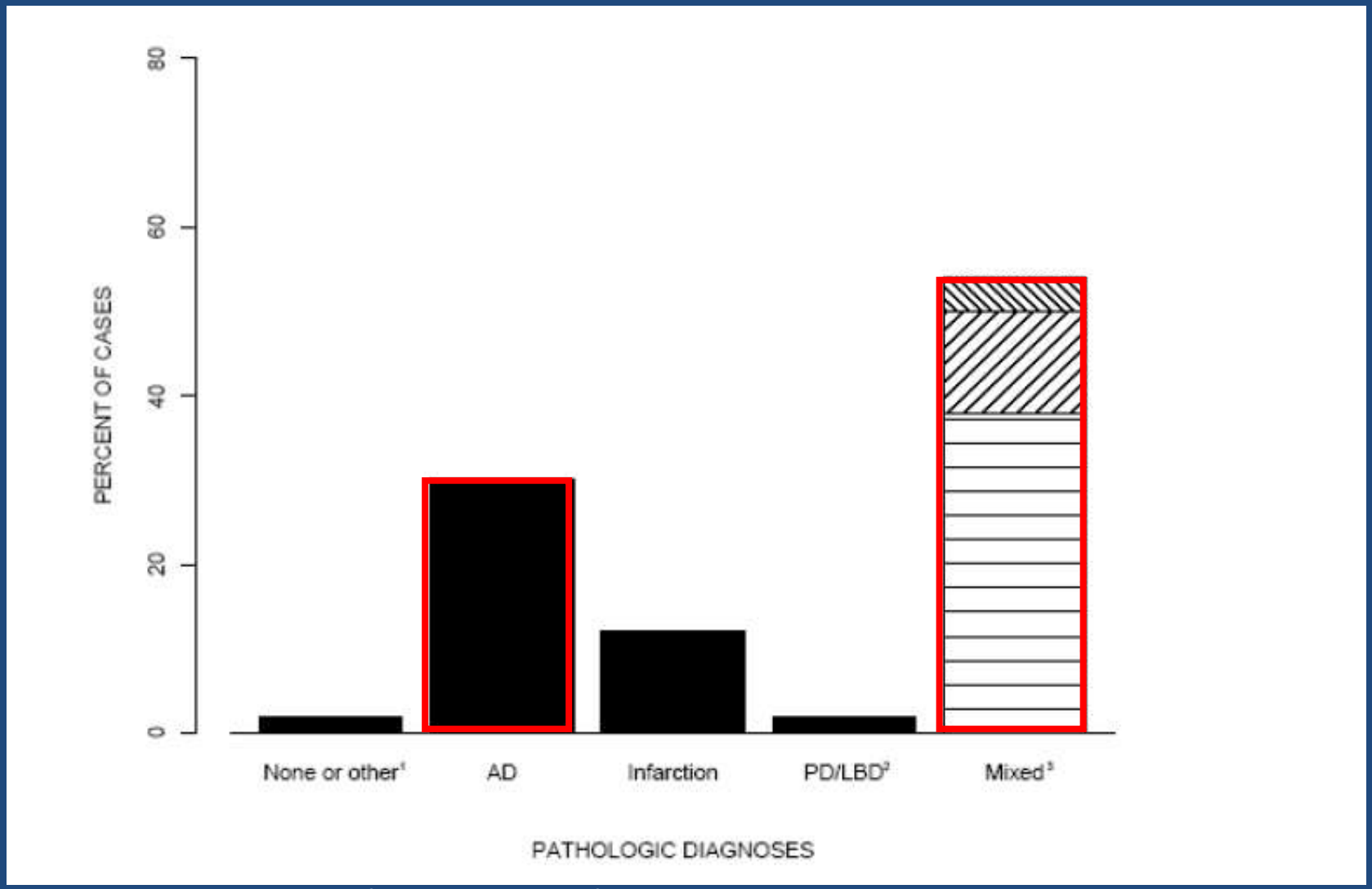
TDP-43 pathology

Lewy bodies

Hippocampal sclerosis

PART (mesial temporal tangles)

Mixed brain pathologies in dementia – common in dementia (141 autopsies– 91 no dementia; 50 dementia)



Rush Memory and Aging Project

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

Mixed brain pathologies common in MCI and probable AD

483 autopsied participants from the Religious Orders Study and the Rush Memory and Aging Project

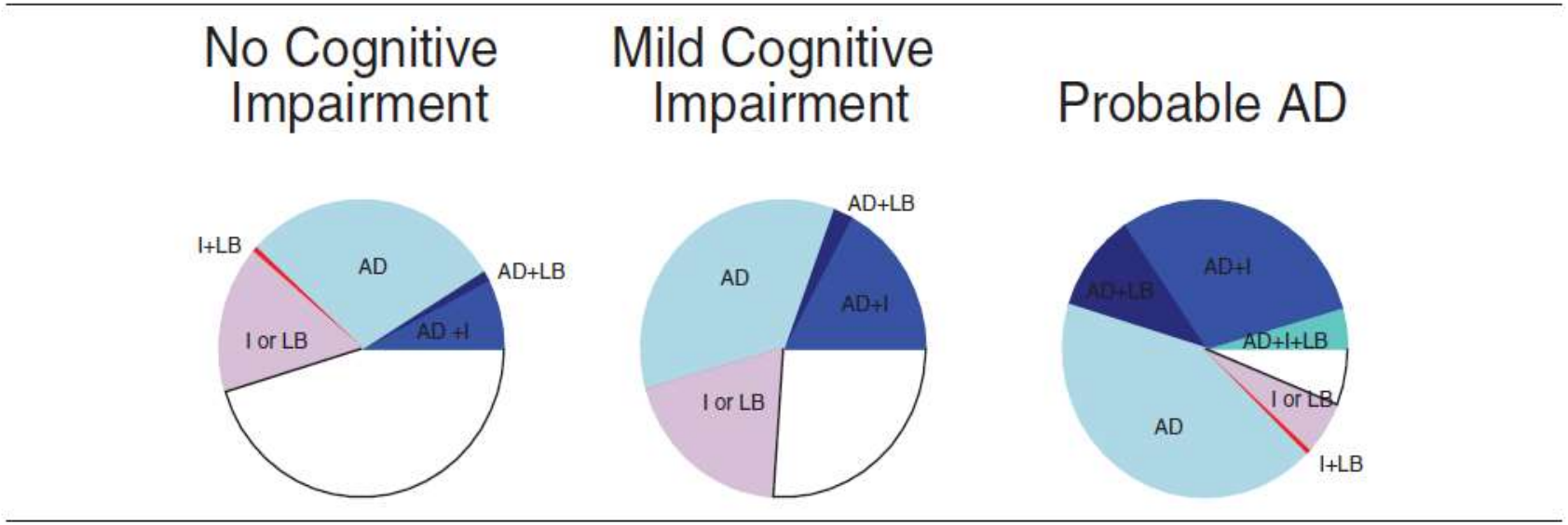


*Fig. Pathology by clinical status proximate to death. (*Blue shades*) Pathologic diagnosis of Alzheimer disease (AD). Clockwise: light blue = pathologic diagnosis of AD only; dark blue = pathologic diagnosis of AD and neocortical Lewy bodies (LB); medium blue = pathologic diagnosis of AD and cerebral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

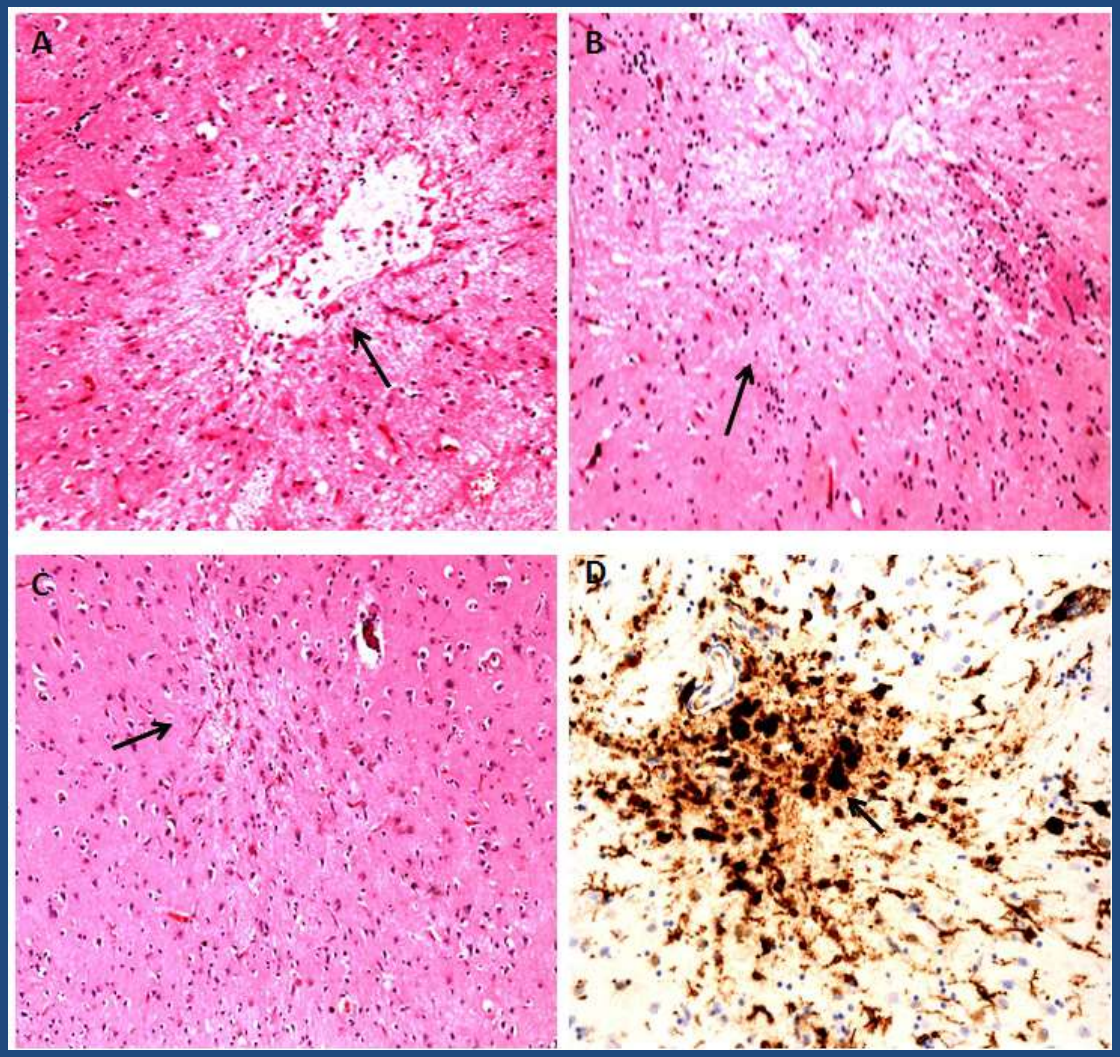
Schneider JA et al. *Ann Neurol* 2009;66:200–208.

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

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

Microscopic infarcts – “invisible lesions”

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

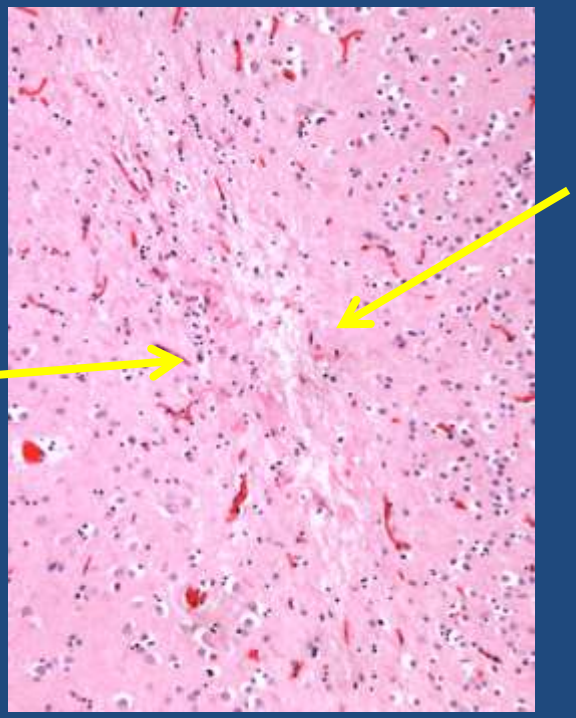


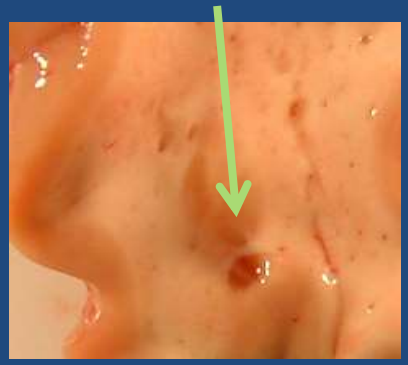
Smith E. et al. The invisible lesions. Lancet Neurology 2012

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





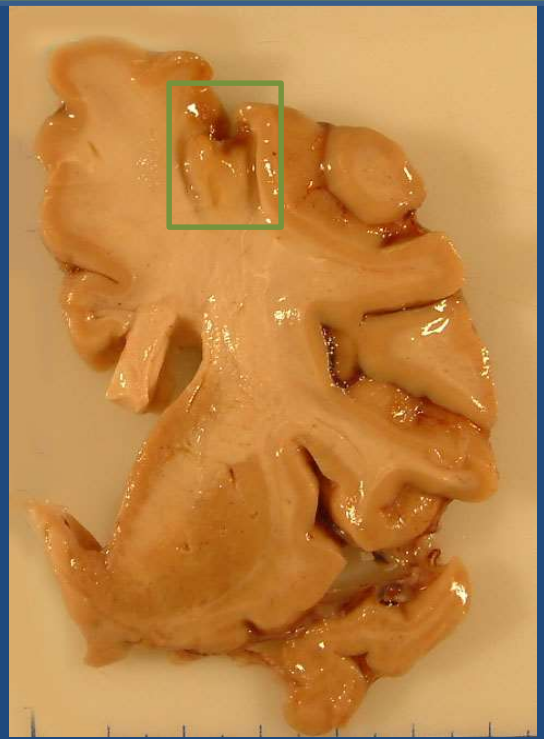


Table 1. Characteristics* of Subjects

	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!

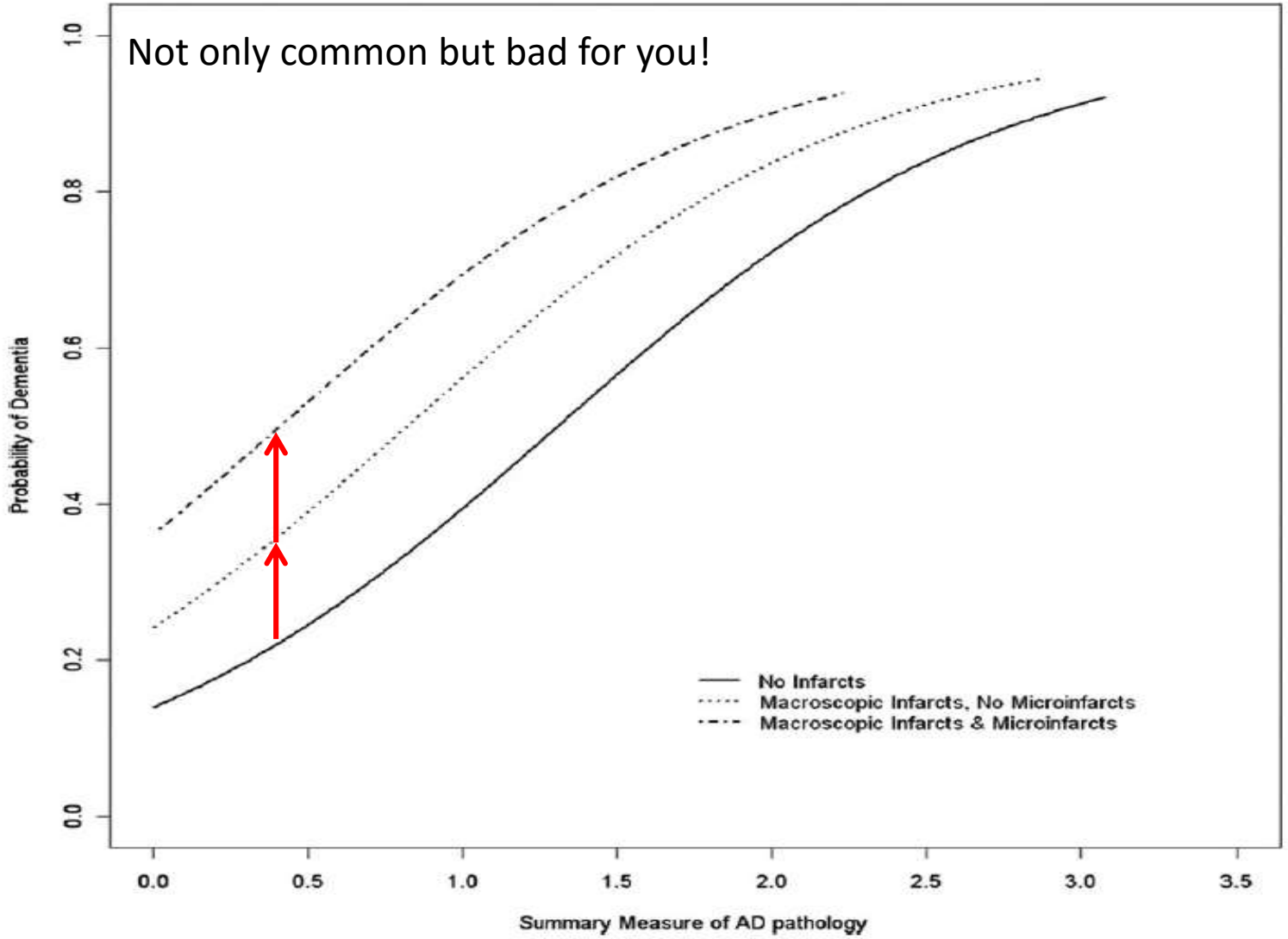


Figure 1. Probability of dementia by Alzheimer disease pathology showing additive effects of macroscopic infarcts and microinfarcts.

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

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.

How about Vessel pathology?

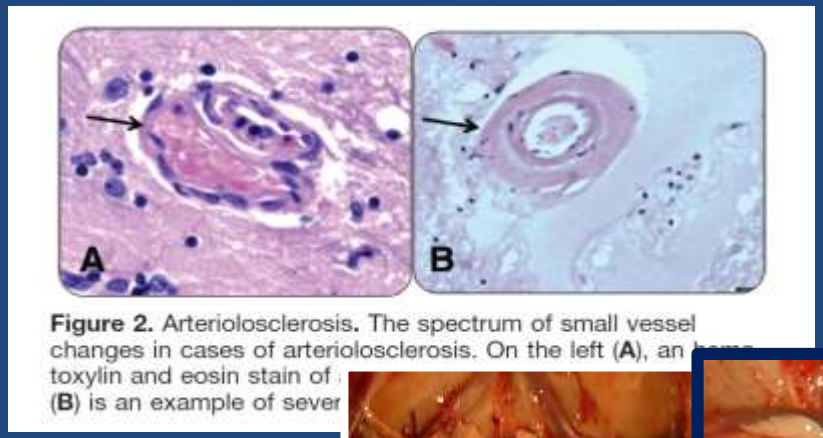
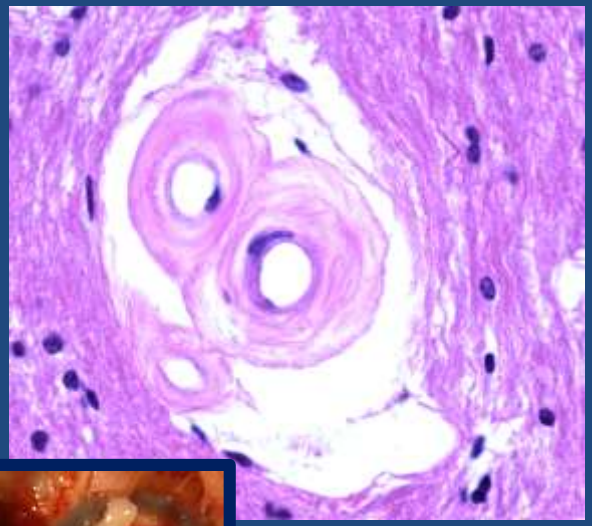
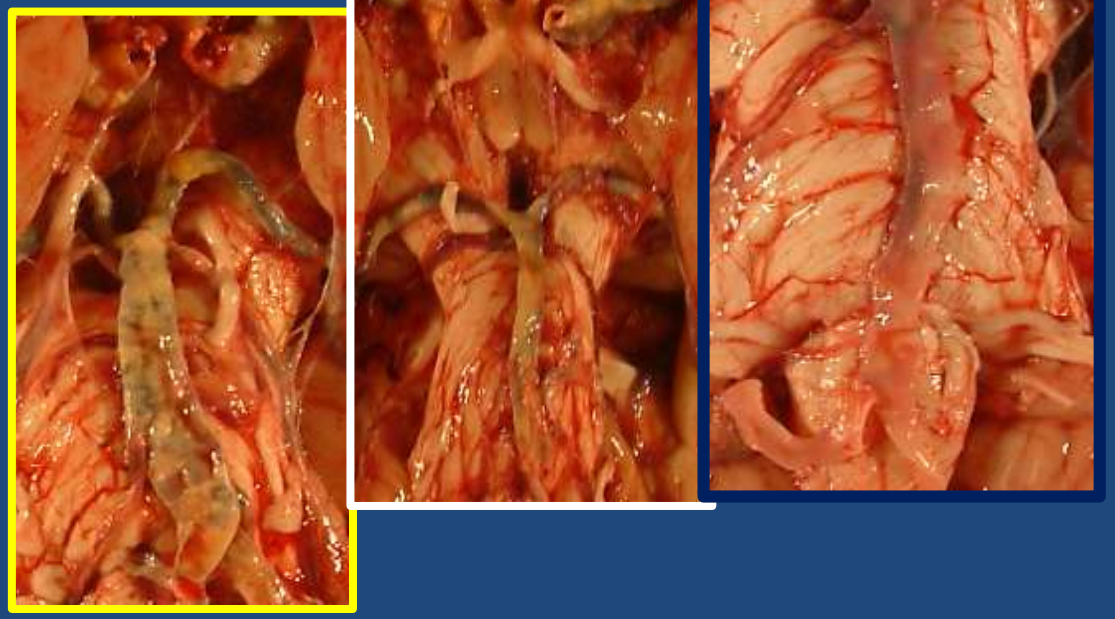


Figure 2. Arteriolosclerosis. The spectrum of small vessel changes in cases of arteriolosclerosis. On the left (**A**), an [illegible] toxylin and eosin stain of [illegible] (**B**) is an example of sever[illegible]





Atherosclerosis and arteriolosclerosis increase odds of gross and microinfarcts but also add to likelihood of dementia

- Cerebral Amyloid Angiopathy – moderate to severe in about 1/3 of older persons

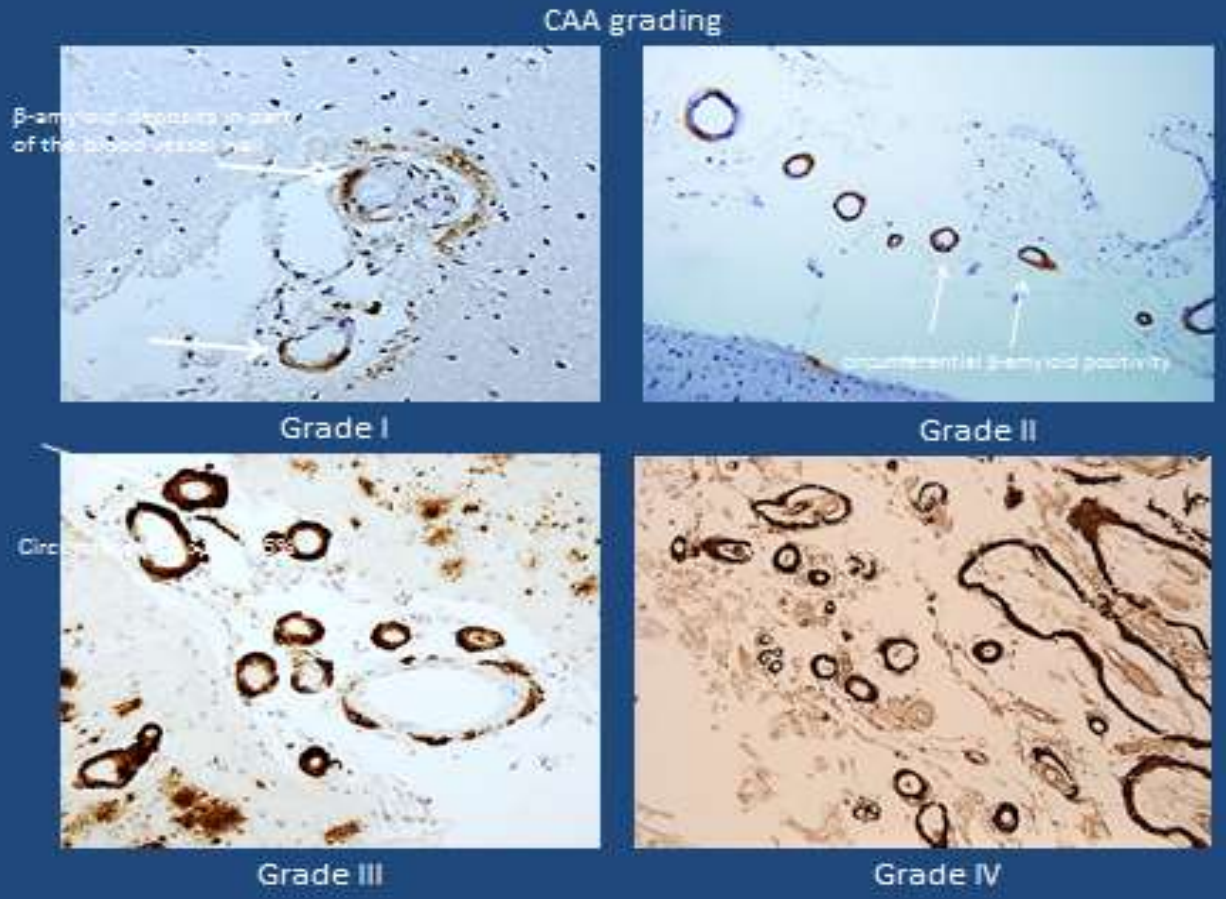


Table 2 Association of CAA with AD dementia[a]

Model terms	OR (95% CI)	OR (95% CI)
Age at death	1.074 (1.052-1.096)	1.070 (1.046-1.095)
Male sex	0.892 (0.679-1.170)	0.970 (0.719-1.307)
Education	1.018 (0.983-1.054)	1.033 (0.994-1.074)
AD	—	3.868 (3.005-4.981)
Macroscopic infarcts	—	1.510 (1.257-1.815)
Microinfarcts	—	1.180 (0.958-1.453)
Lewy bodies	—	2.176 (1.567-3.023)
CAA	1.523 (1.352-1.715)	1.237 (1.082-1.414)

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; CI = confidence interval; OR = odds ratio.
[a] Derived from separate logistic regression models.

Table 3 Association of CAA with decline in global cognition[a]

Model terms	β (SE), *p* value	β (SE), *p* value
Age at death	−0.0009 (0.0007), 0.183	−0.000007 (0.0006), 0.9061
Male sex	0.013 (0.009), 0.165	0.005 (0.008), 0.533
Education	0.002 (0.001), 0.118	0.001 (0.001), 0.230
AD	—	−0.087 (0.007), <0.0001
Macroscopic infarcts	—	−0.022 (0.005), <0.0001
Microinfarcts	—	−0.002 (0.006), 0.703
Lewy bodies	—	−0.046 (0.009), <0.0001
CAA	−0.029 (0.004), <0.0001	−0.012 (0.004), 0.0001

Abbreviations: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; SE = standard error.
[a] Derived from separate mixed-effects models.

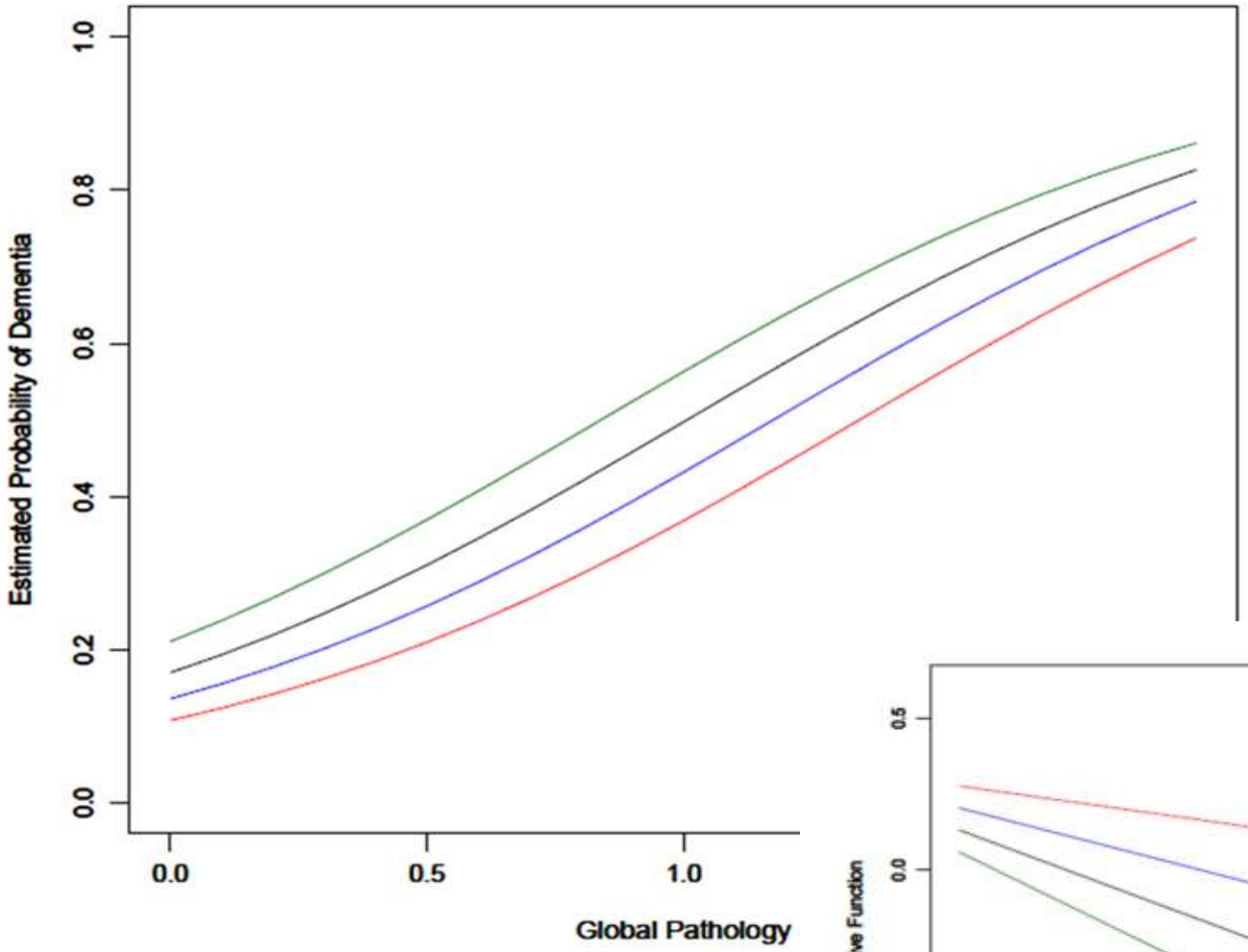
Boyle et al. Neurology. 2015 Dec 1;85(22):1930-6.

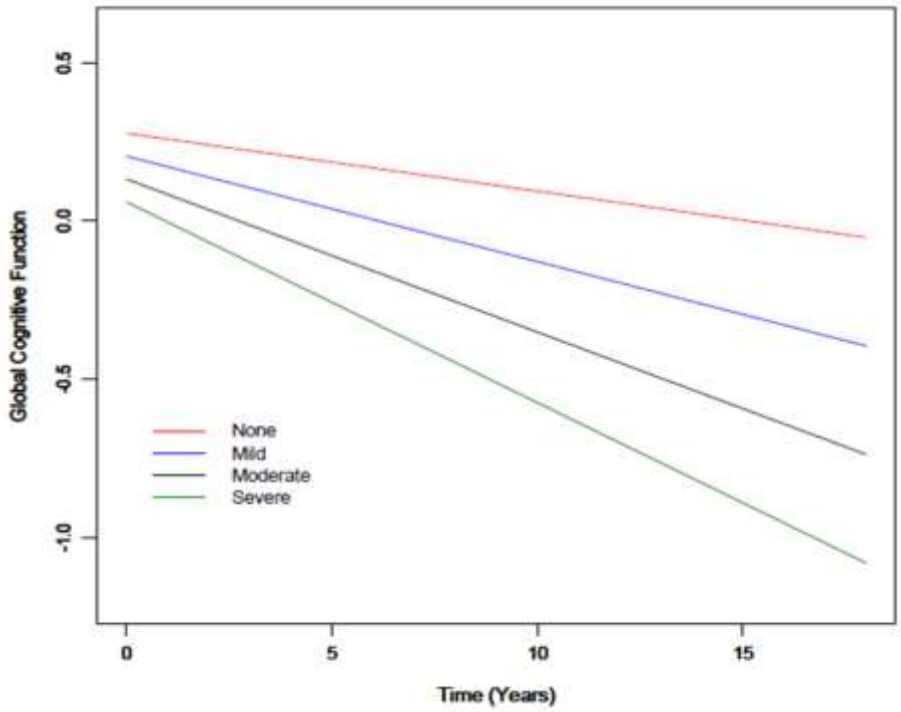
CAA

DEMENTIA

AND

COGNITIVE DECLINE





Boyle et al. Neurology. 2015 Dec 1;85(22):1930-6.

Association of CAA with decline in 5 specific cognitive systems

- CAA related to rate of decline in episodic memory ($p=0.006$), semantic memory ($p<0.0001$), and perceptual speed ($p=0.032$)

- Not significantly related to working memory ($p=0.114$) or visuospatial skills ($p=0.148$)

APOE and cerebral amyloid angiopathy in community-dwelling older persons

Lei Yu [a,b,*], Patricia A. Boyle [a,c], Sukriti Nag [a,d], Sue Leurgans [a,b,e], Aron S. Buchman [a,b], Robert S. Wilson [a,b,c], Zoe Arvanitakis [a,b], Jose M. Farfel [d,f], Philip L. De Jager [g,h,i], David A. Bennett [a,b], Julie A. Schneider [a,b,d]

Neurobiology of Aging 36 (2015) 2946–2953

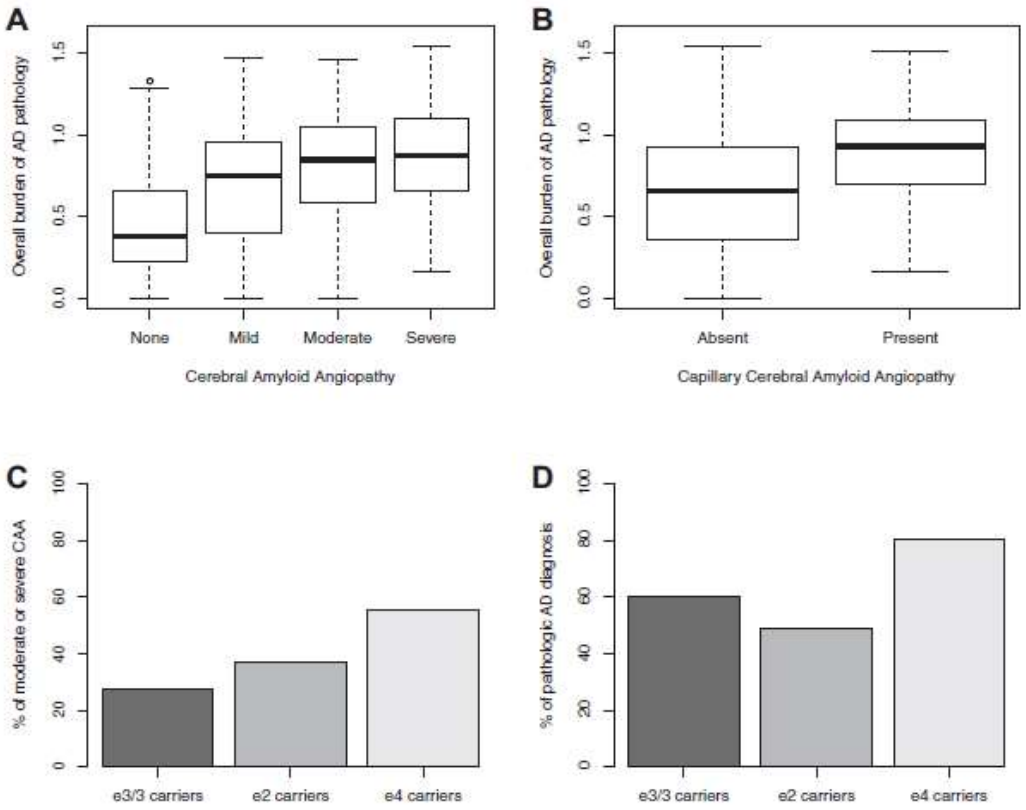


Fig. 2. Relationship of AD pathology, CAA, and *APOE* genotypes. (A and B) Distribution of the composite measure of AD pathology by CAA. The association of CAA with more burden of AD pathology is evident. (C) The percentages of moderate to severe CAA by *APOE* genotypes. The figure illustrates isoform-dependent pattern of *APOE* (i.e., ε4 > ε2 > ε3) in relation to CAA. (D) The percentages of pathologic AD diagnosis by *APOE* genotypes. Here, we observe a different pattern in relation to AD (i.e., ε4 > ε3 > ε2), as compared with CAA (C). Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy.

Role for other pathologies in cognitive impairment in aging, MCI, dementia

- Lewy bodies - Neocortical LB increase odds of dementia and associated with all cognitive domains.
  - Limbic Lewy bodies related to impaired visuospatial skills

- TDP-43 – very common proteinopathy associated with aging, AD pathology, and HS; lowers episodic memory fxn and increases odds of dementia.

- Hippocampal sclerosis - very common in the oldest old and when associated with TDP-43 increases odds of MCI and dementia

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

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.

Very common abnormal protein deposit in aging

Approximately 50% of cohort with TDP-43 pathology

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

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

Effect size similar to tangles in mixed effect models on cog decline

Hippocampal Sclerosis and TDP-43 Pathology in Aging and Alzheimer Disease

Sukriti Nag, MD, PhD,[1,2] Lei Yu, PhD,[1,3] Ana W. Capuano, PhD,[1,3] Robert S. Wilson, PhD,[1,3,4] Sue E. Leurgans, PhD,[1,3] David A. Bennett, MD,[1,3] and Julie A. Schneider, MS, MD[1,2,3]

ANN NEUROL 2015;77:942–952

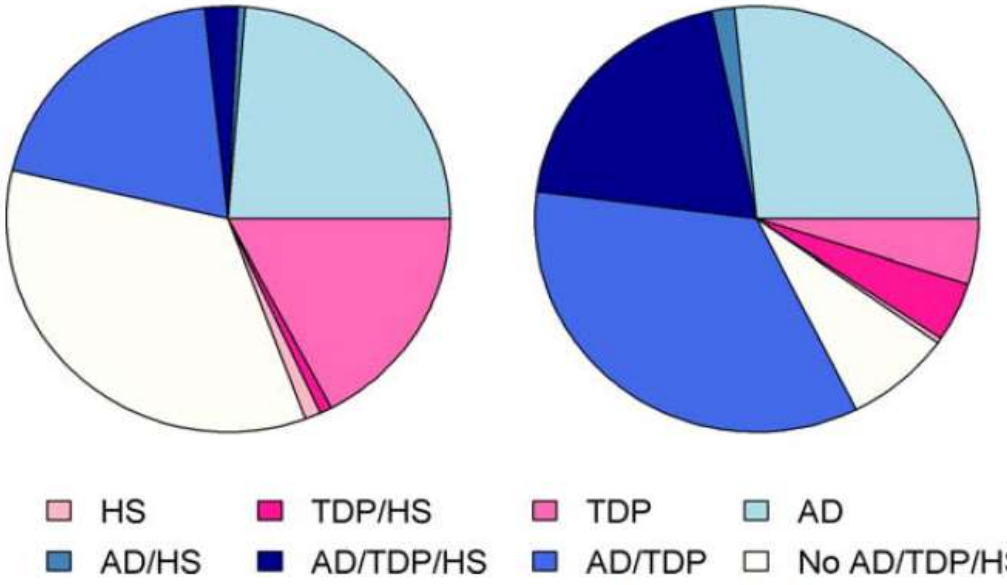


FIGURE 2: Blue shades represent the pathologic diagnosis of Alzheimer disease (AD) with or without coexisting hippocampal sclerosis (HS) and/or TDP-43 pathology, whereas pink shades represent the pathologic diagnosis of HS and/or TDP without pathology AD.

TMEM 106B and TDP43 pathology

The *TMEM106B* locus and TDP-43 pathology in older persons without FTLD

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ABSTRACT

Objective: To determine the independent association of the *TMEM106B* variants with transactive response DNA binding protein 43 (TDP-43) pathology in older persons without frontotemporal lobar degeneration (FTLD) and to explore functional pathways that link the risk variants to the pathology, including a *GRN* mRNA pathway.

Methods: Data came from 544 autopsied participants without FTLD in 2 community-based studies of aging. Participants underwent uniform neuropathologic evaluations, including TDP-43 cytoplasmic inclusions. We examined the association of *TMEM106B* variants with a semiquantitative measure of TDP-43 pathology in a series of regression analysis. We explored potential pathways by leveraging genetic, brain DNA methylation, miRNA, and transcriptomic data collected from this same group of participants.

Results: TDP-43 pathology was identified in 51.7% of the participants. The index single-nucleotide polymorphism (SNP), rs1990622[A], was associated with more advanced TDP-43 pathology. Top hits from fine mapping of the locus were in linkage disequilibrium of the index SNP. The association remained significant after adjustment for other neuropathologies including Alzheimer disease and hippocampal sclerosis (odds ratio = 1.351, 95% confidence interval = 1.068–1.709, $p = 0.012$). *GRN* expression was upregulated in rs1990622[AA/AG] carriers, and was associated with more advanced TDP-43 pathology. The *TMEM106B* variants were associated with lower level of DNA methylation in an active enhancer in *GRN*.

Conclusions: Common variants in *TMEM106B* serve as a distinct risk factor for TDP-43 pathology in older persons without FTLD. The role of *GRN* expression and epigenetic mechanisms associating *TMEM106B* in the accumulation of TDP-43 in older persons require further study.

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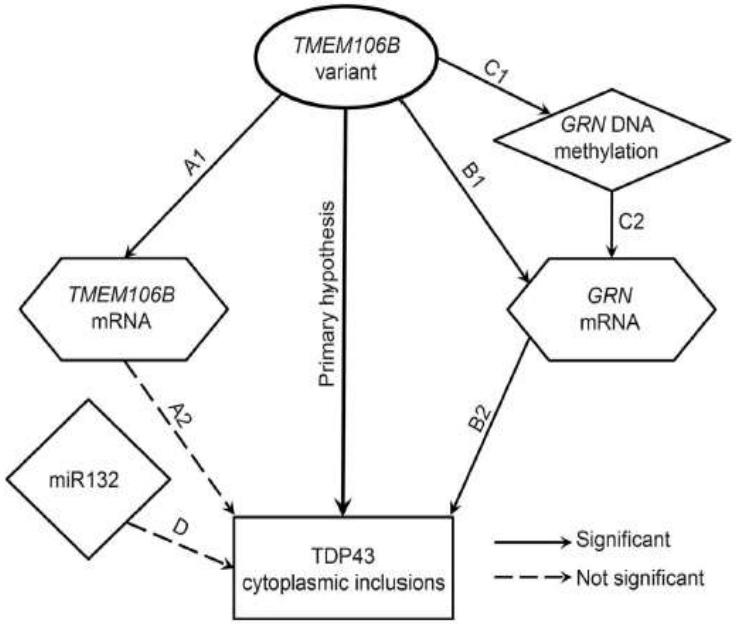
Figure 1 Relationship and potential pathways linking *TMEM106B* variant and transactive response DNA binding protein 43 pathology



Each line in the figure represents a hypothesis tested in this study. The primary hypothesis is that transmembrane protein 106B (*TMEM106B*) variants are related to transactive response DNA binding protein 43 (TDP-43) pathology in aging after controlling for other common age-related pathologies. A (1 and 2) indicates the *TMEM106B* expression pathway; B (1 and 2) indicates granulin expression pathway; and C and D indicate potential epigenetic pathways. Solid lines indicate those relationships that were found to be significant. Dashed lines show relationships that did not reach significance (note miR132 pathway was not significant after controlling for other neurodegenerative pathologies).

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CONSENSUS PAPER

Primary age-related tauopathy (PART): a common pathology associated with human aging

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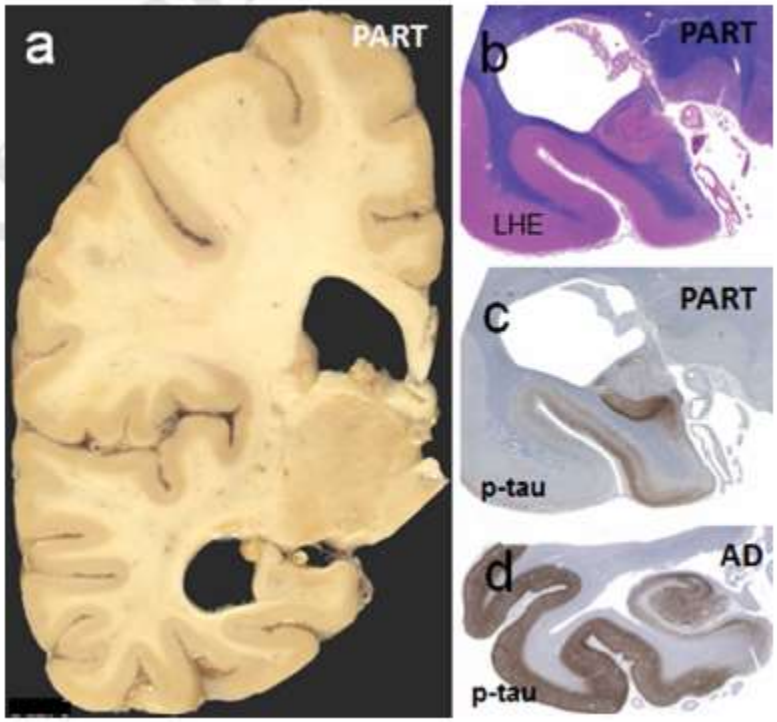

Table 2 Primary age-related tauopathy (PART): working classification

1. Requires

NFTs present with Braak stage ≤IV (usually III or lower)

2. Then subclassify as follows

Category	Thal Aβ Phase[a]	Other disease associated with NFT[b]
Definite	0	Absent
Possible	1–2	Absent

Examples

Primary age-related tauopathy (PART), Definite, Braak stage II

Primary age-related tauopathy (PART), Possible, Braak stage III, Thal Aβ phase 2

3. Ancillary studies (not required)

Immunohistochemistry: 3R and 4R tau-positive

Electron microscopy: paired helical filaments present

Genetics: absence of pathogenic FTLD-tau mutation

[a] See [116, 135]. Laboratories using the CERAD neuritic plaque density score [96, 97] may classify subjects with neuritic plaque frequency of "None" as "Definite" and "Sparse" as "Possible"

[b] For example, "progressive supranuclear palsy", "corticobasal degeneration", "Pick's disease", "frontotemporal lobar degeneration with *MAPT* mutation", and "chronic traumatic encephalopathy"

Implications

1. **Need to start thinking about sporadic AD dementia as a multifactorial syndrome**

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. Episodic memory - primary domain affected by AD pathology, but also primary domain effected by TDP-43 pathology, HS, and PART, and also affected by vascular pathologies, and LB

4. Genetic factors may increase risk across diverse degenerative diseases.

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