

Prodromal Onset Presentations, Clinical Features, and Longitudinal Cognitive Trajectories in Dementia with Lewy Bodies: insights from the CLIMB-DLB cohort

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INTRODUCTION

Despite growing recognition of the prodromal stage of Dementia with Lewy Bodies (DLB), its clinical heterogeneity and prognostic implications remain poorly understood. Although **three main onset patterns (OPs, namely MCI-LB, psychiatric, and delirium-onset)** have been proposed, their distribution, relationship with core and supportive clinical features, as well as their impact on longitudinal cognitive decline have not been comprehensively characterized yet.

AIMS AND METHODS

- 1
- To systematically characterize onset patterns (OPs) and the distribution of core and supportive clinical features in prodromal stages of DLB, and their reciprocal association.
- 2
- To evaluate whether baseline clinical features and their interaction with different OPs predict longitudinal cognitive decline

Clinical assessment

- Core and supportive features, Feature Burden Score (FBS, 0–6)
- Longitudinal MMSE (up to 8 years follow-up)

Statistical analysis

- Feature association network (Phi coefficients)
- Linear mixed-effects models: **time × feature** and **time × feature × OP**

Table 1. Baseline characteristics and prevalence of clinical features in patients stratified according to most prominent onset presentation

	All (n=75)	MCI-LB (n=51)	Psychiatric (n=18)	Delirium (n=6)	Effect size	p value
Age (y)	73.16 ± 6.43	73.86 ± 6.52	71.00 ± 5.55	73.67 ± 7.81	$\varepsilon^2=0.041$	0.0827
Sex (F%)	20/75 (26.7%)	12/51 (23.5%)	7/18 (38.9%)	1/6 (16.7%)	V=0.094	0.379
MMSE V1	24.32 ± 3.95	24.23 ± 3.68	24.57 ± 3.53	24.22 ± 6.95	$\varepsilon^2<0.001$	0.825
FBS	1.39 ± 1.15	1.43 ± 1.24	1.22 ± 0.81	1.50 ± 1.38	$\varepsilon^2<0.001$	0.937
Fluctuations (%)	5/75 (6.7%)	2/51 (3.9%)	2/18 (11.1%)	1/6 (16.7%)	V<0.001	0.341
Hallucinations (%)	22/75 (29.3%)	15/51 (29.4%)	5/18 (27.8%)	2/6 (33.3%)	V<0.001	0.967
RBD (%)	40/75 (53.3%)	30/51 (58.8%)	6/18 (33.3%)	4/6 (66.7%)	V=0.161	0.140
Parkinsonism (%)	23/75 (30.7%)	15/51 (29.4%)	7/18 (38.9%)	1/6 (16.7%)	V<0.001	0.559
Dysautonomia (%)	10/75 (13.3%)	7/51 (13.7%)	2/18 (11.1%)	1/6 (16.7%)	V<0.001	0.932
Hyposmia (%)	4/75 (5.3%)	4/51 (7.8%)	0/18 (0.0%)	0/6 (0.0%)	V=0.007	0.370

Data are presented as mean ± SD for continuous variables and n/N (%) for categorical variables. Group comparisons are based on one-way ANOVA (continuous) and χ^2 test (categorical). Effect sizes: η^2 for ANOVA, Cramér's V for χ^2 .

Get in touch!



References

- McKeith IG, et al - Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium - Neurology - 2017
- McKeith IG, et al - Research criteria for the diagnosis of prodromal dementia with Lewy bodies - Neurology - 2020
- Mastenbroek SE, et al - Disease progression modelling reveals heterogeneity in trajectories of Lewy-type α -synuclein pathology - Nature Communications - 2025

Abbreviations

CF, cognitive fluctuations; RBD, REM sleep behaviour disorder; VH, visual hallucinations; FBS, Feature Burden Score; MMSE, Mini-Mental State Examination; β , beta coefficient; CI, confidence interval.

RESULTS and DISCUSSION

CROSS-SECTIONAL RESULTS

- MCI-LB was the most frequent prodromal onset pattern** (68%), followed by psychiatric (24%) and delirium-onset (8%).
- Overlapping presentations** were common (35.6%), particularly the combination of cognitive and psychiatric symptoms
- No differences in baseline clinical features across onset patterns.
- Parkinsonism emerged as the central node** within the symptom network, showing the strongest association with hallucinations.

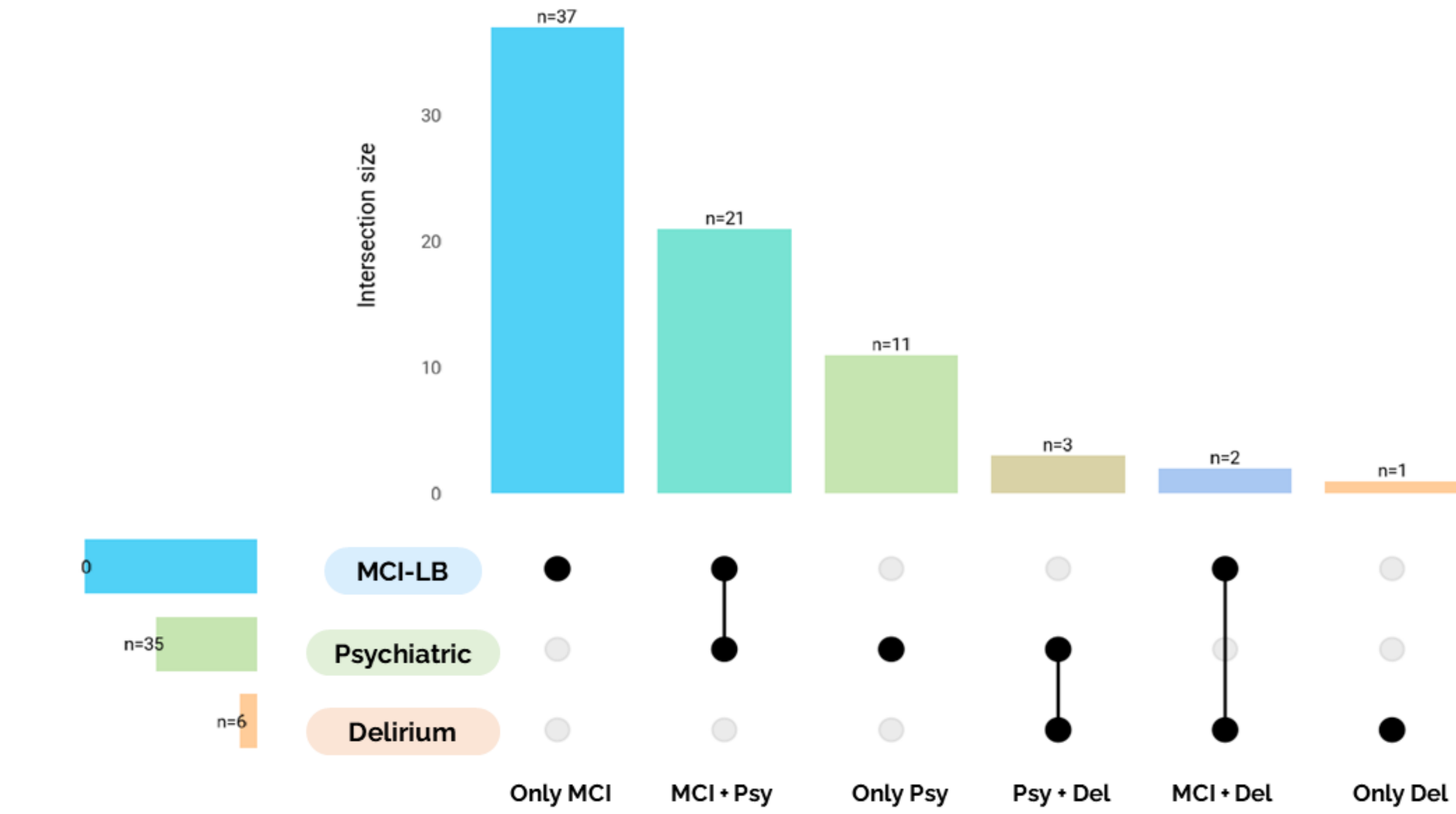


Figure 1. UpSet plot summarizing Onset Presentations and overlaps
Upper: size of each intersection, ordered by decreasing frequency. Lower: combination of OPs. Filled circles denote the presence of a given presentation, vertical lines indicate co-occurrence within the same subgroup.

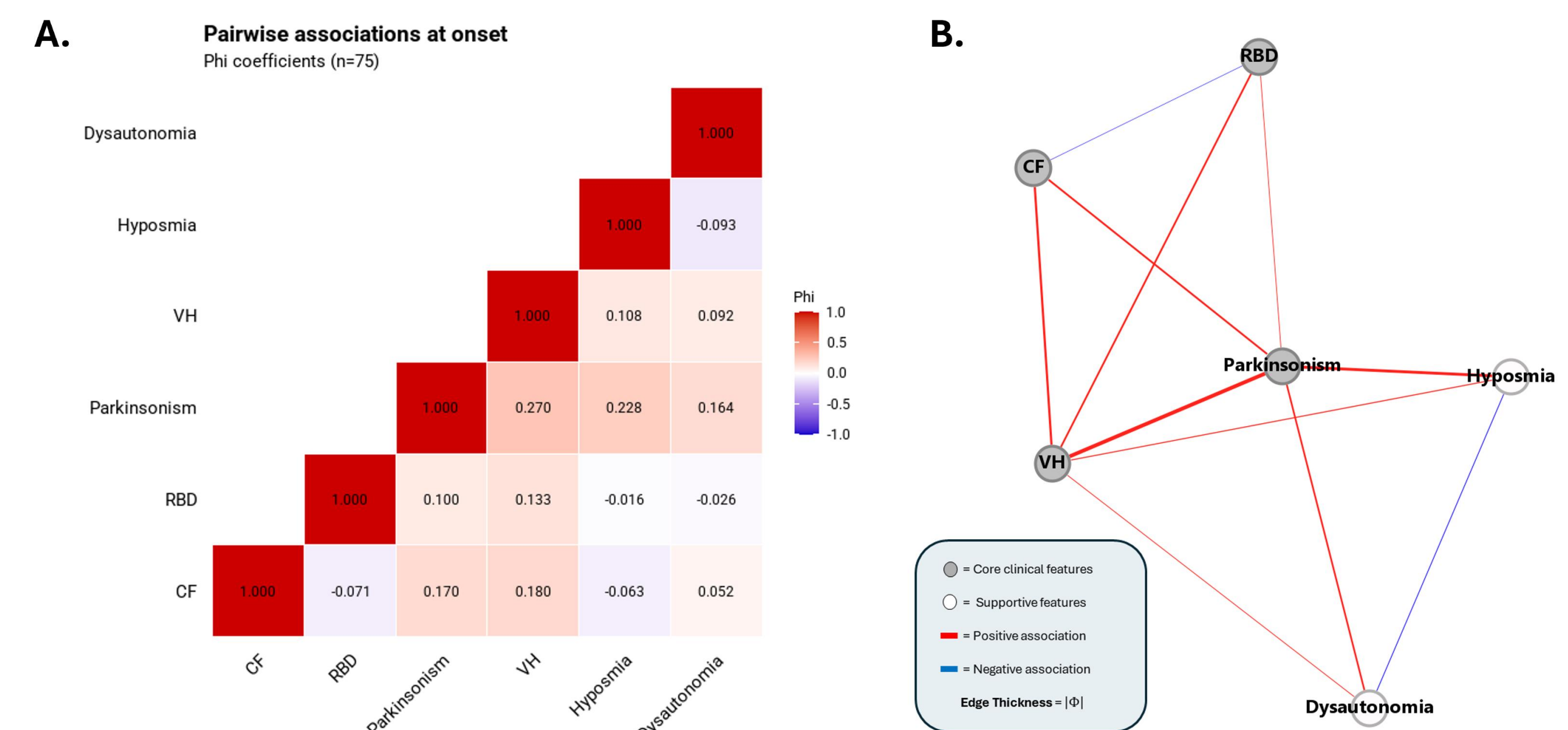


Figure 2. Pairwise and network-based associations between core and supportive clinical features at onset.
(A) Heatmap of pairwise positive (red) and negative (blue) associations. Color intensity reflect magnitude (phi range: -1 to +1).
(B) Network representation of associations.

Table 2. Linear mixed-effects model examining the interaction between time and baseline clinical features with and without considering the effect of onset presentation

Baseline Feature	β (time × feature)	SE	95% CI	β (time × feature × OP)	SE	95% CI
Fluctuations	-0.072	1.126	[-2.279, 2.134]	-2.191	3.462	[-8.977, 4.594]
Hallucinations	-0.457	0.469	[-1.376, 0.461]	-2.338	1.159	[-4.610, -0.066]
RBD	-0.446	0.403	[-1.236, 0.343]	-0.749	1.166	[-3.036, 1.537]
Parkinsonism	1.077	0.449	[0.198, 1.956]	0.316	1.129	[-1.897, 2.529]
Dysautonomia	0.455	0.698	[-0.912, 1.823]	1.417	1.608	[-1.735, 4.569]
Hyposmia	1.445	0.890	[-0.299, 3.190]	n.a.*	n.a.*	n.a.*
FBS	0.112	0.197	[-0.274, 0.498]	-0.902	0.898	[-2.663, 0.858]

Models included random intercepts and slopes and were adjusted for age and sex. *Interaction terms not estimable due to limited variability across onset groups. Bold values indicate statistical significance.

LONGITUDINAL RESULTS

- MMSE declined by approximately 1.1 pts/y, with marked inter-individual variability.
- Baseline parkinsonism was associated with slower cognitive decline over time.**
- Overall FBS and OPs alone did not predict cognitive progression.
- Visual hallucinations** predicted **faster decline only in patients with psychiatric-onset DLB**, suggesting a context-dependent prognostic role.

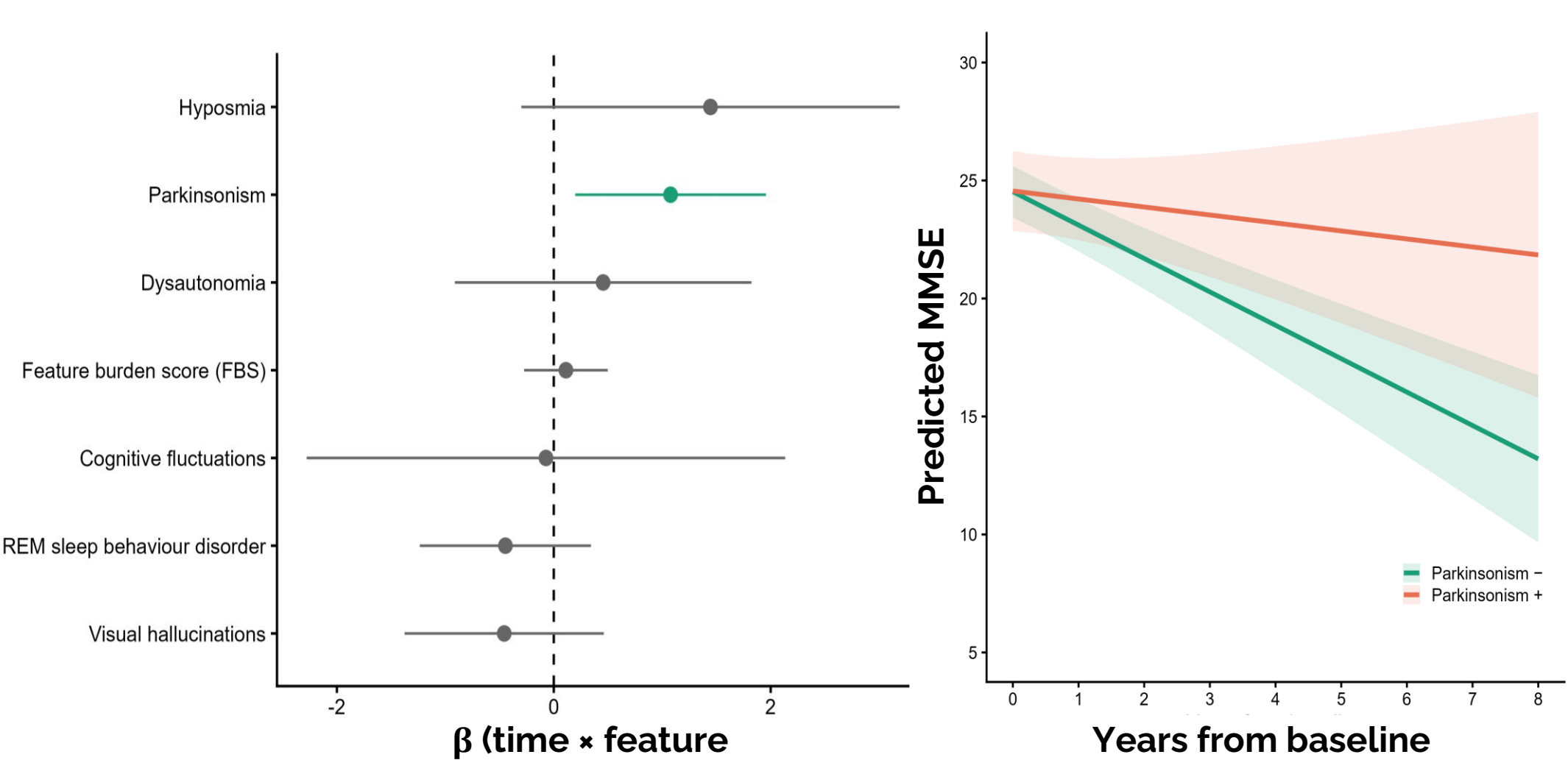


Figure 3. Longitudinal associations between baseline clinical features and cognitive decline.
Left: Forest plot of β coefficients for time × features interactions. Error bars indicate 95% CIs. green denotes statistically significant associations. Right: Predicted MMSE trajectories according to baseline parkinsonism status, shaded areas represent 95% CIs.

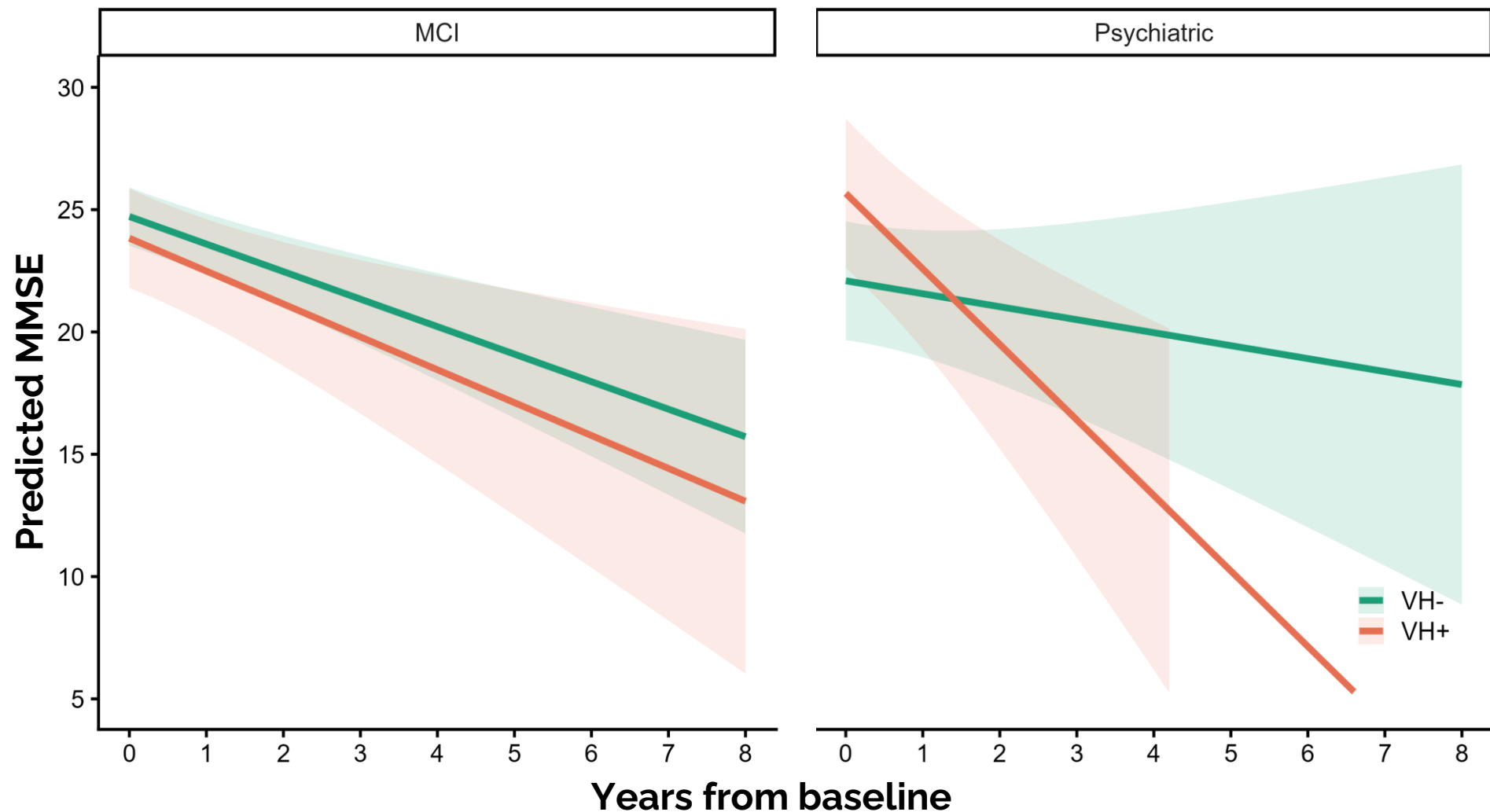


Figure 4. Predicted MMSE trajectories by visual hallucinations and onset category (MCI vs Psychiatric)
Trajectories were estimated from a linear mixed-effects model including time × VH × onset interaction, adjusted for age and sex, with random intercepts and slopes. Shaded areas represent 95% confidence intervals. VH: Visual Hallucinations.

KEY MESSAGES

- Prodromal DLB is a heterogeneous but partially structured clinical spectrum, where **onset presentation alone has limited prognostic value**
- Prognosis is better explained by the interaction between individual clinical features and phenotypic context.**
- Early phenotypic characterization may improve patient stratification and support personalized prognostic assessment in prodromal DLB.

