

# Collaborative work on characteristics of asymptomatic people with Alzheimer's disease neuropathologic change

## Team:

Wash U: J Morris, C Roe, N Cairns, J Hassenstab,

Mt. Sinai: S Bertelson, A Goate

U Kentucky: D Fardo, S Ellingson

NACC: S Monsell, C Mock, W Kukull

# Characteristics of asymptomatic persons with AD neuropathology as defined by the NIA-AA Guidelines

## Comparison of symptomatic and asymptomatic persons with Alzheimer disease neuropathology

Sarah E. Monsell, MS  
Charles Mock, MD, PhD  
Catherine M. Roe, PhD  
Nupur Ghoshal, MD,  
PhD  
John C. Morris, MD  
Nigel J. Cairns, PhD,  
FRCPath  
Walter Kukull, PhD

### ABSTRACT

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**Methods:** We studied 82 asymptomatic (Clinical Dementia Rating global score = 0) and 824 symptomatic subjects (Clinical Dementia Rating score >0) with low to high AD neuropathologic changes at autopsy who were assessed at 1 of 34 National Institute on Aging-funded Alzheimer's Disease Centers. All subjects underwent a clinical examination within 1 year of death. Logistic regression was used to evaluate factors associated with the odds of being asymptomatic vs symptomatic.

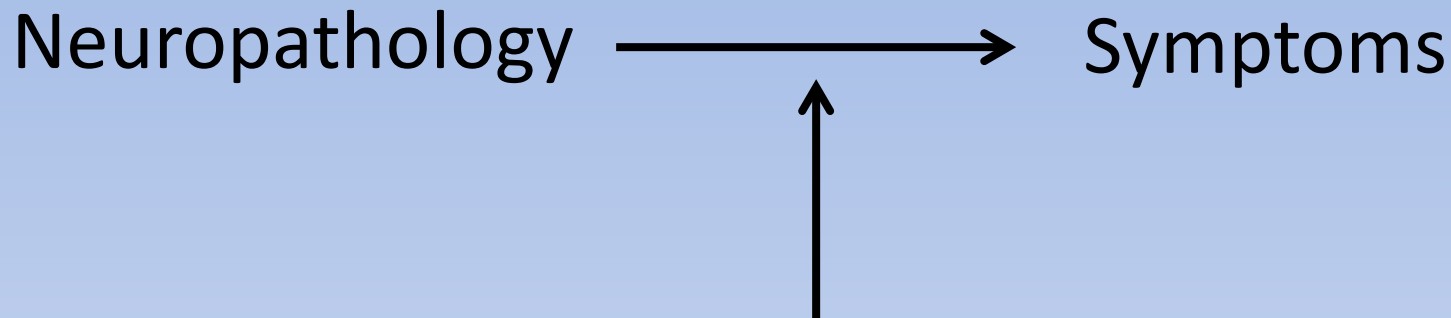
**Neurology® 2013;80:2121-2129**

Basic model  
of sx vs asx

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Genetic differences:  
sx vs asx

From ADGC



Demographics

Genetic status

Comorbid conditions (e.g. vascular disease)

Environmental influences

Cognitive reserve

## 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 A $\beta$ 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

**Table 3** “ABC” score for level of AD neuropathologic change

AD neuropathologic change		B <sup>a</sup>		
A <sup>b</sup>	C <sup>c</sup>	0 or 1	2	3
0	0	Not <sup>d</sup>	Not <sup>d</sup>	Not <sup>d</sup>
1	0 or 1	Low	Low	Low <sup>e</sup>
	2 or 3 <sup>f</sup>	Low	Intermediate	Intermediate <sup>e</sup>
2	Any C	Low <sup>g</sup>	Intermediate	Intermediate <sup>e</sup>
3	0 or 1	Low <sup>g</sup>	Intermediate	Intermediate <sup>e</sup>
	2 or 3	Low <sup>g</sup>	Intermediate	High

Inclusion:

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

OR

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

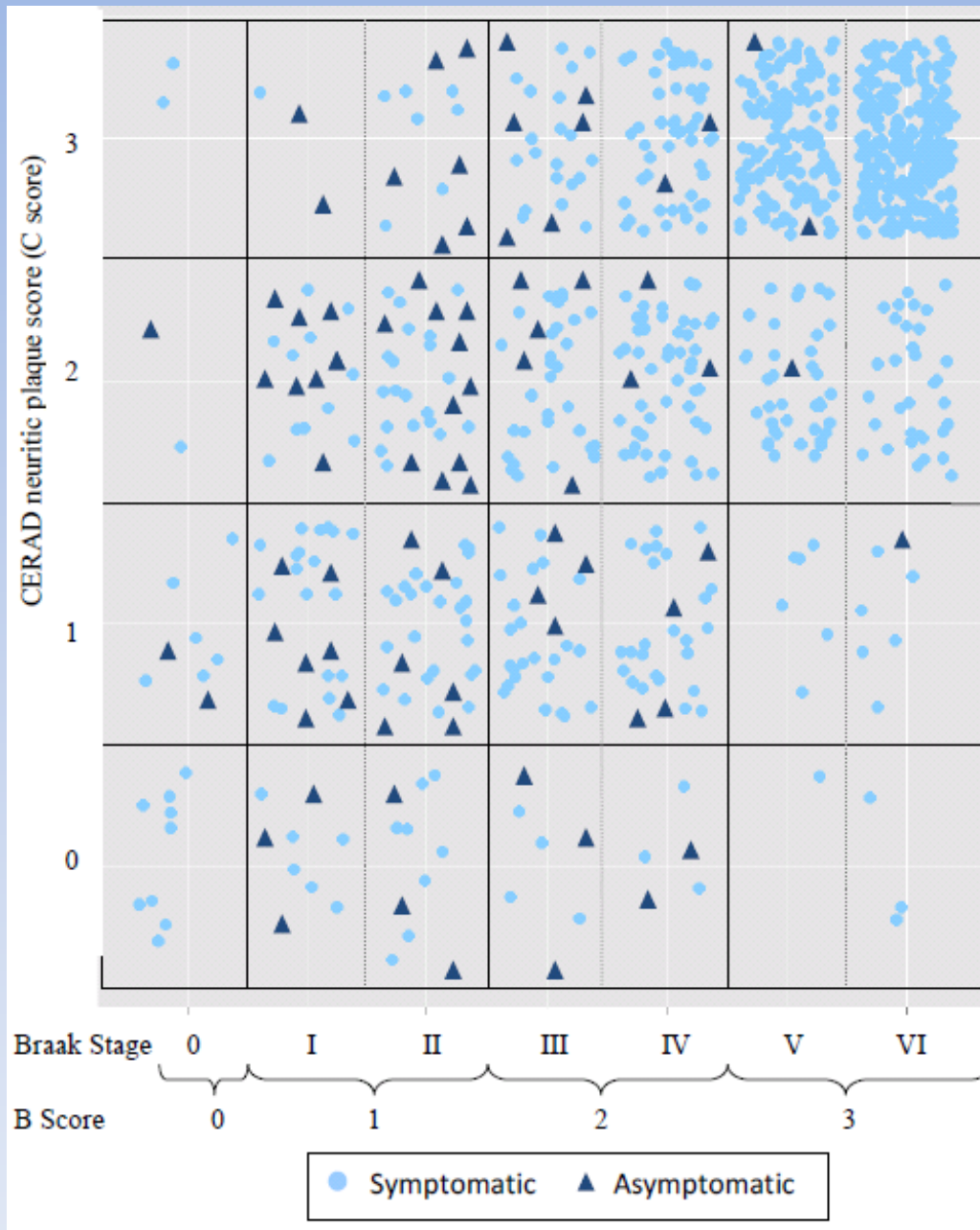
# Clinical status

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

- 0 = asymptomatic
- 0.5 or higher = symptomatic

$\leq 1$  year between last clinical assessment and autopsy.

# Scatter-plot by B and C score



893 (91.5%) CDR  $\geq$  0.5  
(symptomatic)

83 (8.5%) CDR = 0  
(asymptomatic)

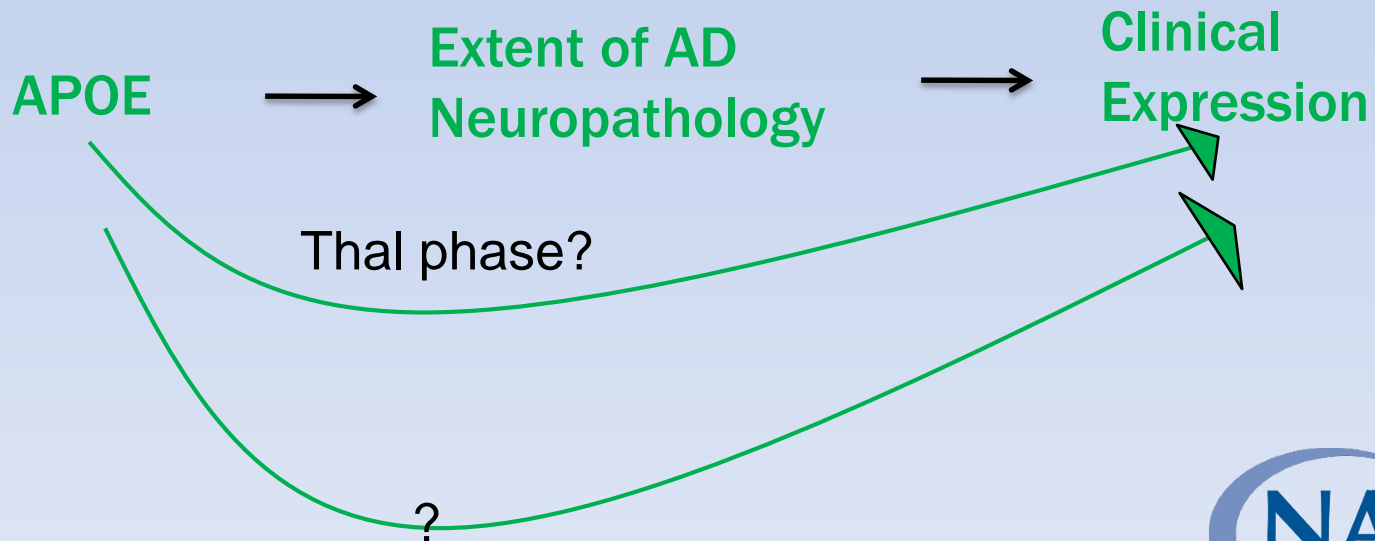
# Multivariable logistic regression: odds of being asymptomatic

Predictor	Full Model (n=559)		Without APOE (n=665)		Without APOE & HIS (n=845)	
	OR	95% CI*	OR	95% CI*	OR	95% CI*
Age at last visit	<b>1.04</b>	<b>(1.01,1.07)</b>	<b>1.05</b>	<b>(1.02,1.08)</b>	<b>1.05</b>	<b>(1.02,1.08)</b>
Education (at least some college vs. no college)	1.46	(0.71,2.99)	1.52	(0.76,3.07)	1.82	(0.91,3.63)
Depression (present within the past 2 years vs. absent)	0.65	(0.33,1.26)	<b>0.51</b>	<b>(0.26,0.99)</b>	<b>0.43</b>	<b>(0.23,0.80)</b>
Sex (female vs. male)	1.21	(0.66,2.21)	1.47	(0.82,2.63)	1.39	(0.81,2.36)
Hachinski Ischemic Score	<b>0.82</b>	<b>(0.69,0.97)</b>	<b>0.81</b>	<b>(0.69,0.96)</b>	-	-
APOE (e4 vs. no e4)	<b>0.36</b>	<b>(0.16,0.83)</b>	-	-	-	-
B score (continuous)	<b>0.28</b>	<b>(0.17,0.45)</b>	<b>0.26</b>	<b>(0.16,0.42)</b>	<b>0.23</b>	<b>(0.15,0.36)</b>
C score (continuous)	0.92	(0.62,1.36)	0.95	(0.64,1.42)	1.04	(0.72,1.51)
Lewy body pathology (present vs. not present)	0.68	(0.24,1.97)	0.67	(0.27,1.65)	0.56	(0.24,1.31)
Amyloid angiopathy (present vs. not present)	0.69	(0.37,1.28)	0.57	(0.32,1.04)	0.66	(0.38,1.15)

# Conclusions

## APOE

Still strong association with outcome even after adjusting for AD NP (B & C scores).



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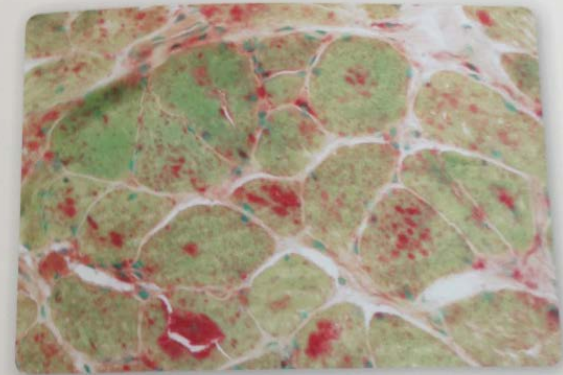
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## SIGNIFICANCE

One of first applications of NIA-AA guidelines

Proposed method for converting existing NP data in NACC database to NIA-AA format (Newer NP10 data have Thal phase, since beginning of 2014).

Useful for future studies on early AD using NACC NP data

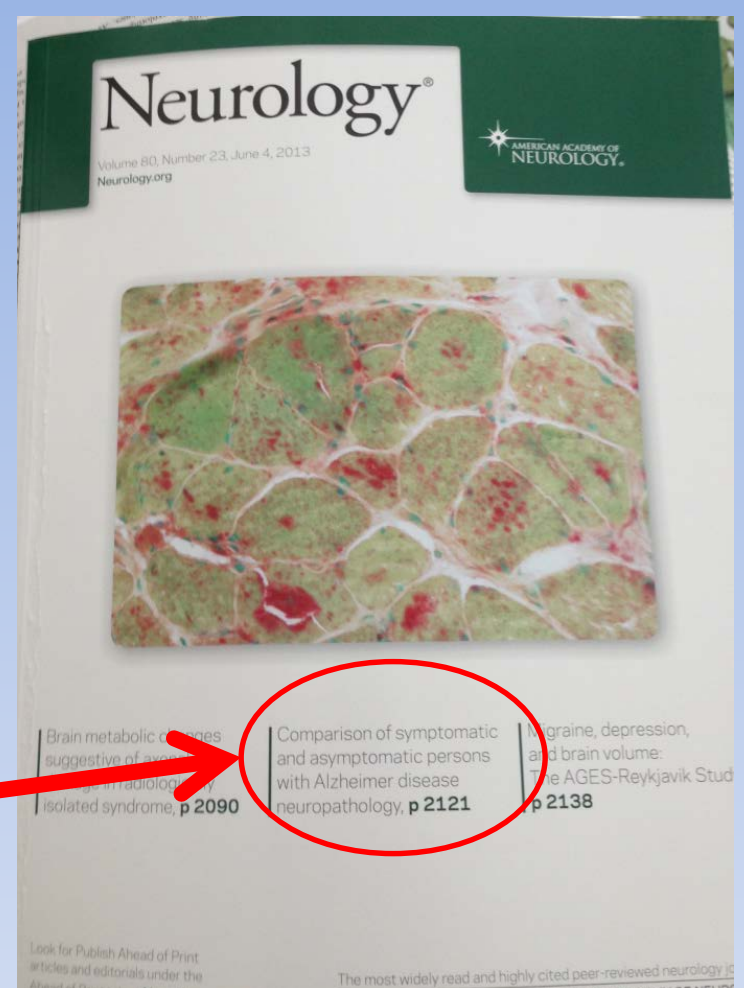
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# I. Performance on neuropsychological tests.

- *Specific aims:*
- 1. To determine whether persons with AD neuropathologic change and CDR global score of 0 have more subtle changes that are detectable by neuropsychological tests.
- 2. To determine the clinical and neuropathologic features affecting these changes.
- 3. To determine the trajectory of these changes over time.
- Secondary specific aim: 4. Determine whether there are any neuropsychological tests that are particularly sensitive as an early sign of AD and which thus might be useful in clinical trials involving preclinical cases of AD.

# Neuropsychological tests

- Three related papers: underway / planned
- 1. Trajectory over time:
  - AD NP vs no AD NP (all with CDR = 0).
- 2. Differences at baseline visit: progressors vs non-progressors.
  - (progressors: AD NP, CDR = 0 on initial visit; but develop MCI or dementia).
- 3. Determinants within AD NP
  - Not so much to show, but negative results might still be useful.

# Cognitive Measures

- Cognitive Composites of UDS Measures  
(Hayden et al. 2011 *ADAD*)
  - Episodic Memory: WMS-R Logical Memory Immediate & Delayed Recall
  - Language: Boston Naming Test, Animal Naming, Vegetable Naming
  - Attention & Working Memory: WMS-R Digit Span Forward & Backwards
  - Executive Function: Trailmaking Test Parts A & B, WAIS Digit-Symbol
  - Global Composite: All measures above

# Monzell et al., 2014 *Neurology*

- 211 participants who were never symptomatic (CDR 0), but died with significant levels of AD neuropathology (n=131), or who had no evidence of AD neuropathology (n=80)
- Working memory/Attention declined faster in AD-NP.

Domain	No. of subject-visits	Annual mean change for AD-NP (95% CI) <sup>a,b</sup>	Annual mean change for non-AD-NP (95% CI) <sup>a,b</sup>	Annual mean difference between AD-NP and non-AD-NP (95% CI) <sup>a</sup>	p Value <sup>a</sup>
Episodic memory	565	0.08 (−0.09, 0.25)	0.17 (0.08, 0.25)	−0.09 (−0.19, 0.02)	0.10
Language	553	−0.04 (−0.18, 0.09)	0.02 (−0.04, 0.08)	−0.07 (−0.15, 0.01)	0.11
Attention	573	−0.09 (−0.23, 0.06)	0.02 (−0.05, 0.09)	−0.11 (−0.19, −0.02)	0.02
Executive function	538	−0.02 (−0.24, 0.19)	0.01 (−0.09, 0.12)	−0.03 (−0.16, 0.09)	0.60
Global composite	511	−0.02 (−0.15, 0.12)	0.06 (−0.01, 0.13)	−0.08 (−0.15, 0.00)	0.06

Abbreviations: AD = Alzheimer disease; CDR = Clinical Dementia Rating; CI = confidence interval; NP = neuropathologic.

<sup>a</sup> Adjusted for age at visit; education; sex; presence of ischemic, hemorrhagic, or vascular pathology; presence of cerebral amyloid angiopathy; and presence of Lewy body pathology.

<sup>b</sup> Interpretation: a negative mean annual change indicates a decline in cognition, whereas a positive slope indicates improvement in scores over time.

# Significance

- Attention/working memory as earliest changes in preclinical AD
  - Balota et al, Psychol Aging, 2010
  - Tse et al, Neuropsychology, 2010
  - Storandt et al, Arch Neurol, 2009
- Subtle changes in preclinical AD more likely to be detected by changes over time
  - Knopman et al, Neurodegener Dis Manag 2012
  - Riley et al, J Alz Dis, 2011

# **Neuropsychological Markers of Cognitive Decline in Persons with Alzheimer's Disease Neuropathology**

**Presented at AAlC2015; In Press JNEN**

**Jason Hassenstab, PhD<sup>1</sup>**; Sarah E Monsell, MS<sup>2</sup>; Charles Mock, MD, PhD<sup>2</sup>; Catherine M Roe, PhD<sup>1</sup>; Nigel J. Cairns, PhD, FRCPath<sup>1</sup>, John C. Morris, MD<sup>1</sup>, and Walter Kukull, PhD<sup>2</sup>

<sup>1</sup>Knight Alzheimer's Disease Research Center, Washington University in St. Louis, St. Louis, USA

<sup>2</sup>National Alzheimer's Coordinating Center, University of Washington, Seattle, USA



Basic model  
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Genetic differences:  
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# GWAS / IGAP genes

- Most studies have compared genetic profiles of clinically-diagnosed cases of dementia or MCI with non-demented controls.
- Recently, several studies have assessed association of these loci with AD NP at autopsy.
  - Genetic profiles of people with clinical dementia and mod to high AD NP vs controls without dementia and no or low AD NP
  - 14 (of 22) loci associated with dementia and AD NP
    - (Shulman 2013; Beecham 2014; Chibnik 2011, Kramer 2011)

- Potential associations between **expression** of existing AD NP and other (non-APOE) loci not yet explored.
- Findings could potentially explain some of the variation in determining whether a person with AD NP would express symptoms or not.
- Identify pathways to disease heterogeneity.

## II. Genetic differences between symptomatic and asymptomatic persons with AD neuropathologic change.

### *Specific aim:*

- 1. To determine the differences in the proportions of persons having different alleles that have been associated with higher risks of AD for symptomatic (CDR global > 0) vs. asymptomatic (CDR global = 0) persons with AD neuropathologic change.

# Data

- NACC UDS and NP data linked with:
- ADGC data for:
  - 9 loci with GWAS defined associations
  - 12 loci identified by IGAP
  - MAPT
- Inclusion criteria: AD NP as per prior 2 studies
  - 521 with symptoms (CDR global > 0)
  - 68 without symptoms (CDR = 0)

Table: Odds ratio (adjusted for age and sex) for symptomatic AD vs. asymptomatic AD for each SNP and stratified by APOE e4 carrier status assuming an additive mode of inheritance

Gene	SNP	OR	OR in APOE e4 carriers	OR in APOE e4 non-carriers
CR1	rs6656401	1.46 (0.85,2.49)	1.56 (0.53,4.53)	1.44 (0.76,2.73)
BIN1	rs6733839	0.96 (0.63,1.46)	1.02 (0.41,2.54)	1.06 (0.65,1.75)
CD2AP	rs10948363	0.73 (0.50,1.09)	<b>0.35 (0.16,0.75)</b>	0.99 (0.62,1.61)
HLA-DRB5/HLA-DRB1	rs9271192	1.01 (0.67,1.50)	0.93 (0.41,2.11)	1.03 (0.64,1.65)
EPHA1	rs11771145	0.96 (0.65,1.41)	1.29 (0.60,2.77)	0.88 (0.56,1.38)
CLU	rs9331896	0.83 (0.55,1.25)	1.18 (0.49,2.87)	0.73 (0.45,1.19)
PTK2B	rs28834970	1.22 (0.85,1.77)	1.38 (0.66,2.88)	1.10 (0.71,1.70)
MS4A4A	rs983392	1.29 (0.88,1.90)	1.57 (0.73,3.40)	1.19 (0.75,1.90)
PICALM	rs10792832	1.16 (0.80,1.70)	1.03 (0.46,2.30)	1.15 (0.75,1.77)
SORL1	rs11218343	1.72 (0.68,4.33)	2.99 (0.76,11.75)	1.45 (0.38,5.49)
SLC24A4/RIN3	rs10498633	1.24 (0.83,1.87)	1.50 (0.66,3.43)	1.15 (0.71,1.85)
DSG2	rs8093731	0.96 (0.12,7.86)	NA	0.94 (0.11,8.20)
ABCA7	rs4147929	<b>1.66 (1.00,2.76)</b>	1.25 (0.52,3.02)	1.81 (0.97,3.40)
CD33	rs3865444	1.26 (0.87,1.83)	1.28 (0.60,2.70)	1.44 (0.93,2.23)
CASS4	rs7274581	1.12 (0.62,2.04)	1.53 (0.54,4.35)	1.03 (0.49,2.17)
NME8	rs2718058	0.77 (0.51,1.15)	0.89 (0.40,2.02)	0.74 (0.46,1.19)
CELF1	rs10838725	0.99 (0.67,1.46)	0.70 (0.34,1.46)	1.14 (0.70,1.85)
FERMT2	rs17125944	1.69 (0.76,3.74)	3.05 (0.39,23.66)	1.41 (0.58,3.40)
INPP5D	rs35349669	0.88 (0.61,1.28)	1.07 (0.50,2.27)	0.75 (0.49,1.15)
MEF2C	rs190982	1.24 (0.84,1.82)	1.03 (0.45,2.36)	1.15 (0.74,1.80)
ZCWPW1	rs1476679	1.31 (0.87,1.96)	<b>2.98 (1.33,6.69)</b>	1.04 (0.63,1.70)
MAPT	rs393152	<b>2.18 (1.26,3.75)</b>	<b>3.73 (1.27,10.97)</b>	1.77 (0.93,3.40)

Gene	SNP	OR	OR in APOE e4 carriers	OR in APOE e4 non-carriers
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ABCA7: Lipid metabolism; immune function

Loci associated with CD2AP:  
neuritic plaque burden; modulating a-beta clearance

Loci associated with ZCWPW1: little known about possible function

MAPT: tau encoding gene

# Conclusions: NACC collaboration with ADCs

- ADCs: use UDS data by themselves.
- Smaller #: consultation with NACC staff.
- Develop ideas collaboratively.

# Extra slides

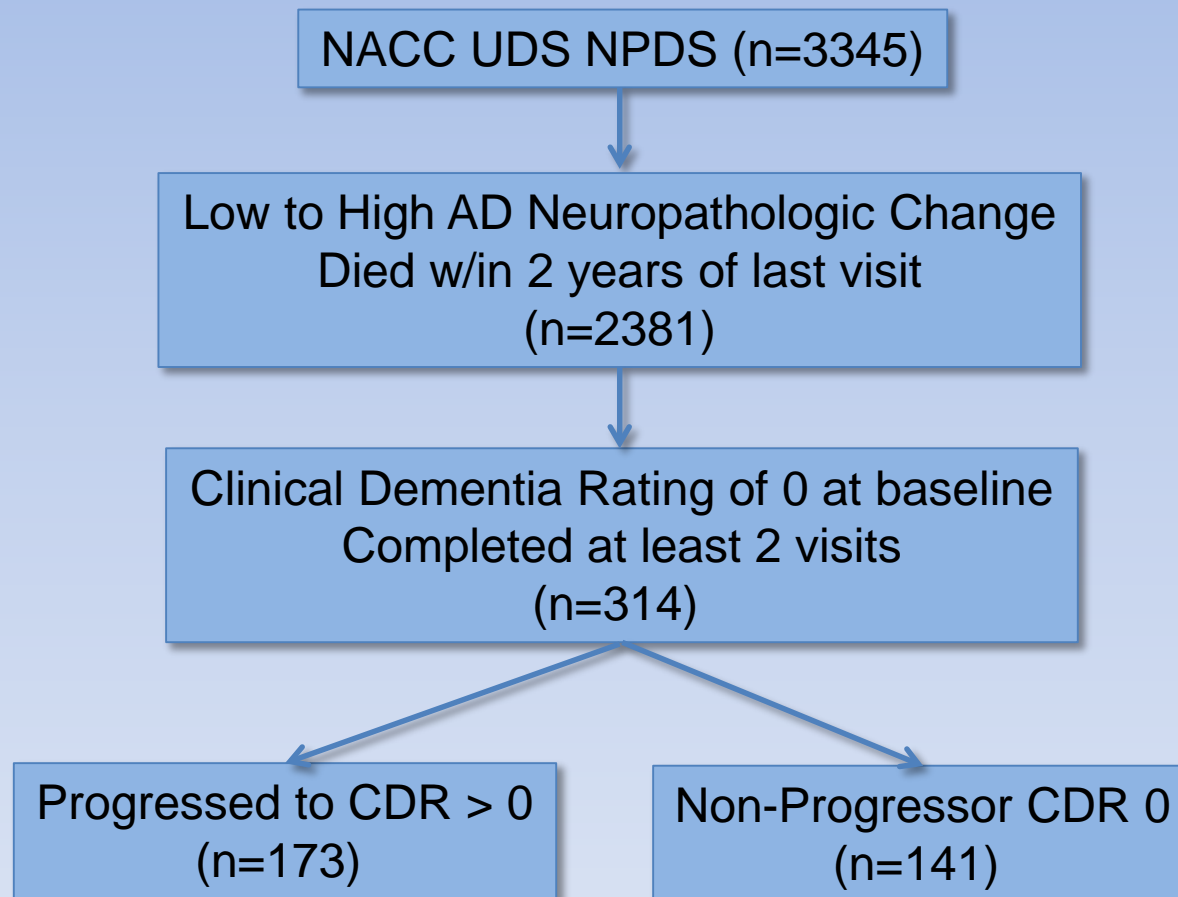
# Statistical analysis

- Table 1: asymptomatic and symptomatic demographic and neuropathologic differences assessed using chi square and t-tests
- Table 2: Additive test to explore association between number of risk alleles and asymptomatic status ( $CDR = 0$ ) for each of the 21 SNPs
- Table 2: Additive to test to explore differences stratified by APOE e4 carrier status

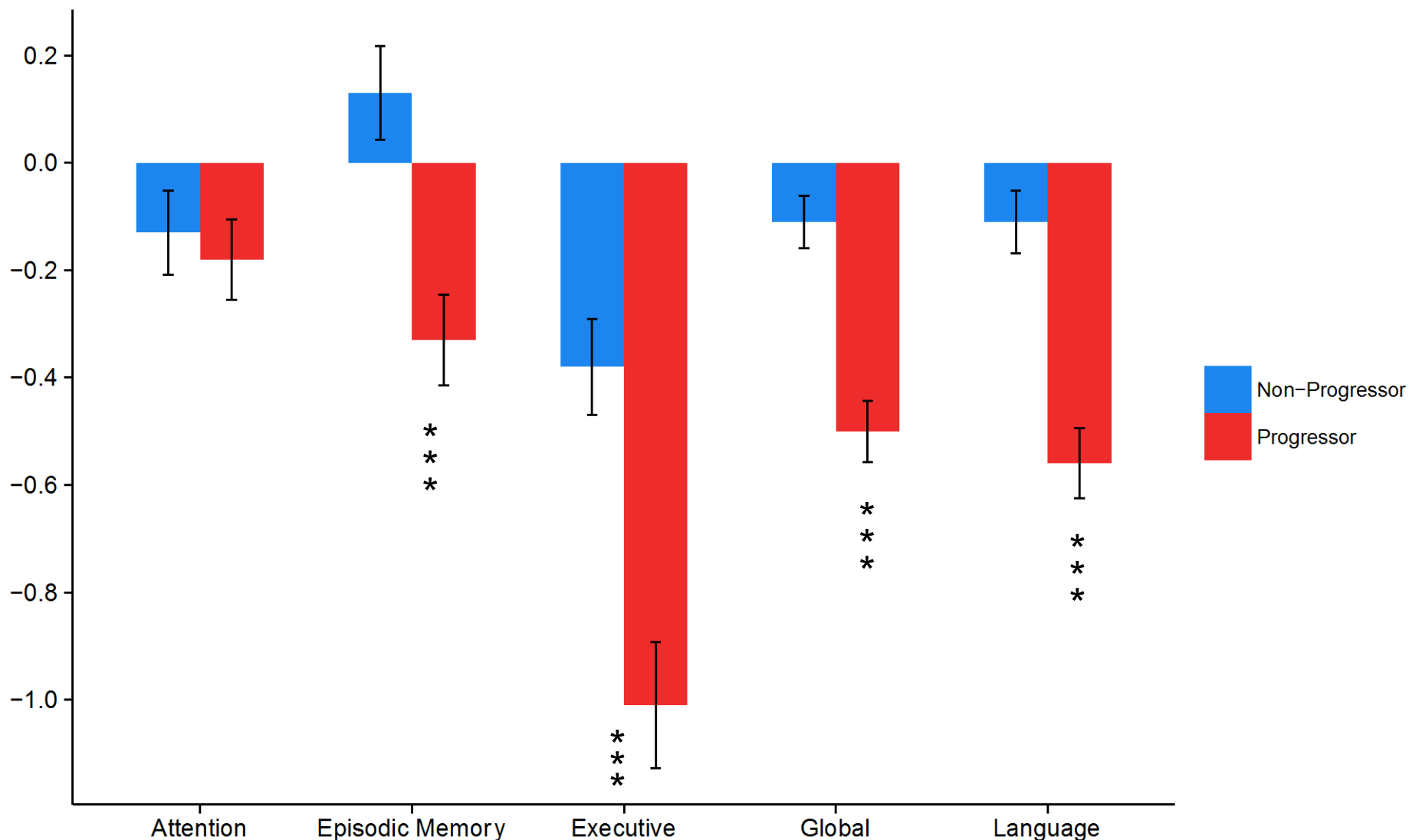
# Risk score data

	19 SNPs with <10% missing data <sup>a</sup>			21 SNPs with <15% missing data <sup>b</sup>			All 22 SNPs		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
All participants	419	2.65	(1.60,4.39)	300	2.14	(1.21,3.80)	184	1.85	(1.00,3.43)
APOE e4 carriers	201	5.27	(1.55,17.92)	143	5.99	(0.99,36.06)	NA		
APOE e4 non-carriers	218	2.31	(1.29,4.13)	157	1.97	(1.03,3.78)	91	1.74	(0.85,3.56)

# Participants



## Model 2: Age, Gender, Education, Infarcts, Lacunes, Hemorrhages, Microbleeds, Arteriosclerosis, Cerebral Amyloid Angiopathy



# Summary

- In a large, autopsy-confirmed AD sample, those who progressed to symptomatic AD during life had **widespread** cognitive deficits at baseline.
- On average, Progressors performed 0.33 SDs worse than Non-Progressors and up to 0.6 SDs worse on Executive Functioning.
- Differences were not related to vascular neuropathology.