Clinical and neuropathological characteristics of symptomatic primary age-related tauopathy (PART)

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What is primary age-related tauopathy (PART)?

- AD: neurofibrillary tangles (NFT) develop secondarily to amyloid pathology
- Primary tauopathies: NFTs develop independent of amyloid pathology
- PART: NFTs - regionally, morphologically, ultra-structurally & biochemically similar to early-moderate AD, yet no evidence of amyloid pathology
  - Cognitively normal, MCI and demented (formerly tangle predominant senile dementia, tangle only dementia, etc.)

Nelson et al (2009)

- UK ADC data: n=26 NFT+/NP-
  - Most 85+ years
  - Most with no MCI/neurodegenerative dx before death
  - Mean MMSE = 26.5
- NACC data: n=219 NFT+/NP- cases
  - Higher likelihood born just before 1918-19 flu pandemic
- Approximately 5% of older individuals are NFT+/NP-
- Given age, suggests not preclinical AD

Crary et al (2014)

- Used NACC data: n=167
- PART: No/sparse neuritic plaques; Braak stage ≤IV
- Compared to those with AD pathology, PART group:
  - Older age at death
  - Better MMSE scores
  - Not associated with APOE ε4

PART and SNAP (Jack, 2014)

- *In vivo* biomarkers suggest some are amyloid-/tau+
- Termed suspected non-Alzheimer pathophysiology (SNAP)
- SNAP parallels PART
  - Lack of amyloid pathology
  - Can include those with / without cognitive impairment
    - Severe dementia is uncommon
  - Relatively common in older adults
  - <30% are *APOE* ε4 carriers

Working classification of PART
(Crary et al, 2014)

Requires:

- Braak stage ≤IV
- absence of other disease associated with NFT

Then subclassify as follows:

Category	Thal Aβ Phase	Alternative: CERAD NP
PART Definite	Phase 0	None (0)
PART Possible	Phase 1 or 2	Sparse (A)

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The debate

- Against PART:
  - no clinical, morphologic, genetic difference w/ early AD
  - PART is part of the AD continuum
  - Would develop amyloid pathology if live long enough
- For PART:
  - Up to 20% of oldest old will not develop amyloid pathology
  - Almost all ≥40 years olds have tau pathology
  - Cannot determine who will develop AD/amyloid pathology or symptomatic PART/other tauopathy; best to classify as PART

Study objective

- Characterize clinical and neuropathological features associated with being symptomatic in those with no or sparse neuritic plaques (NP)
- Given debate whether PART is separate neuropath. process
  - Assess cut-points for NP score (No NP v. Sparse NP) and Braak stage

Study sample

- UDS subjects w/ neuropath data:
  - No NP; n = 170
  - Sparse NP; n = 207
- Restricted to:
  - Those w/ clinical visit ≤1 year of autopsy
- Excluded subjects with:
  - parkinsonian signs, higher cortical visual problems, NPH, LBD, MSA, DS, HD, prion disease, clinical or neuropathological FTLD
- Data from 26 ADCs

Study methods

- Logistic regression with generalized estimating equations
- Outcome: symptomatic (CDR>0) vs. asymptomatic (CDR=0)
- Separate models for No and Sparse NP groups
- Each potential predictor entered into unadjusted model
- Multivariable models incl. significant variables (α=0.10) in unadjusted models

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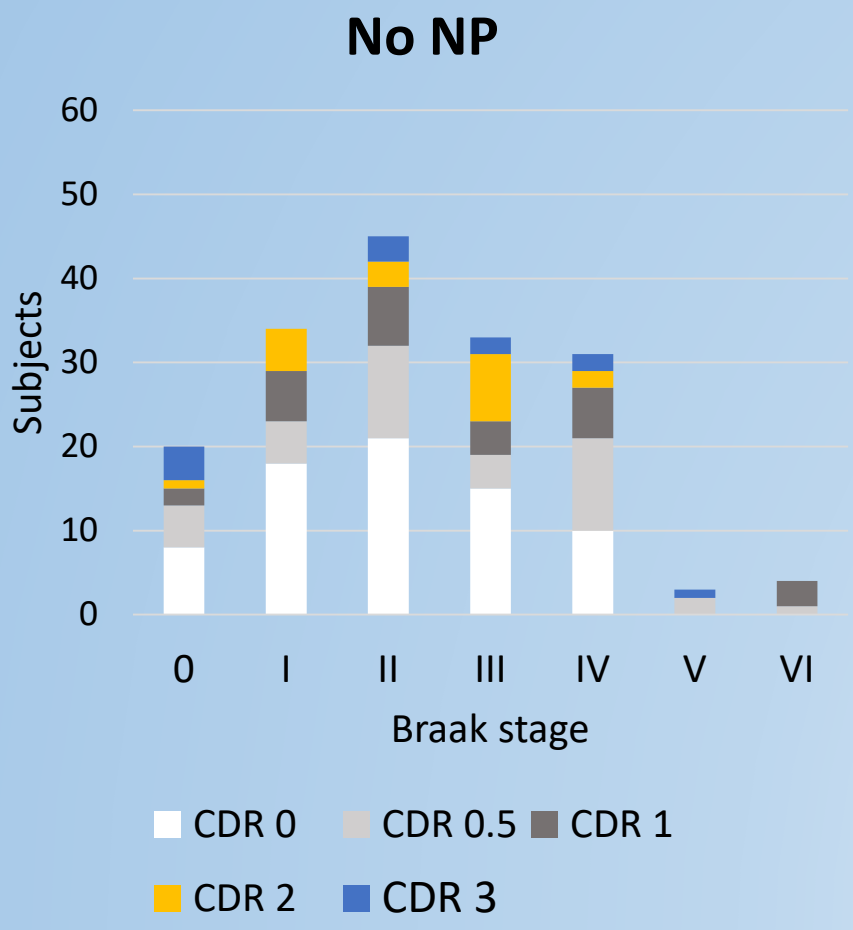
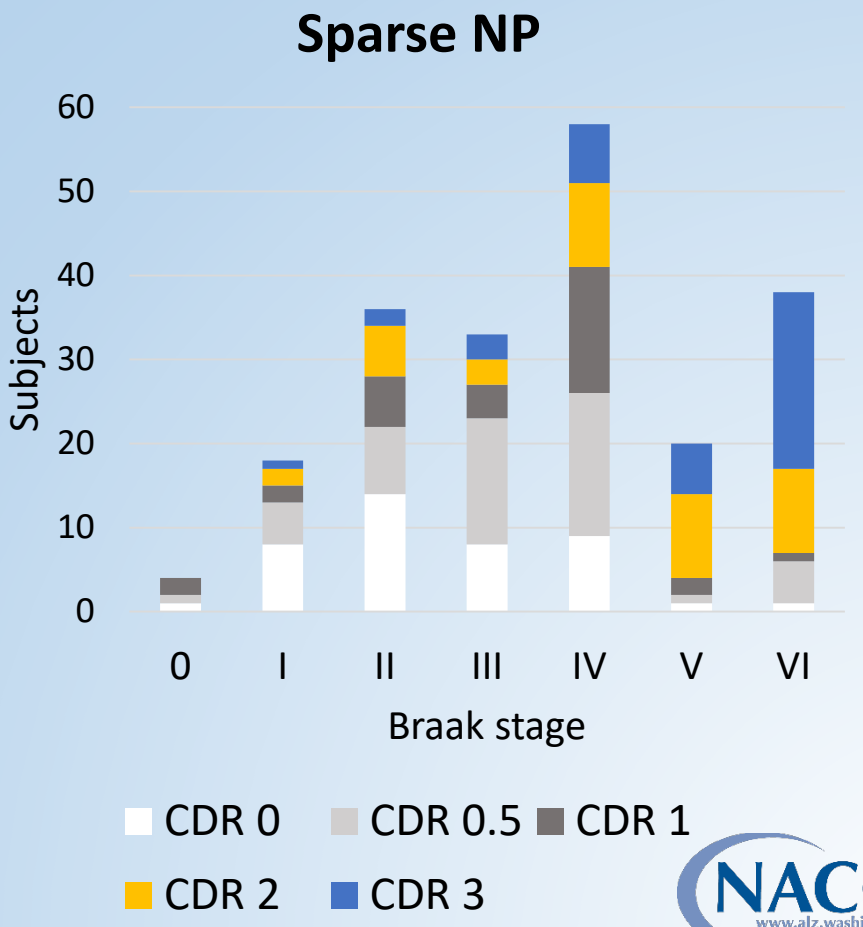
Sample by Braak stage

CERAD NP score		Braak Stage							
		0	I	II	III	IV	V	VI	Total
No NP	CDR=0	8	18	21	15	10	0	0	72
	CDR>0	12	16	24	18	21	3	4	98
Sparse NP	CDR=0	1	8	14	8	9	1	1	42
	CDR>0	3	10	22	25	49	19	37	165

CDR by Braak stage





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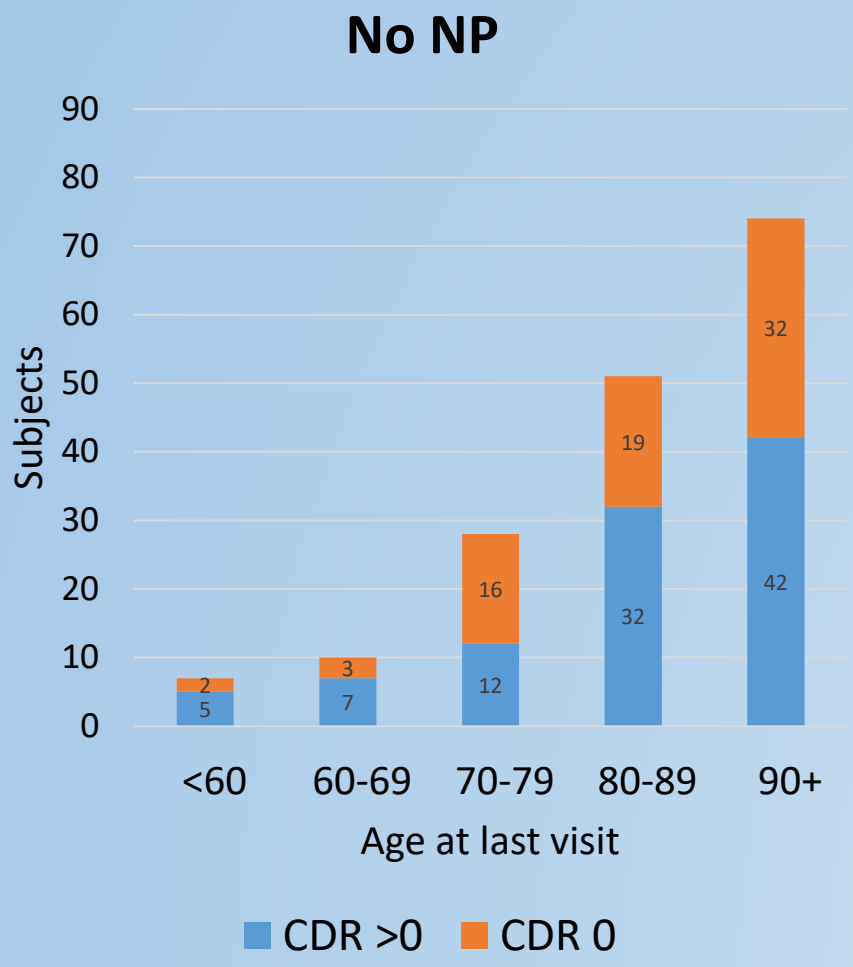
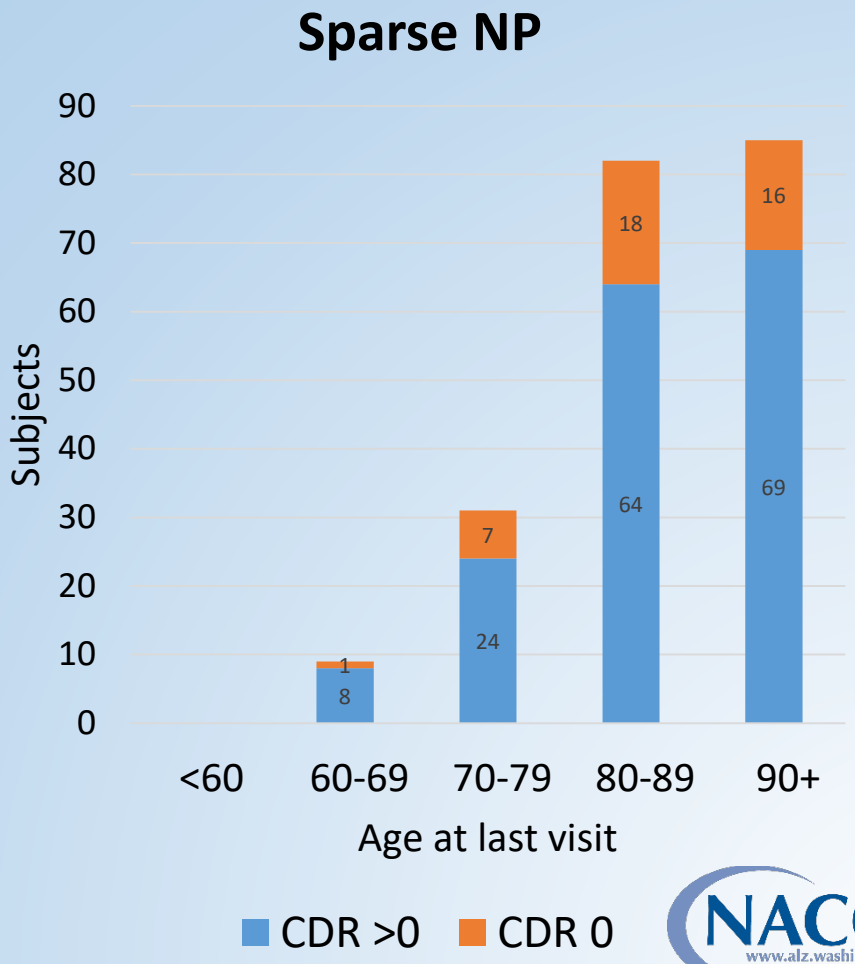
Age and CDR





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Demographic & clinical characteristics

Groups were similar in:

- Age
- Education
- race (>90% white)
- Family hx of cognitive impairment
- Hx - diabetes, stroke, hypertension, TBI

	No NP		Sparse NP	
	CDR>0	CDR=0	CDR>0	CDR=0
Male	53%	39%	51%	36%
APOE ε4 carrier	19%	8%	48%	16%
Depression	59%	31%	44%	17%
Clinical AD diagnosis	65%	-	82%	-

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Neuropathology

Groups were similar in % with:

- Microinfarcts
- Hemorrhages/microbleeds
- Atherosclerosis
- Arteriolosclerosis

	No NP		Sparse NP	
	CDR>0	CDR=0	CDR>0	CDR=0
Diffuse plaques				
None	70%	66%	1%	5%
Sparse	21%	19%	67%	61%
Moderate	5%	7%	11%	13%
Frequent	4%	9%	21%	21%
Medial temp. lobe sclerosis	13%	0%	12%	0%
Amyloid angiopathy	20%	19%	60%	32%

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Multivariable model

	No NP		Sparse NP	
	Odds ratio	95% CI	Odds ratio	95% CI
Age (years)	**0.97**	**0.94-1.00**	1.05	0.97-1.13
Depression	**3.47**	**2.13-5.66**	5.67	0.78-41.22
APOE e4 carrier	1.79	0.87-3.70	2.14	0.55-8.36
History of diabetes	0.61	0.21-1.78	1.81	0.47-7.02
Braak stage	**1.34**	**1.07-1.67**	**1.61**	**1.07-2.41**
Any diffuse plaques	0.55	0.28-1.08	0.64	0.03-13.62
Microinfarct	1.52	0.72-3.20	1.93	0.73-5.09
Amyloid angiopathy	1.29	0.58-2.84	**2.65**	**1.40-5.01**

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Summary

- Few in no NP group had Braak V-VI
- In sparse NP group, CDR=2 or 3 increased from Braak 0 to Braak 6
- Sparse NP group had more symptomatic subjects in each age group, vs. no NP group
- In both NP groups, symptomatic subjects more often male, depressed, APOE e4 carriers
- 65% of symptomatic no NP group diagnosed with clin. AD
- Being symptomatic associated with:
  - Braak stage & depression in no NP group
  - Braak stage & amyloid angiopathy in sparse NP group

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