Clifford Jack, David Knopman, Ronald Petersen & William Jagust - selected joint publications

1 Jack, C. R., Jr., Wiste, H. J., Weigand, S. D., Rocca, W. A., Knopman, D. S., Mielke, M. M. et al. (2014). Age-specific population frequencies of cerebral beta-amyloidosis and neurodegeneration among people with normal cognitive function aged 50-89 years: a cross-sectional study. *Lancet Neurology, 13,* 997-1005.
Notes: BACKGROUND: As preclinical Alzheimer's disease becomes a target for therapeutic intervention, the overlap between imaging abnormalities associated with typical ageing and those associated with Alzheimer's disease needs to be recognised. We aimed to characterise how typical ageing and preclinical Alzheimer's disease overlap in terms of beta-amyloidosis and neurodegeneration. METHODS: We measured age-specific frequencies of amyloidosis and neurodegeneration in individuals with normal cognitive function aged 50-89 years. Potential participants were randomly selected from the Olmsted County (MN, USA) population-based study of cognitive ageing and invited to participate in cognitive and imaging assessments. To be eligible for inclusion, individuals must have been judged clinically to have no cognitive impairment and have undergone amyloid PET, (18)F-fluorodeoxyglucose ((18)F-FDG) PET, and MRI. Imaging results were obtained from March 28, 2006, to Dec 3, 2013. Amyloid status (positive [A(+)] or negative [A(-)]) was determined by amyloid PET with (11)C Pittsburgh compound B. Neurodegeneration status (positive [N(+)] or negative [N(-)]) was determined by an Alzheimer's disease signature (18)F-FDG PET or hippocampal volume on MRI. We determined age-specific frequencies of the four groups (amyloid negative and neurodegeneration negative [A(-)N(-)], amyloid positive and neurodegeneration negative [A(+)N(-)], amyloid negative and neurodegeneration positive [A(-)N(+)], or amyloid positive and neurodegeneration positive [A(+)N(+)]) cross-sectionally using multinomial regression models. We also investigated associations of group frequencies with APOE varepsilon4 status (assessed with DNA extracted from blood) and sex by including these covariates in the multinomial models. FINDINGS: The study population consisted of 985 eligible participants. The population frequency of A(-)N(-) was 100% (n=985) at age 50 years and fell to 17% (95% CI 11-24) by age 89 years. The frequency of A(+)N(-) increased to 28% (24-32) at age 74 years, then decreased to 17% (11-25) by age 89 years. The frequency of A(-)N(+) increased from age 60 years, reaching 24% (16-34) by age 89 years. The frequency of A(+)N(+) increased from age 65 years, reaching 42% (31-52) by age 89 years. The results from our multinomial models suggest that A(+)N(-) and A(+)N(+) were more frequent in APOE varepsilon4 carriers than in non-carriers and that A(+)N(+) was more, and A(+)N(-) less frequent in men than in women. INTERPRETATION: Accumulation of amyloid and neurodegeneration are nearly inevitable by old age, but many people are able to maintain normal cognitive function despite these imaging abnormalities. Changes in the frequency of amyloidosis and neurodegeneration with age, which seem to be modified by APOE varepsilon4 and sex, suggest that pathophysiological sequences might differ between individuals.

2 Jack, C. R., Jr., Wiste, H. J., Knopman, D. S., Vemuri, P., Mielke, M. M., Weigand, S. D. et al. (2014). Rates of beta-amyloid accumulation are independent of hippocampal neurodegeneration. *Neurology, 82,* 1605-1612.
Notes: OBJECTIVE: To test the hypotheses predicted in a hypothetical model of Alzheimer disease (AD) biomarkers that rates of beta-amyloid (Abeta) accumulation on PET imaging are not related to hippocampal neurodegeneration whereas rates of neurodegenerative brain atrophy depend on the presence of both amyloid and neurodegeneration in a population-based sample. METHODS: A total of 252 cognitively normal (CN) participants from the Mayo Clinic Study of Aging had 2 or more serial visits with both amyloid PET and MRI. Subjects were classified into 4 groups based on baseline positive/negative amyloid PET (A+ or A-) and baseline hippocampal volume (N+ or N-). We compared rates of amyloid accumulation and rates of brain atrophy among the 4 groups. RESULTS: At baseline, 148 (59%) were amyloid negative and neurodegeneration negative (A-N-), 29 (12%) amyloid negative and neurodegeneration positive (A-N+), 56 (22%) amyloid positive and neurodegeneration negative (A+N-), and 19 (8%) amyloid positive and neurodegeneration positive (A+N+). High rates of

Abeta accumulation were found in those with abnormal amyloid at baseline and were not influenced by hippocampal neurodegeneration at baseline. In contrast, rates of brain atrophy were greatest in A+N+. CONCLUSIONS: We describe a 2-feature biomarker approach to classifying elderly CN subjects that is complementary to the National Institute on Aging-Alzheimer's Association preclinical staging criteria. Our results support 2 key concepts in a model of the temporal evolution of AD biomarkers. First, the rate of Abeta accumulation is not influenced by neurodegeneration and thus may be a biologically independent process. Second, Abeta pathophysiology increases or catalyzes neurodegeneration

3 Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Petersen, R. C., Weiner, M. W., Aisen, P. S. et al. (2013). Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurology, 12,* 207-216.
Notes: In 2010, we put forward a hypothetical model of the major biomarkers of Alzheimer's disease (AD). The model was received with interest because we described the temporal evolution of AD biomarkers in relation to each other and to the onset and progression of clinical symptoms. Since then, evidence has accumulated that supports the major assumptions of this model. Evidence has also appeared that challenges some of our assumptions, which has allowed us to modify our original model. Refinements to our model include indexing of individuals by time rather than clinical symptom severity; incorporation of interindividual variability in cognitive impairment associated with progression of AD pathophysiology; modifications of the specific temporal ordering of some biomarkers; and recognition that the two major proteinopathies underlying AD biomarker changes, amyloid beta (Abeta) and tau, might be initiated independently in sporadic AD, in which we hypothesise that an incident Abeta pathophysiology can accelerate antecedent limbic and brainstem tauopathy
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4 Jack, C. R., Jr., Wiste, H. J., Lesnick, T. G., Weigand, S. D., Knopman, D. S., Vemuri, P. et al. (2013). Brain beta-amyloid load approaches a plateau. *Neurology, 80,* 890-896.
Notes: OBJECTIVE: To model the temporal trajectory of beta-amyloid accumulation using serial amyloid PET imaging. METHODS: Participants, aged 70-92 years, were enrolled in either the Mayo Clinic Study of Aging (n = 246) or the Mayo Alzheimer's Disease Research Center (n = 14). All underwent 2 or more serial amyloid PET examinations. There were 205 participants classified as cognitively normal and 55 as cognitively impaired (47 mild cognitive impairment and 8 Alzheimer dementia). We measured baseline amyloid PET-relative standardized uptake values (SUVR) and, for each participant, estimated a slope representing their annual amyloid accumulation rate. We then fit regression models to predict the rate of amyloid accumulation given baseline amyloid SUVR, and evaluated age, sex, clinical group, and APOE as covariates. Finally, we integrated the amyloid accumulation rate vs baseline amyloid PET SUVR association to an amyloid PET SUVR vs time association. RESULTS: Rates of amyloid accumulation were low at low baseline SUVR. Rates increased to a maximum at baseline SUVR around 2.0, above which rates declined-reaching zero at baseline SUVR above 2.7. The rate of amyloid accumulation as a function of baseline SUVR had an inverted U shape. Integration produced a sigmoid curve relating amyloid PET SUVR to time. The average estimated time required to travel from an SUVR of 1.5-2.5 is approximately 15 years. CONCLUSION: This roughly 15-year interval where the slope of the amyloid SUVR vs time curve is greatest and roughly linear represents a large therapeutic window for secondary preventive interventions

5 Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W. et al. (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology, 9,* 119-128.
Notes: Currently available evidence strongly supports the position that the initiating event in Alzheimer's disease (AD) is related to abnormal processing of beta-amyloid (Abeta) peptide, ultimately leading to formation of Abeta plaques in the brain. This process occurs while individuals are still cognitively normal. Biomarkers of brain beta-amyloidosis are reductions in CSF Abeta(42) and increased amyloid PET tracer retention. After a lag period, which varies

from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Biomarkers of neuronal injury and neurodegeneration are increased CSF tau and structural MRI measures of cerebral atrophy. Neurodegeneration is accompanied by synaptic dysfunction, which is indicated by decreased fluorodeoxyglucose uptake on PET. We propose a model that relates disease stage to AD biomarkers in which Abeta biomarkers become abnormal first, before neurodegenerative biomarkers and cognitive symptoms, and neurodegenerative biomarkers become abnormal later, and correlate with clinical symptom severity

6 Jack, C. R. (2003). Magnetic resonance imaging. In R.C.Petersen (Ed.), *Mild cognitive impairment. Aging to Alzheimer's disease* (pp. 105-132). New York: Oxford University Press.

7 Jack, C. R. & Petersen, R. C. (2000). Structural imaging approaches to Alzheimer's disease. In L.F.M.Scinto & K. R. Daffner (Eds.), *Early diagnosis of Alzheimer's disease* (pp. 127-148). Totowa,NJ: Humana Press.

8 Jack, C. R. (1998). Anatomic neuroimaging in the dementias. In J.H.Growdon & M. N. Rossor (Eds.), *The dementias* (pp. 189-218). Boston: Butterworth-Heinemann.