Comparison of Symptomatic and Asymptomatic Persons with AD Neuropathology as defined by the new NIA-AA Guidelines

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Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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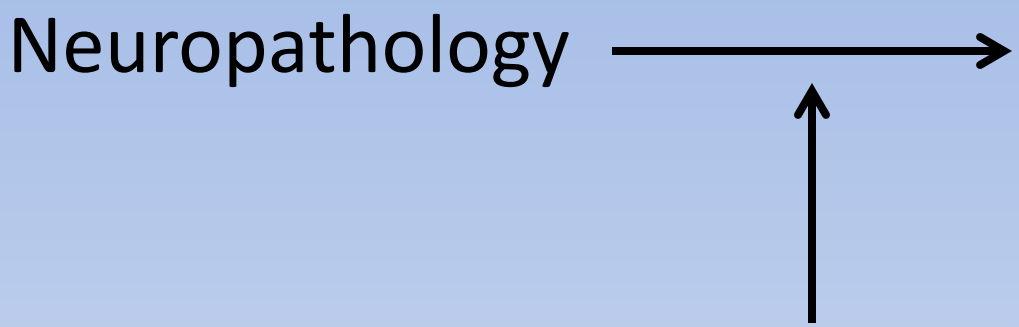
"we need to further elucidate the link between the pathological cascade of AD and the emergence of clinical symptoms."

"to determine the factors which best predict the risk of progression from "normal" cognition to MCI and AD dementia"



Demographics

Genetic status

Comorbid conditions (e.g. vascular disease)

Environmental influences

Cognitive reserve

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Prior NP classification schemes

Khachaturian

NIA / Reagan

CERAD (Consortium of Establish a Registry for Alzheimer's Disease)

All emphasized the presence of clinical symptoms in addition to NP changes.

Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas G. Beach · Eileen H. Bigio · Nigel J. Cairns · Dennis W. Dickson · Charles Duyckaerts · Matthew P. Frosch · Eliezer Masliah · Suzanne S. Mirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rudolf Thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

Table 2 "ABC" score for AD neuropathologic change

"A"	Thal Phase for Aβ plaques [57]	"B"	Braak and Braak NFT stage [14,15]	"C"	CERAD neuritic plaque score [41]
0	0	0	None	0	None
1	1 or 2	1	I or II	1	Sparse
2	3	2	III or IV	2	Moderate
3	4 or 5	3	V or VI	3	Frequent

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Objectives

Identify factors associated with clinical manifestations of MCI and dementia in a large database of persons with autopsy findings consistent with AD by the new NIA-AA criteria.

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METHODS

Uniform Data Set (UDS): 2005 - 2012

Neuropathology Data Set (NP)

A: Thal phase not available in NP.

- Diffuse plaques: Plaques with non-compact amyloid and no dystrophic neurites:

  Proxy for Thal

- Sparse, moderate, or frequent diffuse plaques:

  Thal phase $\geq$ 1.

B: Braak stages collapsed 6 to 3 to increase inter-rater reliability

C: Same as before.

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NP inclusion criteria

A: Thal phase ≥ 1 (any diffuse plaque: Sparse, moderate, or frequent diffuse plaques).

OR

C: Neuritic plaque C ≥ 1 (any neuritic plaques: sparse, moderate, or frequent neuritic plaques)

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Clinical status

CDR (Clinical Dementia Rating) global score at last clinical assessment:

- 0 = asymptomatic
- 0.5 or higher = symptomatic

≤ 1 year between last clinical assessment and autopsy.

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Covariates

- Demographics (age, sex, race, education).
- Depression
- Family history of dementia
- APOE E4 allele status
- Modified Hachinski Ischemic Score (HIS)
- Neuropathology:
  - Any vascular pathology
  - Microinfarcts
  - Lewy Body pathology

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Statistical methods

Logistic regression with GEE

Bivariate

Multivariable

- Those factors found to be associated with outcome (sx vs asx) at $p < 0.05$ on bivariate analysis included.

RESULTS

Patient population

UDS: (Sept 2005 – June 2012)

- 1702 subjects with autopsy data
- 1375 had at least some diffuse or neuritic plaques
- 976 with $\leq$ 1 year between last clinical assessment and death
  - 893 (91.5%) CDR $\geq$ 0.5 (symptomatic)
  - 83 (8.5%) CDR = 0 (asymptomatic)

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Demographic characteristics

Characteristic	Asymptomatic (n=83)	Symptomatic (n=893)
Age at last visit	86.1 (8.3)	81.0 (10.9)
Years of education*	15.4 (2.9)	14.9 (3.4)
Sex: female	47 (56.6%)	379 (42.4%)
Race*		
White	82 (98.8%)	838 (94.4%)
African-American	0 (0.0%)	34 (3.8)
American Indian, Alaskan	0 (0.0%)	1 (0.1%)
Asian	0 (0.0%)	7 (0.8%)
Multiracial	1 (1.2%)	8 (0.9%)
APOE : at least one Ɛ4 allele*	14 (19.7%)	394 (54.7%)

*13 subjects with missing data on education; 5 subjects with missing data on race; 185 subjects with missing data on APOE Ɛ4 frequency

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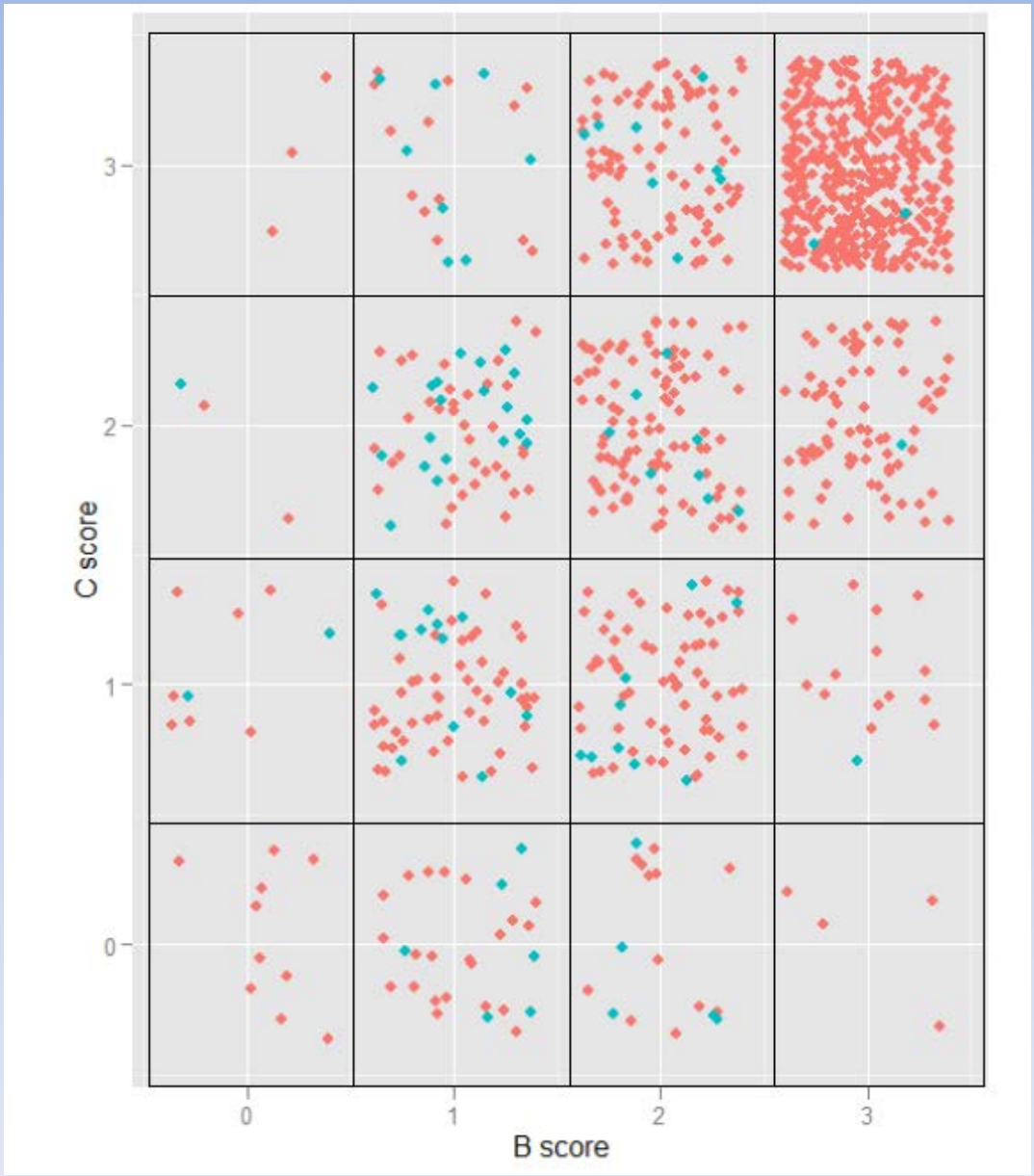
Scatter-plot by B and C score



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Frequency (%) of neuropathologic comorbidities

Characteristic	Asymptomatic (n=83)	Symptomatic (n=893)
Any vascular pathology	15 (18%)	159 (18%)
Microinfarcts	66 (80%)	727 (81%)
Lewy body pathology	9 (11%)	322 (36%)

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Bivariate: Odds of being asymptomatic

Predictor	OR	95% CI*	p-value*
Age at last visit	**1.05**	**(1.03,1.08)**	**<.0001**
Education (some college vs. no college)	**1.78**	**(1.02, 3.12)**	**0.04**
Sex (female vs. male)	**1.77**	**(1.15, 2.73)**	**.01**
Family history (present vs. absent)	0.68	(0.43, 1.06)	0.09
Depression (past 2 years)	**0.34**	**(0.20, 0.59)**	**.0001**
Hachinski Ischemic Score	**0.87**	**(0.75, 1.00)**	**0.05**
APOE (at least one Ɛ4 vs. no Ɛ4)	**0.20**	**(0.11, 0.37)**	**<.0001**
B score (continuous)	**0.30**	**(0.23, 0.38)**	**<.0001**
C score (continuous)	**0.52**	**(0.43, 0.63)**	**<.0001**
Vascular pathology	0.99	(0.53,1.81)	0.96
Multiple microinfarcts	1.14	(0.65,1.99)	0.64
Lewy body pathology	**0.21**	**(0.11,0.43)**	**<.0001**

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Multivariable logistic regression: odds of being asymptomatic

Predictor	Full Model (n=620)	
	OR	95% CI*
Age at last visit	**1.04**	**(1.01,1.07)**
Education (some college vs. none)	1.48	(0.76,2.90)
Sex (female vs. male)	1.34	(0.74,2.43)
Depression	0.66	(0.34,1.27)
Hachinski Ischemic Score	**0.81**	**(0.67.0.97)**
APOE (e4 vs. no e4)	**0.41**	**(0.20,0.83)**
B score (continuous)	**0.31**	**(0.20,0.50)**
C score (continuous)	0.83	(0.58,1.20)
Lewy body pathology	**0.30**	**(0.11,0.77)**

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Multivariable logistic regression: odds of being asymptomatic

Predictor	Without APOE (n=750)		Without APOE & HIS (n=939)	
	OR	95% CI*	OR	95% CI*
Age at last visit	**1.05**	**(1.02,1.08)**	**1.05**	**(1.02,1.08)**
Education (some college vs. none)	1.70	(0.86,3.38)	**2.03**	**(1.03,3.99)**
Sex (female vs. male)	1.66	(0.94,2.96)	1.63	(0.96,2.79)
Depression	**0.46**	**(0.24,0.87)**	**0.40**	**(0.22,0.73)**
Hachinski Ischemic Score	**0.81**	**(0.69,0.96)**	-	-
APOE (e4 vs. no e4)	-	-	-	-
B score (continuous)	**0.25**	**(0.16,0.40)**	**0.24**	**(0.16,0.37)**
C score (continuous)	0.96	(0.67,1.39)	1.02	(0.72,1.44)
Lewy body pathology	**0.33**	**(0.15,0.74)**	**0.35**	**(0.17,0.73)**

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Limitations

A. Diffuse plaques vs amyloid:

- Not able to get Thal phase (A score)

B. Sample size and missing values (HIS, APOE)

- Sensitivity analysis:
    - Repeating analysis without these variables
- Similar results to full model.

C. Biases inherent in database

- Asx controls: more likely to be college educated

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Conclusions

1. Strong effect of pathology
- Yet some asx subjects with high B and C scores.

2. Coexisting pathology
- Lewy body
- Vascular: pathology vs HIS

3. Depression; education

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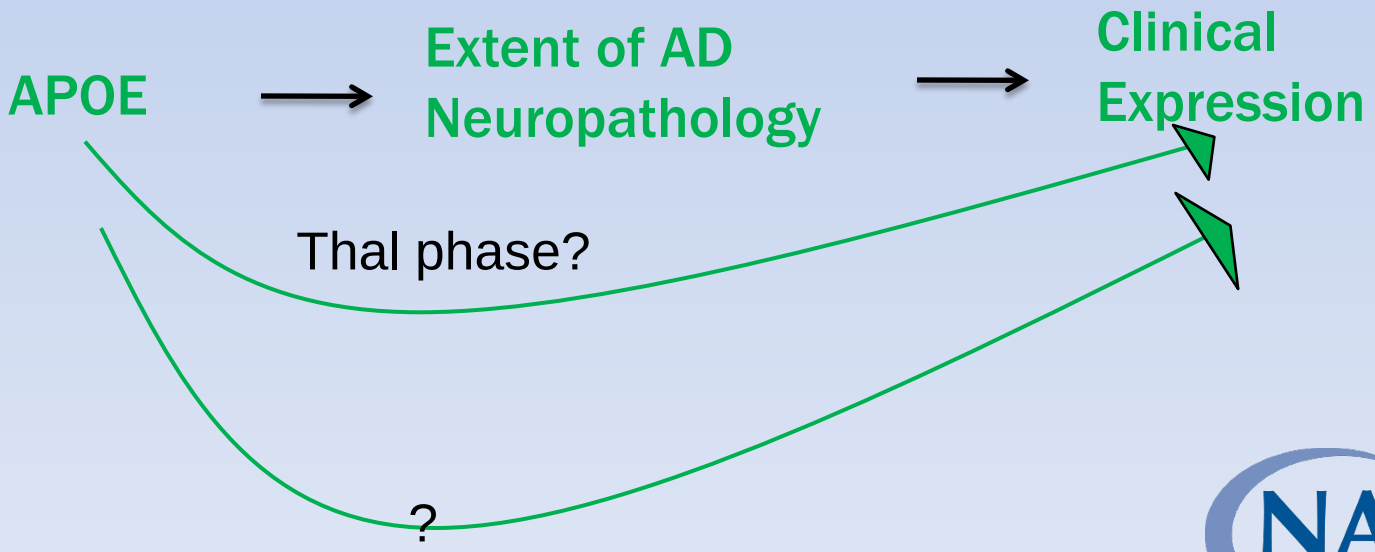
Conclusions

4. APOE

Still strong association with outcome even after adjusting for NP.



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No conflicts.

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Education and Alzheimer disease without dementia

Support for the cognitive reserve hypothesis

Catherine M. Roe, PhD; Chengjie Xiong, PhD; J. Phillip Miller, AB; and John C. Morris, MD

Neurology, 68: 223-8, 2007

MDS, NP
2372 people, autopsy within 1 year of a clinical evaluation
Compared demented vs non-demented persons, all with AD NP
Central finding:

higher education status associated with lower dementia risk

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Table 3 "ABC" score for level of AD neuropathologic change

AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	Not[d]
1	0 or 1	Low	Low	Low[e]
	2 or 3[f]	Low	Intermediate	Intermediate[e]
2	Any C	Low[g]	Intermediate	Intermediate[e]
3	0 or 1	Low[g]	Intermediate	Intermediate[e]
	2 or 3	Low[g]	Intermediate	High

Inclusion:

A: Thal phase $\geq$ 1 (any diffuse plaque)

OR

C: C $\geq$ 1 (any neuritic plaques)

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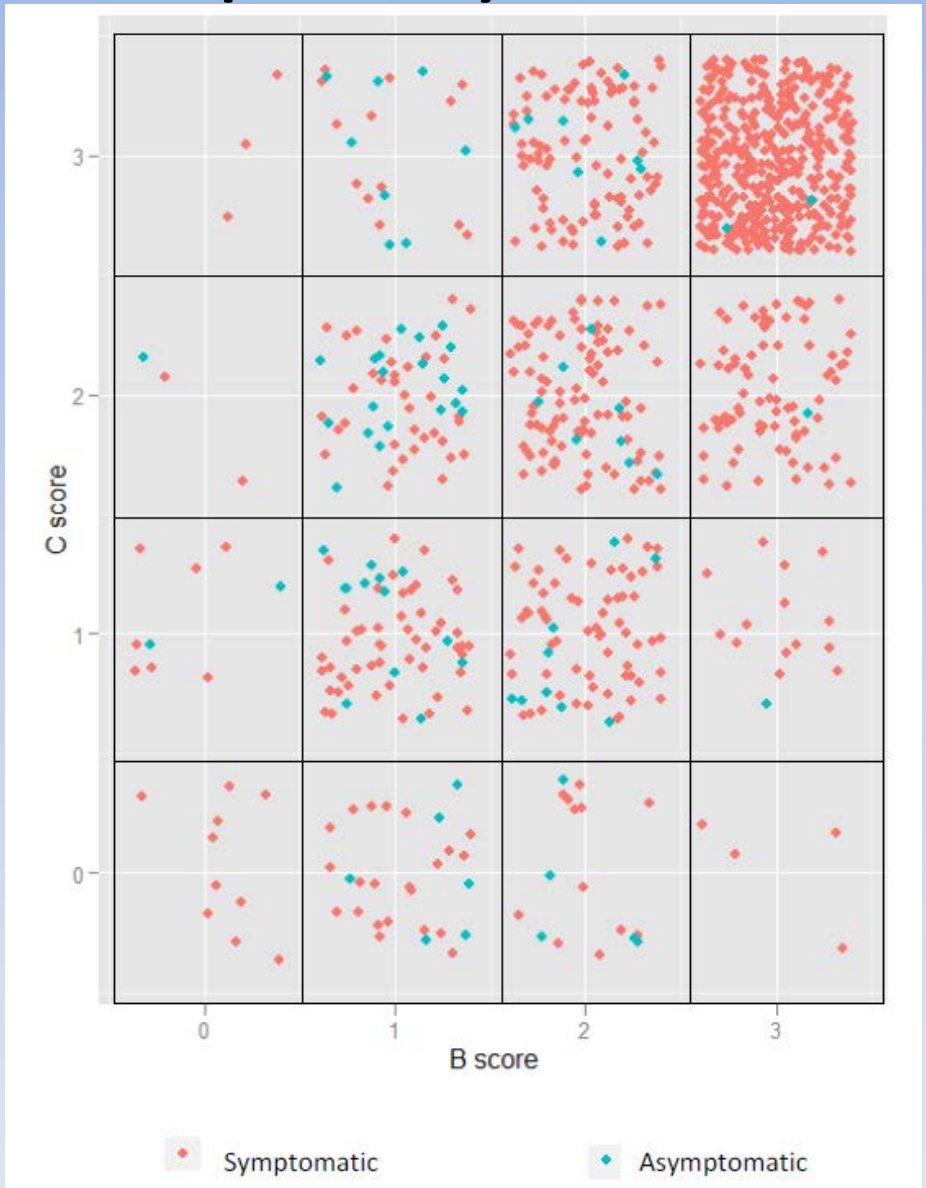
Scatter-plot by B and C score



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