

The Syn-D Study: Detection of Cutaneous Phosphorylated Alpha-Synuclein in Mild Cognitive Impairment

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Background

- Dementia with Lewy Bodies (DLB) is a neurodegenerative disease characterized by progressive accumulation of phosphorylated alpha-synuclein (P-SYN)
- Cutaneous assessment of P-SYN using skin punch biopsies can identify, visualize, and quantify the presence of P-SYN within cutaneous nerve fibers, facilitating diagnosis of neurological disease and offering a potential biomarker of target engagement
- Up to 50% of patients with Alzheimer’s disease (AD) may exhibit synuclein co-pathology in the central nervous system; the prevalence and quantity of peripheral synuclein deposition in these cases is unknown
- We sought to determine the frequency of biomarker support for mixed pathology in the MCI stage of patients with MCI with the DLB phenotype (MCI-DLB) and MCI AD phenotype (MCI-AD).

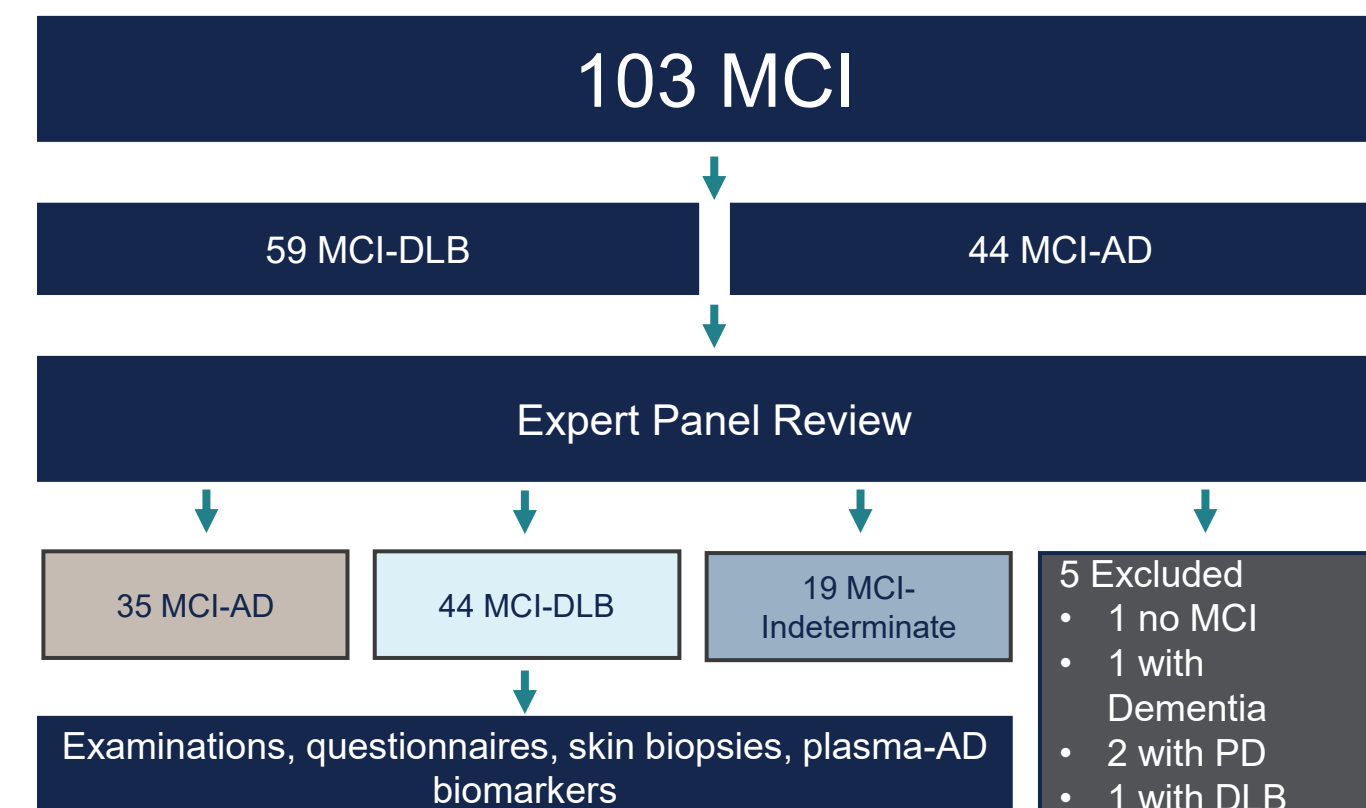
Objective

- To quantify the deposition of cutaneous phosphorylated alpha-synuclein (P-SYN) in patients with MCI-DLB and MCI-AD
- To determine peripheral biomarker co-pathology with plasma P-Tau217 in patients with MCI-DLB and MCI-AD
- Determine the rates of P-SYN change over time, and determine correlations with disease severity

Methods

- 103 participants with MCI-AD and MCI-DLB completed neurological examinations, medical history screening, and motor assessments
- Clinical review by an expert panel blinded to pathology established the clinical diagnosis
- Skin biopsies at the distal leg, distal thigh and posterior cervical sites were performed with quantitation of P-SYN
- Blood plasma was collected for quantification of phosphorylated-Tau217 (p-tau217)
- A total of 79 patients completed their 12-month follow-up assessment and repeated the study procedures and skin biopsies

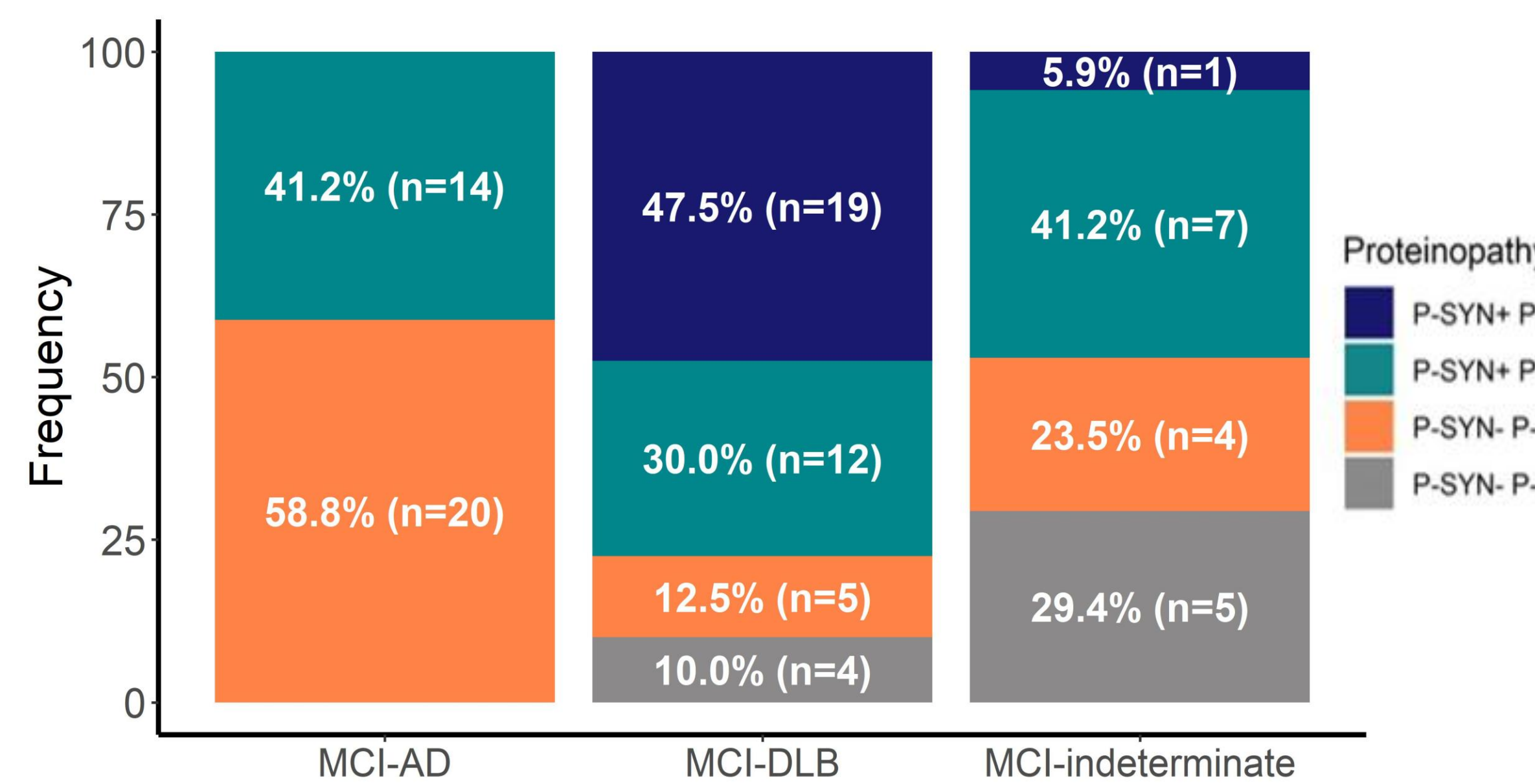
Participant Flow Diagram



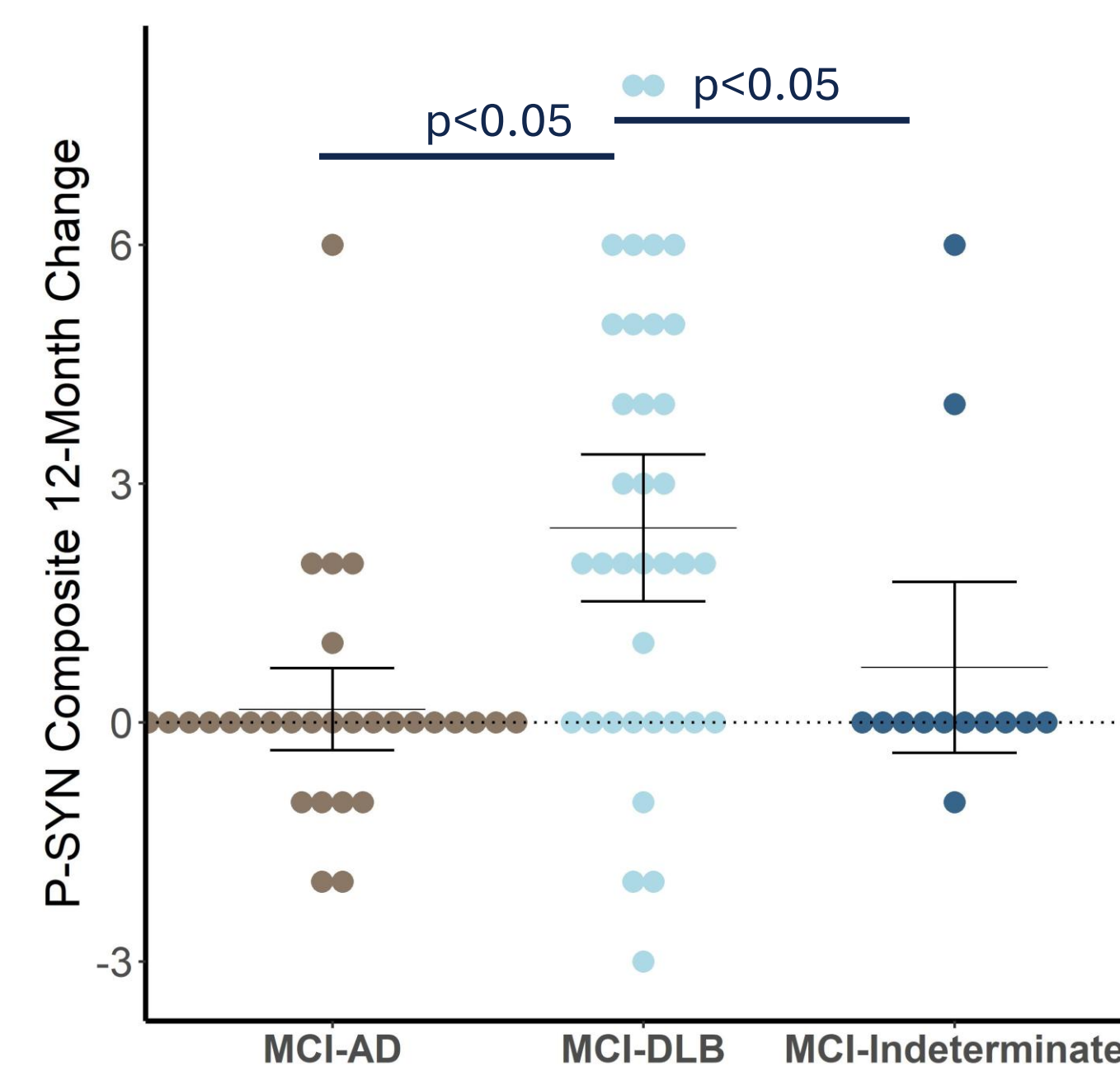
	Total Cohort		MCI-AD (n=35)		MCI-DLB (n=44)		MCI-indeterminate (n=19)		ANOVA between groups (baseline)
	Baseline (n=98)	12M Follow Up (n=79)	Baseline (n=35)	12M Follow Up (n=30)	Baseline (n=44)	12M Follow Up (n=36)	Baseline (n=19)	12M Follow Up (n=13)	
Age ± SD	73.3 ± 6.9	73.9 ± 6.6	73.0 ± 5.1	73.3 ± 5.1	73.3 ± 8.3	73.8 ± 7.9	74.0 ± 6.3	75.5 ± 6.0	p=0.88
Sex (M:F)	61:37	48:31	17:18	15:15	33:11	25:11	11:8	8:5	p=0.05
UPDRS Part 2-3 Mean ± SD	19.6 ± 17.8	22.0 ± 20.5	5.5 ± 5.2	5.8 ± 5.2	26.8 ± 15.6	32.9 ± 20.5	28.9 ± 20.8	29.1 ± 19.7	p<0.0001
Global CDR ± SD	0.51 ± 0.1	0.70 ± 0.40	0.50 ± 0.0	0.67 ± 0.2	0.51 ± 0.08	0.75 ± 0.5*	0.53 ± 0.1	0.62 ± 0.3	p=0.42
CDR Sum of Boxes ± SD	2.2 ± 1.1	3.2 ± 2.4	1.8 ± 1.2	2.9 ± 2.3*	2.3 ± 1.0	3.5 ± 2.6*	2.4 ± 1.2	3.1 ± 2.3	p=0.06

* Indicate Group-specific significant change from Baseline to Follow-up

P-Syn and p-Tau217 Frequency by MCI Diagnostic Group



Change in P-SYN Over 12 Months



12-Month Changes in P-SYN by Group

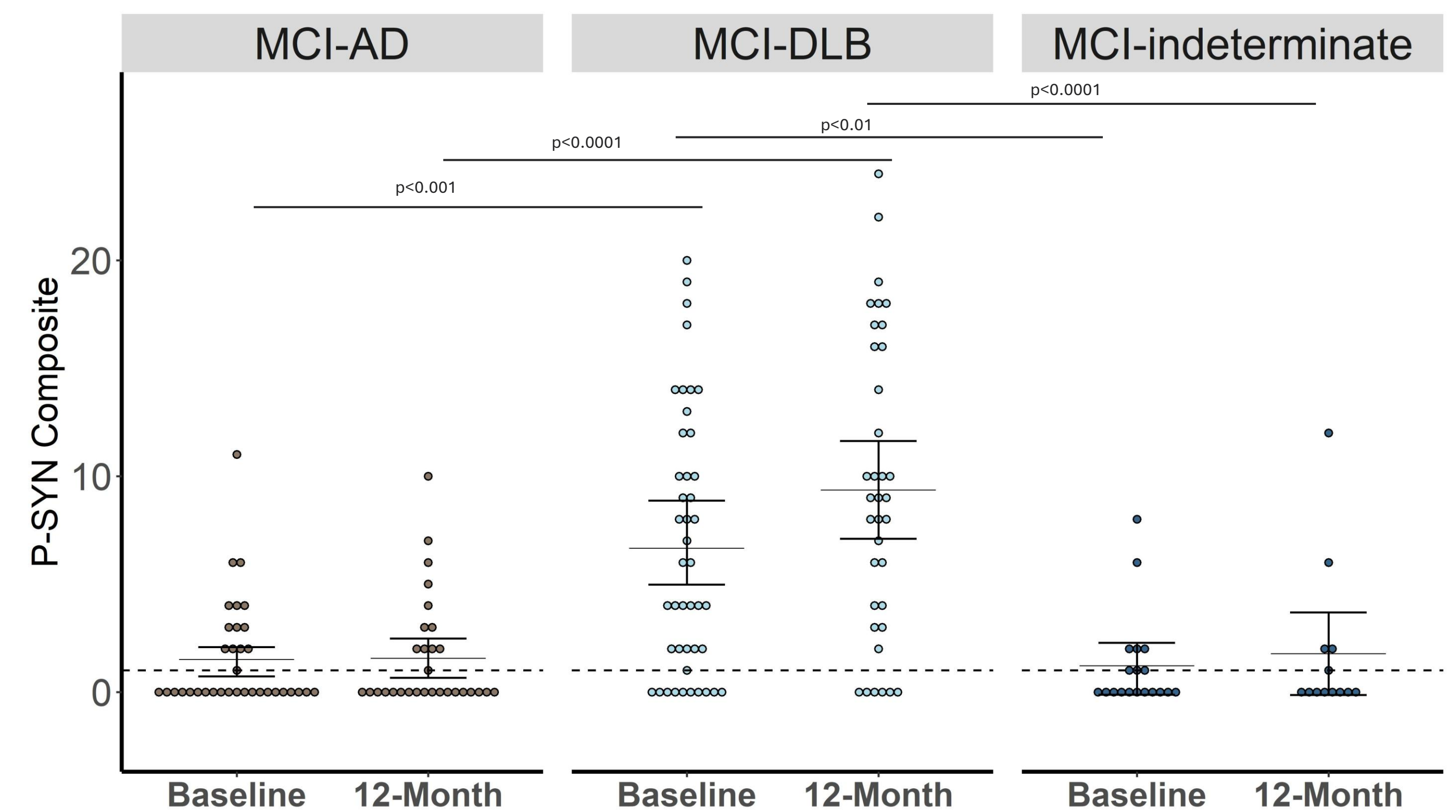
	MCI-AD	MCI-DLB	MCI-Indeterminate
Increase (n)	5	24	2
Decrease (n)	6	4	1
No Change (n)	19	8	10

Results

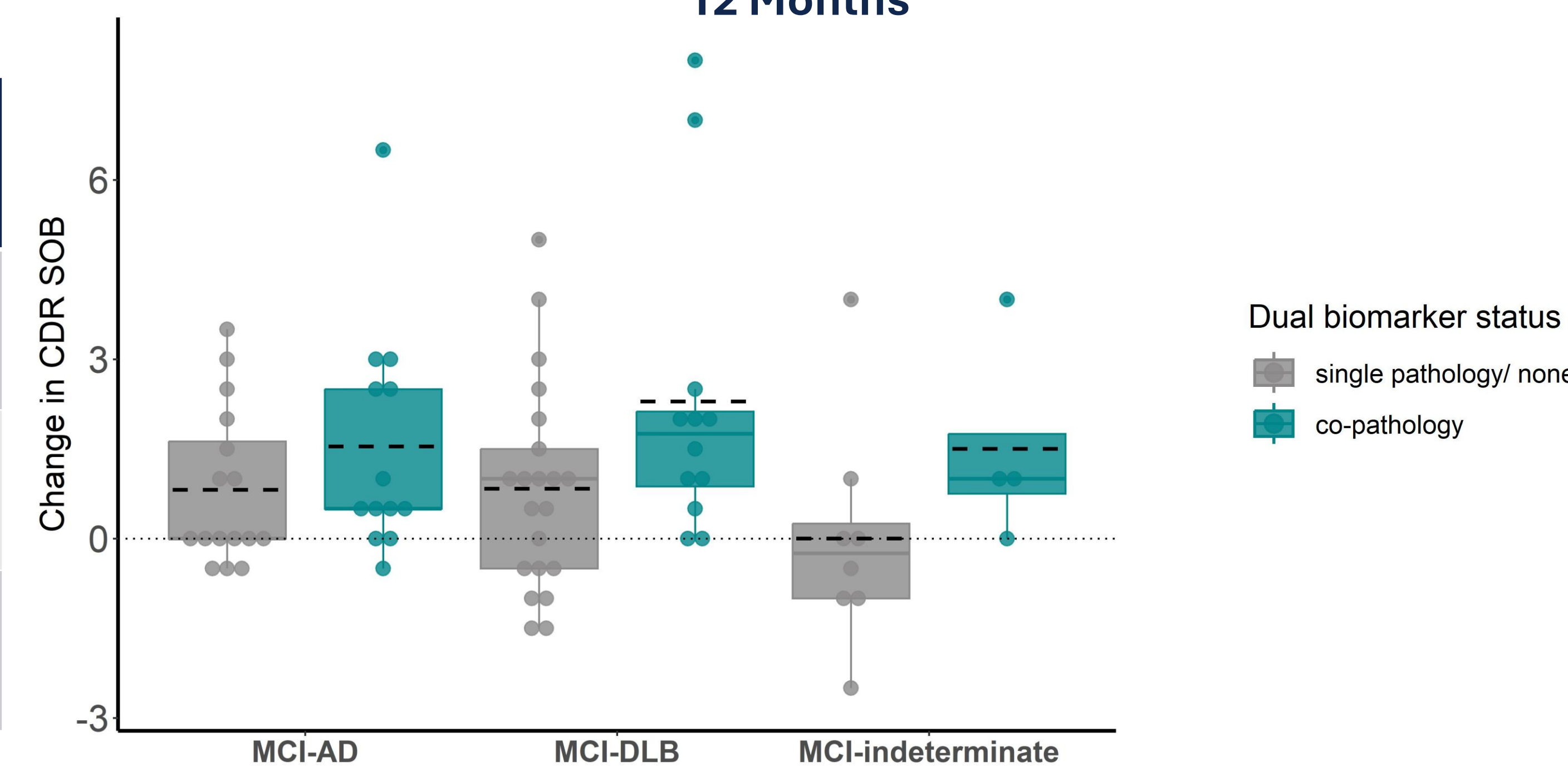
Basic Demographics

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P-SYN at 12 Months and Baseline by Group



Presence of biomarkers and change in CDR Sum of Boxes over 12 Months



Conclusion

- This prospective blinded study of patients with MCI extends the results of the previously reported Syn-One study¹ and a recent pilot study in patients with recent onset cognitive impairment² that validated the detection of cutaneous P-SYN as a diagnostic test of synucleinopathies
- At the 12-month follow-up, consistent with autopsy studies, P-SYN was detected in 83% of MCI-DLB and 41% of MCI-AD patients
- The individuals with both p-tau217 and P-SYN biomarkers had the greatest 12-month decline in cognitive function as measured by CDR sum of boxes**
- Rate of cutaneous P-SYN increases may distinguish between dementia subtype trajectories
- Ongoing analysis and longitudinal follow-up will define the relevance of P-SYN deposition in patients with suspected AD and DLB at the MCI stage

References

- Gibbons CH, et al. Synuclein-One study: skin biopsy detection of phosphorylated α-synuclein for diagnosis of synucleinopathies. *Biomarkers in Medicine*. 2022
- Furia A, et al. Identification of Dementia With Lewy Bodies by Skin Biopsy in Recent-Onset Cognitive Impairment. *Ann Clin Transl Neurol*. 2025