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Progression to Dementia in Mild Cognitive Impairment With Lewy Bodies or Alzheimer Disease

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Abstract:

Objective: To determine whether mild cognitive impairment with Lewy bodies or Alzheimer's disease differ in their rates of clinical progression to dementia, we undertook longitudinal observation of mild cognitive impairment cases with detailed clinical assessment of Lewy body diagnostic characteristics.

Methods: Two prospective longitudinal cohorts combining to 111 individuals aged 60 years or older with mild cognitive impairment were assessed annually to track cognitive and clinical progression, including the presence or absence of core clinical features and proposed biomarkers of dementia with Lewy bodies. Multi-state modelling was used to assess the associations of diagnostic characteristics of dementia with Lewy bodies with clinical progression from mild cognitive impairment to dementia, with death as a competing outcome.

Results: After a mean follow-up of 2.2 yrs (range = 1-6.7 yrs), 38/111 (34%) of the participants progressed to dementia: 10 with AD, 3 with possible dementia with Lewy bodies and 25 with probable dementia with Lewy bodies. The presence of any Lewy body disease characteristic was associated with an increased hazard of transition to dementia; this risk further increased as more diagnostic characteristics were observed (Hazard ratio = 1.33 per characteristic, 95% CI: 1.11–1.60), and was especially high for those experiencing complex visual hallucinations (Hazard ratio = 1.98, 95% CI: 0.92-4.29) or cognitive fluctuations (Hazard ratio = 3.99, 95% CI: 2.03-7.84).

Conclusions: Diagnostic characteristics of Lewy body disease are associated with an increased risk of transition from mild cognitive impairment to dementia.

Introduction

Dementia with Lewy bodies (DLB) has a worse prognosis than Alzheimer's disease (AD), with increased hospitalization[1] and shorter survival time.[2] We have previously found[3] that the cognitive prodrome of DLB, MCI with Lewy bodies (MCI-LB) for which research diagnostic criteria were recently published[4], was more likely to demonstrate a progressive cognitive decline than MCI due to AD (MCI-AD). The respective cognitive prodromes may therefore progress at different rates, as in dementia. However, it remains unclear as to whether an MCI with core clinical features of DLB (REM sleep behaviour disorder (RBD), parkinsonism, complex visual hallucinations, and cognitive fluctuations) has a worse clinical prognosis with faster dementia onset than MCI-AD, and whether progression risk differs between those with different clinical features.

RBD and Parkinson's disease are risk factors for neurodegenerative disease and dementia, but may remain as isolated diagnoses without cognitive decline for many years[5, 6] and may not manifest in greater risk over the short term of this study. Psychiatric symptoms in an amnestic MCI are associated with faster conversion to dementia,[7] and faster decline in AD[8, 9] so MCI with core neuropsychiatric symptoms of DLB (visual hallucinations or cognitive fluctuations) may progress to dementia faster than those without these features.

We hypothesised that 1) MCI-LB would have a greater annual risk of clinical transition to dementia than MCI-AD; 2) Specific characteristics of DLB would confer differing risks of dementia onset; cognitive fluctuations and visual hallucinations would be associated with increased dementia risk, whereas RBD and parkinsonism would not.

Methods

Participants

Participants were included from two prospective longitudinal cohorts, for which recruitment has been described previously in detail[10, 11], with the second cohort differing only in its inclusion of an additional indicative biomarker for MCI-LB: 123I-metaiodobenzylguanidine (MIBG) cardiac scintigraphy. Prospective participants were recruited from local memory and secondary care psychiatric services, older people's medical services, neurology and specialist Lewy body clinics in North-East England, where they had received a recent health service diagnosis of MCI and had either any core feature of Lewy body disease, or other supportive symptoms associated with the presence of Lewy body diseases, but also found in AD, e.g. a history of falls, general sleep disturbance, or hyposmia. Exclusion criteria were the presence of a possible frontotemporal or vascular aetiology (where clinical features suggested the patient might fit the possible behavioural variant frontotemporal dementia clinical criteria, or evidence of clinical stroke in clinical notes or MRI) at either baseline or after follow-up, parkinsonism predating onset of cognitive symptoms by over one year, and either dementia or absence of objective cognitive impairment. Inclusion criteria were: age 60 years or older and a diagnosis of MCI according to NIA-AA criteria;[12] that is, subjective and objective evidence of cognitive decline with retention of independent function, and therefore not meeting clinical criteria for dementia.[13, 14] Participants from both cohorts were selected for inclusion when they had at least two observations available, or had died prior to second observation. A self-selected subset of participants participated in both studies; these are included within the 'LewyPro' cohort, but had additional imaging results available from the 'SUPErB' cohort (see below).

Measures and diagnoses

Participants underwent semi-structured interview and neurological examination with a board-certified medical doctor at baseline, and at annual re-assessment. Where available, an informant was also interviewed to provide additional information. Clinical notes from these assessments were independently reviewed by a panel of experienced old age psychiatrists (AJT, PCD, JPT) who confirmed the clinical diagnosis as MCI according to NIA-AA criteria.[12] The same panel independently rated the presence or absence of each of the four core diagnostic features of DLB.[14] Assessments of core diagnostic features of DLB (complex visual hallucinations, cognitive fluctuations, RBD, and parkinsonism) were guided by standardised scales: the Clinician Assessment of Fluctuations and Dementia Cognitive Fluctuations Scale, the North-East Visual Hallucinations Inventory, the Mayo Sleep Questionnaire, and the Revised Unified Parkinson's disease Rating Scale Motor Sub-Scale. However, the presence/absence of core clinical features was a clinical judgement utilising these scales and all available information from the health service and research records (including neurological examination), rather than on cut-off scores alone. Clinical review was repeated annually, including re-assessment of diagnosis (MCI or dementia), and repeated rating of the presence or emergence of any core symptoms of DLB.

Dopaminergic 123I-N-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) single-photon emission computed tomography (FP-CIT) imaging was undertaken as detailed previously,[15] with images independently rated as normal or abnormal by an experienced trained panel, blind to clinical information. Those included from the second study (n = 64 total, which included 23 from the first study) also underwent MIBG scintigraphy to assess cardiac denervation as an additional biomarker for prodromal DLB. Delayed images were processed blind to clinical information and quantified to provide a heart:mediastinum uptake ratio (HMR), and a cut-off for abnormality was

derived from locally-recruited cognitively healthy older adults: HMRs of two or more standard deviations below the healthy mean were rated as abnormal. Symptomatic heart failure was cause for exclusion to prevent diagnostic false positives. The results of both imaging modalities were included in diagnoses.

Diagnosis of mild cognitive impairment with Lewy bodies (MCI-LB) was operationalised as outlined in the current consensus research criteria[4] for diagnosis of prodromal DLB. Cases with MCI, no DLB core clinical features or indicative biomarkers, and no features of other potential causes of dementia, e.g. vascular or frontotemporal aetiology, were diagnosed as MCI due to Alzheimer's disease (MCI-AD), in accordance with NIA-AA criteria.[12] MCI cases with either any one core DLB clinical feature and no indicative biomarker, or no core clinical features but an indicative biomarker present were diagnosed as possible MCI-LB. Individuals with MCI and either two or more DLB core clinical features, or one core clinical feature and an indicative biomarker, received a diagnosis of probable MCI-LB. For direct comparison in the multi-state modelling analysis all MCI sub-groups were included as a single MCI group, with their clinical characteristics as covariates.

When judged to meet NIA-AA criteria for all-cause dementia,[13] participants received a diagnosis of dementia and ended involvement in the study. Diagnosis of all-cause dementia was based on reported loss of independent function along with evidence of cognitive decline as judged by the panel. Core symptom presence and abnormal biomarkers were subsequently assessed as above, and their final dementia diagnosis was rated according to current consensus clinical criteria for DLB or AD.[13, 14]

Cognitive assessments were undertaken with a detailed panel of neuropsychological tests administered separately from the clinical interview, with a median of 12 days between these assessments. In-depth cognitive profiles of this cohort have been detailed previously;[10] the Addenbrooke's Cognitive Examination – Revised (ACE-R) provided global cognitive scores reported here, and a derived Mini-Mental State Examination (MMSE) score to contextualise the mental status of this cohort on study entry. Cognitive profile was not incorporated into differential diagnosis, which was based on clinical assessment only. Instrumental Activities of Daily Living (IADL) were recorded, and the Movement Disorder Society Unified Parkinson's Disease Rating Scale – Part III: Motor Examination was administered to quantify motor impairments; quantified scores of these were included for research purposes, but review of functional impairment and parkinsonism were based on clinical reasoning, not score cut-offs.

Socio-economic background was anticipated to be a confounding variable; local-community deprivation has been directly associated with cognitive dysfunction in older age, and indirectly via other deprivation-related factors associated with increased risk of conversion to dementia from MCI.[16] English indices of multiple deprivation (IMD) deciles were therefore derived from publicly-available national statistics,[17] based on each participant's home address at the time of study enrolment. Neighbourhood deprivation scores are nationally ranked, and these were sorted into deciles; decile rank of 1 as presented here corresponds to the 10% most deprived neighbourhoods in England, and a rank 10 is amongst the 10% least deprived neighbourhoods.

Analysis

A competing risks multi-state model was assembled with the *msm* package for *R* software.[18] This approach provides a flexible framework in which to undertake survival analysis with multiple

states (two competing end-state risks in this case, but may be extended to include more complex transition structures) and time-varying covariates (e.g. emergence of clinical features). Three states were defined: MCI, dementia, and death. Dementia and death were treated as competing absorbing states with no subsequent transitions allowed; since participants ceased involvement in the study after conversion to dementia, then no further information was available after clinical conversion. Exact dates were recorded for all deaths. Observation times were recorded as a continuous variable (i.e. days since individual baseline assessment/365) to account for any variability in follow-up schedule, with the zero-point at the participant's first enrolment in their respective cohort.

All MCI diagnoses were included under the same MCI state. Likewise, all dementia diagnoses were included within a single dementia state. At each observation, participants could either remain as MCI, with or without some change in any covariates (see below), or progress to dementia or death. The emergence of Lewy body disease characteristics later in the MCI course, and their association with subsequent dementia transitions, could therefore be assessed in this model in a flexible manner.

Covariates theorised to have an association with clinical conversion were included to assess the association of DLB features and other demographic variables with risk of death or dementia: age, deprivation, sex, education (all previous time-invariant, assessed at baseline), and number of DLB diagnostic characteristics (time-varying). An additional analysis included the same, with each of six specific characteristics included as individually present or absent (time-varying except for MIBG imaging): complex visual hallucinations, cognitive fluctuations, parkinsonism, RBD, FP-CIT and MIBG abnormalities.

Model fit was assessed by Akaike Information Criterion (AIC) with a lowered AIC value indicating better model fit, with a penalty for inclusion of additional parameters. Covariates were chosen by forwards selection leading to the best-fitting models reported here. In the event that a covariate did not improve model fit, it was excluded to favour parsimony. As MIBG imaging was available only for a subset of the sample, a sensitivity analysis was conducted including only those with this imaging available (either normal or abnormal) to assess if including this improved model fit. Interaction effects were considered for retained main effects, assessed with the same criteria (model improvements observed with AIC).

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was given by the National Research Ethics Service Committee North East – Newcastle and North Tyneside 2 (Research Ethics Committee No. 12/NE/0290 and 15/NE/0420), and written informed consent was obtained from all participants.

Data Availability

Data supporting this analysis are available by request through the Medical Research Council Dementias Platform UK, study references: ‘LewyPro’ and ‘SUPErB’.

Results

Demographics and baseline

One-hundred and eleven participants were suitable for inclusion (see Figure 1). Baseline demographic and clinical information is summarised for the overall MCI group, and differential diagnostic sub-groups in **Table 1**. The mean follow-up time was 2.2 years (SD = 1.39, median = 2.05) from baseline, with a range of 1-6.7 years of follow-up from baseline. Participants had a median of 3 observations each. While all met criteria for MCI at baseline, probable MCI-LB had slightly greater daily functional impairment; IADL scores were not significantly correlated with global cognitive function (Pearson's r(98) = 0.16, p = .11) but had a weak negative association with motor impairment (r(98) = -0.29, p = .003). Despite comparable cognitive function, probable MCI-LB were more likely to be in receipt of cholinesterase inhibitors at baseline, consistent with local use and recent statements supporting these in the treatment of neuropsychiatric symptoms of Lewy body disease[19].

Dementia diagnoses and deaths

Thirty-eight participants (34%) had progressed to dementia, and an additional seven had died (6%) at the time of analysis. Ten had a diagnosis of AD; all ten had previously been diagnosed with MCI-AD (30% of MCI-AD cases developed dementia). Three had a diagnosis of possible DLB; all had previously been diagnosed as possible MCI-LB (18% of possible MCI-LB cases developed dementia). Twenty-five cases met criteria for a diagnosis of probable DLB; all were previously diagnosed as probable MCI-LB (41% of probable MCI-LB cases developed dementia). Two MCI-AD (6%), one possible MCI-LB (6%), and four probable MCI-LB (7%) had died with a last recorded diagnosis as MCI. Despite similar incidence of death or dementia in the two broad groups (total of 36% death or dementia in MCI-AD, 42% in possible or probable

MCI-LB) the multi-state models indicated that time of onset of these varied by diagnostic characteristics.

Overall DLB feature count

The best-fitting model included age and DLB core feature or indicative biomarker count as main effect covariates, without interactions (**Table 2**). Higher age was associated with an increased risk of death, and a small non-significant increase in dementia per year. In comparison to MCI-AD, each DLB clinical feature or biomarker observed conferred a linearly increasing yearly risk of transition to dementia or death. An increasingly Lewy body-like clinical profile in MCI was therefore associated with worse prognosis as evidenced by an increased annual risk of conversion to dementia or death.

Specific DLB features

The best fitting model favoured inclusion of age, visual hallucinations, and cognitive fluctuations as covariates (**Table 2**), without interactions. Increased age was associated with an increased hazard of both dementia and death. The presence of visual hallucinations was associated with increased hazard of death and non-significant increased risk of dementia, while cognitive fluctuations were associated with a significantly increased hazard of dementia, but not of death. Inclusion of parkinsonism, RBD, abnormal FP-CIT or MIBG imaging did not improve model fit and so may not be associated with an increased transition risk to dementia or death compared to MCI-AD.

Supplementary analysis – death or dementia, and cholinesterase inhibitor use

Given the low death rates, a supplementary analysis was undertaken incorporating death and dementia into a single end-state outcome to provide a more precise estimate of the general prognosis in MCI. This analysis provided agreement with the main analysis that the presence of

DLB clinical features, specifically cognitive fluctuations and visual hallucinations, were associated with increased risk of progression from MCI to a more severe clinical state (**Table 3**). This simple signal is illustrated for each risk factor in **Figure 2**.

In an additional analysis controlling for cholinesterase inhibitor use, the associations between cognitive fluctuations and dementia onset (HR = 2.6, 95% CI: 1.3 – 5.0), and between visual hallucinations and death (HR = 15.2, 95% CI: 2.7 – 84.7) remained. Visual hallucinations were not clearly associated with dementia risks (HR = 1.3, 95% CI: 0.5 – 3.0), but this comparison is limited by a high degree of collinearity between visual hallucination presence and cholinesterase inhibitor use (only 3 of 17 visual hallucinators not using cholinesterase inhibitors at baseline).

Discussion

We found, as hypothesised, that the presence of DLB characteristics in MCI was associated with a greater annual risk of dementia onset, with death as a competing risk; this risk increased as more characteristics were observed. Cognitive fluctuations in particular were associated with faster dementia onset, while RBD and parkinsonism were not. Visual hallucinations were associated with increased risk of death, and with higher but non-significant transition to dementia. Parkinsonism and RBD were not individually associated with increased risk of dementia in comparison to those without these symptoms, nor were dopaminergic and cardiac sympathetic imaging. The data therefore supported the hypotheses that an MCI with diagnostic characteristics of DLB would be associated with a worse prognosis than MCI-AD, and suggests that different clinical presentations of MCI-LB may also be associated with different rates of clinical progression.

These results mirror recent findings on the prognosis of DLB or AD, and in their cognitive prodromes: it appears that in both MCI and dementia,[20] the presence of DLB-specific diagnostic characteristics is associated with a worse prognosis. DLB is associated with increased hospitalization,[1] shorter time to full-time care, shorter survival time,[2] and worse quality of life for patients and carers than AD.[21] In a subset of this cohort, we have also previously found that those with MCI-LB were more likely to feature a progressive decline in cognitive scores than MCI-AD.[3] Our results here indicate that this also manifests in a greater annual risk of developing dementia than MCI-AD.

The specific association between cognitive fluctuations and visual hallucinations, and a poorer prognosis in MCI may indicate that these are symptomatic of a more aggressive clinical phenotype. Both fluctuations[22] and visual hallucinations[23] are hypothesised to reflect particular patterns of neurodegeneration within Lewy body disease which may share a link;[24] that is, the

prominent cholinergic deficiency which may be more typical of DLB[25] due to denervation of the basal forebrain[26] and which may already be present at the MCI stage[27]. Over the short term, people with Parkinson's disease will not necessarily experience cognitive decline or progress to dementia[28], and amongst those who do, cholinergic denervation is more common[29], which is in line with our findings that parkinsonism, and associated dopaminergic imaging findings, may not be associated with a particularly increased risk of dementia within an MCI group, at least within the time-frame of this study. Similarly while RBD may often lead to DLB, this may take several years to develop,[5] consistent with the presence of RBD not being associated with increased risk of dementia in the short term as observed here. Drawing from a prospective cohort with in-depth and repeated assessment by an experienced clinical panel, this study has been able to characterise the dynamic clinical progression of MCI to dementia, and so provides clear evidence of the risks associated with specific clinical symptoms which may be identified in an MCI syndrome.

We previously identified that visual hallucinations were associated with a poorer cognitive prognosis in a subset of this cohort (n = 70), but this association was not observed with fluctuating cognition[3]; the daily variation in cognitive function characteristic of this symptom may obscure progressive decline in cognitive measures, but still manifest in more clinically-relevant functional declines as seen here (i.e. someone may score better on the day of a research cognitive assessment but at home show increased reliance on caregivers as a direct consequence of the intermittent but significant 'lows' associated with this clinical symptom).

While RBD and parkinsonism are recognised risk factors for dementia within an older population in general,[5, 6] these were not observed to be risk factors over the shorter term in this study, relative to those with MCI but without these symptoms. In contrast to the general population, within the context of MCI these symptoms alone may confer no greater risk of transition to dementia than in AD; since both RBD and Parkinson's disease may exist as isolated

diagnoses without cognitive impairment for many years (a decade or longer in the case of RBD). Alternatively, any additional increased risk may only manifest over the longer term, or may be too small or under-powered to translate into meaningful effects without considering the broader clinical picture (e.g. when RBD or parkinsonism are present alongside other symptoms of DLB, as described in the first model), since DLB diagnostic characteristics in general do appear to be associated with increased risk of dementia onset.

Current consensus criteria[12] are such that MCI cases without apparent Lewy body, frontotemporal, vascular, or other differential diagnostic features, meet criteria for a diagnosis of MCI-AD, and so these cases are described as such here. Despite the detailed and repeated assessment, it also remains possible that a number of these MCI cases may reflect non-neurodegenerative aetiologies, which would not be expected to convert to dementia.[30]

These clinical diagnoses are limited by an absence of biomarkers specific to AD, and consequent uncertainty in the association between observed features such as cognitive fluctuations or visual hallucinations and underlying Lewy body disease. While a subset of those who died underwent autopsy, to date only five have entered our brain bank. Two with probable MCI-LB, both had neocortical Lewy body disease, and three diagnosed with MCI-AD who all met pathology criteria for AD, including being Braak stages 5 and 6. Whilst numbers are limited this provides some 'gold standard' validation for our diagnoses. Ultimately, fuller retrospective study of patients with neuropathologically-confirmed Lewy body disease and/or AD could provide clearer evidence for the disease-specific (rather than symptom-specific) associations with dementia onset.

MIBG imaging was undertaken in only a subset of the full cohort; while this was not found to be a predictor of decline in this sub-group, our ability to draw broader conclusions for this measure are limited as this was not available for all, and it remains possible that those who did not

undergo MIBG imaging could have a less accurate clinical characterisation. Additionally, presence of RBD was judged based on clinical interview, with polysomnography not available; while the use of clinical interview is strongly supported (sensitivity/specificity: 98/74%[31])in assessing RBD for DLB and MCI-LB diagnosis[4, 14], it remains possible that an unknown number of this sub-group could be experiencing a non-REM parasomnia which would not be indicative of a synucleinopathy being present.

Overall mortality was low, with only seven deaths by the time of data locking for this analysis, reflecting the early stage of disease in this cohort. The confidence intervals around the effect sizes of predictors of death were therefore wide and the magnitude of these effects are more uncertain in contrast with the predictors of dementia. This may also account for the lack of observed associations with other expected covariates, such as sex or local deprivation.

Diagnostic predictors (both biomarkers and clinical features) were included as binary absent/present variables in this analysis. Continuous quantifications of both biomarkers and clinical features may be more sensitive to mild differences in these, and to any longitudinal change (e.g. worsening FP-CIT abnormalities over time) which may anticipate dementia onset.

Probable MCI-LB had slightly greater daily functional impairment than MCI-AD at baseline, though all had only mild impairment as reflected in their MCI diagnoses. Functional impairments were associated with motor, but not cognitive, impairments at baseline, suggesting that these reflect other barriers to independence in Lewy body disease. Probable MCI-LB were also more likely to be in receipt of cholinesterase inhibitors at baseline despite comparable cognitive function, consistent with recommendations and their local use in treating neuropsychiatric symptoms of Lewy body disease.[19] Due to the observational nature of this study and collinearity with clinical variables we were limited in our ability to assess the influences of cholinesterase

inhibitors in dementia onset; addressing this research question would naturally require a randomised study with larger numbers.

Conclusions

An individual with MCI with clinical characteristics of DLB has a worse prognosis than MCI-AD, with increased annual risk of clinical conversion to dementia. The presence of cognitive fluctuations or visual hallucinations in particular are associated with worse prognosis. There may therefore be value in seeking information on the presence or absence of diagnostic features of Lewy body disease in MCI to aid the prospective identification of those at risk of further clinical decline.

Appendix 1: Author locations and contributions

Name	Location	Contribution
Calum A Hamilton, MSc	Newcastle University, Newcastle upon Tyne	Analyzed the data; codesigned the statistical analysis plan; drafted the manuscript for intellectual content
Fiona E Matthews, PhD	Newcastle University, Newcastle upon Tyne	Interpreted the data; codesigned the statistical analysis plan; revised the manuscript for intellectual content
Paul C Donaghy, PhD	Newcastle University, Newcastle upon Tyne	Design and conceptualization of the study; major role in data acquisition; revised the manuscript for intellectual content
John-Paul Taylor, PhD	Newcastle University, Newcastle upon Tyne	Design and conceptualization of the study; major role in data acquisition; revised the manuscript for intellectual content
John T O'Brien, DM	University of Cambridge, Cambridge	Design and conceptualization of the study; revised the manuscript for intellectual content
Nicola Barnett, MSc	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Kirsty Olsen, MSc	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Rory Durcan, MBBS	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Gemma Roberts, PhD	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Joanna Ciafone, PhD	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Sally AH Barker, BSc	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Michael Firbank, PhD	Newcastle University, Newcastle upon Tyne	Major role in data acquisition; revised the manuscript for intellectual content
Ian G McKeith, MD	Newcastle University, Newcastle upon Tyne	Design and conceptualization of the study; revised the manuscript for intellectual content
Alan J Thomas, PhD	Newcastle University, Newcastle upon Tyne	Design and conceptualization of the study; major role in data acquisition; interpreted the data; revised the manuscript for intellectual content

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Figure 1. Inclusion and exclusion of participants in cohorts used for this analysis.

<Figure 1>

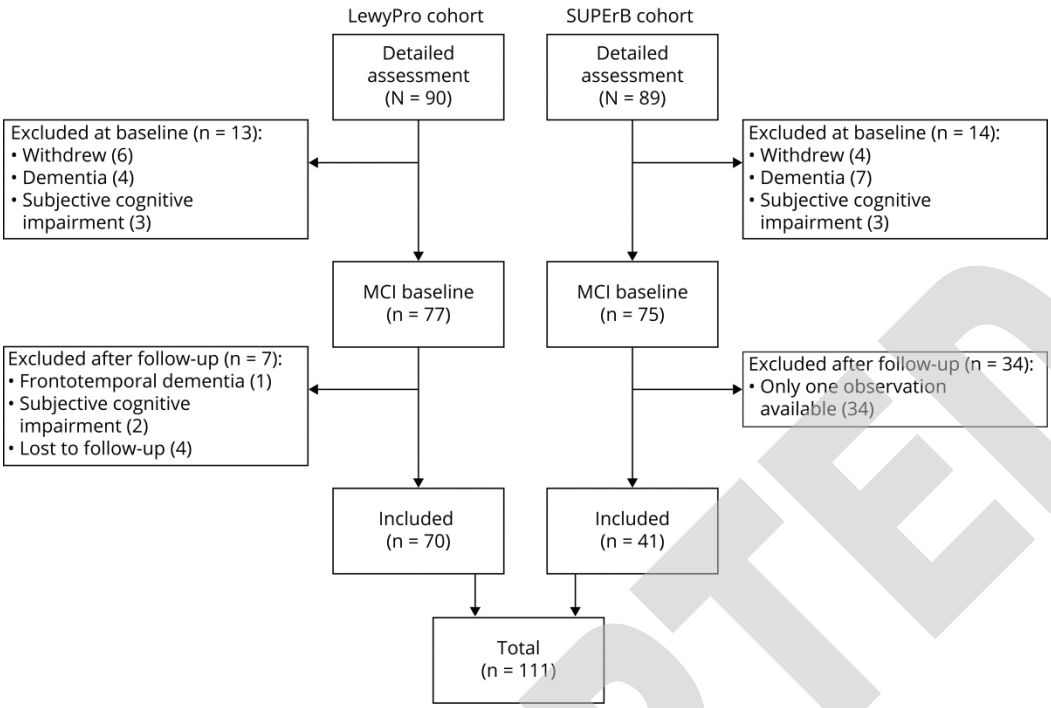


Table 1. Baseline characteristics of overall MCI cohort, and diagnostic sub-groups which make up this cohort (diagnostic group incorporating any later emergence of symptoms or change in imaging findings prior to dementia onset).

		Diagnostic Group			Group Comparison
	MCI Overall (n=111)	**MCI-AD (n=33)**	**Poss. MCI-LB (n=17)**	**Prob. MCI-LB (n=61)**	***p***
Female[a]	42 (37.8%)	22 (66.7%)	7 (41.2%)	13 (21.3%)	< .001
Age (Years)[b]	75.7 (7.30)	77.5 (7.63)	74.9 (7.58)	75.0 (7.00)	.260
Clinical Dementia Rating (0-3)[c]	0.5 [0, 0.5]	0.5 [0.5, 0.5]	0. [0.5, 0.5]	0.5 [0, 0.5]	.395
Mini-Mental State Examination (0-30)[b]	26.7 (2.1)	26.8 (2.36)	26.1 (2.12)	26.7 (1.93)	.497
Addenbrooke's Cognitive Examination – Revised, Total (0-100)[b]	81.3 (9.20)	81.9 (9.87)	78.6 (9.31)	81.8 (8.81)	.425
Instrumental Activities of Daily Living (0-8)[c]	7 [2, 8]	7.5 [5, 8]	7 [3, 8]	6 [2, 8]	.020
Years of Education[b]	11.8 (3.16)	12.4 (3.27)	11.6 (4.12)	11.6 (2.80)	.343
Deprivation Decile (1-10)[c]	5 [1, 10]	6 [1, 10]	4 [1, 10]	5 [1, 10]	.659
Cholinesterase Inhibitor Use[a]	37 (33.3%)	5 (15%)	1 (6%)	31 (51%)	< .001
Parkinsonism Present[a]	26 (23%)	0 (0%)	0 (0%)	26 (43%)	-
REM Sleep Behaviour Disorder Present[a]	41 (37%)	0 (0%)	3 (18%)	38 (62%)	-

		Diagnostic Group			Group Comparison
	MCI Overall (n=111)	**MCI-AD (n=33)**	**Poss. MCI-LB (n=17)**	**Prob. MCI-LB (n=61)**	***p***
Cognitive Fluctuations Present[a]	34 (31%)	0 (0%)	3 (18%)	31 (51%)	-
Visual Hallucinations Present[a]	17 (15%)	0 (0%)	1 (6%)	16 (26%)	-
Abnormal Dopaminergic Imaging[a]	45 (41%)	0 (0%)	5 (29%)	39 (64%)	-
Abnormal Delayed Cardiac mIBG[a]	24/64 (38%)	0/20 (0%)	4/11 (36%)	20/33 (61%)	-

MCI, mild cognitive impairment; MCI-AD, mild cognitive impairment due to Alzheimer's disease; MCI-LB, mild cognitive impairment with Lewy bodies. Group omnibus tests: Chi-squared test[a] (*df* = 2), ANOVA F-test[b] (*df* = 2, 108), Kruskal-Wallis rank sum test[c] (*df* = 2). [a]Count (%), [b]Mean (SD) or [c]Median [Range].

Table 2. Associations between age and presence of Lewy body features in transitions from MCI to death or dementia: variables included which improved model fit. Sample n = 111, observations = 323.

Baseline Annual Transition Probabilities from MCI [95% CI]	Covariates - Hazard Ratios [95% CI]		
Model 1. Overall Feature Count	**Age**[a]		**Lewy Body Features (0-6)**
to MCI	**0.89** [0.82 - 0.93]		
to Dementia	**0.10** [0.06 - 0.17]	**1.05** [1.00 - 1.10]	**1.33** [1.11 - 1.60]
to Death	**0.01** [0.001 - 0.04]	**1.24** [1.08 - 1.42]	**1.39** [0.90 - 2.14]
Model 2. Specific Features	**Age**	**Visual Hallucinations**	**Cognitive Fluctuations**
to MCI	**0.91** [0.85 - 0.95]		
to Dementia	**0.08** [0.05 - 0.14]	**1.06** [1.01 - 1.11]	**1.98** [0.92 - 4.29]	**3.99** [2.03 - 7.84]
to Death	**0.01** [0.001 - 0.03]	**1.25** [1.09 - 1.44]	**7.30** [1.53 - 34.97]	**2.29** [0.49 - 10.82]

CI, Confidence Interval; MCI, mild cognitive impairment

[a]Mean-centered, hazard per year

Model 1: Accumulation of Lewy body disease characteristics as predictor. Model 2: Individual characteristics considered as separate predictors. Considered predictors which did not improve fit

and were not retained: sex, deprivation, education, MIBG abnormality, FP-CIT abnormality, REM sleep behaviour disorder, parkinsonism.

Table 3. Supplementary analysis of associations between age and presence of Lewy body features in transitions from MCI to death or dementia (single outcome). Sample n = 111, observations = 323.

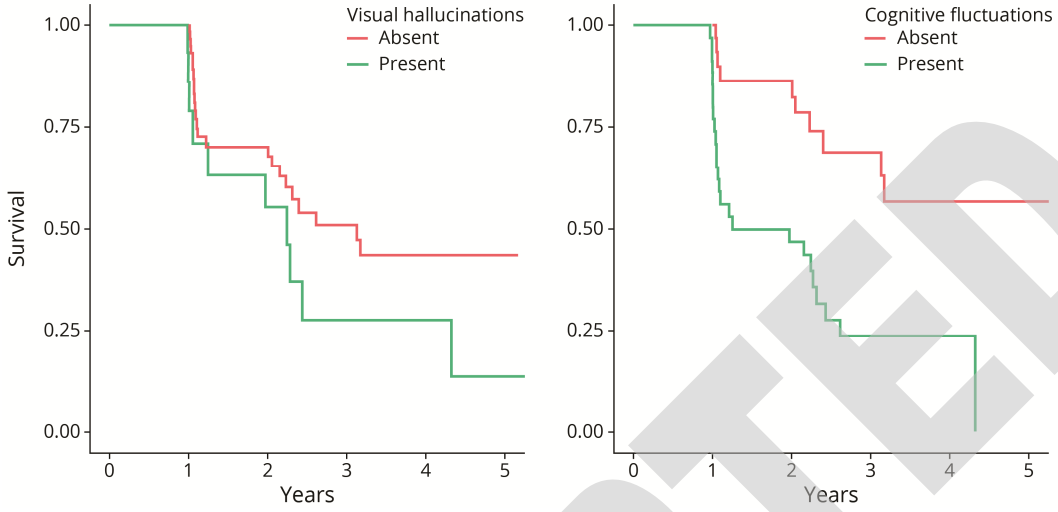
Baseline Annual Transition Probabilities from MCI [95% CI]	Covariates - Hazard Ratios [95% CI]		
Model 1. Overall Feature Count	**Age**[a]		**Lewy Body Features (0-6)**
to MCI	**0.89** [0.82 - 0.93]		
to Dementia/Death	**0.11** [0.07 - 0.18]	**1.08** [1.03 - 1.13]	**1.35** [1.14 - 1.59]
Model 2. Specific Features	**Age**	**Visual Hallucinations**	**Cognitive Fluctuations**
to MCI	**0.91** [0.85 - 0.94]		
to Dementia/Death	**0.09** [0.06 - 0.15]	**1.09** [1.04 - 1.14]	**2.69** [1.35 - 5.38]	**3.77** [2.04 - 6.98]

CI, Confidence Interval; MCI, mild cognitive impairment

[a]Mean-centered, hazard per year

Figure 2. Survival curves in mild cognitive impairment with visual hallucinations or cognitive fluctuations at baseline.

<Figure 2>



Progression to Dementia in Mild Cognitive Impairment With Lewy Bodies or Alzheimer Disease

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