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Frailty and Sensory Impairment in Lewy Body Dementia: Multidomain Frailty Index Development and Characterisation of Clinical Phenotypes

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Declaration of Authorship

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All participants in the studies gave explicit, full and informed consent. All studies adhered to the World Medical Association Declaration of Helsinki on ethical principles for heath research involving human subjects. Ethical approval for this research work was obtained from the St. James's Hospital and Tallaght University Hospital Joint Research Ethics Committee.

Adam Roche

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To Catherine, for everything, always

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Table of Contents

Declaration of Authorship ..... **i**

Acknowledgements ..... **iii**

Dissemination of Research ..... **iv**

List of Figures ..... **viii**

List of Tables ..... **ix**

List of Abbreviations ..... **x**

Abstract: **1**

Lay Abstract: **2**

Chapter 1. Introduction **4**

1.1 Global Ageing and Dementia Burden *4*

1.2 The Current Clinical Context of Lewy Body Dementia *8*

1.3 Frailty and Sensory Impairments *10*

1.4 Knowledge Gaps in Lewy body dementia *12*

1.5 Study Rationale *13*

1.6 Study Aims, Objectives and Hypotheses *15*

1.7 Thesis Structure and Outline *18*

Chapter 2. Literature Review **20**

2.1 Introduction *20*

2.2 Epidemiology of Lewy Body Dementia *21*

2.3 Clinical Features and Diagnostic Frameworks in Lewy Body Dementia *25*

2.4 Lewy Body Dementia Prognosis and Natural History *34*

2.5 Neuropathology of Lewy Body Dementia *37*

2.6 Management of Lewy Body Dementia *41*

2.7 Frailty in Neurodegenerative Disease and in Lewy Body Dementia *47*

2.8 Sensory Impairment in Ageing and Lewy Body Dementia *55*

2.9 Integrating Frailty and Sensory Impairment *59*

Chapter 3. Methods 64
3.1 Study Design and Setting 64
3.2 Ethical Approval and Governance 66
3.3 Participant Eligibility and Recruitment Strategy 67
3.4 Diagnostic Classification and Subgroup Definitions 70
3.5 Assessment Protocol and Study Measures 72
3.6 Development of the Lewy Body Dementia Frailty Index (LBD-FI) 81
3.7 Data Management and Quality Assurance 85
3.8 Statistical Analysis Plan 87
3.9 Methods Summary 90
Chapter 4. Frailty in Lewy Body Dementia (Results I) 91
4.1 Participant Characteristics 91
4.2 Development of the Lewy Body Dementia Frailty Index 92
4.3 Distribution and Descriptive Statistics of the LBD-FI 93
4.4 Associations Between Frailty and Clinical Outcomes 96
4.5 Frailty Differences by Clinical Subtypes 99
4.6 Preliminary Frailty and Sensory Correlations 102
4.7 Summary of Frailty Findings 102
Chapter 5. Sensory Impairment in Lewy Body Dementia (Results II) 104
5.1 Sensory Impairment Prevalence and Profiles 104
5.2 Objective Sensory Measures: Distribution and Diagnostic Performance 105
5.3 Associations Between Sensory Impairment and Frailty 108
5.4 Sensory Impairment and Clinical Outcomes 109
5.5 Sensory Profiles Across Frailty Tertiles 110
5.6 Diagnostic Group Differences in Sensory Impairment 113
5.7 Summary of Sensory Findings 115
Chapter 6. Discussion 116
6.1 Overview and Key Findings 116
6.2 Frailty in Lewy Body Dementia 117
6.3 Sensory Impairment and Its Clinical Significance 119
6.4 Integrating Frailty and Sensory Impairment 120
6.5 Diagnostic and Phenotypic Implications 121
6.6 Methodological Considerations and Limitations 122

6.7 Strengths of the Study *126*
6.8 Implications for Clinical Practice, Research and Policy *127*
6.9 Discussion Summary *128*
Chapter 7. Conclusion **130**
7.1 Overview and Conceptual Integration *130*
7.2 Clinical and Translational Implications *131*
7.3 Methodological and Theoretical Contributions *131*
7.4 Future Directions and Conclusion *132*
References: **134**
Appendices **158**

List of Figures

Figure 1.1. Global population aged ≥ 65 years in 2015 and projected for 2050.....5
Figure 1.2. Projected proportion of Ireland's population aged ≥ 65 years, 2024–2050. .6
Figure 1.3. Projected old-age dependency ratio for Ireland, 2024 to 2050.....6
Figure 1.4. The clinical and pathological spectrum of Lewy body disease.....9
Figure 1.5. Conceptual Framework for the Study.....14

Figure 2.1. Patterns of α-synuclein pathology progression across the Lewy body disease spectrum.....39
Figure 2.2. Conceptual Models of Frailty.....48
Figure 2.3. Pattern of Frailty.....50
Figure 2.4. Domains contributing to frailty. 51

Figure 3.1. Peek Acuity smartphone app assessment.....76
Figure 3.2. Siemens HearCheck Device.....78
Figure 3.3. Example of Hear Check assessment results recording.....78
Figure 3.4. 40-item University of Pennsylvania Smell Identification Test. 80

Figure 4.1. Histogram of LBD Frailty Index Distribution 95
Figure 4.2. Scatterplot of LBD-FI vs MoCA.....98
Figure 4.3. Scatterplots of LBD-FI vs NPI Severity.....98
Figure 4.4. Scatterplots of LBD-FI vs EQ-5D-5L Utility score 99
Figure 4.5. Boxplots of Frailty Index by LBD Diagnostic Group.....101

Figure 5.1. Number of Sensory Impairments Per Participant.. 105
Figure 5.2. Distribution of Objective Sensory Performance Scores..... 107
Figure 5.3. Sensory Scores Across Frailty Tertiles. 112
Figure 5.4. Sensory Scores Across Diagnostic Groups..... 114

List of Tables

Table 2.1. Clinical Features of Lewy Body Dementia 27
Table 2.2. Revised criteria for the clinical diagnosis of probable and possible DLB 29
Table 2.3. MDS Consensus Criteria for a Clinical Diagnosis of PDD 30
Table 2.4. Diagnostic Imaging Biomarkers in LBD.....33
Table 2.5. Pharmacological management strategies for Lewy body dementia 45

Table 3.1. Clinical Research Forms A to F 72
Table 3.2. Sensory testing for Vision, Hearing and Olfactory domains.....75
Table 3.3. Classification of Visual Acuity Using WHO logMAR Criteria. 77
Table 3.4. Interpretation of Siemens HearCheck™ Screening Results.....79
Table 3.5. Composition of the Lewy Body Dementia Frailty Index.....83

Table 4.1. Participant Characteristics by Diagnostic Group.....92
Table 4.2. Summary Statistics of LBD-FI Scores by Diagnostic Group.....94
Table 4.3. Distribution of LBD-FI Tertiles by Diagnosis Group 94
Table 4.4. Spearman's Correlations Between LBD-FI and Clinical Outcome 96
Table 4.5. Linear Regression Models: LBD-FI as a Predictor of Clinical Outcomes 97
Table 4.6. LBD-FI Scores Across Diagnostic Groups (DLB- vs PDD-spectrum groups)..100
Table 4.7. Spearman's Correlations Between LBD-FI and Objective Sensory Scores ..102

Table 5.1. Prevalence of Sensory Impairment across diagnostic groups (DLB-spectrum and PDD-spectrum groups) 104
Table 5.2. Continuous Sensory Scores by Diagnostic Group 106
Table 5.3. Spearman's Correlations Between Sensory Scores and Clinical Outcomes ... 108
Table 5.4. Prevalence of Sensory Impairment Across Frailty Tertiles..... 109
Table 5.5. Continuous Sensory Scores Across Frailty Tertiles..... 111
Table 5.6. Continuous Sensory Scores by Diagnostic Group 113

List of Abbreviations

Abbreviation	Definition
α-syn	Alpha-synuclein
Aβ	Amyloid Beta
ACE-III	Addenbrooke's Cognitive Examination-III
AD	Alzheimer's Disease
ADL	Activities of Daily Living
APOE	Apolipoprotein E
AT(N)	Amyloid/Tau Neurodegeneration biomarker framework
BADLS	Bristol Activities of Daily Living Scale
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CNS	Central Nervous System
CRF	Clinical Research Form
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DAT	Dopamine Transporter
DLB	Dementia with Lewy Bodies
DLT	Degraded Letter Test
EEG	Electroencephalography
EQ-5D-5L	EuroQol Five-Dimension Five-Level Instrument
FI	Frailty Index
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation

HADS	Hospital Anxiety and Depression Scale
HRB	Health Research Board
HSE	Health Service Executive (Ireland)
IBM SPSS	International Business Machines Statistical Package for the Social Sciences
IQR	Interquartile Range
JREC	Joint Research Ethics Committee (St James's & Tallaght University Hospitals)
LBD	Lewy Body Dementia
LBD-FI	Lewy Body Dementia Frailty Index
logMAR	Logarithm of the Minimum Angle of Resolution
MDS	Movement Disorder Society
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MIBG	Metaiodobenzylguanidine Cardiac Scintigraphy
MISA	Mercer's Institute for Successful Ageing
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
n	Sample Size
NMSS	Non-Motor Symptoms Scale
NPI	Neuropsychiatric Inventory
NPI-Q	Neuropsychiatric Inventory Questionnaire
NS	Not Significant
p	Probability value
ρ	Spearman's Rank Correlation Coefficient
PD	Parkinson's Disease
PD-MCI	Parkinson's Disease with Mild Cognitive Impairment
PDD	Parkinson's Disease Dementia
PET	Positron Emission Tomography
PIL	Participant Information Leaflet

QoL	Quality of Life
QoL-AD	Quality of Life in Alzheimer's Disease Scale
RBD	Rapid Eye Movement Sleep Behaviour Disorder
REM	Rapid Eye Movement
SPECT	Single-Photon Emission Computed Tomography
SD	Standard Deviation
SENSE-Cog	Sensory-Cognitive Interaction Programme
SPSS	Statistical Package for the Social Sciences
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TCD	Trinity College Dublin
UPSIT	University of Pennsylvania Smell Identification Test
USA	United States of America
USD	United States Dollar
VAS	Visual Analogue Scale
WHO	World Health Organisation
ZBI	Zarit Burden Interview

Abstract:

Background: Lewy body dementia (LBD), comprising dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is a progressive neurodegenerative disorder involving cognitive, motor, autonomic and neuropsychiatric systems. Although core clinical features such as cognitive fluctuation, parkinsonism, hallucinations and REM sleep behaviour disorder are well recognised, broader systemic contributors to disease burden remain poorly understood. Frailty and sensory impairment are major determinants of morbidity, functional decline and quality of life in older adult populations, yet their prevalence, interrelationship and combined impact within LBD remain poorly characterised. A clearer understanding of these multidomain features may offer new insights into vulnerability, prognosis and potential intervention targets across the LBD spectrum.

Aims: This study sought to characterise the multidimensional nature of Lewy body dementia by quantifying both frailty and objective sensory impairment, examining how these domains relate to cognitive, neuropsychiatric, functional and quality of life outcomes, and exploring whether such patterns differ between diagnostic subtypes. Through the development and application of a novel Lewy Body Dementia Frailty Index (LBD-FI) and comprehensive sensory testing, the study aimed to establish whether frailty and sensory dysfunction represent measurable and interrelated dimensions of systemic vulnerability within LBD.

Methods: A cross-sectional observational study was conducted at Mercer's Institute for Successful Ageing, St James's Hospital, Dublin. Fifty-one participants with clinically diagnosed LBD (DLB-spectrum: probable and prodromal DLB; PDD-spectrum: PDD and Parkinson's disease with mild cognitive impairment) underwent a comprehensive assessment incorporating cognition, function, neuropsychiatric symptoms, quality of life and caregiver burden. Objective sensory testing included olfaction (University of Pennsylvania Smell Identification Test), hearing (HearCheck Screener) and vision (Peek Acuity with logMAR scoring). An LBD Frailty Index (LBD-FI) was developed using a

cumulative deficit model to quantify multidomain vulnerability. Statistical analyses included descriptive summaries, non-parametric group comparisons, correlation analyses using Spearman's rank correlation coefficient (ρ) and multivariable regression models adjusted for age, sex, and diagnostic subtype.

Results: Frailty was highly prevalent and of moderate severity across the cohort, with a median LBD-FI of 0.23 (interquartile range 0.19 – 0.28). Higher frailty scores were associated with greater neuropsychiatric symptom burden (ρ = 0.42, p = 0.003) and lower health-related quality of life (ρ = −0.37, p = 0.008), but not with cognitive or functional outcomes in multivariable models. Frailty levels did not differ between DLB-spectrum and PDD-spectrum groups (p = 0.81). Sensory impairment was widespread: olfactory loss was universal, hearing impairment affected 97.9% of participants, and visual impairment affected 39.6%. Multimodal sensory loss involving two or more modalities occurred in 71% of cases. Lower olfactory scores were associated with greater frailty (ρ = −0.48, p = 0.001) and with lower quality of life (ρ = 0.31, p = 0.035). Better hearing performance correlated with higher cognitive scores (ρ = 0.33, p = 0.021) and lower neuropsychiatric symptom burden (ρ = −0.38, p = 0.008). No significant sensory differences were observed between DLB-spectrum and PDD-spectrum groups.

Conclusion: Frailty and sensory dysfunction are quantifiable, interrelated and clinically meaningful dimensions of Lewy body dementia. The association between frailty and olfactory loss supports the integration of sensory assessment within future diagnostic and management strategies. These findings position LBD as a multisystem disorder in which frailty and sensory decline contribute to clinical heterogeneity and quality of life outcomes.

Lay Abstract:

Lewy body dementia (LBD) is a progressive neurological disorder that causes problems with thinking, movement, sleep, and mood. It includes both dementia with Lewy bodies and Parkinson's disease dementia and is the second most common cause of degenerative dementia after Alzheimer's disease. While problems such as memory loss

and movement difficulties are well known, other factors that influence how the disease affects people are not as well understood. Frailty and changes in the senses, including loss of sense of smell, hearing and vision, may play an important role in both overall health and quality of life outcomes.

This study examined how common frailty and sensory problems are in people with Lewy body dementia, and how these factors relate to thinking ability, behaviour and wellbeing. Fifty-one people with a clinical diagnosis of LBD took part. Each person completed detailed assessments of memory, movement, mood, daily function and quality of life. Tests were also carried out to measure their ability to smell, hear and see. A frailty score was developed to capture overall health and vulnerability across physical, mental and social areas.

Frailty was very common and of moderate severity. Almost all participants had some degree of hearing or smell loss and around four in ten had visual problems. Many had more than one sensory difficulty. People who were frailer tended to have greater mood and behaviour symptoms and lower quality of life. Loss of smell was particularly linked with higher frailty and poorer wellbeing, while hearing loss was related to lower thinking scores and more behavioural symptoms.

These results show that frailty and sensory loss are common and clinically important features of Lewy body dementia. Improved recognition and assessment of these factors could help advance understanding and management of the condition, leading to better diagnosis, care planning and quality of life for people living with Lewy body dementia.

Chapter 1. Introduction

1.1 Global Ageing and Dementia Burden

The global population is ageing rapidly. Adults aged 65 years and older are the fastest growing demographic group worldwide, with the proportion of the population in this age category predicted to approach one in six by 2050, as reflected in United Nations (UN) projections (see Figure 1.1) [1, 2].

This significant demographic shift is reshaping global health priorities, as diseases of later life, including neurodegenerative disorders such as dementia, account for an increasing share of global morbidity and disability [3]. In response to this demographic shift, the World Health Organisation (WHO), in collaboration with the UN, launched the "Decade of Healthy Ageing (2021–2030)" initiative within the WHO global strategy and action plan on ageing and health [4-6].

In Ireland, the number of adults aged 65 years and older is projected to rise from approximately 800,000 in 2022 to over 1.3 million by 2050 (Figure 1.2). During the same period, the population aged 80 years and above is expected to more than double, with the old-age dependency ratio increasing from one in four to one in two, meaning there will be just two working age adults for every older person in Ireland (Figure 1.3) [7-9]. This demographic shift is already exerting sustained pressure on Ireland's health and social care systems and is expected to substantially increase the national burden of age-related diseases nationwide.

Dementia is not a normal part of the ageing process, although the risk of developing dementia increases substantially with age. An ageing global population means that the number of individuals with dementia is also expected to increase substantially. Dementia is now recognised as a critical public health challenge, with profound clinical, societal and economic burdens worldwide.

In 2017, an estimated 50 million people were living with dementia, a figure projected to reach 75 million by 2030 and 132 million by 2050 [10]. Approximately ten million new cases of dementia are diagnosed each year, equivalent to one new case every three seconds [11, 12].

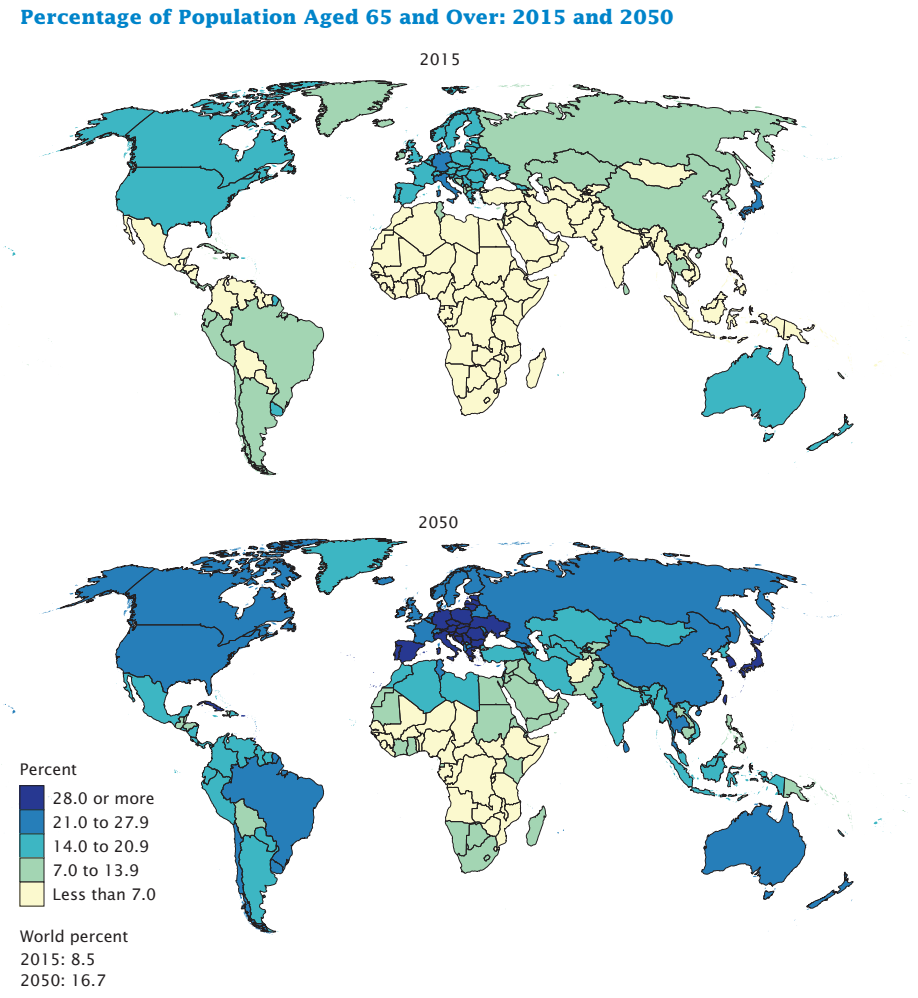

Figure 1.1. Global population aged ≥ 65 years in 2015 and projected for 2050. The proportion of older adults is expected to nearly double worldwide. Adapted from: An Aging World (2015), National Institutes of Health. Source: U.S. Census Bureau, Washington DC, 2016.

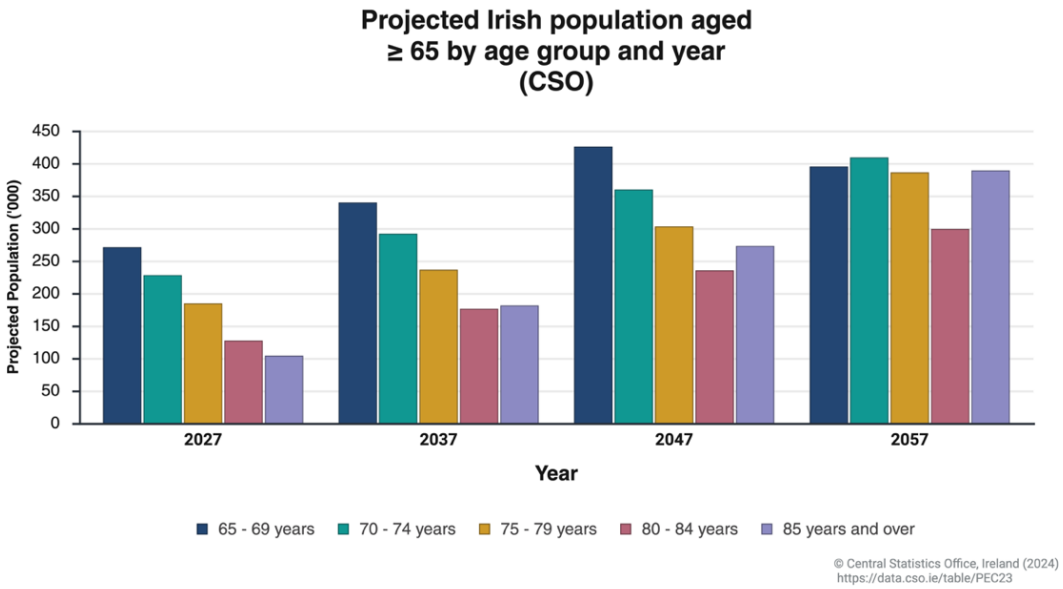

Figure 1.2. Projected proportion of Ireland's population aged ≥ 65 years, 2024–2050. The percentage of older adults is expected to rise steadily from approximately 15% in 2024 to over 25% by 2050. Source: Central Statistics Office (CSO), 2024.

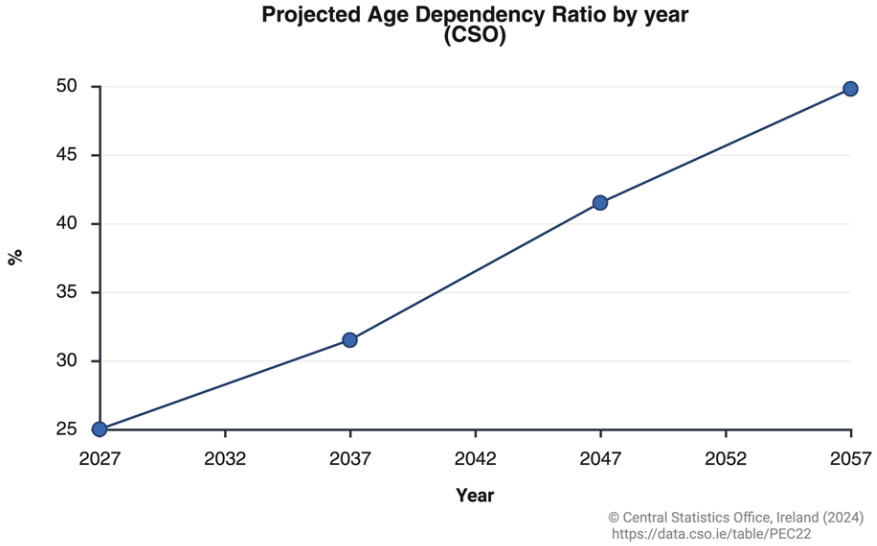

Figure 1.3. Projected old-age dependency ratio for Ireland, 2024 to 2050. The ratio of adults ≥ 65 years to those aged 15–64 is forecast to increase sharply, reflecting population ageing and lower birth rates. Source: Central Statistics Office (CSO), 2024.

From a global perspective, most people with dementia now live in low-income and middle-income countries, where the disease burden is rising fastest [10]. In Ireland, dementia continues to increase in prevalence, with an estimated 64,000 people living with dementia and approximately 7,750 new cases diagnosed every year [13, 14]. If these trends continue, the prevalence of dementia in Ireland is projected to increase to approximately 150,000 people by 2045 [13].

The WHO identifies dementia as a leading cause of disability and dependency in older adults, contributing a substantial share of years lived with disability from non-communicable disease. Global costs were estimated at US$818 billion in 2015 and are projected to exceed US$2.8 trillion by 2030, reflecting not only medical and social care costs but also the contribution of family carers [15, 16]. These costs encompass direct medical and social care and the substantial contribution of informal carers, with marked regional variation that exacerbates inequities in between high and low resource settings [17].

Although Alzheimer's disease accounts for most dementia cases, Lewy body dementia (LBD) is widely recognised as the second most common cause neurodegenerative dementia. Despite LBD's characteristic clinical features, under-recognition of the disease remains common, restricting access to appropriate management and increasing the risk of adverse patient outcomes. Improved diagnostic recognition is therefore essential to capture the true global dementia burden and to inform effective clinical practice [18-20].

1.2 The Current Clinical Context of Lewy Body Dementia

Lewy body dementia is a clinically complex and heterogeneous neurodegenerative syndrome characterised by the accumulation of intraneuronal aggregates of abnormal α-synuclein, termed "Lewy bodies" [21]. LBD encompasses two closely related disorders: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) [22].

LBD is estimated to account for approximately 10% to 15% of all dementia diagnoses worldwide and is associated with a substantial disease burden, progressive morbidity, marked cognitive and functional decline and significant caregiver strain [20, 23-27]. Prevalence estimates vary considerably across a wide range of clinical, epidemiological and neuropathological studies, reflecting limitations in clinical and diagnostic recognition and frequent overlap with Alzheimer's disease pathology [28-30].

In addition to initial diagnosis, differentiating between the two disease subtypes of LBD, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), also represents a significant diagnostic challenge. Both syndromes share overlapping cognitive, neuropsychiatric and motor profiles that often impede accurate classification [31, 32]. Current diagnostic conventions rely on the temporal relationship between the onset of motor and cognitive symptom, referred to as the "one-year rule" [33, 34]. Under this operational definition, dementia developing within one year of parkinsonism supports a diagnosis of DLB, while onset beyond one year defines PDD [35, 36]. Although practical, this time-based rule lacks biological validity and may not reflect the underlying continuum of α-synuclein pathology [37, 38].

Emerging evidence supports a "spectrum model" of Lewy body disease, in which DLB and PDD represent phenotypic expressions within a single clinicopathological continuum (Figure 1.4) [39-42]. Longitudinal and multicentre studies demonstrate that, once dementia is established, trajectories of cognitive and motor decline are broadly comparable across both LBD subtypes [43-45].

This spectrum framework emphasises the importance of considering factors beyond neuropathology in shaping clinical outcomes. Multimorbidity, frailty and sensory impairment have each been identified as independent determinants of disease trajectory, hospitalisation and mortality in older adults [46-48]. Incorporating these core geriatric domains into models of LBD progression may enhance prognostication and inform more individualised care planning for those with the disease.

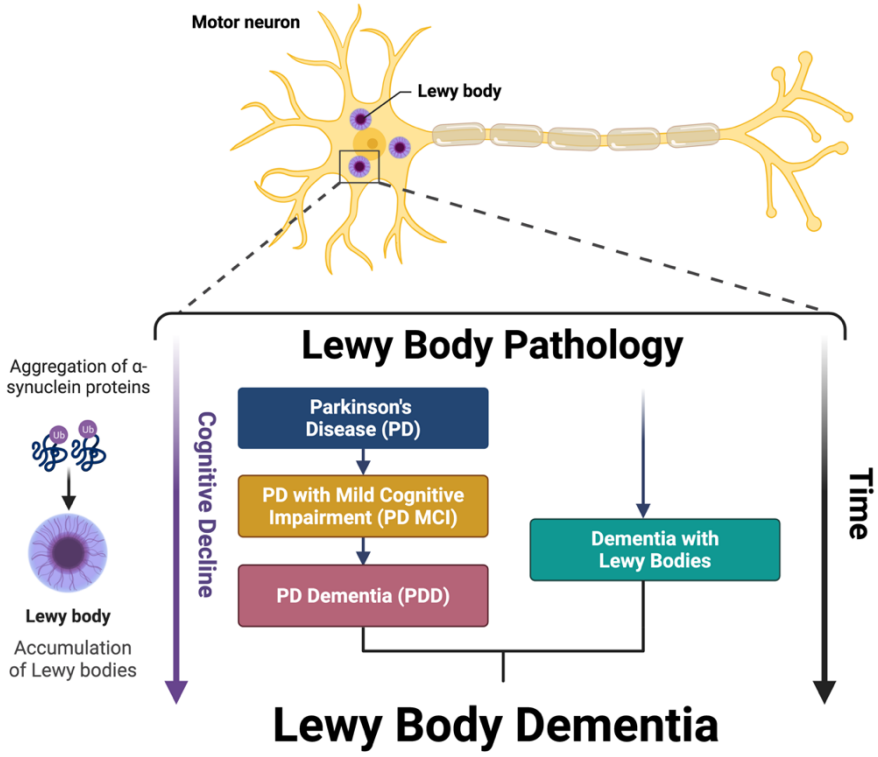

Figure 1.4. The clinical and pathological spectrum of Lewy body disease. Progressive intraneuronal aggregation of α-synuclein gives rise to Lewy body pathology and leads to overlapping syndromes of PDD and DLB. Created with BioRender.

1.3 Frailty and Sensory Impairments

Frailty is a multidimensional age-related clinical syndrome characterised by a decline in physiological capacity across multiple systems, which increases vulnerability to sudden health status changes after relatively minor stressors [49]. It reflects the cumulative effects of biological ageing across multiple physiological systems, including inflammatory, endocrine and metabolic pathways [50]. Between one quarter and one half of people aged over 85 years meet the criteria for frailty, leading to significantly elevated risks of falls, disability, long-term care and death [46, 51].

Two dominant frailty models have shaped the field:

The "**Phenotypic model"** (Fried, 2001) defines frailty as a clinical syndrome characterised by unintentional weight loss, slowness, weakness, exhaustion and low physical activity [52, 53]. Individuals are categorised as "frail" if they meet three out of a possible five physical characteristics. This model reflects a **biological frailty syndrome** of sarcopenia and energy dysregulation.

In contrast, the **"Cumulative deficit model"** (Rockwood et al, 2002) operationalises frailty as the proportion of accumulated health deficits, producing a continuous **Frailty Index (FI)** that provides a measure of biological ageing and vulnerability [54, 55].

Both models have been widely validated in ageing populations and linked to outcomes relevant to dementia, including accelerated cognitive decline, greater caregiver burden and increased health service use with more frequent hospitalisations [56-59].

Despite the wide use of frailty models disease of ageing, frailty in the context of LBD remains underexplored [60, 61]. Existing frailty instruments, developed largely in general older adult or Alzheimer's disease populations, inadequately capture some of the core domains central to LBD disease burden, including attentional fluctuation, visual and perceptual impairment, neuropsychiatric symptoms and sleep disturbance [62-64].

As a result, both the prevalence and impact of frailty in the setting of LBD are poorly understood, despite the potential implication on disease prognosis and future care

planning. Addressing this knowledge gap requires an approach tailored for the distinctive multisystem involvement in α-synuclein diseases such as LBD.

Sensory impairment has also emerged as an important but often neglected domain in dementia research. Sensory impairment can include both objectively measured sensory deficits, such as audiometry, visual acuity assessments and olfactory testing, as well as subjectively reported sensory difficulties, which may diverge in their prognostic implications [65-67]. Epidemiological evidence demonstrates that hearing, vision and olfactory loss are each independently associated with cognitive decline and dementia risk [67-70]. When multiple sensory systems are affected, adverse effects on function, mood and social engagement are magnified [71, 72].

In LBD, sensory impairment is of particular relevance. Olfactory dysfunction is among the earliest and most consistent prodromal markers of α-synucleinopathy, often preceding both motor and cognitive symptoms [73]. Visual deficits are also common and closely linked to key clinical features such as visual hallucinations and visuospatial impairment [74]. Hearing loss, although less extensively studied in LBD, is highly prevalent in older adults and may exacerbate attentional fluctuations and misperceptions, thereby compounding neuropsychiatric symptoms [75]. Yet despite their clear clinical relevance, sensory domains are rarely incorporated into routine clinical assessments or prognostic frameworks in LBD, leaving a core domain of vulnerability incompletely characterised.

Both frailty and sensory impairment are established determinants of poor prognosis in older adults, but their combined role in LBD has also not been well characterised. Emerging evidence indicates that these domains interact to amplify vulnerability, a feature especially relevant in a multisystem disorder such as LBD [65, 76].

My doctoral thesis aims to develop and evaluate a multidomain frailty index in an LBD cohort and consider objective measures of hearing, vision, and olfaction and their association with conventional clinical outcomes.

1.4 Knowledge Gaps in Lewy Body Dementia

Despite increasing recognition as a distinct neurodegenerative disease entity, LBD remains significantly underdiagnosed and inconsistently characterised across both clinical and research settings [77]. Prevalence estimates for LBD vary widely, reflecting limitations in clinical recognition, overlap with Alzheimer's disease pathology and reliance on diagnostic conventions such as the "one-year rule", which may obscure the underlying continuum of α-synuclein pathology [78-80].

Prognosis in LBD is similarly difficult to predict. Disease trajectories are variable, and neuropathological burden alone does not fully explain differences in outcomes such as cognitive decline, functional loss, hospitalisations or survival time [81, 82]. Existing prognostic tools focus largely on cognitive or motor impairment, neglecting broader determinants of intrinsic capacity, resilience and decline [83-85]. These limitations constrain the ability to provide individualised care planning for those with LBD, and are inconsistent with international policy frameworks such as the WHO Global Action Plan on Dementia as well as Ireland's National Dementia Strategy [10, 86, 87].

Frailty is a powerful predictor of adverse outcomes in older adults, but remains underexplored in the context of LBD. Current frailty measurement tools have a tendency to omit key features which are central to LBD, including cognitive fluctuation, perceptual deficits, neuropsychiatric symptoms, autonomic dysfunction and REM sleep behaviour disorder and other sleep disturbances [88, 89].

Similarly, sensory impairment is increasingly recognised as a modifiable contributor to dementia risk, not only as early manifestation of disease but also through its interaction with neuropsychiatric and functional domains [90, 91].
In LBD, sensory loss is particularly relevant, as olfactory dysfunction is an early marker of synucleinopathy, visual impairment is closely linked to worsening hallucinations and visuospatial deficits and hearing loss may exacerbate attentional fluctuations [73, 92-94].
Despite this relevance, sensory domains are largely absent from current frailty

assessments and prognostic models, leaving an important dimension of vulnerability incompletely characterised.

Finally, the impact of the combination of frailty and sensory impairment have rarely been examined within the same cohort, despite evidence that they interact to influence cognitive and functional decline. In LBD, these domains have not been systematically characterised or compared within the same cohort, and no studies have examined their relative or combined contributions to prognosis.

Addressing these limitations in current knowledge is essential to advance understanding of multidomain vulnerability in LBD and to inform more precise, mechanism-based approaches to risk stratification and care planning.

1.5 Study Rationale

The current knowledge gaps in the field of LBD highlight the need for a more comprehensive and integrated approach to the characterisation of the disease. Existing diagnostic and prognostic frameworks do not adequately capture the disorder's heterogeneity, remaining mostly narrowly focused on either cognitive or motor symptoms [18, 60, 64]. These limitations have potentially constrained both clinical management and research by limiting the ability to accurately predict outcomes and to identify individuals at greatest risk of rapid disease progression.

Frailty provides a robust framework for addressing this need. As a multidimensional measure of biological and functional reserve, frailty summarises the cumulative effects of deficits across multiple physiological systems and predicts mortality and disability in later life [95, 96]. Within dementia research, frailty has been demonstrated to not only accelerate cognitive decline but also moderate the relationship between neuropathological burden and clinical expression [97]. However, its role in LBD remains insufficiently defined and existing instruments fail to account for distinctive clinical and biological features specific to synucleinopathies.

Sensory impairment represents a second, complementary domain of interest. Hearing, vision and olfactory loss are highly prevalent in ageing populations and strongly associated with dementia risk and mechanistically linked to hallmark features of LBD [72, 98]. Despite their prognostic value and potential modifiable impact, sensory measures are rarely incorporated into existing disease models of LBD, leaving an important dimension of vulnerability underrepresented.

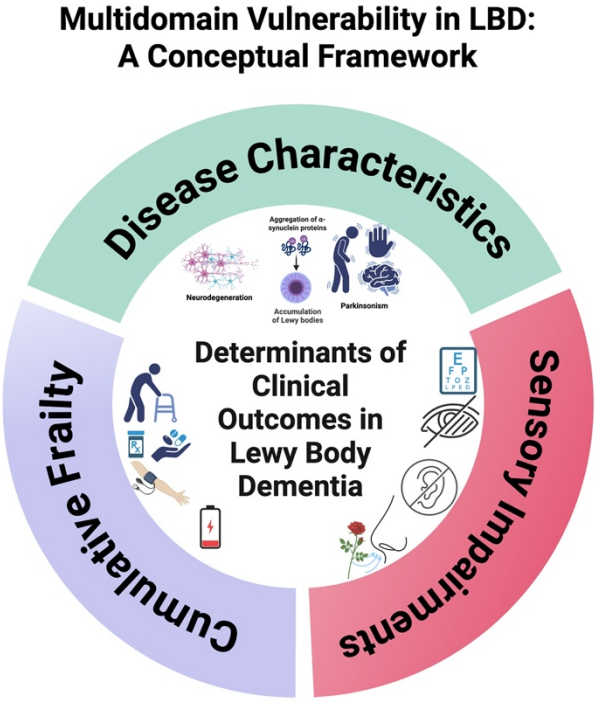

Figure 1.5. Conceptual Framework for the study illustrating multidomain vulnerability in LBD. Frailty and sensory impairment are examined as distinct but interrelated domains contributing to multidomain vulnerability and clinical outcomes in Lewy body dementia. linking frailty and sensory impairment to clinical outcomes in LBD

Although typically studied separately, frailty and sensory loss may exert additive effects on cognition, function and quality of life. Frailty can magnify the impact of sensory deficits, while sensory loss may accelerate frailty through reduced activity, isolation and diminished cognitive reserve [99, 100]. Integrating these constructs may therefore provide a more complete understanding of multidomain vulnerability in LBD.

Accordingly, my doctoral thesis develops and applies a novel multidomain **Lewy Body Dementia Frailty Index (LBD-FI)** based on the cumulative deficit model of frailty, and investigates its relationship and associations with both objectively measured sensory impairment and key clinical outcomes.

Through this dual domain approach, this study aims to improve the characterisation of vulnerability, enhance prognostic precision and identify potential targets for intervention in LBD. The conceptual framework underpinning my thesis is illustrated in Figure 1.5, summarising the hypothesised relationships between frailty, sensory impairment and clinical outcomes in Lewy body dementia

1.6 Study Aims, Objectives and Hypotheses

1.6.1. Background to Study Aims and Objectives

The previous sections have outlined the considerable disease burden, clinical heterogeneity and prognostic uncertainty associated with LBD. These limitations highlight the need for multidimensional frameworks that capture the full range of vulnerability in affected individuals beyond core neuropathological profiles. My study aims to address this unmet need by integrating both frailty and sensory assessment within a single analytical framework in LBD.

My approach aligns with both national and international dementia policy priorities that emphasise comprehensive, person-centred and risk-based approaches to care [101, 102]. It extends the conceptual framework of frailty into a synucleinopathy population, where it has been underexamined to date and also aims to provide new evidence on the clinical relevance of sensory loss in individuals with LBD [103]. In doing so, this study aims to inform multidomain prognostic assessment and clinical phenotyping across the Lewy body disease spectrum.

Frailty and sensory impairment are two clinically important domains in ageing and dementia research, but remain insufficiently characterised in LBD. Frailty reflects reduced physiological reserve and predicts a wide range of adverse outcomes, while

sensory impairment has emerged as both a marker and potential driver of cognitive and functional decline. Examining these domains together provides an opportunity to improve phenotypic resolution, refine prognostic accuracy and identify modifiable contributors to adverse outcomes in LBD.

1.6.2. Study Aims

Primary Thesis Aims:

The primary aims of my doctoral thesis are: to develop and apply a Lewy body dementia Frailty Index (LBD-FI), examine the prevalence and clinical relevance of sensory impairment in an LBD cohort, and to further characterise associated clinical phenotypes within this disease population. Taken together, these components aim to improve the characterisation of clinical vulnerability, account for heterogeneity of disease expression and refine prognostic modelling across cognitive, functional, neuropsychiatric and quality of life outcomes in LBD patients.

To achieve this aim, my study pursued the following objectives:

1. **LBD Frailty Index Development:** Construct a cumulative deficit frailty index specific to Lewy body dementia (LBD-FI), incorporating clinical, functional, neuropsychiatric and non-motor variables.
2. **LBD-FI Construct Validity:** Examine associations between the LBD-FI and established clinical measures and outcomes, including cognition, activities of daily living, neuropsychiatric symptoms, quality of life and caregiver burden.
3. **LBD-FI Predictive Validity:** Evaluate the capacity of the LBD-FI to explain variance in key clinical outcomes, including functional dependence, health-related quality of life and caregiver burden, using cross-sectional regression models adjusted for age and diagnosis. Compare the performance of the LBD-FI with existing generic frailty indices to assess its relative predictive utility within this population.
4. **Subtype Comparisons:** Explore differences in frailty severity between DLB-spectrum and PDD-spectrum groups, characterise phenotypic differences in these groups and consider the implications of these differences for disease prognosis and management.

5. **Sensory Impairment Analyses:** Determine the prevalence and impact of hearing, vision and olfactory impairments in an LBD cohort and examine their associations with both frailty and adverse outcomes.

These objectives inform the core research questions, as outlined below.

1.6.3. Research Questions

Primary Research Question:

The primary research question which informed my doctoral thesis was:
What is the prevalence and clinical impact of frailty in individuals with Lewy body dementia, and how is frailty associated with the presence and severity of sensory impairments?

Secondary Research Questions:

My secondary research questions were as follows:

1. To what extent is frailty severity associated with cognitive, functional, neuropsychiatric and quality of life outcomes in LBD?
2. Does the inclusion of sensory impairment as a complementary domain enhance the prediction of adverse outcomes compared with frailty alone?
3. Do frailty and sensory profiles differ between DLB and PDD, and what are the implications for prognosis and clinical management?
4. Which of the sensory modalities measured (hearing, vision and olfaction) show the strongest associations with frailty severity and clinical outcomes in LBD?

1.6.4. Research Hypotheses

My four key research hypotheses for this study were:

1. **Frailty Prevalence and Subtype Differences:** Frailty is highly prevalent in Lewy body dementia, with greater frailty severity expected in DLB than in PDD, reflecting differences in clinical phenotype and disease trajectory.
2. **Frailty and Clinical Outcomes:** Higher frailty scores are associated with poorer cognitive performance, greater functional dependence, more severe neuropsychiatric symptoms, lower quality of life and increased caregiver distress.

3. **Frailty and Sensory Impairments:** Sensory impairments are common in LBD and are positively correlated with frailty severity, contributing to worse cognitive, functional and quality of life outcomes.
4. **Multidomain Predictive Modelling:** Incorporating sensory impairment alongside frailty improves prediction of adverse outcomes compared with frailty alone, supporting a multidomain model of vulnerability in LBD that can inform clinical phenotyping.

1.7 Thesis Structure and Outline

My doctoral thesis contains seven core chapters, which each aim to address a distinct component of my research process:

- **Chapter 1. Introduction:** Provides background and context for the study and outlines the epidemiology, clinical features, and spectrum model of LBD. Introduces frailty and sensory impairment as emerging and inter-related constructs. The chapter concludes by identifying knowledge gaps, presenting the study rationale, and defining my study aims, objectives, and hypotheses.

- **Chapter 2. Literature Review:** Presents a comprehensive synthesis of current evidence on LBD, frailty and sensory impairment. Reviews the epidemiology, clinical features, natural history, neuropathology and management of LBD, before critically examining frailty and sensory domains in dementia and their integration within multidomain models.

- **Chapter 3. Methods:** Describes study design, participant recruitment, data collection, variable selection and construction of the LBD specific frailty index (LBD-FI). Outlines the analytical strategy for testing construct and predictive validity, comparing subtypes and examining sensory impairment as a complementary domain.

- **Chapter 4. Frailty in Lewy Body Dementia (Results I):** Presents descriptive and inferential analyses of the LBD-FI, including frailty prevalence and distribution, and its association with cognition, daily function, neuropsychiatric symptoms, quality of life and caregiver burden. Reports the predictive validity analyses and comparisons between the DLB-spectrum group and PDD-spectrum group.

- **Chapter 5. Sensory Impairment and Multidomain Integration (Results II):** Examines the prevalence and clinical correlates of hearing, vision and olfactory impairment in LBD. Analyses assess the associations of sensory impairment with frailty burden and key clinical outcomes, and evaluates the added predictive value of incorporating sensory measures within multidomain vulnerability modelling.

- **Chapter 6. Discussion:** Interprets the findings in the context of existing literature, addressing the construct validity of LBD-FI as a customised frailty index, the prognostic utility of frailty and sensory measures, and their combined influence on vulnerability. Discusses potential implications for clinical practice, future research design and health policy, while considering study strengths and limitations.

- **Chapter 7. Conclusion:** Summarises the main contributions of the research, emphasises its novelty, and outlines potential directions for future investigation into multidomain vulnerability in LBD.

Chapter 2. Literature Review

2.1 Introduction

This chapter presents a narrative review of the current Lewy body dementia literature, with specific focus on the topics of frailty and sensory impairment as emerging but underexplored modifiers in the disease course of LBD.

Chapter 1 outlined the global and clinical context of LBD, described the spectrum model of LBD and introduced frailty and sensory impairment as potentially important domains. The purpose of **Chapter 2**, therefore, is to outline and critically appraise the existing body of LBD literature, highlight areas of consensus as well as uncertainty and identify key knowledge gaps that will inform the rationale of this study.

The first part of this chapter is focused on the disease process of Lewy body dementia itself, reviewing the current literature and outlining LBD epidemiology, clinical features, diagnostic framework, disease course, neuropathology and current best practices in disease management. The second part of the chapter examines both frailty and sensory impairment as potentially useful domains in the setting of LBD.

All literary evidence discussed in this chapter was identified through structured searches of MEDLINE, Embase, CINAHL, PsycINFO and the Cochrane Library up to June 2025, supplemented by citation tracking of key consensus reports, systematic reviews and large clinical or neuropathological cohort studies.

Each section of this chapter concludes by highlighting key issues, providing the foundation for the final analysis of current knowledge gaps in LBD research.

This chapter also establishes the intellectual framework for the methodological approach further described in **Chapter 3**, informing the development of a novel frailty index for LBD and the examination of sensory impairments as a potentially complementary domain of vulnerability.

2.2 Epidemiology of Lewy Body Dementia

2.2.1 Background and Definitions

Lewy body dementia is recognised as the second most common cause of neurodegenerative dementia after Alzheimer's disease, representing a substantial proportion of the global dementia burden [104, 105]. Despite this, the true prevalence of LBD remains uncertain, reflecting differences in diagnostic criteria, case detection and study design [20, 28, 78]. Diagnostic heterogeneity observed between the two disease processes within the LBD spectrum, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), further complicates interpretation of epidemiological data. LBD is therefore best conceptualised as a clinicopathological spectrum of diseases within the broader family of synucleinopathies [18, 106].

2.2.2 Determinants of Heterogeneity in Estimates

Variation in prevalence estimates for LBD arises primarily from variability and differences in diagnostic frameworks. In 1996, the first **Dementia with Lewy Bodies Consortium** guidelines established a clinical criteria for the diagnosis of DLB. Notably the earlier DLB Consortium criteria required multiple core features, producing very high specificity for diagnosis but limited overall disease sensitivity [18, 107].

The **Fourth DLB Consortium** report, as outlined by McKeith *et al.* in 2017, subsequently expanded the diagnostic criteria for DLB by incorporating indicative biomarkers, such as dopamine transporter (DAT) imaging and polysomnography for REM sleep behaviour disorder (RBD). These revisions have had the effect of significantly improving disease recognition in both research and specialist clinical settings, yet their applications remain inconsistent [18, 37, 108]. Co-pathology with Alzheimer-type changes or cerebral vascular lesions also influences apparent disease prevalence [80, 106, 109].

In contrast, prevalence estimates for PDD are more consistent, with most studies reporting similar prevenances of dementia in between 20% and 30% of individuals with established Parkinson's disease [110, 111].

Across the LBD spectrum, other methodological factors including recruitment setting, use of specialist clinical expertise and reliance on neuropathological confirmation further contribute to epidemiological heterogeneity [78, 79]. Notably, tertiary referral centres, where diagnostic familiarity and biomarker access are greater have been shown to report higher prevalence [20, 112, 113].

2.2.3 Prevalence in Clinical and Community Cohorts

Specialist clinical cohort studies typically report that LBD accounts for between 7–10% of all dementia diagnoses [114-116]. These estimates derive mainly from specialist memory or movement disorder clinics in tertiary clinical settings and may therefore overstate prevalence relative to community populations [108, 117]. Community based epidemiological studies report lower figures, with LBD comprising approximately 4–7% of dementia cases in these studies [28, 78, 118].

Regional variation is pronounced. European and North American studies report prevalence around 5%, while East Asian estimates are lower [112, 119]. Data remains limited from Latin America, Africa and South Asia, which are all regions where dementia surveillance infrastructure remains broadly underdeveloped [120-122]. Given that more than 70% of all dementia cases are projected to occur in low- and middle-income countries by 2050, this lack of representation constitutes a major gap in global surveillance and dementia epidemiology [17].

Changes in diagnostic definitions, with the introduction of biomarker based criteria by the 2017 DLB Consortium, has increased case detection, particularly in specialist and research settings with access to dopaminergic imaging [18, 37].

2.2.4 Incidence

Incidence data for LBD are limited when compared with Alzheimer's disease. Longitudinal population studies indicate rates of between 0.1 and 0.4 per 1,000 person per year among the older adult population, with rates rising sharply after 70 years of age and peaking in the oldest cohorts [20, 23, 123] . Some studies have suggested higher incidence in men, but this was not consistently observed across the literature [78].

Incidence data to date has been almost exclusively derived from higher income populations, with near complete absence of disease estimates from Africa and South America base studies.

These limitations largely reflect methodological constraints. Routine clinical diagnosis underestimates true incidence owing to misclassification of disease type and the absence of widespread access to biomarkers. In addition, prospective community-based cohorts with neuropathological diagnostic verification are rare, leaving the current global incidence estimates of LBD provisional at best.

2.2.5 Neuropathological and Clinical Prevalence Discordance

Autopsy studies consistently report that Lewy body pathology is more frequent than clinical diagnosis suggests, with cortical or limbic Lewy bodies aggregation identified in approximately 15–25% of all dementia brains post-mortem [29, 124]. Many such cases were not clinically recognised as LBD during the individual's life, underscoring the limited sensitivity of current clinical diagnostic practice [82, 106].

Mixed pathology disease appears to be the rule rather than the exception. Alzheimer-type amyloid and tau pathology co-occur in most autopsy-confirmed LBD cases, while vascular lesions and TDP-43 inclusions also occurred just as frequently in the reviewed literature [80, 106]. This overlap complicates both diagnostic boundaries and attribution of clinical features to a single disease pathology.

2.2.6 Underdiagnosis, Misclassification and Disparities

The discrepancy between clinical and neuropathological prevalence contributes to persistent under-diagnosis and misclassification of Lewy body dementia. Many individuals with substantial Lewy body pathological burden may be labelled as having Alzheimer's disease, particularly when parkinsonism or hallucinations are absent [108]. Conversely, some clinically defined LBD cases show only minimal Lewy body pathology at autopsy [106].

Sociodemographic disparities are noted to further contribute to the under recognition of DLB disease. Underdiagnosis of LBD in individuals who identify as Black, as well as other minority groups, has been well documented and likely reflecting inequitable access to specialist assessment and biomarker testing [113]. Addressing such disparities will be essential for accurate LBD prevalence estimates and equitable planning of future healthcare needs.

2.2.7 Risk Factors for Lewy Body Dementia

Age remains the dominant risk factor for LBD, with disease prevalence rising sharply after 65 year old and peaking in those over 80 years [24]. Genetic susceptibility overlaps with that for Alzheimer's and Parkinson's disease, the APOE ε4 allele confers increased risk and poorer prognosis [24]. GBA mutations, associated with lysosomal dysfunction, are also important susceptibility factors across the synucleinopathies [35]. Variants in SNCA, encoding α-synuclein, further implicate shared molecular mechanisms [40].

Vascular and lifestyle factors appear less influential than in Alzheimer's disease, though they remain relevant to overall health and survival. Higher educational attainment, physical activity and social engagement may confer modest protection, in keeping with the broader dementia literature [1, 11]. Environmental exposures such as pesticides, previously linked to Parkinson's disease, have been suggested but remain poorly characterised in LBD [24].

2.2.8 Epidemiological and Clinical Implications

Epidemiological uncertainty has significant implications for both prognosis and care. Under-recognition delays diagnosis, limits access to specialist support and increases the risk of inappropriate pharmacotherapy or inadequate management. Patients with unrecognised LBD may be prescribed inappropriate antipsychotics, such as haloperidol, which can result in severe or even life-threatening sensitivity [125]. Conversely, failure to identify dementia in Parkinson's disease cohorts prevents early anticipatory management and caregiver preparation.

Misclassification also can significantly impair research progress. Trials often enrol heterogeneous populations, diluting treatment effects and slowing the development and evaluation of disease-modifying therapies for LBD [85]. At a policy level, inaccurate prevalence data can hinder workforce and service planning, particularly in low- and middle-income settings, which are projected to experience the steepest increases in dementia burden over the next number of years [17, 122].

2.2.9 Critical Summary of LBD Epidemiology

Epidemiological findings in LBD are characterised by wide variability in prevalence and incidence, driven by inconsistent criteria, methodological heterogeneity and frequent Alzheimer-type co-pathology.

Clinical studies typically identify LBD in 5% to 10% of all dementia cases, while neuropathological series suggest higher frequencies. Under-diagnosis, misclassification, and regional data gaps persist. Age and genetic factors are established contributors, but vascular and lifestyle determinants remain less defined.

These uncertainties highlight the need for multidimensional frameworks that capture systemic vulnerability beyond neuropathological burden. This context provides the rationale for investigating frailty and sensory impairment as complementary domains in the characterisation of LBD phenotypes.

2.3 Clinical Features and Diagnostic Frameworks in Lewy Body Dementia

2.3.1 Core Clinical Phenotype

LBD presents with a heterogeneous combination of cognitive, neuropsychiatric, motor and autonomic symptoms that collectively distinguish it from Alzheimer's disease and other dementias (See Table 2.1) [36, 126].

Typical cognitive impairment involves early deficits in attention, executive and visual perceptual processing, while episodic memory is often relatively preserved in early disease stages [42]. Fluctuating cognition, characterised by episodic variation in alertness or concentration, represents a defining but clinically under recognised feature [126, 127].

Recurrent and well-formed complex visual hallucinations, often manifesting as "pareidolia", in which complex visual illusions involving ambiguous forms that are perceived as meaningful objects, occur in up to 80% of LBD cases and are strongly predictive of underlying α-synuclein pathology [93, 128, 129]. These perceptual disturbances are strongly mechanistically linked to disrupted visuospatial processing and altered visual-cortical excitability [130-132].

Extrapyramidal features such as bradykinesia, rigidity and rest tremor are very common across the LBD spectrum and typically reflect nigrostriatal involvement [31]. Rapid eye-movement (REM) sleep behaviour disorder (RBD) frequently precedes or accompanies cognitive decline and is now recognised as a core clinical feature of LBD [18]. Autonomic dysfunction, which results in symptoms including orthostatic hypotension, urinary incontinence and constipation, is also prevalent in LBD and contributes to care complexity [36]. Neuropsychiatric symptoms such as apathy, depression and delusions further increase functional impairment and caregiver burden [26, 38].

Table 2.1. Clinical Features of Lewy Body Dementia

Domain	Clinical Features or Deficits
Cognitive	Visuospatial and perception
	Episodic memory deficits that improve with cued recall
	Timed attention tasks
	Executive tasks
	Visual tracking and attention
	Construction tasks
	Verbal and psychomotor initiation
	Cognitive fluctuations
Movement	Bradykinesia
	Rigidity (with or without cogwheeling)
	Festinating gait
	Postural instability with falls
	Rest, postural, or action tremor
Behavioural	Well-formed visual hallucinations
	Delusions (e.g. Capgras or misidentification)
	Depression
	Anxiety
	Apathy
	Hallucinations in other modalities
	REM sleep behaviour disorder
Autonomic or Constitutional	Orthostatic hypotension
	Sense of smell loss
	Constipation
	Sialorrhea or rhinorrhoea
	Sexual dysfunction
	Urinary incontinence
	Hyperhidrosis
	Seborrheic dermatitis

2.3.2 Diagnostic Criteria for DLB and PDD

Consensus criteria provide the cornerstone for clinical diagnosis. The **Third and Fourth DLB Consortium reports** established the current diagnostic framework [18, 133]. The consortium report defines **dementia with Lewy bodies** as: Progressive cognitive decline accompanied by a combination of core clinical features, fluctuating cognition, recurrent visual hallucinations, RBD, and spontaneous parkinsonism.

Supportive features include severe antipsychotic sensitivity, repeated falls, autonomic dysfunction and systematised delusions.
Indicative biomarkers comprise reduced striatal dopamine-transporter uptake on SPECT or PET, abnormal cardiac MIBG uptake, and polysomnographic confirmation of RBD [18, 134].

"Probable DLB" requires two or more core features or one core feature with an indicative biomarker, whereas **"Possible DLB**" requires a single core feature or biomarker alone. See **Table 2.2** for more details.

The **Movement Disorder Society (MDS)** criteria for **Parkinson's disease dementia** require a well-established diagnosis of Parkinson's disease followed by insidious, gradually progressive dementia [35, 135, 136]. Cognitive impairment typically affects attention, executive and visuospatial domains, often accompanied by behavioural or psychiatric symptoms. By convention, dementia arising within one year of parkinsonism supports a DLB diagnosis, whereas dementia emerging after one year defines PDD [18, 35]. Although practical for clinical use, the "one-year rule" remains an operational rather than biological distinction [32, 34].

Table 2.2. Revised criteria for the clinical diagnosis of probable and possible DLB

Central Features	• Dementia with a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions. • Memory impairment may not necessarily occur but usually develops with progression. • Deficits on tests of attention, executive function, and visual-spatial ability may be prominent.
Core Features	**Two core features sufficient for a diagnosis of probable DLB, one for possible DLB:** • Fluctuating cognition pronounced variations in attention and alertness. • Recurrent visual hallucinations, typically well-formed and detailed. • Spontaneous motor features of parkinsonism. • REM sleep behaviour disorder, which may precede cognitive decline. • One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.
	If one or more present, along with one or more core features, a diagnosis of probable DLB can be made. **In absence of core features, ≥1 suggestive features sufficient for possible DLB.** **Probable DLB should not be diagnosed on the basis of suggestive features alone.** • REM sleep behaviour disorder • Severe neuroleptic sensitivity • Reduced dopamine transporter uptake in basal ganglia on SPECT or PET imaging
Supportive clinical features	• Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET. • Abnormal (low uptake) ^{123}Iodine-MIBG myocardial scintigraphy. • Relative preservation of medial temporal lobe structures on CT/MRI scan • Prominent posterior slow-wave activity on EEG with temporal lobe transient sharp waves • Postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction • Hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression
DLB is less likely:	• In the presence of cerebral infarcts evident as focal neurological signs on examination or brain imaging • In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical presentation • If parkinsonism are the only core clinical feature and appear for the first time at a stage of severe dementia.
Temporal Sequence of Symptoms:	• DLB is diagnosed when dementia precedes or is concurrent with parkinsonism. • Parkinson disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson disease. • For research studies that distinguish between DLB and Parkinson disease dementia, a 1-year rule is recommended for a diagnosis of DLB, such that dementia should begin no later than 1 year after onset of parkinsonism.

Table 2.3. Movement Disorder Society (MDS) Consensus Criteria for a Clinical Diagnosis of Parkinson Disease Dementia.

I. Clinical Features	
Core features (Both 1 and 2 must be present)	**1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria** • **Bradykinesia** and at least one of the following: muscular rigidity, 4-6 Hz rest tremor, postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction • **No exclusion criteria** (e.g. history of repeated strokes with stepwise progression of parkinsonian features, supranuclear gaze palsy, cerebellar signs, or early severe dementia) • **At least three supportive criteria of the following:** Unilateral onset, rest tremor present, progressive disorder, persistent asymmetry, excellent response to L-dopa, severe L-dopa-induced chorea, L-dopa response for at least 5 years, clinical course at least 10 years, hyposmia, or visual hallucinations
	2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical and mental examination, defined as: • Impairment in more than one cognitive domain • Representing a decline from premorbid level • Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms
A. Associated clinical features	**1. Cognitive features:** • **Attention:** Impairment may fluctuate during the day and from day to day • **Executive Functions:** Impairment often associated with impaired mental speed (bradyphrenia) • **Visual-spatial Functions:** Impairment in tasks requiring visual-spatial orientation, perception, or construction • **Memory:** Impairment in free recall of recent events; memory usually improves with cueing, and recognition is usually better than free recall ***Note that core language functions are largely preserved; however, word-finding difficulties and impaired comprehension of complex sentences may be present*** **2. Behavioural features:** • **Apathy:** Decreased spontaneity and loss of motivation, interest, and effortful behaviour • Changes in personality and mood including depressive features and anxiety • **Hallucinations:** Mostly visual; usually complex, formed visions of people, animals, or objects • Delusions • Excessive daytime sleepiness

B. Features that make the diagnosis of PDD uncertain	• Coexistence of any other abnormality that may by itself cause cognitive impairment, but is judged not to be the cause of dementia (e.g. relevant vascular disease on imaging) • Time interval between the development of motor and cognitive symptoms is not known
C. Features that make the diagnosis of PDD unreliable	• Cognitive and behavioural symptoms appearing solely in the context of other conditions such as acute confusion due to systemic diseases or abnormalities or due to drug intoxication • Major depression according to the DSM-5 **Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN:** *Dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging **AND** a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)*
II. Diagnostic Criteria for the Diagnosis of Probable and Possible PDD	
A. Probable PDD	**1. Core features: Both 1 and 2 must be present** **2. Associated clinical features:** • Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing) • The presence of at least one behavioural symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PDD, lack of behavioural symptoms, however, does not exclude the diagnosis **3. None of the Group C features present** 4. **None of the Group D features present**
B. Possible PDD	**1. Core features: Both must be present** **2. Associated clinical features:** Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention Behavioural symptoms may or may not be present **OR** **3. One or more of the group ill features present** **4. None of the group IV features present**

2.3.3 Indicative and Supportive Biomarkers

Neuroimaging and physiological biomarkers have substantially improved diagnostic specificity but remain limited in availability and validation. Dopamine-transporter imaging with ^{123}I FP CIT SPECT demonstrates high sensitivity and specificity for differentiating DLB from Alzheimer's disease [137, 138]. Cardiac MIBG scintigraphy, reflecting post-ganglionic sympathetic denervation and discriminates DLB from non-synucleinopathic dementias [139]. Table 2.4 summarises diagnostic imaging biomarkers in LBD. In addition to imaging, polysomnographic confirmation of RBD is a highly specific biomarker and often precedes clinical dementia by several years [41].

Additional supportive measures include posterior slow-wave activity and fluctuating pre-alpha EEG patterns [131] . Visual evoked-potential abnormalities and quantitative visuospatial testing may further enhance early detection [132, 140]. Olfactory assessment using standardised tools such as the University of Pennsylvania Smell Identification Test (UPSIT) can distinguish DLB from Alzheimer's disease [73, 141]. Emerging research incorporating multimodal biomarkers, including dopaminergic imaging, cardiac autonomic testing, and olfactory measures, through international collaborative initiatives such as the European DLB Consortium promises to refine diagnostic staging and facilitate biologically defined subtypes [40, 44, 142].

2.3.4 Operational Challenges and Diagnostic Accuracy

Despite well-established criteria, diagnostic performance remains suboptimal in routine clinical practice. Up to half of clinically diagnosed Alzheimer's disease cases show substantial Lewy pathology at autopsy, while some clinically defined LBD cases reveal minimal neuropathological changes [106, 143]. Co-existing amyloid and tau pathology contributes further to misclassification [109].

Standardised instrumental tests such as Addenbrooke's Cognitive Examination-III (ACE-III) and Lewy Body Composite Risk Score (LBCRS) can enhance bedside diagnostic recognition, however these remain underused outside specialist centres [144, 145]. Broader implementation of standardised assessment protocols and alignment of biomarker frameworks are needed to bridge the gap between research criteria and clinical practice [37, 84].

Table 2.4. Diagnostic Imaging Biomarkers in LBD

Imaging modality	PDD	DLB	Comments
Structural imaging (preferably MRI)	Frontal atrophy, enlargement of posterior horn of the lateral ventricle, atrophy of the caudate head	Widespread frontal and parietal atrophy with relatively less medial temporal atrophy	Relative preservation of medial temporal lobe is a supportive biomarker in the 2017 DLB criteria
SWI sequence on high-resolution MRI (3T or 7T)	Loss of the healthy swallowtail appearance of nigrosome 1 in the substantia nigra is known as the *swallow tail sign*; diagnostic sensitivity and specificity are high for PD; sensitivity low and specificity high for DLB		Not in any current diagnostic criteria; the 3T MRI platform is widely available now
FDG-PET/SPECT	Extension of occipital hypometabolism from the primary to the visual association cortices and precuneus hypometabolism, are the earliest cortical metabolic signature of incident dementia in PD	Hypometabolism in the lateral and medial occipital cortices as well as posterior parietal areas, with relative preservation of the med-and posterior cingulate cortex, is known as the "cingulate island" sign	Reduced occipital activity with or without the cingulate island sign is a supportive biomarker in the 2017 DLB criteria
Striatal ^{123}I-FP-CIT scan	The tracer is taken up symmetrically by caudate and lentiform nuclei to create the "double comma" sign, which is normal; first sign of an early neurodegenerative Parkinsonian syndrome is loss of the putaminal "tail"		Reduced dopamine transporter uptake in the basal ganglia on SPECT or PET is an indicative biomarker in the 2017 DLB criteria
MIBG myocardial scan	High sensitivity and specificity to differentiate PD from APS	Differentiates DLB from AD dementia with high sensitivity but low specificity	Upgraded from a supportive to an indicative biomarker in the 2017 DLB criteria: more reliable and accurate than ^{123}I-FP-CIT scan for excluding other dementias

2.3.5 From Categorical to Spectrum Models

Accumulating clinical and neuropathological evidence supports viewing DLB and PDD as points along a single α-synucleinopathy continuum rather than distinct disorders [21, 32, 34]. Differences in phenotype largely reflect regional distribution and interaction of Lewy, amyloid, and tau pathologies [106]. The proposed neuropathological continuum suggests that DLB and PDD represent regionally weighted expressions of a common α-synucleinopathy, with cortical-predominant pathology driving DLB phenotypes and nigrostriatal involvement characterising PDD [146]. This framework aligns with current efforts to develop biologically defined staging systems that integrate clinical, biomarker,

and pathological data, rather than relying solely on temporal distinctions between motor and cognitive onset [22, 40].

2.3.6 Critical Summary of Clinical Features and Diagnostic Frameworks

The clinical and diagnostic literature demonstrates substantial progress but enduring limitations. Consensus criteria have standardised case definition, yet sensitivity and specificity remain suboptimal outside expert settings. Overlap with Alzheimer-type pathology and variable biomarker availability continue to restrict accuracy.

The shift towards multimodal, biologically integrated diagnostic frameworks represents a major conceptual advance, though implementation remains limited in clinical practice. Understanding this diagnostic complexity is essential for interpreting variability in disease trajectory and forms the basis for the prognostic analyses presented in the next section.

2.4 Lewy Body Dementia Prognosis and Natural History

2.4.1 Overview

Lewy body dementia follows a variable yet typically aggressive clinical course, characterised by rapid functional decline, pronounced neuropsychiatric symptoms and reduced survival compared with Alzheimer's disease. Prognostic heterogeneity reflects the interplay between α-synuclein pathology, Alzheimer-type and vascular co-pathologies, and systemic factors such as frailty and multimorbidity [24, 83, 114].

LBD is now recognised to include a prolonged prodromal phase preceding the onset of dementia, characterised by non-cognitive symptoms such as REM sleep behaviour disorder, autonomic dysfunction and olfactory loss [41, 127]. Recognition of this stage has refined understanding of disease evolution and permitted earlier identification of at risk individuals. The transition from prodromal to overt dementia typically spans several years and is influenced by neuropathological burden, comorbid disease and systemic vulnerability [147].

2.4.2 Survival and Mortality

Population based and clinical cohort studies consistently report median survival time ranging from four to eight years from diagnosis, substantially shorter than in Alzheimer's disease but comparable to Parkinson's disease dementia [24, 27]. Reported survival times vary depending on age, comorbidity and co-pathology [117, 148]. Mortality risk is approximately two to three times higher than age-matched controls and remains elevated after adjustment for comorbidities and cognitive severity [114]. Earlier onset of hallucinations, fluctuating cognition and autonomic dysfunction have all been shown to predict reduced survival [24, 82]. In contrast, younger age at diagnosis, a more gradual progression of motor symptoms and preserved attention function are associated with longer survival trajectories [83].

2.4.3 Functional Decline and Institutionalisation

Functional impairment in LBD develops rapidly once cognitive symptoms appear. Loss of independence in instrumental activities of daily living occurs earlier in LBD than in Alzheimer's disease, driven by concurrent motor, cognitive and behavioural impairments [33, 83]. Gait disturbance, visual and perceptual dysfunction and postural instability accelerate falls, hospitalisation and dependency [149]. Median time to residential or nursing-home placement is estimated at 3 to 5 years in specialist cohorts, considerably shorter than for Alzheimer's cohorts [25, 26]. Increased caregiver burden, behavioural disturbance and fluctuating cognition are the strongest predictors of early institutionalisation [77].

2.4.4 Cognitive and Neuropsychiatric Progression

Cognitive decline in LBD progresses more rapidly than in Alzheimer's disease during the early and middle stages, with annual decreases of approximately two to four points on the Mini-Mental State Examination or Montreal Cognitive Assessment [24, 33]. Attention and visuospatial domains show the steepest early decline, while memory loss may remain relatively stable until later disease stages. Neuropsychiatric symptoms, including hallucinations, delusions, apathy and anxiety, occur in more than 80% of patients and fluctuate with disease progression [38, 150]. These symptoms often precede measurable

cognitive deterioration and contribute substantially to functional loss, quality of life and caregiver distress.

2.4.5 Motor Progression

Motor features evolve variably. Parkinsonian signs typically emerge concurrently with or within a year of cognitive onset, but their progression is faster and more disabling than in idiopathic Parkinson's disease [31, 33]. Axial rigidity, gait freezing, and falls are common early, while rest tremor is less prominent. Levodopa responsiveness is modest and treatment can worsen hallucinations or confusion, further complicating management [79]. The combination of motor and neuropsychiatric deterioration accelerates overall disability.

2.4.6 Comorbidity, Frailty and Systemic Vulnerability

Physical comorbidities and frailty exert a strong influence on outcomes. Hospital-based studies report higher rates of delirium, infection and cardiovascular instability in LBD compared with Alzheimer's disease [64, 151] . Frailty prevalence among individuals with mild LBD has been estimated at 60–70%, substantially higher than in Alzheimer's cohorts of similar age and cognitive severity [60, 64]. Frailty and multimorbidity predict mortality and dependency independent of cognitive status, underscoring the need for holistic assessment of systemic vulnerability.

2.4.7 Quality of Life and Caregiver Outcomes

Quality of life studies demonstrate pronounced reductions in both patient and caregiver reported wellbeing compared with other dementia subtypes, largely driven by behavioural and autonomic symptoms rather than cognitive impairment alone [77, 83]. Depression, anxiety and psychosis correlate more closely with patient reported quality of life measures than cognitive scores, indicating that non-cognitive symptoms of LBD are the primary determinants of the patient lived experience [26, 116]. Caregivers report higher psychological distress and lower satisfaction with healthcare support, reflecting the fluctuating and unpredictable nature of the condition [77].

2.4.8 Predictors of Outcome

Across cohorts, consistent predictors of adverse prognosis include older age at diagnosis, greater functional dependence, autonomic instability, hallucinations, and antipsychotic sensitivity [24, 114]. Neuroimaging and biomarker studies link reduced striatal dopamine-transporter binding, cortical hypoperfusion, and amyloid burden with accelerated cognitive and functional decline [109, 152]. Systemic frailty and co-existing vascular pathology further worsen prognosis, highlighting the importance of multidimensional assessment.

2.4.9 Critical Summary of Prognosis and Natural History

LBD is associated with shorter survival, earlier loss of independence, and higher neuropsychiatric and caregiver burden than Alzheimer's disease. Prognosis is shaped by the interaction of neuropathological, functional, and systemic factors, yet longitudinal studies remain few and geographically limited.

Most existing work focuses narrowly on cognition or motor function and seldom incorporates frailty, sensory loss, or other geriatric domains. The absence of multidomain prognostic frameworks limits predictive accuracy and the development of tailored interventions.

Recognising frailty and sensory impairment as modifiable contributors offers a potential pathway to explain inter-individual variability and improve outcome prediction, an approach which is explored further in the subsequent sections.

2.5 Neuropathology of Lewy Body Dementia

2.5.1 Overview

LBD is defined neuropathologically by the abnormal aggregation of misfolded α-synuclein within neuronal cell bodies (Lewy bodies) and neuronal processes (Lewy neurites). The regional distribution and density of these inclusions determine the clinical phenotype across the LBD spectrum. Although α-synuclein accumulation is the hallmark pathology, co-existing Alzheimer-type amyloid-β and tau lesions, vascular changes and

TDP-43 inclusions are frequent, producing complex mixed pathologies that blur clinicopathological boundaries [106, 124].

2.5.2 α-Synuclein Pathology and Staging

α-Synuclein pathology follows a stereotyped but variably expressed progression. Early involvement of the dorsal motor nucleus of the vagus and locus coeruleus is typically followed by spread to limbic and neocortical regions, correlating with the onset of cognitive, behavioural, and neuropsychiatric symptoms [124].

Recent computational progression modelling studies demonstrated that α-synuclein propagation follows multiple trajectories rather than a single linear sequence, offering an explanation for the phenotypic variability between DLB and PDD [81]. Cortical and limbic involvement, particularly in the temporal and occipital association cortices, correlates with visuospatial deficits and hallucinations [42, 153, 154]. Figure 2.1 summarises the regional distribution of α-synuclein pathology across Lewy body disease subtypes.

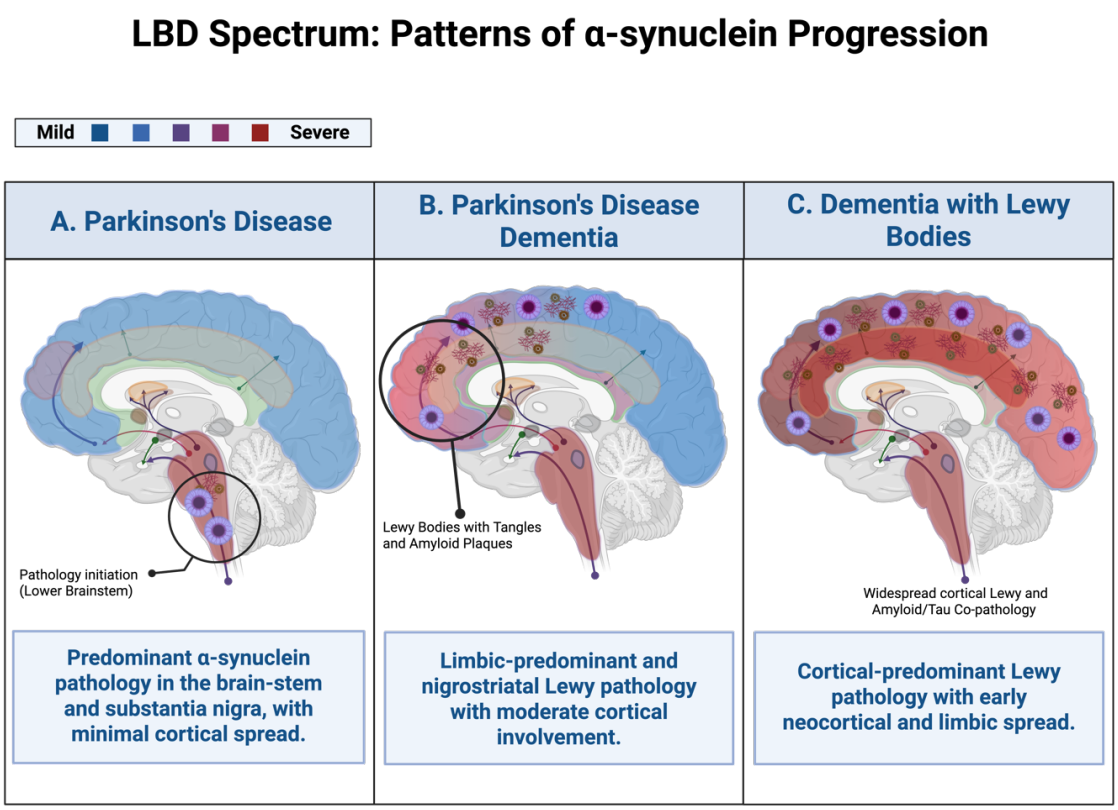

Figure 2.1. Patterns of α-synuclein pathology progression across the Lewy body disease spectrum. *Cortical, limbic, and nigrostriatal patterns of Lewy pathology correspond to the clinical phenotypes of Parkinson's disease (PD), Parkinson's disease dementia (PDD), and dementia with Lewy bodies (DLB). Increasing cortical involvement is associated with greater cognitive and neuropsychiatric impairment, while predominant brain-stem involvement produces a motor-dominant presentation. Adapted from Fu and Halliday (2025).*

2.5.3 Overlap with Alzheimer Pathology

Amyloid-β plaques and tau neurofibrillary tangles are identified in up to 80% of autopsy-confirmed LBD cases [29, 80]. Co-existent Alzheimer pathology is associated with greater cortical Lewy burden and more rapid cognitive decline [106]. Donaghy et al. (2020) reported that amyloid-positive DLB patients exhibit faster progression on cognitive and functional measures than amyloid-negative cases [152].

Neuropathological studies indicate that combined α-synuclein and tau pathology exerts synergistic toxicity, amplifying synaptic dysfunction beyond additive effects [132]. This frequent co-occurrence complicates diagnostic interpretation and underlines the biological continuum between LBD and Alzheimer's disease.

2.5.4 Vascular and TDP-43 Co-pathology

Cerebrovascular lesions, including small-vessel disease, microinfarcts, and amyloid angiopathy, are reported in in 40–60 % of LBD brains [80]. Although vascular burden is not the primary driver of the syndrome, it lowers the threshold for clinical dementia and may exacerbate fluctuations through impaired cerebral autoregulation [109].

TDP-43 inclusions, identified in approximately 15–30% of cases, are associated with hippocampal sclerosis and more rapid memory decline [106]. The cumulative impact of these secondary pathologies reinforces the concept of LBD as a multidimensional neurodegenerative disorder rather than a single protein disease.

2.5.5 Clinicopathological Correlation

Correlation between clinical diagnosis and autopsy findings remains limited. Merdes *et al.* (2003) demonstrated that over 40% of clinically diagnosed Alzheimer's disease cases showed significant cortical Lewy pathology at autopsy, while a subset of clinically defined LBD patients exhibited minimal inclusion burden [143].

These discrepancies reflect limitations in current clinical criteria and the masking effect of co-pathology. Importantly, cortical rather than limbic Lewy distribution is most predictive of cognitive impairment and hallucinations [128].

This imperfect correlation reflects the masking effect of mixed pathology and highlights the need for biologically integrated diagnostic models linking clinical and pathological findings [40].

2.5.6 Emerging Mechanistic Insights

Recent transcriptomic and proteomic analyses reveal that co-pathologies are not merely additive but mechanistically intertwined. Amyloid and tau deposition appear to facilitate α-synuclein aggregation via cross-seeding mechanisms, while microglial and astroglial activation propagate pathology through inflammatory cascades [81]. Vascular dysfunction and impaired glymphatic clearance may further accelerate protein spread.
Collectively, these mechanisms point to a systems-level process of network disintegration rather than isolated proteinopathy.

2.5.7 Critical Summary of LBD Neuropathology

The neuropathology of LBD is complex and multidimensional. α-Synuclein aggregation defines the disorder, but most cases exhibit concurrent Alzheimer-type, vascular, or TDP-43 pathologies that shape the clinical phenotype and accelerate decline.

Cortical and limbic involvement is closely associated with hallucinations, visuospatial deficits, and global cognitive deterioration. Traditional lesion-based models insufficiently capture this interplay of molecular and systemic processes.

A multidomain framework integrating neuropathological, systemic and functional dimensions, encompassing frailty and sensory domains, offers a more complete understanding of vulnerability in LBD and informs the conceptual basis of this thesis.

2.6 Management of Lewy Body Dementia

2.6.1 Overview and General Principles of Management

Management of Lewy body dementia (LBD) is complicated by multisystem involvement and narrow therapeutic window due to drug sensitivities. In practice, treatment aims are symptom control, risk reduction and maintenance of function and quality of life through

medication optimisation and structured non-pharmacological care [126, 155-157]. Health economic analyses underscore the need for proactive, coordinated care as disease complexity and behavioural symptoms drive higher utilisation and costs compared with other dementias [158].

2.6.2 Pharmacological management

Cognition and Global Function:

Cholinesterase inhibitors are the mainstay for cognitive and neuropsychiatric symptoms in LBD, with consistent symptomatic benefits reported across trials and practice summaries. Memantine has more mixed effects and is typically used as second line or adjunctive treatment [155, 156].

Donepezil, rivastigmine and galantamine have comparable efficacy profiles, while memantine demonstrates variable benefit and is typically used as an adjunct. Observational data suggest that cholinesterase inhibitor use is associated with lower mortality in community-dwelling dementia populations, supporting their continued use when tolerated [97].

Motor Symptoms:

Levodopa remains the principal agent for parkinsonism in LBD. Therapy should begin at the lowest effective dose with gradual titration to minimise neuropsychiatric complications. Motor benefit is usually modest compared with idiopathic Parkinson's disease and treatment may exacerbate hallucinations or confusion[79, 125]. Dopamine agonists, monoamine-oxidase B inhibitors, and anticholinergics are generally avoided due to poor tolerability and high risk of behavioural side effects [79, 159].

Psychosis and Agitation:

Visual hallucinations and delusions are common in LBD and correlate with network-level perceptual dysfunction [129, 160]. When symptoms are distressing or dangerous, first steps are to remove reversible triggers, such as infection, pain and sleep deprivation. It is key to avoid or minimise centrally acting anticholinergic and sedative hypnotic agents and optimise cholinesterase inhibition [155, 156]. If an antipsychotic is unavoidable, cautious use

of agents with the lowest dopamine receptor antagonism and careful monitoring is advised due to neuroleptic sensitivity, which has been well described in LBD [157].

Sleep and Autonomic Symptoms:

REM sleep behaviour disorder, insomnia, orthostatic hypotension, and constipation are common and require targeted, symptom-based management.

Melatonin is first-line for REM sleep behaviour disorder, with clonazepam as a second-line option. Non-pharmacological interventions such as sleep hygiene, environmental safety modifications, and head-up sleeping position should precede pharmacotherapy [38].

For orthostatic hypotension, conservative measures such as hydration, compression stockings, slow posture change are prioritised. If persistent, pharmacological agents such as midodrine or fludrocortisone may be used with careful monitoring for hypertension and electrolyte imbalance [156, 161].

Polypharmacy and Anticholinergic Load:

Polypharmacy is prevalent and clinically important in LBD, heightening the risk of delirium, falls, and functional decline. Regular structured medication reviews are recommended, with particular attention to cumulative anticholinergic burden given its association with frailty and cognitive vulnerability in older adults [156, 162]. Anticholinergic cognitive burden can be calculated using validated anticholinergic burden scales such as the Anticholinergic Cognitive Burden (ACB) scale, enabling structured deprescribing and rationalisation of therapy [163, 164].

Emerging and Disease-Modifying Approaches:

Current disease-modifying strategies target α-synuclein aggregation, neuroinflammation, and synaptic dysfunction, but none have yet demonstrated clinical efficacy. Advances in biomarker-based patient stratification may facilitate future therapeutic trials by enabling more homogeneous recruitment and endpoint definition [85, 165].

A summary of recommended pharmacological agents and key clinical considerations for each major symptom domain is presented **in Table 2.5.**

2.6.3 Non-Pharmacological and Rehabilitation Strategies

While evidence the evidence base for non-pharmacological interventions in LBD is smaller than that for Alzheimer's disease or Parkinson's disease, available studies support structured, multidomain interventions to maintain function and limit secondary complications.

Small clinical trials in LBD populations demonstrate benefit from supervised exercise and comprehensive programmes combining progressive resistance training, dietary optimisation and deprescribing [166, 167].

More broadly, geriatric guidance recommends routine frailty identification and management, strength and balance training, adequate protein intake, optimisation of vision and hearing optimisation and proactive falls prevention, delivered through primary care and specialty services [168-171].

Table 2.5. Pharmacological management strategies for Lewy body dementia. Summary of common therapeutic agents, typical dosing approaches, and key clinical considerations across cognitive, motor, behavioural, sleep, autonomic and mood domains.

Symptom Domain and Target	Agent (Class)	Typical Use and Key Considerations
Cognition and Behaviour	**Donepezil** (cholinesterase inhibitor)	First-line for cognitive and behavioural symptoms. Start 5 mg once daily for ≥4 weeks; increase to 10 mg once daily if tolerated. May improve hallucinations; monitor for bradycardia, syncope, and gastrointestinal upset.
	Rivastigmine (cholinesterase inhibitor)	Oral or transdermal formulations. Start 1.5 mg twice daily or 4.6 mg patch daily. Useful when donepezil not tolerated; patch form causes fewer gastrointestinal effects.
	Galantamine (cholinesterase inhibitor)	Alternative oral agent; titrate slowly. Similar efficacy; monitor for nausea and weight loss.
	Memantine (NMDA receptor antagonist)	Add-on or second-line for cognitive or behavioural symptoms. Start 5 mg daily, titrate to 10 mg twice daily. Mixed evidence of benefit.
Motor symptoms (Parkinsonism)	**Levodopa / Carbidopa**	First-line for bothersome rigidity or bradykinesia. Start low (e.g. 62.5 mg three times daily) and titrate slowly. Monitor for hallucinations and orthostatic hypotension.
	Dopamine agonists (e.g. pramipexole, ropinirole)	Generally **avoid** due to high risk of hallucinations, sleep attacks, and impulse-control disorders.
Psychosis and Agitation	**Quetiapine** (atypical antipsychotic)	If antipsychotic essential, start 12.5–25 mg at night and titrate cautiously. Preferred due to low dopamine-receptor antagonism.
	Clozapine (atypical antipsychotic)	Effective for refractory psychosis; start 12.5 mg nightly under haematology monitoring. Risk of agranulocytosis and orthostasis; specialist supervision required.
	Avoid: haloperidol, olanzapine, risperidone	Contraindicated due to severe neuroleptic sensitivity.
Sleep disturbance (RBD, insomnia)	**Melatonin**	2–6 mg at bedtime; first-line for REM sleep behaviour disorder. Safe and well tolerated.
	Clonazepam	0.25–1 mg at bedtime if melatonin ineffective. Monitor for sedation, falls, and confusion.
	Trazodone / Mirtazapine	Low-dose bedtime use for insomnia if comorbid depression; avoid polypharmacy.
Autonomic dysfunction	**Midodrine**	2.5–10 mg three times daily (daytime only) for orthostatic hypotension. Contraindicated in severe hypertension.
	Fludrocortisone	0.1 mg once daily to expand plasma volume. Monitor blood pressure and electrolytes.

	Oxybutynin, Tolterodine, Solifenacin	Used for urinary urgency or incontinence but **avoid if possible** due to high anticholinergic load. Consider **mirabegron** as safer alternative.
	Polyethylene glycol, Lactulose, Senna	For constipation; titrate to effect. Combine with hydration and dietary fibre.
Mood / Apathy	**SSRIs** (e.g. sertraline, citalopram)	For comorbid depression or anxiety. Avoid tricyclic antidepressants due to anticholinergic effects.
	Bupropion / Modafinil	Occasionally used for apathy or daytime somnolence. Limited evidence; specialist initiation only.
Other supportive agents	**Rivastigmine patch**	Useful in patients with swallowing difficulty or gastrointestinal intolerance.
	Avoid high-risk agents	Benzodiazepines, anticholinergics, typical antipsychotics, opioids, and bladder antimuscarinics exacerbate confusion and falls risk.

2.6.4 Care Models and Outcome Measurement

Comprehensive geriatric assessment (CGA) provides a structured foundation for managing the multidimensional needs of people with LBD. CGA anchored management integrates neurological and geriatric expertise, enabling personalised goal setting, minimisation of medication risk, and coordination across care transitions [172].

In both research and clinical contexts, outcome measurement should extend beyond cognitive scales to include frailty indices, functional metrics, falls, and caregiver outcomes. The incorporation of patient-centred and system-relevant endpoints strengthens translational value and informs health-service planning [85, 158, 173].

2.6.5 Practical Priorities and Evidence Gaps

The literature identifies several consistent priorities for clinical practice:

- Systematic medication review with minimisation of anticholinergic exposure and cautious titration of dopaminergic and cholinesterase therapies.
- Stepwise management of psychosis, favouring non-pharmacological approaches and the lowest-risk antipsychotics only when essential.
- Integration of structured exercise, nutrition, and rehabilitation programmes targeting strength, balance, and independence.
- CGA-based multidisciplinary care and structured caregiver education.
- Clinical trials designed to capture frailty, functional outcomes, and real-world effectiveness rather than cognitive endpoints alone.

Despite progress, high-quality randomised trials of non-pharmacological and integrated interventions remain scarce. Head-to-head comparisons of psychosis management strategies balancing efficacy and safety are limited, and implementation studies of CGA-anchored care within neurology services are rare. Addressing these evidence gaps will be critical for improving both patient and caregiver outcomes in LBD.

2.7 Frailty in Neurodegenerative Disease and in Lewy Body Dementia

2.7.1 Conceptual Models of Frailty

Frailty describes a state of multisystem dysregulation that involves inflammatory, endocrine, and mitochondrial pathways, producing reduced physiological reserve and increased vulnerability to external stressors, leading to disproportionate risk of adverse health outcomes [46, 49]. Two principal conceptual models dominate current gerontological research: the phenotypic model and the cumulative deficit model.

The Frailty Phenotype Model:

The **frailty phenotype model**, introduced by Fried *et al.* (2001), defines frailty as a clinical syndrome of observable physical characteristics or criteria which include: weakness (measure via grip strength), unintentional weight loss, self-reported exhaustion, slow walking speed and low physical activity. Frailty is defined as a clinical syndrome in which three or more of the above criteria are present. The model was originally proposed to identify individuals at heightened risk of poor outcomes in community cohorts [52].

The Cumulative Deficit Model:

In contrast, the **cumulative deficit model**, developed by Rockwood and Mitnitski, conceptualises frailty as the accumulation of age-related health deficits across physiological, psychological and functional domains. This approach is expressed as a Frailty Index (FI), which provides a continuous measure of biological ageing and vulnerability [54].

While both models predict mortality and functional decline, the deficit accumulation approach offers greater flexibility for epidemiological and clinical use, allowing frailty to be quantified using routinely collected variables and incorporated into multidimensional datasets. Comparative analyses show that phenotypic measures emphasise physical performance and sarcopenia, whereas deficit-based models capture broader multidomain vulnerability, including comorbidity, polypharmacy, cognitive impairment, and psychosocial stressors [56, 57].

Figure 2.2 summarises the key distinctions between the phenotypic and cumulative deficit models, highlighting their differing conceptual and operational foundations.

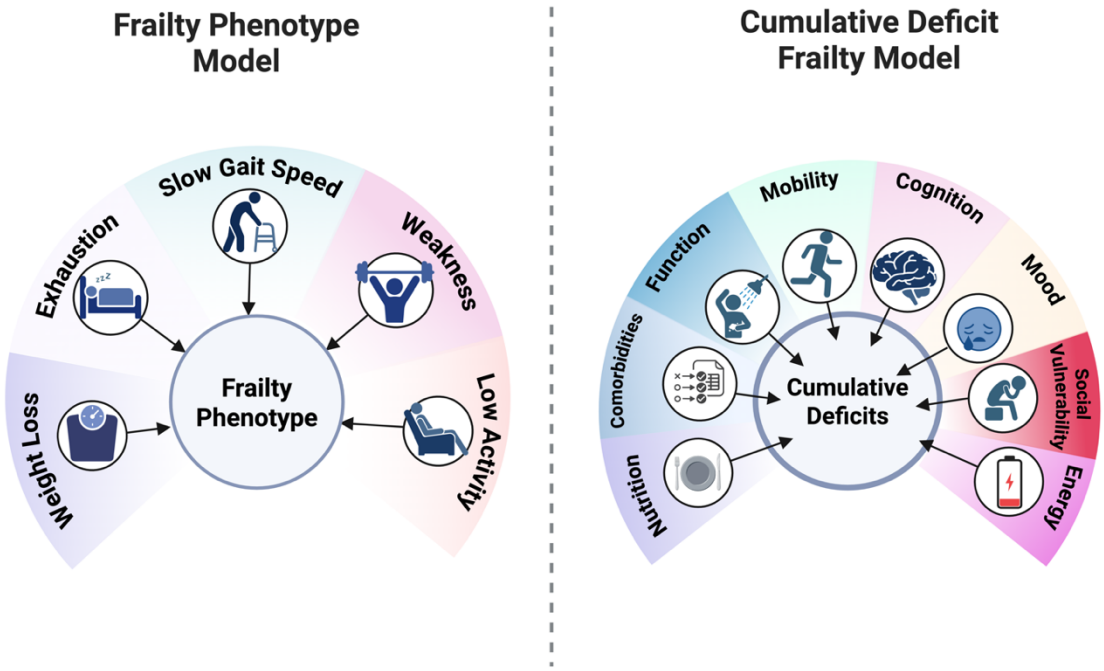

Figure 2.2. Conceptual Models of Frailty. *Comparison of the two principal frailty frameworks: the phenotypic model describing a clinical syndrome defined by physical criteria, and the cumulative deficit model conceptualising frailty as the proportion of health deficits accumulated across multiple domains (adapted from Fried et al., 2001 and Rockwood and Mitnitski, 2002).*

In neurodegenerative disease, the multidimensional FI approach is particularly useful because motor, autonomic and neuropsychiatric symptoms overlap with frailty domains and evolve dynamically over time [174]. The critical challenge remains construct validity, differentiating frailty as an age-related constructs from overlapping manifestations of neurological disease itself [103].

2.7.2 Frailty as a Predictor of Adverse Outcomes

Across ageing populations, frailty has been shown to be an independent predictor of higher mortality, institutionalisation and cognitive decline. Longitudinal studies in community dwelling older adults show that both phenotypic and deficit-based frailty independently predict mortality and nursing home admission after adjustment for age and comorbidity [59, 88].

Meta-analyses indicate that frailty approximately doubles dementia risk, implicating shared mechanisms such as vascular burden, inflammation and impaired homeostatic regulation [175]. Neurodegeneration contributes to the development of frailty, while frailty exacerbates the clinical impact of neuropathological burden by reducing cognitive and physiological reserve [176].

Figure 2.3 illustrates the typical progression of this process, showing how accumulated deficits gradually reduce resilience and functional capacity.

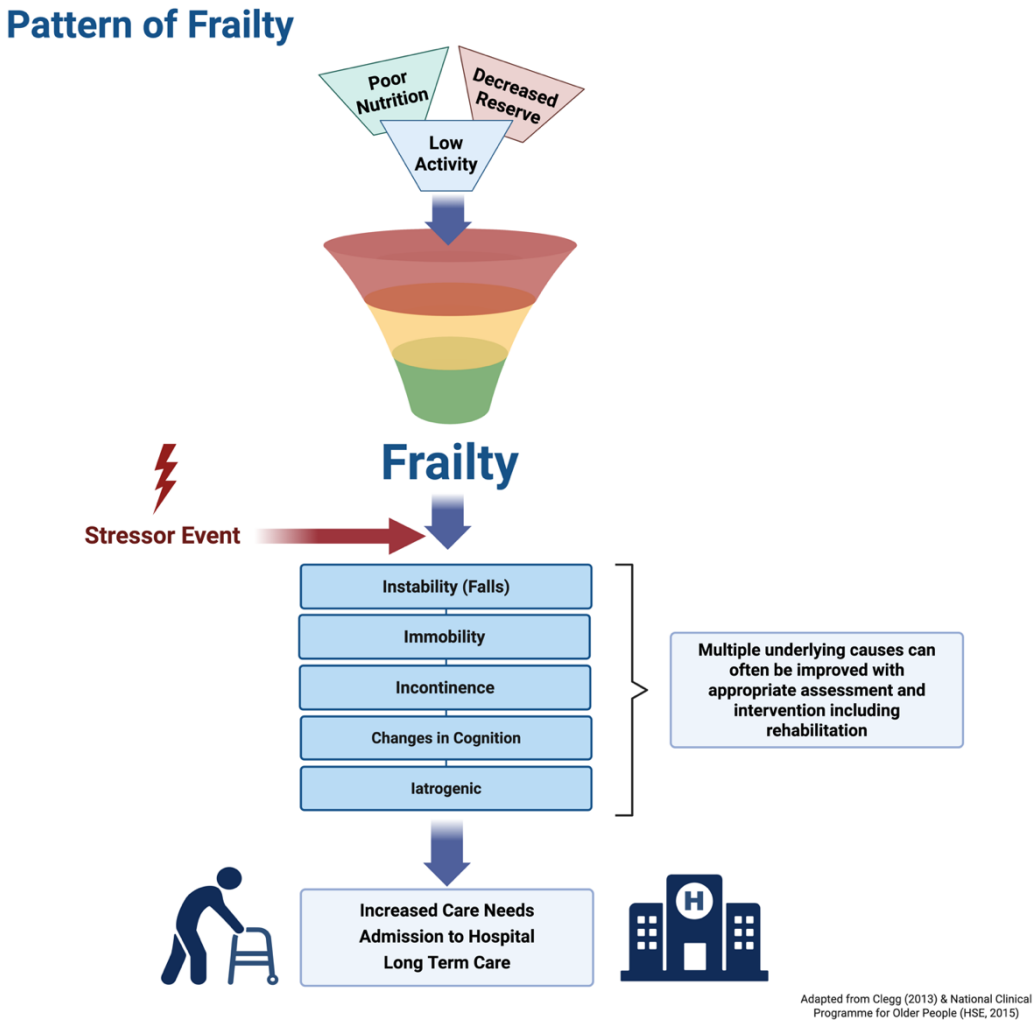

Figure 2.3. Pattern of Frailty. *Frailty develops through progressive accumulation of deficits across physiological, cognitive and functional systems, leading to reduced reserve, increased vulnerability to stressors and higher likelihood of adverse outcomes (adapted from Clegg 2013).*

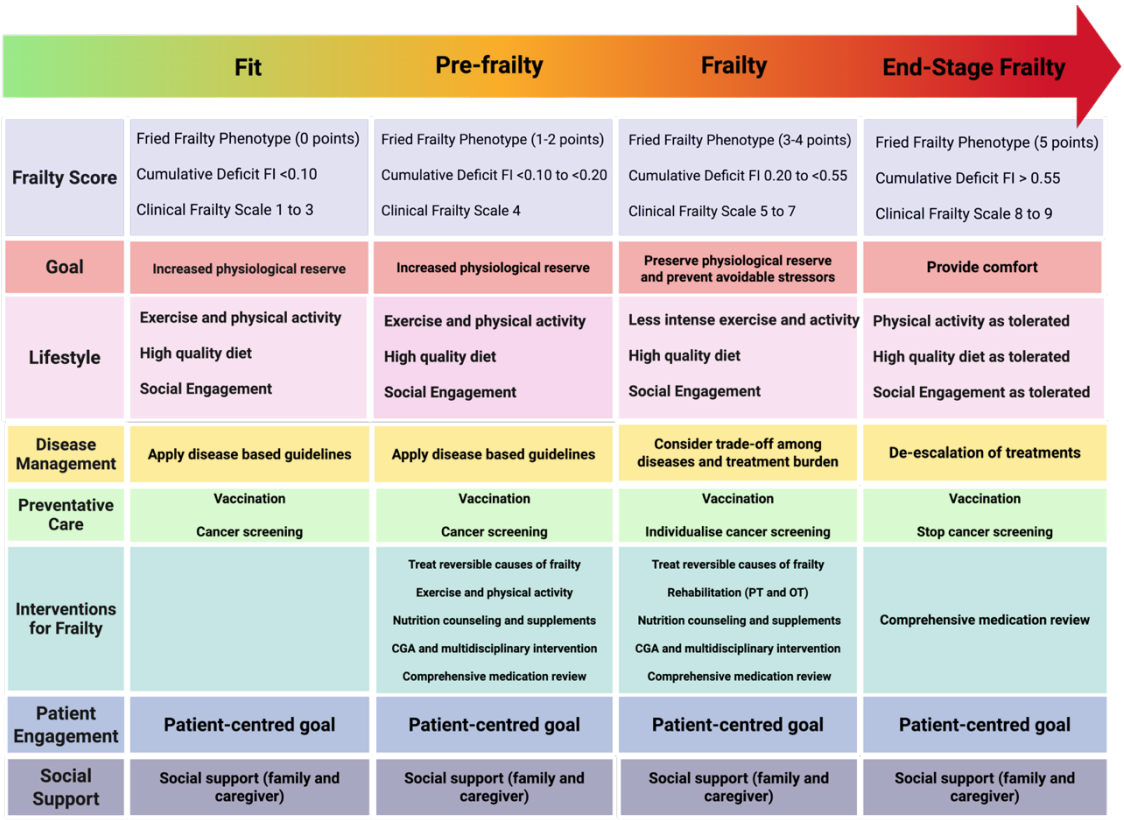

Figure 2.4. Domains contributing to frailty. *Frailty arises from the cumulative interaction of biological, psychological, cognitive, and social domains that together determine resilience to stressors and risk of adverse outcomes (adapted from Kim and Rockwood, 2024).*

Figure 2.4 illustrates the multidomain framework proposed in recent work, which conceptualises frailty as an emergent property of interacting biological, functional, and psychosocial processes rather than a purely physical syndrome.

In neurological disease, frailty provides prognostic information beyond conventional staging. In Parkinson's disease, higher frailty scores correlate with increased falls, hospitalisation and mortality independent of motor severity [177, 178]. In Alzheimer's disease, frailty predicts faster cognitive and functional decline, supporting the view that systemic resilience modifies neurodegenerative disease trajectories [62, 179].

Collectively, these findings establish frailty as a dynamic and potentially modifiable biological state influencing both disease expression and prognosis rather than merely a marker of comorbidity[180].

2.7.3 Frailty Indices in Dementia and Parkinson's Disease

The application of frailty indices in dementia research has expanded rapidly over the past decade. The Multidimensional Prognostic Index (MPI), derived from the comprehensive geriatric assessment (CGA), has demonstrated predictive validity for mortality and hospitalisation among outpatients with cognitive impairment and dementia [96]. Similarly, the Survey of Health, Ageing and Retirement in Europe Frailty Instrument (SHARE-FI) provides large scale frailty quantification in epidemiological cohorts and correlates with both physical and cognitive outcomes [59].

In Parkinson's disease, frailty is highly prevalent even in early stages and associated with disability, reduced quality of life and mortality [167]. Although frailty overlaps with motor symptoms such as bradykinesia, gait instability and autonomic dysfunction, it remains an independent prognostic indicator for hospitalisation and mortality [103]. Prospective trials such as the PRIDE study demonstrate that multidomain interventions combining exercise, nutrition and medication review can improve functional capacity and self-efficacy in both Parkinson's disease and dementia with Lewy bodies [167].

2.7.4 Emerging Evidence for Frailty in Lewy Body Dementia

Despite the significant clinical overlap between Parkinson's disease and dementia with Lewy bodies, frailty remains under-studied in LBD. In a cross-sectional comparative analysis, Borda et al. (2019) found that frailty was significantly more prevalent in DLB than in Alzheimer's disease, even after adjustment for age and comorbidity [64]. This pattern implies that systemic vulnerability develops early within the synucleinopathy spectrum and may contribute to clinical heterogeneity.

Subsequent studies have extended these observations, showing that frailty correlates with neuropsychiatric burden and poorer quality of life even in early or mild LBD, consistent with the view that systemic vulnerability is intrinsic to the disorder rather than a late consequence of disability.

The first structured frailty assessment in DLB, reported by D'Antonio et al. (2025), demonstrated significant associations between higher frailty index scores and poorer cognitive performance, greater neuropsychiatric burden and reduced quality of life [181]. Importantly, the study demonstrated feasibility of frailty assessment in this population, but also highlighted methodological limitations, including small sample size and incomplete validation of the index against functional outcomes.

Similarly, Wyman-Chick et al. (2024) observed that highly frailty scores in the year preceding DLB diagnosis correlated with higher anticholinergic burden, implying that medication effects and prodromal neurodegeneration contribute jointly to systemic vulnerability [61]. Preliminary interventional reports suggest that addressing frailty domains through measures like regular exercise, increase protein intake and medication deprescribing, can stabilise functional trajectories and reduce dependence [166, 171].

Collectively, these studies support the hypothesis that frailty is common in LBD and influences clinical outcomes and highlights the need for a validated disease-specific frailty index, which integrates the motor, autonomic, sleep and neuropsychiatric domains characteristic of this disorder.

2.7.5 Methodological and Conceptual Challenges

Several methodological issues complicate frailty measurement in neurodegenerative disease:

Deficit Selection: Many candidate items overlap with disease manifestations such as bradykinesia, orthostatic hypotension or cognitive fluctuation. This overlap risks circularity and inflating frailty scores. Construct validity requires clear separation of disease symptoms from systemic vulnerability [56, 162].

Measurement Heterogeneity: Frailty instruments differ in domain composition, scoring thresholds and inclusion criteria, leading to inconsistent prevalence and predictive strength across studies [88, 182]. Construct validity requires that frailty be distinguished from disease manifestations such as rigidity or cognitive fluctuation while still capturing their cumulative effect on resilience.

Population Bias. Research cohorts often exclude the oldest old and those with multimorbidity, underestimating frailty's true impact in clinical populations [49]. Acute hospitalisation and immobility contribute further to functional decline, with hospital-associated deconditioning recognised as both a cause and a consequence of frailty in older adults

Construct Overlap: Frailty, sarcopenia and cognitive decline share biological pathways, involving inflammation, mitochondrial dysfunction and hormonal dysregulation, complicating causal interpretation. Whether frailty represents an independent ageing process or a downstream manifestation of neurodegeneration remains unresolved [176].

2.7.6 Critical synthesis and rationale for an LBD specific frailty construct

Evidence across geriatric, dementia, and Parkinson's disease research confirms that frailty is measurable, clinically relevant, and prognostically significant. Yet existing instruments, developed for general ageing populations, inadequately capture the multisystem features that define LBD.

The combination of parkinsonism, dysautonomia, sleep-wake disturbance, visual-perceptual impairment and cognitive fluctuation creates a distinctive vulnerability pattern only partly represented by current measures.

Two key knowledge gaps remain. Firstly, Lewy body dementia lacks a validated, disease-specific frailty index capable of quantifying the combined burden of motor, autonomic, cognitive and neuropsychiatric deficits. Second, the mechanistic relationship between frailty, systemic ageing, and neurodegenerative expression is incompletely defined.

Developing an LBD specific cumulative deficit frailty index offers a methodological pathway to address both gaps by operationalising multisystem vulnerability within a single quantitative framework. This approach aligns with contemporary geriatric and neurological paradigms that conceptualise resilience and decline as multidimensional, interdependent processes.

2.8 Sensory Impairment in Ageing and Lewy Body Dementia

2.8.1 Epidemiology of Sensory Loss in Ageing

Hearing, vision, and olfaction decline progressively with age and represent three of the most prevalent chronic conditions of later life. Global data indicate that nearly one third of adults aged 65 years and older live with clinically significant hearing loss, while more than 200 million live with moderate to severe visual impairment [183, 184]. Olfactory dysfunction, though less frequently recognised, affects up to one quarter of individuals over 60 years of age and is independently associated with increased mortality and cognitive decline, independent of age and comorbidity [185].

Dual sensory impairment, involving concurrent loss of hearing and vision, is increasingly common. Longitudinal cohort studies demonstrate that individuals with multisensory deficits have a twofold risk of functional disability, depression and dementia compared with those affected in a single modality [90].

Population-based analyses emphasise that sensory impairment rarely occurs in isolation but clusters with frailty, multimorbidity and cognitive decline [98, 99]. These patterns suggest that sensory loss is not only an organ-specific deficit but also a systemic marker of vulnerability relevant to brain health and neurodegenerative risk.

2.8.2 Mechanistic links between sensory loss and cognition

Several complementary mechanisms explain the strong association between sensory decline and cognitive impairment.

The **"Sensory Deprivation Hypothesis"** proposes that reduced afferent sensory input leads to cortical under-stimulation, structural cerebral atrophy and compensatory reorganisation of neural networks [100, 186, 187]. Functional imaging studies demonstrate that hearing loss correlates with reduced grey-matter volume in auditory and prefrontal cortices and with compensatory increases in neural activation, contributing to cognitive fatigue [188, 189].

The **"Common Cause Hypothesis"** suggests that shared neurodegenerative or vascular processes underlie both sensory and cognitive decline, supported by neuropathological evidence of small-vessel disease and α-synuclein deposition in sensory pathways [190-192].

Olfactory impairment occupies a distinct position within this framework. The olfactory bulbs and anterior olfactory nuclei are among the earliest sites of α-synuclein aggregation, often preceding cognitive or motor symptoms [92, 193, 194].
Visual and auditory processing areas are also vulnerable to Lewy-related pathology, which may disrupt integration across sensory modalities.

These findings indicate a reciprocal relationship in which sensory loss both reflects and intensifies neurodegenerative change.

2.8.3 Sensory Dysfunction in Lewy body Dementia

Sensory dysfunction is integral but under recognised deficit in Lewy body dementias.

Olfaction: Anosmia and hyposmia frequently precede motor and cognitive symptoms by several years, distinguishing prodromal DLB and Parkinson's disease dementia (PDD) from Alzheimer's disease [73]. Pathological studies confirm dense α-synuclein deposition in olfactory tracts and amygdala correlating with disease severity [92, 194, 195]. Quantitative olfactory testing such as the University of Pennsylvania Smell Identification Test (UPSIT) can achieve diagnostic discrimination between DLB and AD even at the mild cognitive impairment stage in some studies [73, 196].

Vision: Visual-perceptual and oculomotor abnormalities are core clinical features central to the LBD phenotype. Patients demonstrate impaired contrast sensitivity, motion perception and visual hallucinations linked to occipital and temporal network dysfunction [74, 93, 197]. Neuroimaging reveals occipital hypometabolism and posterior cortical atrophy corresponding to visuospatial deficits, while electrophysiological studies demonstrate abnormal visual evoked potentials and altered cortical excitability [132, 198, 199].

Hearing: Hearing loss is increasingly recognised as relevant in synucleinopathies. Epidemiological data show higher rates of hearing impairment in Parkinson's disease compared with controls and emerging data suggest similar associations in LBD [94]. The mechanism likely include a combination of peripheral presbycusis and central auditory processing deficits, with attentional fluctuation contributing to misinterpretation of auditory stimuli and increased hallucination susceptibility.

Collectively, these findings position sensory dysfunction as both a clinical manifestation and mechanistic component of LBD. Deficits in olfaction, vision, and hearing not only reflect the spread of Lewy pathology but also interact with cognitive and neuropsychiatric symptoms informing expression of disease.

2.8.4 Clinical and Prognostic Implications

Sensory impairment exerts a measurable influence on function, quality of life, and disease trajectory in dementia. Individuals with combined hearing and vision loss experience faster cognitive decline, earlier institutionalisation, and greater depressive

symptomatology than those with single modality loss [67, 69]. In LBD, greater sensory dysfunction correlates with higher caregiver burden and reduced quality of life, paralleling the effects of motor and neuropsychiatric symptoms [48].

Despite its relevance, sensory assessment remains marginal in standard clinical evaluation. Cognitive screening tools such as the Mini-Mental State Examination (MMSE) or Addenbrooke's Cognitive Examination (ACE) are rarely adjusted for uncorrected sensory loss, potentially underestimating residual cognitive capacity and contributing to diagnostic misclassification. Unrecognised hearing or visual impairment may be misinterpreted as cognitive fluctuation or psychosis, leading to inappropriate pharmacological intervention.

Interventional data, though limited, indicate that correcting sensory deficits can improve clinical outcomes. Studies in mixed dementia populations demonstrate that hearing aids, cataract surgery and environmental adaptations improve cognition, communication, and social participation [48, 65]. These findings suggest that sensory rehabilitation represents a feasible and potentially modifiable target for enhancing quality of life and delaying decline in LBD.

2.8.5 Mechanistic and Research Implications

The convergence of clinical, neuropathological and mechanistic evidence supports the conceptualisation of sensory dysfunction as a multidimensional vulnerability domain in LBD. Sensory deficits arise from direct α-synuclein pathology within peripheral and central processing pathways and contribute to attentional fluctuation, visual misperception and neuropsychiatric symptomatology.

From a research perspective, sensory impairment offers a promising avenue for biomarker development and prognostic modelling. Objective measures of hearing, vision, and olfaction are quantifiable, repeatable and mechanistically linked to disease progression. Incorporating these variables into longitudinal studies may enhance prediction of functional decline and aid identification of prodromal LBD.

Sensory impairment also intersects conceptually with frailty. Both constructs reflect loss of physiological reserve across systems and predict adverse outcomes independent of chronological age. Integrating sensory variables into frailty assessment frameworks could improve the granularity of vulnerability profiling in LBD, bridging neurological and geriatric domains. This conceptual linkage forms the basis for the integrated multidomain model explored in the following section.

2.8.6 Critical Summary

Sensory impairment is common in ageing and nearly universal in Lewy body dementia, where it arises from both peripheral and central mechanisms. Olfactory dysfunction represents an early marker of synucleinopathy, while visual and auditory deficits contribute to the characteristic perceptual and attentional disturbances of the disease.

Despite strong mechanistic and clinical evidence, sensory domains remain under-assessed in diagnostic and prognostic models. Their omission limits understanding of disease heterogeneity and precludes identification of modifiable contributors to poor outcomes.

Integrating sensory measures into multidimensional frailty frameworks may improve prognostic precision and support development of targeted interventions. The next section examines this intersection in detail, outlining the emerging concept of “Sensory Frailty” and its implications for modelling multidomain vulnerability in LBD.

2.9 Integrating Frailty and Sensory Impairment

2.9.1 Conceptual Foundations

Frailty and sensory impairment, although often studied separately, share a common biological basis of multisystem decline. Both reflect loss of physiological reserve and reduced capacity to adapt to environmental or internal stressors [76, 200]. Sensory impairment directly affects mobility, balance, and communication, thereby accelerating social isolation and inactivity, key drivers of frailty [201, 202]. In turn, frailty may worsen sensory function through vascular, metabolic, or inflammatory pathways that damage

ocular, cochlear or olfactory structures [203-205]. These reciprocal interactions have prompted calls for an integrated construct, “sensory frailty”, describing the interaction between sensory and systemic ageing processes [100, 206].

Within the cumulative deficit model, sensory decline can be understood as one dimension within a broader network of physiological impairments [207, 208]. This aligns with modern gerontological frameworks in which sensory, cognitive, and physical deficits interact through shared mechanisms involving mitochondrial dysfunction, oxidative stress, and neuroinflammation [204, 209]. The convergence of these mechanisms suggests that sensory decline is not merely correlated with frailty but represents one of its clinical expressions.

2.9.2 Epidemiological evidence for sensory frailty interactions

Large cohort studies consistently show strong associations between sensory loss and frailty progression. In the English Longitudinal Study of Ageing, new-onset hearing impairment was associated with a twofold increase in frailty risk over four years, independent of comorbidity and socioeconomic status [95, 210].

Similar findings have been reported for vision loss in Asian and North American cohorts [211, 212]. Individuals with both hearing and visual impairment show the steepest increases in frailty and mortality, suggesting additive or synergistic effects [69, 99].

Meta-analysis data indicates that sensory loss accounts for up to 15% of variance in physical frailty after adjusting for age and multimorbidity [213]. Importantly, these associations persist when sensory impairment is measured objectively rather than self-reported, reinforcing the biological rather than psychosocial link [72]. Mechanistically, reduced sensory input limits environmental engagement and locomotor activity, precipitating sarcopenia and balance instability, while chronic sensory deprivation imposes sustained cognitive load and stress reactivity that accelerate physiological exhaustion [212].

2.9.3 Shared Pathways and Mechanistic Models

The overlap between frailty and sensory impairment extends to molecular and neural pathways. Vascular dysfunction, including microangiopathy and endothelial senescence, compromises perfusion of both sensory organs and skeletal muscle[204].

Inflammatory activation, reflected by elevated interleukin-6 and tumour necrosis factor-α, is common to frailty, age-related hearing loss and retinal degeneration [214, 215]. Neurodegenerative propagation through α-synuclein or amyloid-β pathology links olfactory and visual circuits with central autonomic and cognitive networks [216, 217]. Together, these processes create the multisystem vulnerability characteristic of Lewy body disease.

Neuroimaging and post-mortem studies demonstrate reduced white-matter integrity in frontostriatal and parietal tracts in both frailty and sensory impairment, regions that integrate sensory and motor function [218]. This evidence supports a model of network-level decline, where reduced connectivity and compensatory resource depletion underpin both conditions.

2.9.4 Implications for Lewy body dementia

LBD is a disorder in which multisystem impairment, including motor, autonomic, cognitive and sensory domains, coexists and fluctuates over time. The intersection of frailty and sensory loss is therefore intrinsic to its clinical phenotype. Olfactory dysfunction is almost universal in individuals with LBD, while visual and auditory deficits contribute to hallucinations and attentional fluctuation and loss of independence [92, 94]. These impairments may compound systemic frailty, leading to greater dependency, higher falls risk and increased caregiver strain.

Despite this overlap, frailty and sensory loss are rarely examined together in LBD research. Most studies address them as separate correlates of disability rather than interacting determinants of vulnerability. Early evidence implicates chronic inflammation, vascular dysfunction and neuroendocrine stress pathways, but these mechanisms have rarely been examined in relation to frailty or sensory decline within

LBD cohorts [204, 219, 220]. The interaction between sensory input, cortical network plasticity and attentional fluctuation, a defining feature of LBD, has not been systematically measured. Integrating these constructs could improve staging and prognostication.

Including sensory variables within frailty indices may detect early multisystem involvement before substantial cognitive decline. This approach reflects the broader goal of precision gerontology, where multidomain metrics replace single-domain measures to improve prediction and clinical relevance [204].

2.9.5 Towards an Integrated Sensory Frailty Framework

Recent evidence supports the development of an integrated sensory frailty framework encompassing structural, functional and behavioural domains. In this model, sensory impairment functions both as a contributing factor and as a measurable component of frailty, linked through shared biological and behavioural mechanisms [100]. Operationally, this framework would combine standard frailty parameters, such as mobility, nutrition, strength, comorbidity, with objective sensory measures of vision, hearing, and olfaction. The resulting sensory frailty index could improve sensitivity to multisystem decline in disorders like LBD, where sensory dysfunction is an early and pervasive feature.

This integration also offers practical benefits. Interventions that restore sensory input, including hearing or vision rehabilitation, may attenuate frailty progression by supporting mobility, cognition and social engagement [210, 221]. Multidomain frailty interventions that target exercise, nutrition, and medication optimisation may preserve or improve sensory performance through better vascular and metabolic resilience [222, 223].

In summary, unifying frailty and sensory impairment within a single construct provides a more comprehensive model of vulnerability in neurodegenerative disease. In LBD, where systemic and sensory deficits intersect, this framework offers both conceptual clarity and methodological direction for the development of multidimensional indices such as the LBD-FI explored in this thesis.

By quantifying frailty and sensory domains together within a single analytical framework, this thesis directly addresses the identified translational gap, advancing understanding of multidomain vulnerability in Lewy body dementia. The next chapter outlines the methodological approach used to operationalise these constructs within the study cohort.

Chapter 3. Methods

3.1. Study Design and Setting

My doctoral thesis project was a cross-sectional observational study performed as part of SENSE-Cog Lewy, which formed the core clinical work package (Work Package 3) of the EMERALD Lewy research programme. EMERALD Lewy is a Health Research Board-funded initiative aimed at improving the early diagnosis, multidomain characterisation and management of Lewy body dementia in Ireland. My role in developing this core clinical work package forms the basis of this doctoral thesis, including the establishment and analysis of a clinical assessment dataset of participants, focusing on quantifying both frailty and sensory impairment in individuals with LBD.

My doctoral thesis project was designed to address two complementary aims:

1. To develop and validate a Lewy body dementia Frailty Index (LBD-FI) as a multidomain measure of vulnerability specific to the LBD population.
2. To characterise the prevalence, severity and clinical correlates of objectively measured sensory impairments (olfactory, auditory and visual impairments) within the same cohort and examine their relationship with frailty and clinical outcomes.

Participants were referred from collaborating specialist movement disorder, memory and geriatric medicine clinics across Ireland. Following eligibility screening, all participants attended a single structured assessment visit at the Mercer's Institute for Successful Ageing (MISA), St James's Hospital, Dublin 8. I performed sensory, cognitive, neuropsychiatric and functional assessments under standardised conditions using a pre-specified operational protocol.

Each participant was accompanied by a co-participant, usually a spouse, relative or close caregiver who was more 18 years of age, who provided collateral information on functional ability, behaviour and neuropsychiatric symptoms. Co-participant inclusion was mandatory for all participants to enable completion of informant-based measures. Recruitment occurred between December 2023 and May 2025. The final analytic sample comprised of 51 participants, who all met inclusion criteria for probable or prodromal

DLB, PDD or PD-MCI. The cross-sectional design enabled simultaneous profiling of frailty, cognition, neuropsychiatric symptoms, function and sensory ability at a single time point, allowing direct analysis of interrelationships among these domains, while controlling for age and diagnostic group.

As the clinical assessor, I was not blinded to participants clinical diagnosis, but I followed detailed standardised protocols and validated instruments to minimise observer bias. Following eligibility screening, I obtained informed consent from all study participants and their nominated co-participant. I then performed study assessments, as outlined in section 3.5, with the participating patients, while co-participant assessments were simultaneously obtained by collaborating trained clinical researchers.

All assessments were performed under harmonised study procedures to ensure methodological consistency and reproducibility. An overview of the study design and workflow, from participant recruitment to data analysis, is presented in Figure 3.1.

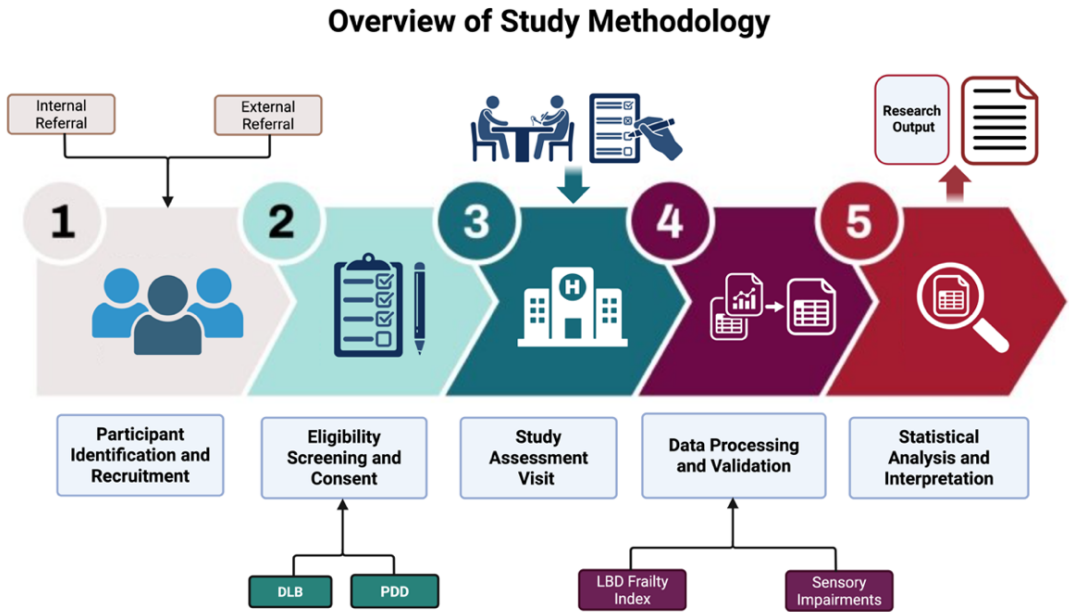

Figure 3.1. Overview of Study Methodology and Stages: Participant identification and recruitment; eligibility screening and consent; study assessment visit; data collection and preparation; and statistical analysis and interpretation.

3.2. Ethical Approval and Governance

Ethical approval for this study was granted by the Joint Research Ethics Committee (JREC) of St James's Hospital and Tallaght University Hospital, with initial approval issued on 5 July 2023 (Reference: 2023-07) and subsequent amendment approval on 14 November 2023 (Reference: 2023-11 Amendment A). Institutional approval was also provided by the St James's Hospital Research and Innovation Office (Appendix 1).
The study was conducted in accordance with the Declaration of Helsinki (2013 revision), the standards and principles of Good Clinical Practice (GCP) and the governance policies of Trinity College Dublin and participating institutions.

All participants provided written informed consent before any study-related procedures. Capacity to consent was a mandatory inclusion criterion and was formally evaluated by trained clinical researchers using a structured, study-specific framework assessing understanding, appreciation, reasoning, and communication of choice. Individuals who lacked capacity were excluded from participation.
Each co-participant also provided independent written consent before completing informant-based questionnaires. Consent forms explicitly authorised the use of pseudonymised data for the present analysis and for future ethically approved research.

All participants received detailed Participant Information Leaflets (PILs) describing study aims, procedures, potential risks and benefits, voluntary participation, and data-handling practices. These documents specified the right to withdraw at any time before anonymisation without consequence and outlined procedures for notifying general practitioners (with consent) and for handling any incidental findings of clinical concern (Appendix 2).

The study was classified as minimal-risk, involving no therapeutic intervention or invasive procedure. Data management complied fully with the General Data Protection Regulation (GDPR; EU 2016/679) and the Data Protection Act 2018. All study data were pseudonymised at source using unique alphanumeric identifiers. The linkage file connecting identifiers to participant codes was stored separately on encrypted, access-

restricted institutional servers. Identifiable data were accessible only to authorised members of the research team directly involved in data collection. All analyses used fully de-identified datasets.

Data retention, storage, and sharing followed the institutional policies of St James's Hospital and Trinity College Dublin. Electronic data were maintained on secure hospital servers with routine encrypted backup, while paper Case Report Forms (CRFs) were stored in locked, access-controlled research offices. A complete audit trail documented ethics approvals, consent procedures and data-management processes throughout the study lifecycle.

3.3. Participant Eligibility and Recruitment Strategy

3.3.1 Eligibility Criteria

Participants were eligible if they met established diagnostic criteria for Lewy body disease, encompassing:

- Probable Dementia with Lewy Bodies according to the 2017 DLB Consortium criteria [18]
- Prodromal DLB as defined by emerging research consensus for prodromal Lewy body syndromes [41, 127]
- Parkinson's Disease Dementia (PDD) meeting Movement Disorder Society (MDS) Task Force guidelines [35]
- Parkinson's Disease with Mild Cognitive Impairment (PD-MCI) fulfilling MDS Level II (Comprehensive Assessment) criteria [224].

Additional inclusion requirements were:

- Age ≥ 50 years;
- Capacity to provide informed consent, formally verified by trained research personnel;
- Availability of an adult (≥ 18 years) co-participant familiar with the participant's health and daily function; and
- Ability to attend the study site and complete assessments conducted in English.

Participants were excluded if they met the following criteria:

- Primary neurodegenerative diagnosis other than LBD (e.g. Alzheimer's disease, frontotemporal dementia);
- Acute delirium or had an unstable medical or psychiatric condition likely to interfere with testing;
- Severe uncorrected hearing or visual impairment that precluded valid sensory testing; or
- Unable to complete validated instruments because of language, comprehension, or motor limitations.

3.3.2 Recruitment Procedures

Participants were recruited through the EMERALD Lewy programme following a standardised recruitment protocol (See Appendix 2). Recruitment took place through two coordinated pathways. The primary pathway operated within St James's Hospital, where potential participants were identified directly by collaborating clinicians during specialist movement disorder, memory and geriatric psychiatry clinics. Eligible individuals expressing interest were recorded in a secure institutional database and subsequently contacted by the research team to arrange assessment at the Mercer's Institute for Successful Ageing (MISA).

The secondary recruitment pathway involved referrals from collaborating hospital sites via a dedicated Trinity College Dublin research email address and a secure Microsoft Forms system linked to a study-specific QR code. Referring clinicians completed electronic referrals through these platforms, which automatically encrypted identifiable data and transmitted it securely to the study team for screening. This approach ensured standardised data capture, traceable documentation and full compliance with GDPR and institutional governance requirements.

Potential participants were also informed through community outreach and study flyers distributed to participating clinical sites (see Figure 3.1). Referrals were made by treating clinicians, with written permission sought before initial contact by the research team.

Figure 3.2. Study Participant Recruitment Flyer distributed to participating collaborators in movement disorder and memory clinics

Each participant and their nominated co-participant received a detailed Participant Information Leaflet (PIL) and provided written informed consent before participation. General practitioners were notified of their patient's involvement using a standardised GP letter, confirming consent and clarifying that study participation would not affect usual clinical care.

Recruitment materials emphasised voluntary participation and withdrawal rights. All recruitment procedures were conducted in accordance with GCP, GDPR, and the study's approved ethical protocol. Recruitment occurred between December 2023 and May 2025.

Following referral, potential participants completed a structured telephone screen to confirm eligibility and capacity. Those meeting inclusion criteria were invited to attend a single comprehensive in-person assessment at MISA, St James's Hospital. I completed all of the participants assessments, while co-participant interviews were performed by trained clinical researchers under standardised conditions in accordance with the operational protocol described in Section 3.5.

3.3.3 Co-Participants

Each participant attended with a co-participant informant, typically a spouse, family member, or close caregiver aged ≥ 18 years. Co-participants provided collateral information on daily function, behaviour, and neuropsychiatric symptoms using structured instruments including the Bristol Activities of Daily Living Scale (BADLS), the Neuropsychiatric Inventory Questionnaire (NPI-Q) and the Zarit Burden Interview (ZBI).

The final analytic sample comprised 51 participants who met inclusion criteria and completed the full assessment protocol. This sample size was adequate for non-parametric, correlational and exploratory multivariable analyses of frailty, sensory impairment and clinical outcomes.

3.4 Diagnostic Classification and Subgroup Definitions

3.4.1 Diagnostic Framework

Diagnostic classification followed internationally recognised consensus criteria for Lewy body disease and was verified by consultant specialists before enrolment.
All participants were assessed within referring clinical services using the following frameworks:

- **Probable DLB:** Defined according to the Fourth Consensus Report of the DLB. Diagnosis required progressive cognitive decline accompanied by one or more core clinical features: fluctuating cognition, recurrent well-formed visual hallucinations, REM sleep behaviour disorder (RBD) or spontaneous parkinsonism with supportive

evidence from indicative biomarkers such as abnormal dopamine transporter imaging or reduced cardiac MIBG uptake [18].

- **PDD:** Diagnosed using the MDS Task Force Criteria. Criteria required a well-established diagnosis of Parkinson's disease followed by gradual onset of dementia, with impairment in at least two cognitive domains and sufficient severity to interfere with daily living [35].

- **Prodromal DLB (pDLB):** Defined using emerging research criteria for prodromal Lewy body syndromes. Participants met criteria for mild cognitive impairment (MCI) together with one or more core or indicative DLB features suggestive of early α-synucleinopathy [41].
- **Parkinson's Disease with Mild Cognitive Impairment (PD-MCI):** Classified according to MDS Level II (Comprehensive Assessment) Criteria, requiring cognitive decline within the context of Parkinson's disease but without significant loss of functional independence [225].

Diagnostic confirmation was undertaken through multidisciplinary consensus at the referring specialist centre and verified by a senior clinician within the study team. All classifications were documented and cross-checked against inclusion criteria before data analysis.

3.4.2 Operational Definitions

Diagnosis was considered stable at the time of assessment. Participants were enrolled only if their most recent clinical evaluation supported one of the four diagnostic categories above. Clinical features and biomarker evidence were documented through standardised data entry forms (CRFs A to F) to ensure reproducibility.
Each diagnosis was treated as mutually exclusive for analytic purposes: cases with mixed, atypical or indeterminate pathology were excluded to preserve internal validity.

3.4.3 Analytical Diagnostic Grouping and Rationale

For statistical analyses, diagnostic categories were consolidated into two a priori diagnostic groups to reflect the Lewy body disease spectrum:

- **DLB-spectrum group**: Probable DLB + Prodromal DLB
- **PDD-spectrum group:** PDD + PD-MCI

This stratification mirrors current neuropathological models distinguishing cortical-predominant (DLB) from nigrostriatal-predominant (PDD) patterns of α-synuclein pathology [154]. Grouping by phenotype enabled examination of whether frailty and sensory impairment differed across cortical and subcortical disease variants while maintaining adequate statistical power in each group.

Diagnostic classifications were finalised prior to data analysis and remained fixed throughout all stages of statistical testing. Verification was independently performed by a senior clinician, ensuring diagnostic accuracy and reproducibility within the dataset.

3.5. Assessment Protocol and Study Measures

3.5.1 Overview

All participants and co-participants completed a single, structured in-person assessment at the Mercer's Institute for Successful Ageing (MISA), St James's Hospital, Dublin 8. The protocol was pre-specified and harmonised with the European DLB Consortium (E-DLB) recommendations for psychometric and clinical characterisation, with additional domains selected to capture frailty and sensory function.

Data were collected using six standardised Clinical Research Forms (CRFs A to F) designed and validated within the EMERALD Lewy programme. Each CRF corresponded to a defined assessment domain (Table 3.1).

A detailed operational manual was established to ensure uniform administration, data entry, scoring, and reproducibility across participant and co-participant assessments. Completed paper forms were reviewed to confirm accuracy before digitisation for analysis. I designed a digital data entry dictionary to facilitate consistent data recording and statistical analysis (see Section 3.7).

Table 3.1. Clinical Research Forms A to F. CRF structure ensured standardised data capture and reproducibility across core domains including demographic, medical, cognitive, motor, psychosocial and sensory domains.

Form	Domains	Core Assessments	Primary Respondent
A.	**Demographics and Social History**	Age, sex, education, occupation, living arrangement, social deprivation indices	Participant
B.	**Medical Co-Morbidities and Medications**	Comorbidities, medication list, ATC codes, polypharmacy, anticholinergic burden	Participant
C.	**Cognitive Performance and Neuropsychiatric Symptoms**	MDS-UPDRS II–III, Hoehn & Yahr Stage, BADLS, NMSS, Mayo Sleep and Fluctuation Scales	Participant and Co-Participant
D.	**Motor Assessments and Functional Capacity**	UPDRS II & III, BADLS, NMSS, Mayo Sleep Questionnaire, Mayo Fluctuations Scale	Participant and Co-Participant
E.	**Quality of Life and Carer Burden**	QOL-AD, EQ-5D-5L, Zarit Caregiver Burden Assessment	Participant and Co-Participant
F.	**Sensory Function**	Sensory History, HearCheck audiometry, Peek Acuity (LogMAR, vision), Olfactory (UPSIT)	Participant

3.5.2 Demographic and Health History (Form A and B)

Form A documented demographic variables included age, sex, education, occupation, marital status and living arrangement. Socio-economic position was quantified using the Pobal HP Deprivation Index and Irish Census 2022 occupational class categories.

Form B captured medical history across cardiovascular, neurological, endocrine, respiratory, renal, hepatic, musculoskeletal and psychiatric systems.
Each condition was coded on a four-level ordinal scale:
(0 = absent, 1 = recent/active, 2 = remote, 999 = unknown).

Medication data were coded by Anatomical Therapeutic Chemical (ATC) classification, enabling derivation of:

- Polypharmacy (≥ 5 regular drugs = 1),
- Anticholinergic Cognitive Burden (ACB) score, and
- Levodopa Equivalent Dose (LED) for dopaminergic therapy.

These variables provided quantitative inputs for the frailty index and secondary analyses.

3.5.3 Cognitive and Neuropsychiatric Assessments (Form C)

Global cognition was assessed with the Montreal Cognitive Assessment (MoCA), total score out of 30. Supplementary measures included semantic and phonemic verbal fluency, the Degraded Letter Test (DLT) for visual–perceptual attention and the Clinical Dementia Rating (CDR) scale.

Affective and behavioural symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q), capturing both symptom severity and associated caregiver distress.

3.5.4 Motor, Autonomic, and Functional Assessments (Form D)

Motor function was evaluated using the MDS Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III and Hoehn and Yahr stage. Functional independence was rated by co-participants on the Bristol Activities of Daily Living Scale (BADLS).

Non-motor and autonomic domains were profiled using the Non-Motor Symptoms Scale (NMSS), the Mayo Sleep Questionnaire for REM-sleep behaviour disorder and the Mayo Fluctuation Scale for daytime alertness and attentional variability.
Together, these measures captured the multisystem clinical signature of Lewy body disease.

3.5.5 Quality of Life and Caregiver Burden (Form E)

Perceived quality of life was assessed with the Quality of Life in Alzheimer's Disease (QoL-AD) scale (Total out of 52) and the EQ-5D-5L, including the visual analogue scale for self-rated health, scored out of 100.
Caregiver strain was measured using the Zarit Burden Interview (ZBI). Total score was marked out of 88, with higher scores indicated greater carer burden.

3.5.6 Sensory Assessments (Form F)

Sensory assessments included self-reported sensory history and objective sensory testing (Table 3.2). All procedures followed the SENSE-Cog research protocol and were counterbalanced to minimise fatigue.

Table 3.2. Sensory testing for Vision, Hearing and Olfactory domains

Modality	Instrument	Measurement and Classification
Vision	Peek Acuity App	**LogMAR acuity** 2-metre distance. Categorised per WHO 2021 criteria: Normal (≤ 0.3), Mild (> 0.3–0.5), Moderate/Severe (> 0.5).
Hearing	Siemens HearCheck™ Screener	Pure-tone detection at 1 kHz and 3 kHz
Olfactory	University of Pennsylvania Smell Identification Test (UPSIT, /40)	Categorised by normative sex- and age-adjusted norms (normosmia, microsmia or anosmia)

1. Vision:

Visual acuity was measured using the Peek Acuity smartphone application which was calibrated for a two-metre testing distance. The tool has been validated against the Early Treatment Diabetic Retinopathy Study (ETDRS) Logarithm of the Minimum Angle of Resolution (logMAR) chart in a cohort of 600 participants over a six-year period, demonstrating excellent agreement with standard logMAR testing [226, 227].

Testing was conducted in the clinic with participants seated at a standardised distance of two metres from the assessor. Those who normally wore distance spectacles, including bifocals, were instructed to wear them; reading glasses were not permitted. The assessor positioned the smartphone at eye level under consistent lighting conditions.

The Peek Acuity app displays a capital letter E that varies in size and orientation. Participants indicated the direction of the letter and the app automatically adjusted optotype size according to performance until it generated a final logMAR score for each eye (See Figure 3.1). Testing was performed binocularly, followed by monocular testing of each eye separately, with the non-tested eye covered by the participant's palm.

LogMAR scores were categorised as normal (≤ 0.3), mild impairment (0.3 to 0.5), or moderate-to-severe impairment (> 0.5) in accordance with World Health Organization (WHO 2021) visual-impairment thresholds [228, 229]:

Figure 3.3. Peek Acuity smartphone app assessment.

Table 3.3 Classification of Visual Acuity Using WHO logMAR Criteria. Adapted from WHO International Classification of Diseases (ICD-11, 2021) and Peek Acuity validation study.

Category	**logMAR Score (Binocular)**	**Functional Description**
Normal vision	≤ 0.3	No significant impairment in daily activities
Mild impairment	> 0.3 – 0.5	Some difficulty with small print or low contrast
Moderate impairment	> 0.5 – 1.0	Marked difficulty recognising faces or navigating unfamiliar environments
Severe impairment	> 1.0 – 1.3	Restricted visual fields, difficulty in most visual tasks
Blindness	> 1.3	No useful vision

2. Hearing:

Hearing was assessed using the Siemens HearCheck™ screener, a portable handheld device for rapid detection of potential hearing impairment (Figure 3.2) [230].
The instrument has been validated as a reliable and user-friendly screening tool for identifying individuals who may benefit from formal audiological assessment [231, 232].

Testing was performed in a quiet clinic room during the initial assessment session. The device was positioned securely over each ear to ensure an adequate acoustic seal. Pure-tone stimuli were presented at 1 kHz and 3 kHz, each delivered twice per ear. Participants signalled detection of each tone by raising a hand.

Responses were recorded as the number of tones detected with maximum number of 6 per ear (Figure 3.2). Failure to detect one or more tones in either frequency band in both ears was coded as hearing impairment. Results were summarised as normal hearing (6/6 tones detected), possible mild impairment (4 or 5/6), or probable hearing impairment (≤ 3/6) according to Siemens user-manual guidance (Table 3.4).

Figure 3.4. Siemens HearCheck™ Device

The lower the score, the more likely the patient will benefit from a hearing aid. Please see below an example of how the results should be recorded.

	No. of tones heard in the 1000Hz test		No. of tones heard in the 3000Hz test		Total no. of tones heard PER EAR
Left ear	2	+	1	=	3

Results

If the patient can hear:

All 6 tones	3, 4 or 5 tones	1 or 2 tones	0 tones
Patient is unlikely to need further hearing assessment. May be discharged after an explanation and advice.	Patient is likely to have a hearing difficulty and would benefit from an assess and fit hearing aid product (e.g. open ear tip or instant fit tip).	Refer patient for instant fit or for assessment and fitting in two sessions.	Refer patient for an assessment in a clinic that can appropriately assess severe hearing impairment.

Score the right ear in exactly the same way.

Figure 3.5. Example of HearCheck™ assessment results recording.

Table 3.4. Interpretation of Siemens HearCheck™ Screening Results

Score per Ear	Interpretation	Recommended Action
6 / 6	Hearing within normal limits	No further assessment required
4 – 5 / 6	Possible mild hearing impairment	Review clinical history and monitor
0 – 3 / 6	Probable hearing impairment	Refer for formal audiology evaluation

Source: Siemens *HearCheck™ Screener User Manual* [230].

3. Olfaction:

Olfactory function was measured using the University of Pennsylvania Smell Identification Test (UPSIT, Sensonics International), a 40-item standardised "scratch-and-sniff" test widely recognised as the most reliable quantitative measure of olfactory performance. The UPSIT demonstrates excellent test–retest reliability (r = 0.94) and strong sensitivity for detecting hyposmia in neurodegenerative disorders [233, 234].

Testing followed the manufacturer's standard protocol. Participants completed four booklets, each containing ten microencapsulated odour stimuli. For each item, they selected one of four response options in a forced-choice format, yielding a total score out of 40 (see Figure 3.4)

Raw scores were converted to age- and sex-adjusted normative categories using reference data provided by Sensonics International. Participants were classified as:

- Normosmia: within or above the normal range
- Mild or moderate microsmia: reduced odour identification relative to norms
- Severe microsmia or anosmia: profound or complete olfactory loss

Testing was conducted face-to-face under controlled environmental conditions with adequate ventilation and minimal background odours. All sensory measures, including the UPSIT, were administered according to the SENSE-Cog operational protocol, with test order counterbalanced to minimise fatigue and attentional bias.

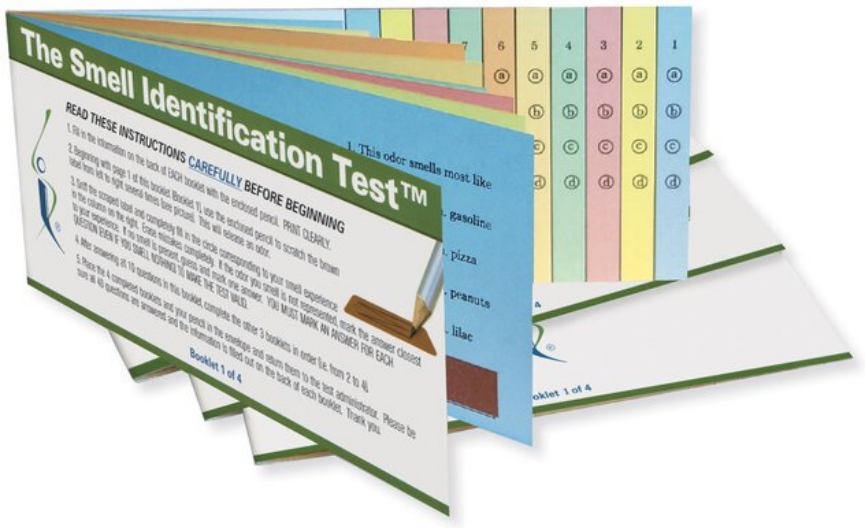

Figure 3.6. 40-item University of Pennsylvania Smell Identification Test (Sensonics International, Haddon Heights, NJ).

Table 3.4. Classification of Olfactory Function Using UPSIT Normative Data

UPSIT Raw Score (0 – 40)	**Interpretation**	**Equivalent Category**
≥ 34 (Male) / ≥ 35 (Female)	Normal olfactory function	Normosmia
26–33 (Male) / 27–34 (Female)	Mild microsmia	Mild smell loss
19–25 (Male)/ 20–26 (Female)	Moderate microsmia	Moderate smell loss
10–18 (Male) / 11–19 (Female)	Severe microsmia	Severe smell loss
≤ 9 (Male) / ≤ 10 (Female)	Anosmia	Complete smell loss

Source: *Sensonics International, University of Pennsylvania Smell Identification Test Manual and Normative Olfactory Data (Doty et al, 1984, 2015)* [234, 235]

3.5.7 Data Integration and Coding

All data were first recorded on paper CRFs, reviewed at source for completeness, and subsequently digitised. Missing values were coded as 999 (Unknown) to preserve audit traceability.

Performance-based measures (e.g. MoCA, UPSIT) and informant scales (e.g. BADLS, ZBI) were integrated into a unified SPSS dataset following the variable definitions in the Data Entry Dictionary. This dataset provided the foundation for the Lewy Body Dementia Frailty Index (LBD-FI) development described in Section 3.6.

3.6. Development of the Lewy Body Dementia Frailty Index (LBD-FI)

3.6.1 Conceptual Framework

The Lewy Body Dementia Frailty Index (LBD-FI) was developed in accordance with the cumulative deficit model, which conceptualises frailty as the proportion of age-related health deficits accumulated across multiple physiological and functional systems [54]. This framework offers a quantitative approach to measuring biological vulnerability, integrating diverse indicators of health deterioration into a single continuous score.

Applied to the clinical context of Lewy body disease, the LBD-FI captures the multisystem nature of this disorder through inclusion of variables reflecting motor, cognitive, neuropsychiatric, autonomic and functional domains. The objective was to generate a single, reproducible measure of cumulative physiological vulnerability and functional decline.

Deficits were selected based on three predefined selection criteria:

- Established association with ageing or disease progression.
- Representation of multiple physiological and functional systems.
- Low rates of missing data (< 20%) and absence of significant floor or ceiling effects.

Each deficit represented a clinically meaningful deviation from normal health rather than a diagnostic entity. The index thereby quantifies overall physiological vulnerability rather than isolated symptoms.

3.6.2 Deficit Selection

Variable selection followed a structured domain-based approach. Thirty four variables were extracted from the SENSE-Cog Lewy dataset after detailed evaluation of completeness, clinical relevance, and construct validity. Each variable corresponded to a binary indicator of health deficit across seven domains: comorbidity, medication use, mood, motor, autonomic, non-motor, sleep fluctuation, function and neuropsychiatric status.

All variables were derived from validated clinical instruments (MoCA, HADS, NMSS, UPDRS, BADLS, NPI-Q, QoL-AD) and coded according to pre-specified thresholds reflecting clinically significant deviation. Sensory variables (UPSIT, Peek Acuity, HearCheck) were analysed separately and intentionally excluded from the frailty index. Although sensory impairment is recognised as an important contributor to vulnerability in older adults, inclusion of these variables within the LBD-FI would have introduced structural overlap between the frailty construct and the sensory analyses described in Section 3.8.

In accordance with cumulative deficit methodology, the index was designed to capture multidomain physiological and functional vulnerability while preserving conceptual independence between frailty and sensory performance. This separation minimises the risk of circular inference and ensures that associations observed between sensory impairment and the LBD-FI reflect relationships between analytically distinct constructs rather than shared component variables.

A valid LBD-FI score required at least 80 per cent complete data (≥ 28 of 34 variables).

The final composition of the LBD-FI is summarised in Table 3.5.

Table 3.5. Composition of the Lewy Body Dementia Frailty Index (LBD-FI)

Domain	Variables Included
Comorbidities and Medical History (10 items)	1. Hypertension 2. Diabetes Mellitus 3. Stroke or TIA 4. Atrial Fibrillation or Arrhythmia 5. History of IHD/Angina/MI 6. Congestive Heart Failure 7. Peripheral Vascular Disease 8. Chronic Kidney Disease 9. Asthma or COPD 10. Cancer (Primary or Secondary)
Medication Use (1 item)	11. Polypharmacy (≥ 5 concurrent medications)
Mood Symptoms (2 items)	12. Anxiety (HADS Anxiety score ≥ 11) 13. Depression (HADS Depression score ≥ 11)
Motor Symptoms (7 items)	**UPDRS Part II:**
	14. Speech Difficulties ≥3 15. Swallowing Difficulties ≥3 16. Tremor Impact ≥3 17. Turning in Bed Difficulties ≥3
	UPDRS Part III:
	18. Rigidity ≥3 19. Bradykinesia ≥3 20. Gait Difficulties ≥3
Autonomic and Non-Motor Symptoms: MDS Non-Motor Symptoms Scale **(6 items)**	21. Urinary Urgency Severity × Frequency ≥4 22. Constipation Severity × Frequency ≥4 23. Light-headedness Severity × Frequency ≥4 24. Fainting Severity × Frequency ≥4 25. Fatigue Severity × Frequency ≥4 26. Difficulty staying asleep (sleep fragmentation) Severity × Frequency ≥4
Sleep and Fluctuation-Related Features (8 items)	**Mayo Sleep Questionnaire (5 items):**
	27. REM Sleep Behaviour Disorder (Acting out dreams) 28. Leg jerks or Restless legs during sleep 29. Breathing Pauses During Sleep 30. Snorting or Choking Themselves Awake 31. Sleepwalking or Unusual Nocturnal Behaviours
	Mayo Fluctuation Scale (3 items)
	32. Daytime Drowsiness or Lethargy 33. Disorganised Flow of Ideas (Cognitive fluctuations) 34. Staring Spells

3.6.3 Deficit Coding and Scoring

Each variable was coded as 0 (no deficit) or 1 (deficit present).

Ordinal symptom measures were dichotomised using validated clinical cut-offs.

Continuous scales (e.g. HADS, QoL-AD subscales) were converted into binary form at established thresholds.

The frailty index was computed for each participant as the ratio of deficits present to the total number of possible deficits:

$$\text{LBD-FI} = \frac{\text{Number of deficits present}}{\text{Total number of assessed variables (Maximum = 34)}}$$

Scores ranged from 0 (no deficits) to 1 (all measured variables abnormal). Higher values indicated greater frailty burden.

For descriptive analyses, scores were divided into tertiles representing low, intermediate, and high frailty categories. A secondary threshold of ≥ 0.25 was used to denote clinically significant frailty, consistent with prior frailty index literature.

3.6.4 Validation and Robustness Testing and Data Integration

Construct validity was assessed by examining correlations between LBD-FI scores and chronological age using Spearman's rank correlation coefficient (ρ). A positive association was expected ($\rho > 0$), reflecting the established relationship between deficit accumulation and biological ageing. The sign of ρ was interpreted in accordance with prespecified reporting conventions, with positive coefficients indicating higher frailty with advancing age. Score distributions were inspected visually (histograms and Q-Q plots) and formally tested for normality using the Shapiro-Wilk statistic.

As anticipated for a cumulative-deficit index, the distribution was right-skewed, indicating that most participants accumulated a moderate number of deficits while a smaller subset exhibited extensive frailty.

Internal consistency across the 34 items was evaluated using Cronbach's α, with coefficients ≥ 0.75 considered acceptable. Item-deletion analysis confirmed that removal of any single variable altered the mean LBD-FI by < 1%, demonstrating stability and absence of overweighting by specific items.

Sensitivity analyses examined the impact of key modelling assumptions, including:

- alternative thresholds for polypharmacy (≥ 4 vs ≥ 5 regular medications),
- exclusion of participants with > 20% missing frailty data, and
- subgroup stratification by diagnostic spectrum (DLB-spectrum group vs PDD-spectrum group) and by sex.

These tests confirmed that index distribution and rank order were consistent across analytical specifications, supporting robustness and reproducibility.

All variables were coded, labelled, and cross-referenced in IBM SPSS Statistics v29.0.2, following a structured data dictionary that documented variable names, coding logic, and transformation rules. The final dataset contained 34 binary variables, one continuous composite LBD-FI score, and categorical derivatives for tertiles and for the 0.25 threshold classification.

These data formed the foundation for the construct- and predictive-validity analyses presented in Chapter 4, where the LBD-FI is evaluated as a multidimensional indicator of systemic vulnerability in Lewy body dementia.

3.7 Data Management and Quality Assurance

All study data were initially recorded on paper-based Clinical Research Forms by the author, assisted trained research personnel during or immediately after each in-person

assessment. The CRFs were pre-piloted, version controlled and designed to minimise ambiguity through structured fields, embedded prompts and predefined coding schemes aligned with study data dictionary.

Each completed CRF was reviewed at source for accuracy and internal consistency, with cross-verification against clinical documentation and co-participant responses where applicable. Physical copies were stored in locked filing cabinets within our restricted-access research office at St James's Hospital. Periodic audits by the study coordinator confirmed compliance with standard operating procedures and ensured prompt resolution of missing or discrepant entries.

Following verification, data were digitised using a double-entry protocol to minimise transcription error. Manual data entry was performed in Microsoft Excel under password protection, accessible only to authorised study personnel. Discrepancies between entries were identified via conditional-formatting and logic checks, then resolved by consensus review of the original CRFs.

All participant identifiers were pseudonymised at source using unique alphanumeric study codes. The linkage key was stored separately in an encrypted, access-restricted file on institutional servers. Electronic files were maintained on secure servers at St James's Hospital, with automatic encrypted backups conducted on a scheduled basis.

Once double entry and verification were complete, datasets underwent systematic data cleaning. Range and logic checks were applied to detect outliers, improbable values, or code inconsistencies. Validated data were then exported into IBM SPSS Statistics v29.0.2 for analysis. The final analysis dataset contained only de-identified variables, ensuring complete separation between participant identity and analytical data.

All procedures adhered to the General Data Protection Regulation (EU 2016/679), the Data Protection Act 2018, and institutional governance policies of St James's Hospital and Trinity College Dublin.

Quality assurance was maintained through documented audit trails, version control logs, and systematic integrity checks throughout all stages of data handling, ensuring full transparency and reproducibility of the dataset used for statistical analysis.

3.8. Statistical Analysis Plan

All statistical analyses were performed using IBM SPSS Statistics (Version 29.0.2).
I designed and created all of the figures and schematic illustrations included in this thesis using BioRender (BioRender.com), unless otherwise stated.

The analytical framework was designed to test the study's core objectives:

1. Validate the newly developed Lewy Body Dementia Frailty Index (LBD-FI);
2. Examine its association with key clinical outcomes including cognitive, functional, neuropsychiatric, quality of life and caregiver outcomes;
3. Explore relationships between frailty and objectively measured sensory impairments; and
4. Evaluate whether combined modelling of frailty and sensory domains improved prognostic precision.

All statistical tests were two-tailed, with $p < 0.05$ considered statistically significant. P-values are reported to three decimal places, with $p < 0.001$ presented where appropriate.
Where relevant, clinical relevance and effect magnitude were emphasised over statistical significance alone.

3.8.1 General Procedures and Preprocessing

Data integrity and completeness were verified before analysis. Range checks, internal logic tests, and inspection of missingness were undertaken across all variables derived from CRFs A to F. Outliers were identified through boxplot inspection and cross-checked against source documentation. Implausible values were corrected or, if unresolved, coded as missing. Participants with more than 20% missing data for frailty items were excluded and no data imputation was applied.

All categorical variables were summarised as frequencies (n, %); continuous variables as means ± standard deviation (if normally distributed) or medians with interquartile ranges (if skewed). Normality was evaluated using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots.

3.8.2 Research Questions and Analytical Framework

The statistical analysis was structured around the study's four core research questions. Analytical methods were selected based on variable measurement levels, distributional properties and sample size constraints. Across all analyses, descriptive statistics, bivariate associations and adjusted models were systematically applied to quantify clinical relationships. For all correlation analyses, both the coefficient (ρ) and corresponding p-value were reported, with interpretation aligned to the sign and magnitude of ρ.

Research Question 1: Frailty Distribution and Subtype Differences

- Distribution of LBD-FI scores summarised using medians, interquartile ranges, and frequency histograms.
- Diagnostic group comparisons (DLB-spectrum group vs PDD-spectrum group) performed using Mann-Whitney U tests.
- Correlation between frailty and age examined using Spearman's rank correlation coefficient (ρ), assessing construct validity of the LBD-FI.

Research Question 2: Frailty and Clinical Outcomes

- Associations between frailty severity and clinical outcomes were evaluated using Spearman's rank correlation coefficient (ρ) for cognition (MoCA total), functional independence (BADLS), neuropsychiatric symptoms (NPI-Q severity), quality of life (EQ-5D-5L utility, QoL-AD) and caregiver burden (Zarit Burden Interview).
- Regression models examining clinical outcomes were adjusted for age and sex (frailty analyses) and for age and diagnosis (sensory analyses).

- Linearity, residual normality and equality of variance were assessed using residual plots and diagnostic tests.

Research Question 3: Frailty and Sensory Impairment

- Relationships between LBD-FI and continuous sensory measures were assessed using Spearman's rank correlation coefficient (ρ): olfaction (UPSIT), vision (Peek logMAR) and hearing (HearCheck tone detection).
- Comparisons of frailty tertiles across sensory scores used Kruskal-Wallis tests, with post-hoc Mann-Whitney U tests when appropriate.
- Categorical sensory impairment prevalence compared across frailty levels using Fisher's Exact tests.

Research Question 4: Sensory Impairment and Clinical Outcomes

- Associations between sensory measures and clinical outcomes were examined using bivariate correlations and linear regression models.
- Stepwise adjustment incorporated age, diagnosis, and subsequently LBD-FI to determine whether sensory impairment independently predicted cognitive, functional or quality of life outcomes.
- Sensory measures were analysed both as continuous variables (UPSIT, logMAR, HearCheck) and as dichotomous indicators (impaired vs non-impaired).
- Model comparison tested whether inclusion of sensory variables improved explanatory power beyond frailty alone.

3.8.3 Exploratory and Sensitivity Analyses

Exploratory analyses evaluated:

- Subgroup differences between prodromal (pDLB, PD-MCI) and dementia-stage (DLB, PDD) participants.
- Interaction effects (frailty x sensory, frailty x diagnosis) in regression models.
- Alternative polypharmacy thresholds (≥ 4 vs ≥ 5 regular medications).

Model diagnostics included variance inflation factors (VIF < 2) for collinearity, Q-Q plots for residual normality, and Breusch-Pagan tests for heteroscedasticity.
Where multiple comparisons were made across secondary outcomes, the Benjamini-Hochberg false discovery rate (FDR < 0.05) procedure was applied.

3.8.4 Reporting and Interpretation

All analyses were performed on fully anonymised datasets following data verification. Analytical procedures were documented to ensure transparency and reproducibility.

Results are reported in accordance with STROBE guidelines for cross-sectional studies, with emphasis on effect direction and magnitude (ρ, β coefficients, 95% confidence intervals and p-values) rather than statistical significance alone. For all correlation analyses, the sign of ρ is reported explicitly, and the narrative description of association (positive or negative) corresponds precisely to the coefficient sign. P-values are reported consistently to three decimal places, with $p < 0.001$ presented where appropriate.

Procedures complied with the General Data Protection Regulation (EU 2016/679), the Data Protection Act 2018 and institutional governance requirements.

3.9 Methods Summary

This chapter has outlined the design, governance, recruitment, assessment procedures, and analytical framework of the SENSE-Cog Lewy study forming the empirical basis of my doctoral thesis.

Participants with dementia with Lewy bodies and Parkinson's disease dementia underwent standardised clinical, functional, neuropsychiatric and sensory assessments, from which a multidomain Lewy Body Dementia Frailty Index (LBD-FI) was developed using the cumulative deficit model.

Data handling adhered to ethical and data-protection standards, and analyses were structured to evaluate the construct and predictive validity of the LBD-FI, its relationship

with sensory impairment, and their combined influence on cognition, function and quality of life.

The next chapter presents the study results, beginning with validation and descriptive analyses of the LBD-FI.

Chapter 4. Frailty in Lewy Body Dementia (Results I)

This chapter addresses my Research Questions 1 and 2, examining the prevalence and distribution of frailty within the LBD cohort and evaluating its association with clinical outcomes across cognitive, functional, neuropsychiatric and quality of life domains.

4.1. Participant Characteristics

Fifty-one participants with clinically confirmed LBD were included (n = 51). Demographic and clinical characteristics, stratified by diagnostic group, are summarised in Table 4.1. The cohort was predominantly male and older (mean age 73.9 years, SD 6.5; median symptom duration 58 months, IQR 42 – 96).

Participants were classified into two diagnostic groups representing the clinical spectrum:

- DLB-spectrum group: probable DLB and prodromal DLB (n = 32).
- PDD-spectrum group: Parkinson's disease dementia (PDD, n = 10) and Parkinson's disease with mild cognitive impairment (PD-MCI, n = 9) (n = 19).

Comorbidity burden was high, with hypertension was present in 62.7%, cardiovascular disease in 31.4%, and diabetes mellitus in 9.8% of participants. Polypharmacy (≥ 5 regular medications) was highly prevalent, affecting 82.4% of the cohort.

The mean Montreal Cognitive Assessment (MoCA) score was 21.3 (SD 4.6). Neuropsychiatric symptoms, functional limitations, reduced quality of life, and high caregiver burden (Zarit Burden Interview) were common across diagnostic groups, consistent with a clinically vulnerable LBD population with multidomain deficits.

Table 4.1. Participant Characteristics by Diagnostic Group (n = 51)

Demographics	**Total** (n = 51)	**DLB-spectrum group** (n = 32)	**PDD-spectrum group** (n = 19)	**p-value** (DLB vs PDD)
Age in Years *Median (IQR)*	74 (70 – 78)	76 (72 – 79)	70 (67 – 75)	**0.029** [a]
Range	58 – 83	58 – 83	61 – 82	
Mean ± SD	73.9 ± 6.5	74.9 ± 6.3	72.1 ± 6.8	
Male, *n (%)*	38 (74.5%)	23 (71.9%)	15 (78.9%)	0.497 [b]
Symptom Duration (Months)	58 (42 – 96)	42 (24 – 72)	72 (48 – 120)	**0.021** [a]
Range	4 – 192	12 – 144	4 – 192	
Mean ± SD	68.7 ± 46.3	57.1 ± 39.5	86.5 ± 52.1	
LBD Frailty Index, 0 – 1 *Median (IQR)*	0.235 (0.147 – 0.294)	0.235 (0.147 – 0.294)	0.220 (0.147 – 0.272)	0.807 [a]
Range	0.030 – 0.441	0.057 – 0.441	0.030 – 0.441	
Mean ± SD	0.229 ± 0.101	0.235 ± 0.097	0.229 ± 0.105	

Values presented as median (IQR); range; mean ± standard deviation, unless specified.

[a] Mann-Whitney U Test (continuous variables)

[b] Fisher's Exact Test (categorical variables).

Bolded p-values indicate statistical significance **($p < 0.05$)**.

4.2. Development of the Lewy Body Dementia Frailty Index

As outlined previously, I developed the Lewy Body Dementia Frailty Index (LBD-FI) using Rockwood's deficit accumulation frailty model.

Thirty-four binary clinical variables were included, encompassing chronic comorbidities, medication burden, motor and non-motor symptoms, mood disturbance, autonomic and

sleep dysfunction and cognitive fluctuations. Each variable was coded 0 (deficit absent) or 1 (deficit present).

The final LBD-FI score was calculated as the sum of deficits present divided by the total number of applicable variables for each participant, to a maximum of 34. The final index value was computed as:

$$\text{LBD-FI} = \frac{\text{Number of deficits present}}{34}$$

A minimum of 80% data completeness required for frailty index calculation.
The resulting scores ranged from 0.00 (no deficits) to 1.00 (all deficits present) with higher scores reflecting greater frailty burden.
Frailty index construction and scoring adhered to published guidelines for frailty index development in neurodegenerative populations, ensuring conceptual and methodological validity.

4.3. Distribution and Descriptive Statistics of the LBD-FI

LBD-FI scores across the 51 participants in the cohort ranged from 0.030 to 0.441. The median was 0.235 (IQR 0.147 – 0.294). Figure 4.1 shows the distribution, and Table 4.2 summarises scores overall and by diagnostic group. Median, range and mean values were comparable between the DLB-spectrum and PDD-spectrum groups, with no significant difference (Mann-Whitney U, $p = 0.807$).

Participants were categorised into low, moderate and high frailty tertiles. The distribution of diagnostic groups across tertiles is shown in Table 4.3.
DLB-spectrum group and PDD-spectrum group participants were proportionally represented across tertiles and between-group differences were not significant ($\chi^2(2) = 0.89$, $p = 0.641$). These comparisons are descriptive and hypothesis generating given the sample size.

Table 4.2. Summary Statistics of LBD Frailty Index Scores by Diagnostic Group

Group	*Median (IQR)*	*Range*	*Mean ± SD*
Full Cohort (n = 51)	0.235 (0.147 – 0.294)	0.030 – 0.441	0.229 ± 0.101
DLB-spectrum group (n = 32)	0.235 (0.147 – 0.294)	0.057 – 0.441	0.235 ± 0.097
PDD-spectrum group (n = 19)	0.214 (0.143 – 0.264)	0.030 – 0.441	0.229 ± 0.105
p-value [a]	0.807		

[a] Group comparison (DLB-spectrum vs PDD-spectrum groups) by Mann-Whitney U

Table 4.3. Distribution of LBD Frailty Index Tertiles by Diagnosis Group [b]

Frailty Tertile	**Total** (n, %)	**DLB-spectrum group** (n, %)	**PDD-spectrum group** (n, %)
Low Frailty	16 (32%)	10 (62.5%)	6 (37.5%)
Moderate Frailty	19 (38%)	11 (57.9%)	8 (42.1%)
High Frailty	15 (30%)	11 (73.3%)	4 (26.7%)
Total [a]	50 (100%)	32 (64%)	18 (36%)

[a] One case was excluded from tertile analyses due to missing frailty index data.

[b] Group comparison by frailty tertile using Pearson's Chi-square test: $\chi^2(2) = 0.89$, $p = 0.641$.

Frailty scores demonstrated a moderately right-skewed distribution, with the majority of participants clustered between 0.20 and 0.30. There was no evidence of bimodal distribution, suggesting a continuous spectrum of frailty severity within the cohort.

When stratified by diagnostic group, frailty scores were broadly comparable. Median LBD-FI scores were 0.24 in the DLB-spectrum group and 0.22 in the PDD-spectrum group ($p = 0.807$), indicating no significant difference in frailty burden by clinical diagnosis. These findings confirm that frailty is a prevalent and clinically meaningful feature across the LBD spectrum, regardless of diagnostic subtype.

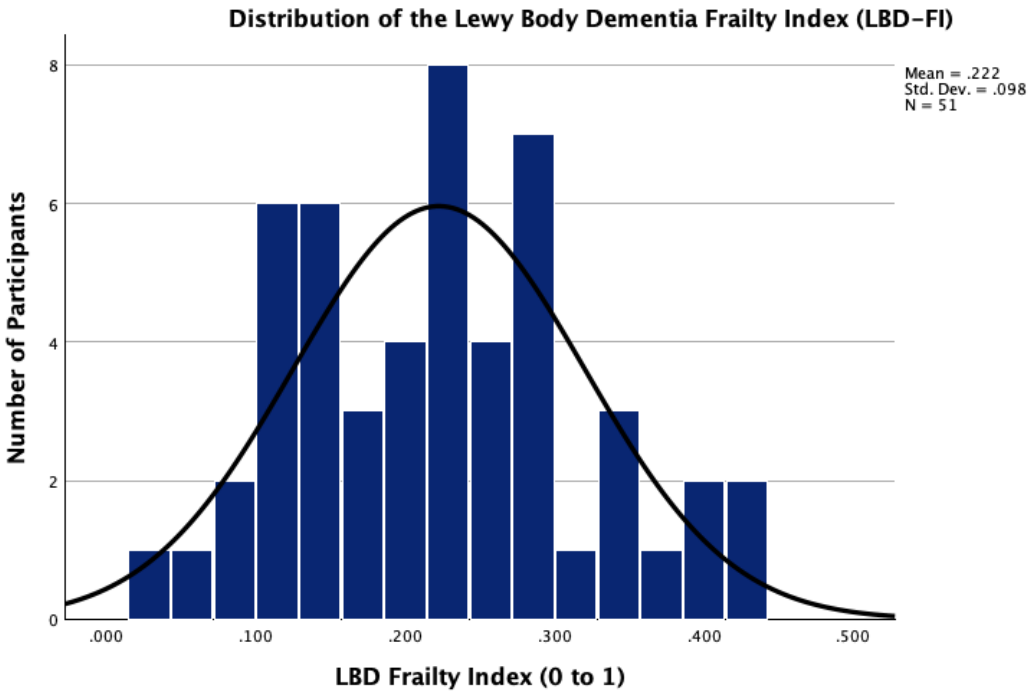

Figure 4.1. Distribution of Lewy Body Dementia Frailty Index (LBD-FI) Scores. Histogram illustrating the distribution of LBD-FI scores for the full cohort (n = 51). Scores ranged from 0.03 to 0.44, with a mean of 0.229 (SD 0.10). The distribution was unimodal and slightly right-skewed, indicating that most participants demonstrated mild to moderate frailty levels across the cohort.

4.4. Associations Between Frailty and Clinical Outcomes

4.4.1 Cognitive, Neuropsychiatric, Functional and Quality of Life Associations

Spearman's rank correlation coefficients are shown in Table 4.4. Higher LBD-FI scores correlated with greater neuropsychiatric symptom burden (NPI-Q severity, ρ = 0.422, p = 0.003) and higher caregiver burden (Zarit total, ρ = 0.621, p < 0.001), and with lower health related quality of life (EQ-5D-5L utility, ρ = −0.369, p = 0.008).

Associations with global cognition (MoCA) and functional independence (BADLS) were not significant (MoCA ρ = 0.067, p = 0.641; BADLS ρ = 0.194, p = 0.186).

Frailty was most strongly associated with neuropsychiatric symptoms, caregiver burden and lower quality of life, with no significant correlations observed with global cognition or functional independence.

Table 4.4. Spearman's rank correlation coefficients (ρ) between LBD-FI and clinical outcome

Clinical Outcomes	Spearman's ρ	p-value
MoCA total score	0.067	0.641
NPI severity total	0.422	**0.003**
BADLS total	0.194	0.186
EQ-5D-5L utility score	−0.369	**0.008**
QoL-AD total score (Participant rated)	−0.212	0.136
Zarit total score (Caregiver burden)	0.621	**< 0.001**

ρ = Spearman's rank correlation coefficient.

Bolded p-values indicate statistical significance **(p < 0.05)**.

4.4.2 Regression Analyses: Adjusted Associations

Linear regression models, as demonstrated in Table 4.5, confirmed the associations observed in bivariate analyses.

In adjusted models accounting for age and sex:

- Caregiver burden: Frailty remained a strong independent predictor of higher Zarit total scores (β = 48.76 [95 % CI 28.65, 68.85], p < 0.001).
- Neuropsychiatric symptoms: Frailty predicted greater NPI severity (β = 24.84 [95 % CI 5.73, 43.96], p = 0.012).
- Health-related quality of life: Frailty was negatively associated with EQ-5D-5L utility (β = −239.69 [95 % CI −1 187.3, 707.0]), though this relationship did not reach statistical significance (p = 0.611).

Table 4.5. Linear Regression Models: LBD Frailty Index as a Predictor of Clinical Outcomes (Univariable and Adjusted for Age and Sex)

Outcome	Model Type	Unstandardised β (95% CI)	Adjusted R^2	p-value
MoCA total score	Univariable	4.17 (−9.48, 17.81)	−0.01	0.542
	Adjusted (age, sex)	8.82 (−3.94, 21.59)	0.20	0.168
NPI severity total	Univariable	26.84 (8.14, 45.55)	0.14	**0.005**
	Adjusted (age, sex)	24.84 (5.73, 43.96)	0.13	**0.012**
BADLS total	Univariable	20.52 (−9.25, 50.29)	0.02	0.176
	Adjusted (age, sex)	18.37 (−13.31, 50.06)	−0.01	0.250
EQ-5D-5L utility score	Univariable	−366.97 (−1263.5, 531.6)	−0.01	0.419
	Adjusted (age, sex)	−239.69 (−1187.3, 707.0)	−0.01	0.611
Zarit total score	Univariable	46.68 (26.86, 63.85)	0.33	**< 0.001**
	Adjusted (age, sex)	48.76 (28.65, 68.85)	0.31	**< 0.001**

β = unstandardised regression coefficient, interpreted as change in outcome per 0.1 unit increase in LBD-FI. 95% CI = confidence interval. Adjusted models include participant age (years) and sex (male/female) as covariates. Adjusted R^2 reflects model explanatory power after correction for covariates.

Bolded p-values indicate statistical significance **(p < 0.05)**.

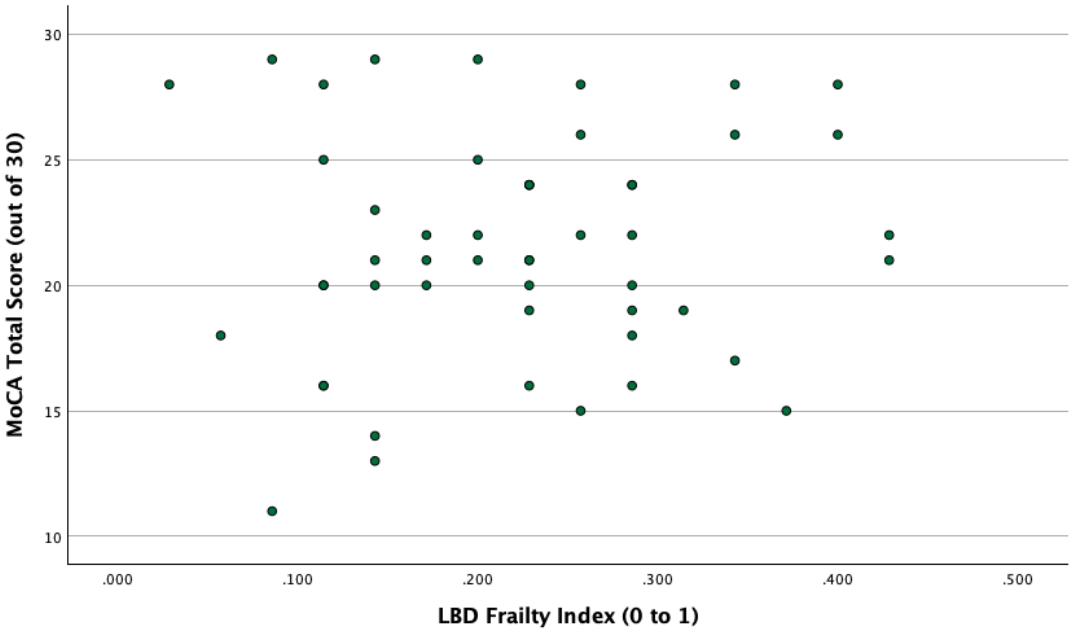

Figure 4.2. Association between frailty (LBD-FI) and global cognitive performance (MoCA total score). No significant association was observed between frailty and global cognition (Spearman's ρ = 0.07, p = 0.64).

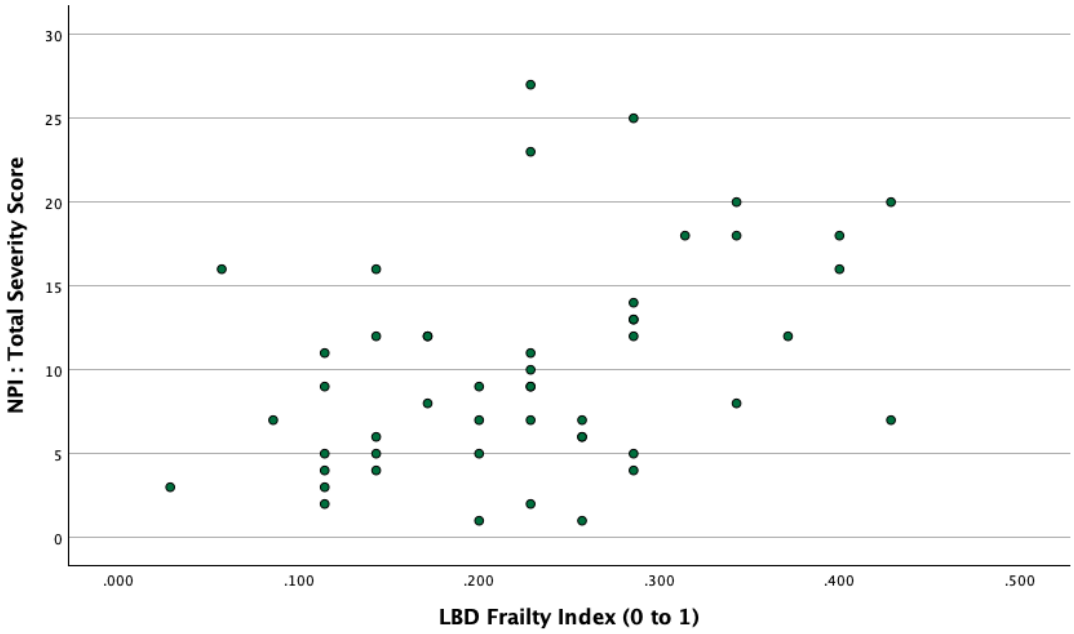

Figure 4.3. Association between frailty (LBD-FI) and neuropsychiatric symptom burden (NPI Total Severity Score). Higher frailty scores were significantly associated with greater neuropsychiatric symptom severity (Spearman's ρ = 0.42, p = 0.003).

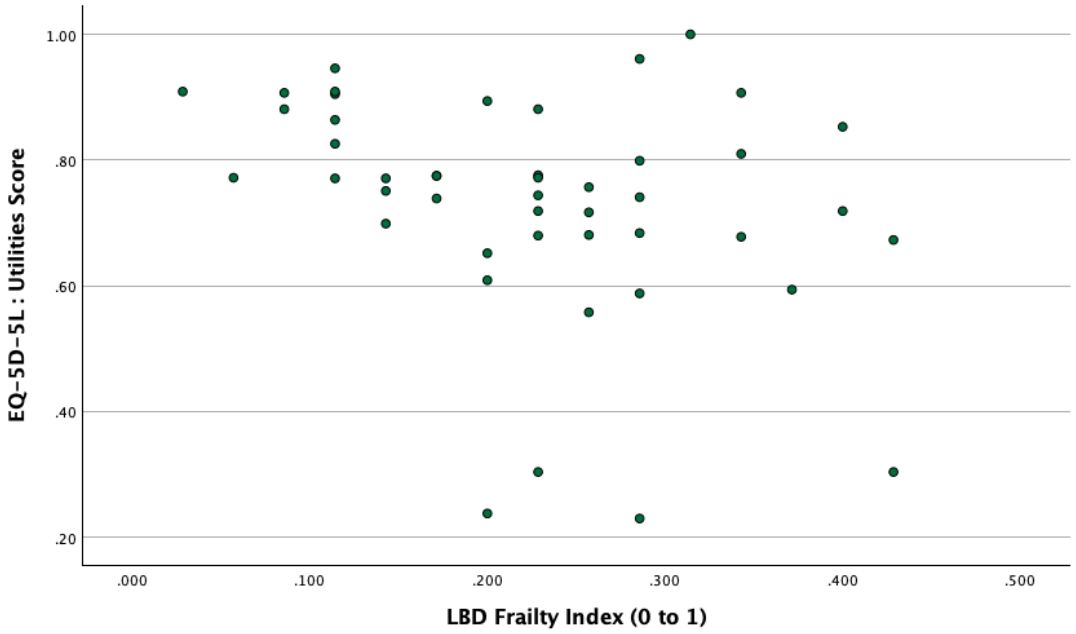

Figure 4.4. Association between frailty (LBD-FI) and health-related quality of life (EQ-5D-5L utility score). Higher frailty was significantly associated with lower EQ-5D-5L utility scores (Spearman's ρ = –0.37, p = 0.008).

No significant association was observed between frailty and MoCA or BADLS in adjusted models. Scatterplots of these associations are presented in Figure 4.2 to 4.4, illustrating the relationships between LBD-FI and key clinical outcomes.

4.5. Frailty Differences by Clinical Subtypes

LBD Frailty Index scores were compared across diagnostic subgroups of DLB-spectrum and PDD-spectrum groups. As shown in Table 4.6 and Figure 4.5, median LBD-FI values were 0.235 (IQR 0.147–0.294) in the DLB-spectrum group and 0.220 (IQR 0.147 – 0.272) in the PDD-spectrum group. The difference was not statistically significant (Mann-Whitney U = 280.5, p = 0.807).

Frailty values ranged from 0.057 to 0.441 in the DLB-spectrum group and 0.030 to 0.441 in the PDD-spectrum group. Mean scores were 0.235 ± 0.097 and 0.229 ± 0.105, respectively. These findings indicate that frailty severity was broadly comparable

between diagnostic groups, with no evidence of systematic differences in frailty distribution across the clinical spectrum of Lewy body disease.

The similarity in frailty profiles supports the interpretation that frailty represents a cumulative multidomain construct inherent to the Lewy body disease process rather than a feature confined to either DLB-spectrum or PDD-spectrum groups.

Table 4.6. LBD Frailty Index Scores by Diagnostic Groups (DLB-spectrum vs PDD-spectrum groups)

Diagnostic Group	***n***	***Median (IQR)***	***Range***	***Mean ± SD***
DLB-spectrum	32	0.235 (0.147 – 0.294)	0.057 – 0.441	0.235 ± 0.097
PDD-spectrum	19	0.220 (0.147 – 0.272)	0.030 – 0.441	0.229 ± 0.105
Group comparison [a]		*U* = 280.5		p = 0.807
[a] Mann-Whitney U test				

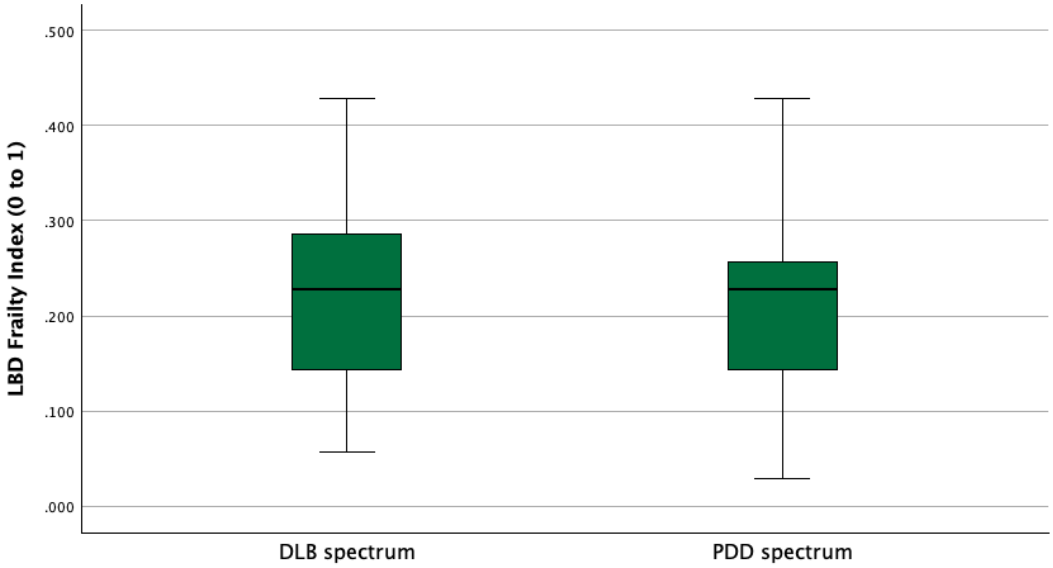

Figure 4.5. Comparison of LBD Frailty Index scores between DLB-spectrum and PDD-spectrum groups. Median frailty scores were similar across groups (DLB-spectrum 0.24 vs PDD-spectrum 0.22; p = 0.807), indicating no significant difference in frailty burden across the LBD spectrum.

4.6. Preliminary Frailty and Sensory Correlations

Preliminary analyses explored associations between frailty parameters and sensory impairment (Table 4.7). Olfactory performance (UPSIT total score) showed a weak but statistically significant inverse correlation with frailty (ρ = −0.299, p = 0.041). Hearing (ρ = −0.169, p = 0.245) and vision (ρ = 0.139, p = 0.341) were not significantly correlated with frailty.

Collectively, these findings suggest that sensory deficits, particularly olfactory impairments, may contribute modestly to frailty vulnerability in LBD. Although preliminary, the pattern of associations points to a potential sensory dimension of the frailty phenotype warranting more detailed investigation. Comprehensive sensory-frailty analyses are presented in Chapter 5.

Table 4.7. Spearman's rank correlation coefficient between LBD Frailty Index and objective sensory scores

Sensory Domain	Spearman's ρ	p-value
Hearing *(HearCheck combined score)*	−0.169	0.245
Vision *(LogMAR, binocular)*	0.139	0.341
Olfaction *(UPSIT score)*	−0.299	**0.041**
ρ = Spearman's rank correlation coefficient. **Bolded** p-values indicate statistical significance **(p < 0.05)**		

4.7. Summary of Frailty Findings

This chapter demonstrated that frailty is a prevalent and clinically meaningful feature of Lewy body dementia. The cohort exhibited a moderate degree of frailty overall, with comparable levels of vulnerability across DLB-spectrum and PDD-spectrum groups. These findings indicate that frailty is a shared characteristic throughout the Lewy body disease continuum rather than a feature restricted to any single diagnostic subtype.

Frailty, measured using the newly developed multidomain Lewy Body Dementia Frailty Index (LBD-FI), was strongly associated with neuropsychiatric symptom burden, reduced

quality of life, and greater caregiver burden. In contrast, no significant relationships were observed with cognitive performance or functional dependence, suggesting that the construct of frailty in this context primarily captures psychosocial and behavioural vulnerability rather than cognitive or physical decline alone.
Preliminary analyses also identified an association between frailty and sensory impairment, particularly olfactory dysfunction, highlighting a potential sensory dimension to the frailty phenotype in Lewy body disorders.

Taken together, these findings establish frailty as an integrated multidomain construct within Lewy body dementia, reflecting the cumulative influence of neuropsychiatric, psychosocial and sensory factors on overall clinical vulnerability. These observations provide a rationale for the subsequent examination of sensory impairment as a related domain of multidimensional decline, presented in Chapter 5.

Chapter 5. Sensory Impairment in Lewy Body Dementia (Results II)

5.1. Sensory Impairment Prevalence and Profiles

Sensory impairment was highly prevalent across the cohort. The prevalence of impairments, defined using standard clinical cut-offs, is summarised in Table 5.1.

Olfactory impairment was almost universal: all forty-six valid cases (100%) demonstrated clinically significant olfactory dysfunction (UPSIT < 26), consistent with hyposmia or anosmia. Hearing impairment was present in 97.9 % of participants, based on HearCheck total scores ≤ 8, reflecting a high prevalence of moderate to severe hearing loss. Visual impairment, defined as binocular logMAR ≥ 0.30, was observed in 39.6 %, representing a smaller but clinically meaningful subgroup with reduced visual acuity.

Overall, 71 % of participants exhibited deficits in two or more sensory modalities (Figure 5.1), confirming that multimodal sensory dysfunction is highly prevalent in Lewy body dementia and occurs across diagnostic subtypes. These findings establish sensory impairment, particularly olfactory and auditory dysfunction, as a pervasive clinical feature of the LBD spectrum.

Table 5.1. Prevalence of Sensory Impairment by diagnostic groups (DLB-spectrum and PDD-spectrum groups)

Sensory Domain	Total n (% valid)	DLB-spectrum n (% valid)	PDD-spectrum n (% valid)	p-value†
Olfactory impairment	46 / 46 (100%)	30 / 30 (100%)	16 / 16 (100%)	Not computed‡
Hearing impairment	47 / 48 (97.9%)	30 / 31 (96.8%)	17 / 17 (100%)	1.000
Vision impairment	19 / 48 (39.6%)	12 / 31 (38.7%)	7 / 17 (41.2%)	1.000

† Fisher's Exact test (two-tailed).

‡ Not computed as all cases in both groups had the same outcome (constant variable).

N values reflect available valid data per domain. Sensory impairment defined using validated clinical cut-offs.

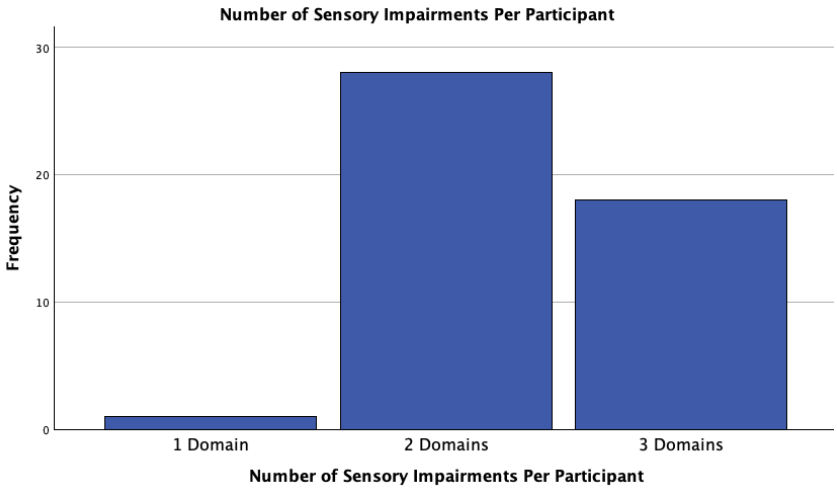

Figure 5.1. Number of Sensory Impairments Per Participant. Distribution of participants according to number of impaired sensory domains. The majority showed multimodal impairment affecting two or more domains.

5.2. Objective Sensory Measures: Distribution and Diagnostic Performance

Objective sensory performance was evaluated across olfactory, visual, and auditory domains. Descriptive statistics for each modality are presented in Table 5.2, and score distributions are illustrated in Figure 5.2.

Olfactory performance (UPSIT total) ranged from 0 to 34 (median 14, IQR 10 – 20; mean 16.3 ± 7.5), indicating marked impairment in nearly all participants. Visual acuity, measured by Peek Acuity under binocular conditions, ranged from 0.00 to 0.90 logMAR (median 0.10, IQR 0.00 – 0.35; mean 0.21 ± 0.25). Hearing performance (HearCheck total) showed a compressed distribution towards the lower end of the scale (median 4.0, IQR 3.0 – 5.0; mean 4.2 ± 1.4), reflecting moderate-to-severe auditory deficit in most participants. The distribution suggested moderate-to-severe hearing loss in many participants, mirroring the high prevalence of auditory impairment described in Section 5.1.

When stratified by diagnostic group, there were no statistically significant differences in sensory performance between the DLB-spectrum and PDD-spectrum groups for any modality. Median and mean values were closely aligned, and no statistically significant differences were observed for any modality (UPSIT p = 0.372; logMAR p = 0.181; HearCheck p = 0.241). Sensory performance was therefore comparable between DLB-spectrum and PDD-spectrum groups.

Table 5.2. Continuous Sensory Scores by Diagnostic Group

Sensory Domain	Total (N = 51)	DLB-spectrum (n = 32)	PDD-spectrum (n = 19)	p-value†
UPSIT Total	14 [10–20], 0–34, 16.3 ± 7.5	14 [10–19], 0–31, 15.8 ± 7.2	17.5 [11–22], 0–34, 17.1 ± 8.2	0.372
Peek Binocular logMAR	0.10 [0.00–0.35], 0.00–0.90, 0.21 ± 0.25	0.10 [0.00–0.35], 0.00–0.90, 0.23 ± 0.26	0.00 [0.00–0.30], 0.00–0.70, 0.17 ± 0.22	0.181
HearCheck Total	4.0 [3.0–5.0], 0–6, 4.2 ± 1.4	4.0 [3.0–5.0], 0–6, 4.1 ± 1.5	5.0 [3.0–6.0], 0–6, 4.3 ± 1.3	0.241

Values are presented as Median [IQR], Range, and Mean ± SD.

† Mann-Whitney U test (exact, two-tailed).

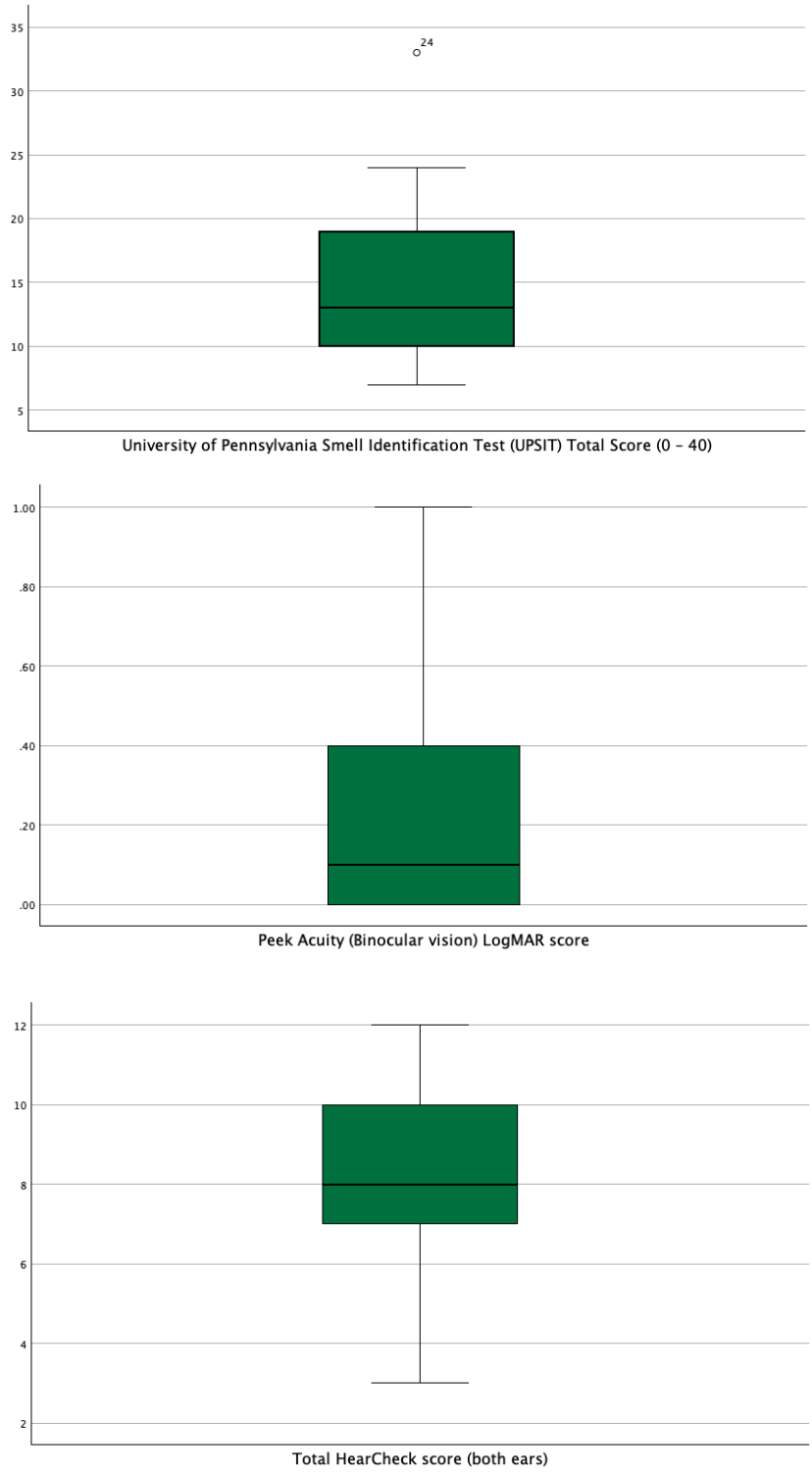

Figure 5.2. Distribution of Objective Sensory Performance Scores. Distribution of continuous sensory performance measures for total cohort. UPSIT total scores; Peek Acuity binocular logMAR scores; HearCheck total scores. Hearing and vision performance demonstrated moderate variability, whereas olfactory scores were uniformly low, reflecting pervasive smell loss across participants.

5.3 Associations Between Sensory Impairment and Frailty

5.3.1. Sensory Scores and LBD-FI

Spearman correlations are summarised in Table 5.3. Olfactory dysfunction (UPSIT score) showed a moderate negative correlation with the Lewy Body Dementia Frailty Index (LBD-FI) ($\rho = -0.482$, $p = 0.001$), indicating greater frailty burden with lower olfactory performance.

Hearing and vision scores were weakly related to frailty (HearCheck $\rho = 0.169$, $p = 0.245$; logMAR $\rho = 0.139$, $p = 0.341$) and did not reach statistical significance.

These results suggest that olfactory, rather than auditory or visual, impairment is the primary sensory correlate of multidomain frailty in LBD.

Table 5.3. Spearman's Correlations Between Sensory Scores and Clinical Outcomes

Clinical Outcome	MoCA Total	NPI Severity	BADLS Total	EQ-5D-5L Utility	QOL-AD (Participant)	Zarit total
HearCheck	ρ = 0.329, **p = 0.021**	ρ = −0.379, **p = 0.008**	ρ = −0.147, p = 0.326	ρ = −0.028, p = 0.856	ρ = 0.111, p = 0.447	ρ = −0.147, p = 0.313
logMAR	ρ = −0.079, p = 0.591	ρ = 0.041, p = 0.784	ρ = 0.060, p = 0.688	ρ = 0.051, p = 0.739	ρ = −0.176, p = 0.227	ρ = 0.168, p = 0.249
UPSIT	ρ = 0.173, p = 0.245	ρ = −0.097, p = 0.522	ρ = −0.213, p = 0.161	ρ = 0.290, p = 0.059	ρ = 0.308, **p = 0.035**	ρ = −0.107, p = 0.474

ρ = Spearman's rank correlation coefficient.
Bolded p-values indicate statistical significance **(p < 0.05)**
Significant associations observed between HearCheck and both MoCA and NPI. UPSIT was positively associated with participant-rated quality of life.

5.3.2. Sensory Impairment Across Frailty Tertiles

Categorical analyses of sensory impairment prevalence across frailty tertiles are shown in Table 5.4. Olfactory dysfunction was universal across all frailty strata. Hearing and vision impairment frequencies were similar between tertiles, and Fisher's Exact tests showed no statistically significant differences (hearing $p = 0.612$; vision $p = 0.936$).

These findings indicate that, although sensory impairments are widespread, their prevalence does not vary significantly across levels of frailty severity within this cohort.

Table 5.4. Prevalence of Sensory Impairment Across Frailty Tertiles

Sensory Domain	Low Frailty Index (n, %)	Moderate Frailty Index (n, %)	High Frailty Index (n, %)	p-value (Fisher's Exact)
Olfactory impairment	14 / 14 (100 %)	18 / 18 (100 %)	15 / 15 (100 %)	Not computed (constant)
Vision impairment	5 / 14 (35.7 %)	8 / 19 (42.1 %)	7 / 16 (43.8 %)	0.936
Hearing impairment	14 / 14 (100 %)	19 / 19 (100 %)	15 / 16 (93.8 %)	0.612
Sensory impairment defined using validated clinical cut-offs. p-values from two-tailed Fisher's Exact tests.				

5.4. Sensory Impairment and Clinical Outcomes

Clinical outcomes measured included cognition, neuropsychiatric symptoms, functional capacity, quality of life and caregiver burden. Lower UPSIT scores (indicating poorer olfactory performance) were significantly associated with greater neuropsychiatric symptom burden (NPI severity $\rho = -0.373$, $p = 0.007$). Conversely, higher UPSIT scores were significantly associated with better health-related quality of life (EQ-5D-5L utility: $\rho = 0.329$, $p = 0.020$). These findings indicate that poorer olfactory function is linked to both increased neuropsychiatric burden and reduced quality of life.

Hearing and vision impairments showed weaker, non-significant associations with clinical outcomes. No sensory domain showed a significant correlation with cognitive

performance (MoCA total score) or caregiver burden (Zarit total). These findings suggest that olfactory dysfunction, in particular, may be linked to the psychosocial aspects of disease burden in LBD.

In adjusted regression models accounting for age and diagnosis, UPSIT scores independently predicted greater neuropsychiatric symptom burden and lower quality of life. Hearing and vision scores did not independently predict clinical outcomes.
These findings suggest that olfactory dysfunction, rather than hearing or visual deficits, reflects a specific dimension of psychosocial vulnerability in LBD.

5.5. Sensory Profiles Across Frailty Tertiles

Sensory scores were compared across frailty tertiles (Table 5.5). Olfactory performance (UPSIT score) showed a stepwise decline from the low to high frailty groups (median UPSIT 16 → 14 → 12), however, this trend did not reach statistical significance (Kruskal-Wallis $H = 5.03$, $p = 0.081$). Hearing (HearCheck total) and vision (binocular logMAR) scores displayed considerable within-group variability, with no significant differences observed across frailty strata ($p = 0.762$ and $p = 0.593$, respectively).

These results indicate a non-significant trend toward poorer olfactory performance with increasing frailty burden, whereas hearing and visual measures appear unrelated to frailty severity within this cohort. The pattern suggests that olfactory dysfunction may be more closely aligned with multidomain vulnerability in Lewy body dementia, but larger samples are required to confirm this association.

Table 5.5. Continuous Sensory Scores Across Frailty Tertiles

Sensory Domain	Frailty Tertile	Mean ± SD	Median (IQR)	Range	p-value (Kruskal–Wallis)
UPSIT Score	**Low**	16.4 ± 4.7	16.0 (10–20)	10–24	0.081
	Medium	15.2 ± 6.9	14.0 (10–19)	7–33	
	High	12.0 ± 3.5	12.0 (9–14)	7–21	
Peek logMAR	**Low**	0.236 ± 0.363	0.10 (0.00–0.35)	0.00–1.00	0.593
	Medium	0.190 ± 0.200	0.10 (0.00–0.35)	0.00–0.60	
	High	0.275 ± 0.286	0.30 (0.00–0.30)	0.00–0.90	
HearCheck Score	**Low**	8.36 ± 1.95	4.0 (3.0–5.0)	3–10	0.762
	Medium	8.11 ± 1.85	4.0 (3.0–5.0)	4–10	
	High	7.94 ± 2.21	4.0 (3.0–5.0)	4–12	
p-values derived from Kruskal-Wallis tests for between-group comparisons.					

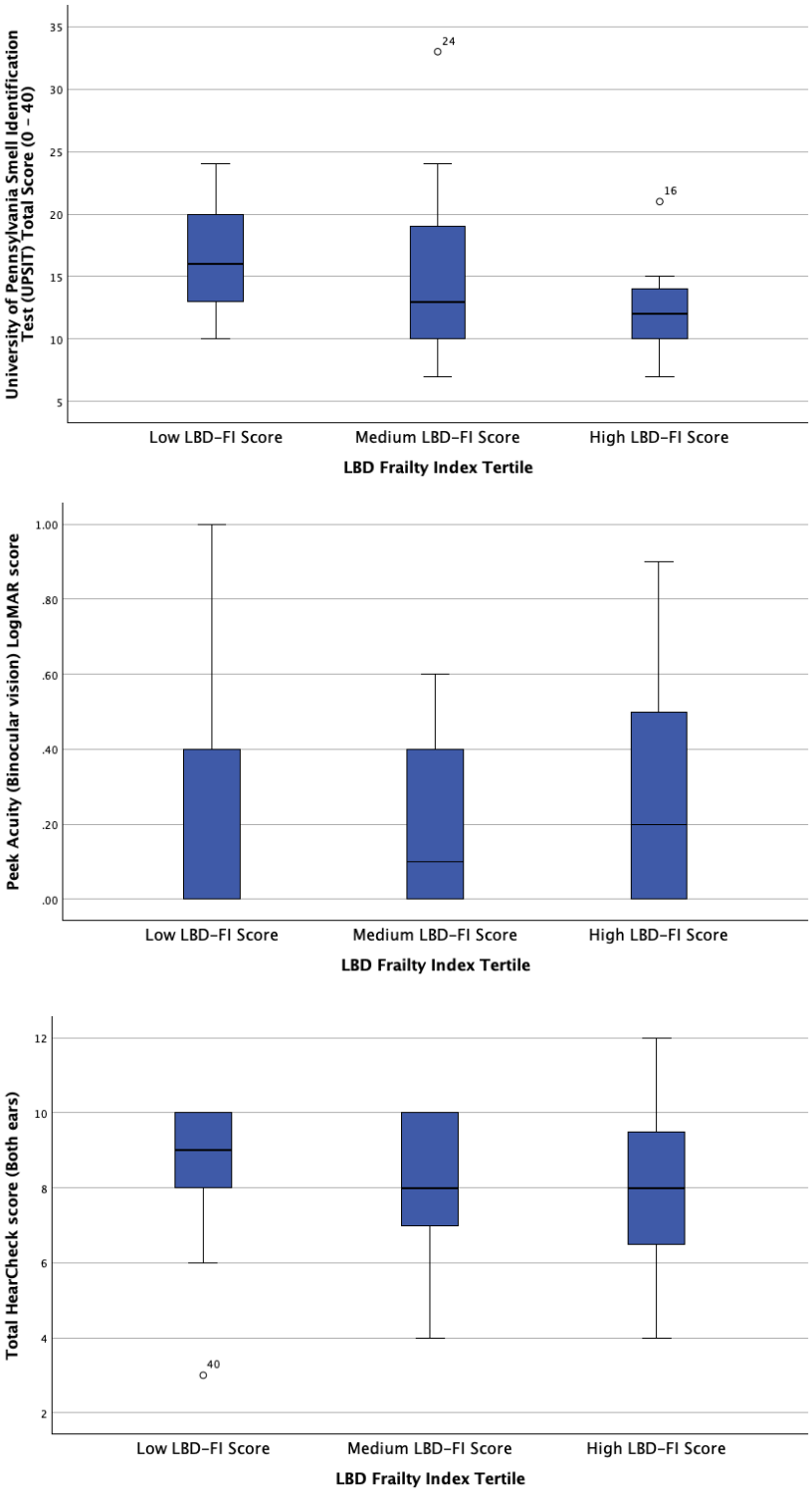

Figure 5.3. Sensory Scores Across Frailty Tertiles. Distribution of UPSIT, Peek Acuity logMAR and HearCheck scores across low, moderate and high frailty tertiles. Olfactory performance declined with increasing frailty (Kruskal-Wallis H = 5.03, p = 0.081), while hearing and vision showed no significant group differences (p > 0.05).

5.6. Diagnostic Group Differences in Sensory Impairment

Sensory impairment prevalence and scores were compared across diagnostic groups of DLB-spectrum and PDD-spectrum groups (Table 5.6 and Figure 5.4). There was no significant differences observed in olfactory, hearing, or vision impairment prevalence.

Continuous sensory scores (i.e. UPSIT, logMAR, HearCheck) were comparable across diagnostic groups. These results indicate that sensory impairment is a shared clinical feature across the Lewy Body Disease spectrum rather than a distinguishing characteristic of diagnostic subtype.

Table 5.6. Continuous Sensory Scores by Diagnostic Group

Sensory Domain	DLB-spectrum (n = 32)	PDD-spectrum (n = 19)	p-value (Mann-Whitney U)
UPSIT Total	14 [10–19], 0–31, 15.8 ±7.2	17.5 [11–22], 0–34, 17.1 ±8.2	0.372
Peek Binocular logMAR	logMAR 0.10 [0.00–0.35], 0–0.90, 0.23 ± 0.26	0.00 [0.00–0.30], 0–0.70, 0.17 ± 0.22	0.181
HearCheck Total	4.0 [3.0–5.0], 0–6, 4.1 ± 1.5	5.0 [3.0–6.0], 0–6, 4.3 ± 1.3	0.241
Values shown as median [IQR], range, and mean ± SD. p-values from two-sided Mann-Whitney U tests.			

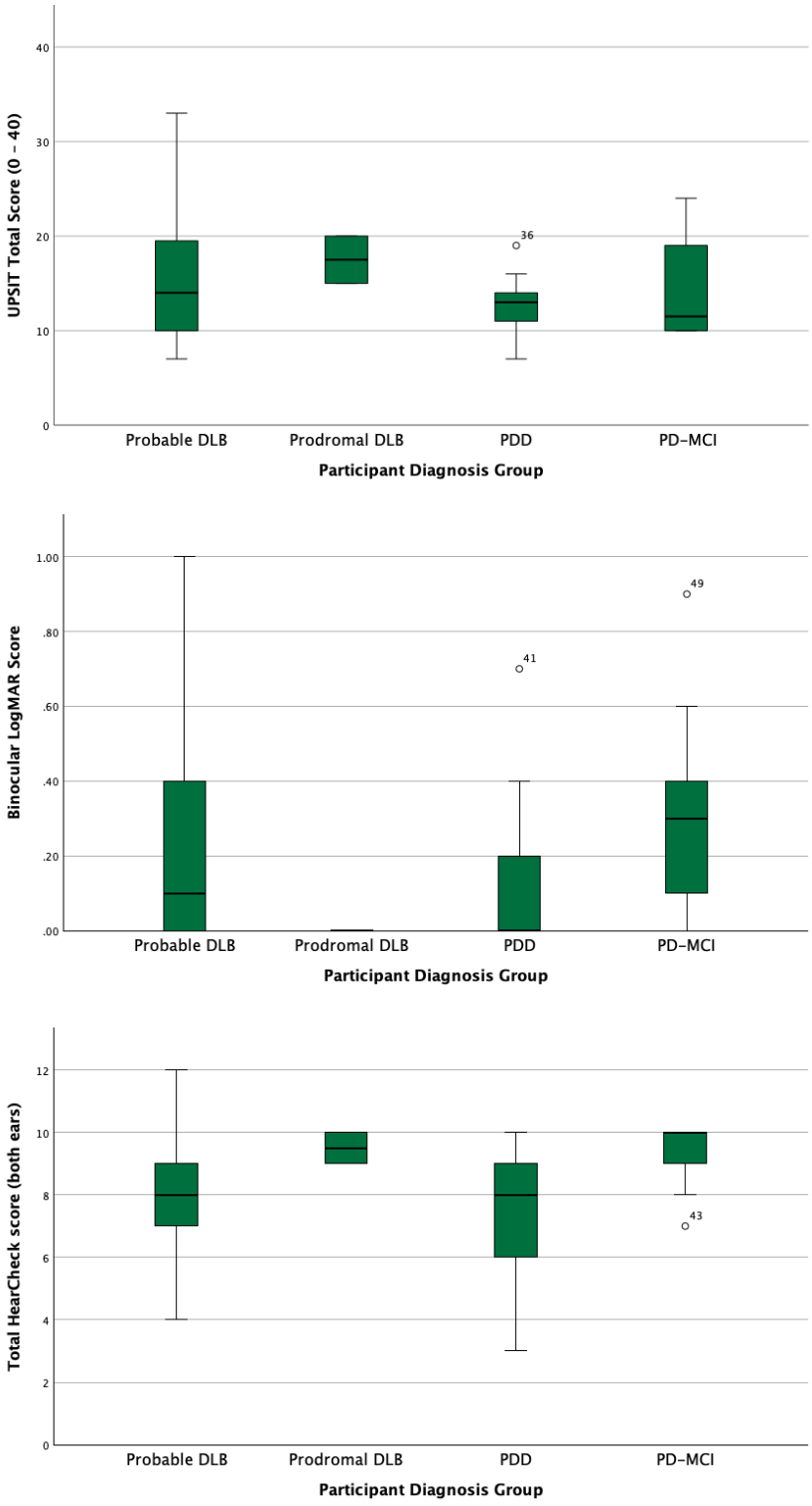

Figure 5.4. Sensory Scores Across Diagnostic Groups. Comparison of UPSIT, Peek Acuity, logMAR, and HearCheck scores between DLB-spectrum and PDD-spectrum groups. Median sensory scores were comparable across subtypes, indicating no significant diagnostic group differences.

5.7. Summary of Sensory Findings

This chapter demonstrated that sensory impairment is a pervasive and clinically significant feature of Lewy body dementia. Objective sensory testing confirmed that olfactory dysfunction was almost universal and typically severe, while hearing and vision impairments were also common. Together, these results emphasise that sensory decline extends beyond the motor and cognitive dimensions traditionally associated with the disorder.

Olfactory performance showed a consistent and clinically relevant association with frailty, as well as with key outcomes including neuropsychiatric symptom burden and health-related quality of life. In contrast, hearing and vision measures exhibited greater variability and only weak correlations with frailty or functional outcomes, suggesting that these modalities may reflect more heterogeneous or secondary processes within the disease spectrum.

Comparisons across diagnostic groups indicated no significant differences in either sensory performance or impairment prevalence between the DLB-spectrum and PDD-spectrum groups. This supports the concept that sensory dysfunction represents a shared clinical vulnerability across the Lewy body disease continuum, rather than a feature confined to any single subtype.

Overall, the findings presented in this chapter position sensory impairment, particularly olfactory dysfunction, as an integral marker of multidomain vulnerability in Lewy body dementia. When interpreted alongside the frailty analyses in Chapter 4, these results highlight the convergence of sensory, neuropsychiatric, and psychosocial factors in shaping disease burden.

Chapter 6. Discussion

The study which formed my doctoral thesis examined both frailty and sensory impairment in Lewy body dementia (LBD) within a cross-sectional cohort. The multidomain Lewy Body Dementia Frailty Index (LBD-FI), constructed using a cumulative-deficit approach, was evaluated against core cognitive, functional, neuropsychiatric and quality-of-life outcomes. Objective olfactory, auditory and visual performance were measured using standardised tools to characterise prevalence and clinical relevance.

My analysis found that in this LBD cohort, frailty burden was substantial and objective sensory impairment was common. The LBD-FI demonstrated construct validity, showing robust associations in particular with severity of neuropsychiatric symptoms and caregiver burden. Higher frailty scores were associated with lower health-related quality of life measures, although these associations did not remain statistically significant after adjustment. Sensory impairment, particularly reduced olfactory performance, was related to greater psychosocial burden and lower quality of life, while hearing and vision measures showed weaker and more variable patterns.

Across the LBD diagnostic groups, frailty burden did not differ between DLB-spectrum and PDD-spectrum groups, and sensory performance was broadly comparable. These findings extend the clinical framing of LBD beyond a purely neurocognitive disorder to one of multisystem vulnerability in which frailty and sensory dysfunction are salient markers of heterogeneity.

6.1 Overview and Key Findings

This study addressed a clear gap in the existing literature by operationalising frailty and sensory impairment within the context of an LBD clinical cohort. While prior research has established the prevalence of cognitive and motor features, few studies have quantified broader systemic vulnerability or examined how these multidimensional deficits interact to shape prognosis.

The principal findings can be summarised as:

- Frailty is highly prevalent in LBD, measurable using a cumulative deficit framework adapted to the multidomain profile of the disease.
- Sensory impairment is common, with olfactory loss near universal, and frequent co-occurrence of auditory and visual deficits.
- Frailty is associated with higher neuropsychiatric and caregiver burden. Associations with health related quality of life were negative but not statistically significant after adjustment and no associated was detected with global cognition or functional dependence.
- Diagnostic groups (DLB-spectrum and PDD-spectrum groups) exhibited comparable frailty burden and similar sensory profiles, but only subtle differences in clinical correlates. This supports frailty as a unifying construct bridging these syndromes, and reinforces a shared vulnerability profile, consistent with the continuum model of Lewy body disease.

The findings collectively support the construct validity of the LBD-FI and provide initial empirical evidence for sensory function as a determinant of frailty and quality of life in LBD. This study moves beyond conventional symptom based characterisations of LBD to frame it as a condition of multisystem dysregulation, integrating neurological, physiological and sensory domains.

By demonstrating that frailty and sensory loss are quantifiable, clinically relevant and interconnected domains of vulnerability in our clinical cohort with LBD, this doctoral thesis reframes the disorder as a multisystem condition rather than a purely neurocognitive disease.

6.2 Frailty in Lewy Body Dementia

6.2.1 Prevalence and Construct Validity

Frailty emerged as a prominent feature in this cohort, with median LBD-FI scores exceeding those typically reported in population-based geriatric studies [236, 237]. The LBD-FI demonstrated acceptable internal consistency and a right-skewed distribution

consistent with established frailty index behaviour. This supports its construct validity and alignment with the cumulative deficit model [54, 55]. The inclusion of multidomain variables, including motor, cognitive, autonomic, neuropsychiatric and sensory variables, enabled comprehensive quantification of vulnerability tailored to the LBD phenotype.

The frailty and age correlation was modest, implying that frailty in LBD reflects disease-specific processes rather than chronological ageing alone. This finding parallels evidence in Parkinson's disease cohorts, where frailty predicts mortality and institutionalisation independently of age and disease duration [178, 238]. The strong association between LBD-FI and functional impairment further supports criterion validity, echoing findings from Alzheimer's and mixed dementia studies in which higher frailty scores predict accelerated decline and reduced survival [176, 239].

6.2.2 Frailty as a Marker of Disease Burden

Frailty provides an integrative framework through which the multisystem nature of LBD can be understood. Its association with neuropsychiatric and autonomic symptoms suggests that it reflects the cumulative impact of widespread neurodegeneration rather than a single domain deficit. The observed correlation between frailty and caregiver burden underscores its relevance beyond biological vulnerability, extending to psychosocial and care-related outcomes.

These findings support the hypothesis that frailty may act as a final common pathway linking neuropathology, clinical phenotype, and real world function in LBD. In this context, frailty is not merely a comorbidity but a dynamic expression of system level decline that captures the heterogeneity often seen between individuals with similar neuropathological loads [240]. Frailty is therefore a valid and multidimensional construct in LBD, reflecting disease-specific multisystem vulnerability and correlating with both functional dependence and caregiver outcomes.

6.3 Sensory Impairment and Its Clinical Significance

6.3.1 Prevalence and Modality-Specific Patterns

Objective testing revealed high rates of sensory impairment across all modalities. Olfactory loss was almost universal, while auditory and visual impairments affected the majority of participants. These rates substantially exceed population based estimates for older adults, indicating that sensory dysfunction in LBD is not merely age-related but disease linked [241-243].

Olfaction was most affected domain, as measured by the UPSIT-40, consistent with early involvement of olfactory pathways in α-synuclein disease. The uniformity of olfactory impairment accords with neuropathological evidence of early α-synuclein deposition in the olfactory bulb and anterior olfactory nucleus in LBD [92, 195].
Unaided hearing loss was frequent on HearCheck, including in participants without prominent subjective complaints, supporting the added value of objective screening in LBD clinics [94].

Visual acuity, measured by Peek logMAR, was also commonly reduced, although typically milder in degree. However, acuity does not capture contrast sensitivity or higher order visuoperceptual deficits relevant to hallucinations and misperceptions. Our visual findings therefore likely underestimate the broader vulnerability of visual processing pathways in LBD [93, 129].

Taken together, these results demonstrate that sensory impairment in LBD is pervasive, multimodal and biologically grounded within the disease process rather than secondary to ageing or comorbidity.

6.3.2 Sensory Impairment as a Marker of Vulnerability

Sensory impairment, most notably olfactory loss, showed significant associations with both frailty and selected clinical outcomes. These findings align with the “common cause” hypothesis, which proposes that shared neurodegenerative or vascular processes drive concurrent declines across sensory and cognitive systems [244]. Alternatively, sensory

deprivation may directly exacerbate cognitive load, social isolation and changes within cortical sensory networks [245]. Both pathways support the interpretation of sensory function as a clinically meaningful and potentially modifiable dimension of disease vulnerability.

The association between sensory loss and poorer quality of life reinforces its clinical relevance. In LBD, this relationship is likely multifactorial, mediated by perceptual uncertainty, attentional fluctuation and communication barriers that compound caregiver stress. Sensory impairment is widespread in LBD and strongly linked to frailty, psychosocial distress and functional decline, supporting its role as both a biomarker and a potentially modifiable component of multidomain vulnerability.

6.4 Integrating Frailty and Sensory Impairment

6.4.1 Conceptual Integration: Sensory Frailty

The observed convergence between frailty and sensory deficits supports the emerging construct of "sensory frailty", defined as the additive or synergistic burden of multiple sensory losses within the broader framework of physiological vulnerability [100]. The positive correlations between LBD-FI and sensory scores (UPSIT, logMAR, HearCheck) in this study provide empirical support for this integrated model.

In older adult populations, dual or multisensory impairment has been shown to predict disability, cognitive decline and mortality independent of traditional frailty markers [69]. Extending this framework to LBD is both logical and clinically relevant: frailty and sensory dysfunction each represent distributed network compromise, loss of reserve and reduced adaptability. Their co-occurrence may therefore capture disease heterogeneity more comprehensively than either domain alone. This framework positions sensory frailty as a unifying construct within LBD, linking systemic and neurological dimensions of disease expression and reinforcing the need for multidomain assessment in both research and clinical contexts.

6.4.2 Mechanistic Implications

Mechanistically, sensory and frailty pathways may intersect through shared substrates such as neuroinflammation, mitochondrial dysfunction and altered synaptic plasticity [245, 246]. In LBD, the widespread distribution of α-synuclein pathology, extending into peripheral autonomic and sensory systems, provides a plausible neurobiological foundation for this overlap. Furthermore, dopaminergic and cholinergic deficits, both core features of LBD pathophysiology, influence sensory gating, attentional regulation and autonomic stability, linking neurotransmitter dysregulation to multisystem frailty expression [100, 206, 247].

Frailty and sensory impairment are mechanistically interlinked in LBD, representing parallel expressions of distributed neural dysfunction, diminished physiological resilience and progressive multisystem decline.

6.5 Diagnostic and Phenotypic Implications

The findings have diagnostic and conceptual implications. The concurrent elevation of frailty and sensory impairment across DLB-spectrum and PDD-spectrum groups suggests that these constructs transcend current disease classification boundaries. Rather than treating DLB and PDD as distinct entities separated by the one-year rule, a combined frailty and sensory framework emphasises their shared vulnerability profile.

Clinically, quantifying frailty and sensory burden could enhance the sensitivity of diagnostic assessment, particularly in prodromal or atypical cases where cognitive and motor criteria are insufficiently discriminatory. The LBD-FI may complement existing diagnostic tools by providing a quantifiable index of systemic involvement, while routine sensory testing could improve the recognition of non-cognitive symptoms and inform supportive interventions targeting hearing or vision rehabilitation.

From a phenotypic perspective, these findings reinforce the concept of multidomain heterogeneity in LBD, where identical pathological substrates produce variable clinical trajectories depending on baseline reserve, comorbidity and frailty state. Integrating

frailty and sensory domains into disease staging models may therefore improve prognostic accuracy and support more refined participant stratification in clinical trials.

Frailty and sensory measures hold diagnostic and staging value, offering a bridge across the spectrum of disease and supporting a multidomain model of LBD heterogeneity that better reflects the true complexity of the disease.

6.6 Methodological Considerations and Limitations

6.6.1 Study Design and Sample Characteristics

The cross-sectional design enabled a detailed multidomain characterisation of LBD but it inherently limits causal inference. Associations between frailty, sensory loss and clinical outcomes cannot be assumed to represent longitudinal trajectories. Future longitudinal validation in incident or early stage cohorts would clarify whether frailty and sensory impairment predict subsequent decline or primarily reflect concurrent disease burden.

The sample size (n = 51) was modest but consistent with other single centre LBD studies employing detailed in-person clinical assessments. While sufficient for correlation and regression analyses, the limited power precluded stratified analyses by sex or comorbidity burden. Recruitment through a specialist national network nonetheless ensured diagnostic rigour and high internal validity.

Participants were recruited from tertiary specialist cognitive and movement disorder services. While this facilitated rigorous phenotyping and recruitment of suitable participants, it may limit the generalisability of findings to the broader population with LBD.

Tertiary referral centres typically manage patients with more complex, diagnostically challenging, or treatment-resistant disease. Individuals referred to such services may therefore represent a subgroup with greater neuropsychiatric burden, atypical symptom profiles or more advanced multisystem involvement. This referral pattern may have influenced the observed prevalence of frailty and sensory impairment within the cohort.

In particular, the high prevalence of multimodal sensory impairment and the moderate overall frailty burden observed in this study may partly reflect case-mix enrichment for patients with more clinically overt or multidomain disease. Community-based or primary care cohorts might include individuals with milder phenotypes, earlier-stage disease or lower overall vulnerability, potentially yielding lower prevalence estimates for both frailty and sensory dysfunction. In addition, tertiary services frequently provide integrated multidisciplinary assessment, which may enhance the identification of comorbid deficits. The structured and objective sensory testing employed in this study may therefore have detected impairments that remain under-recognised or undocumented in non-specialist or community settings. Consequently, both referral bias and enhanced ascertainment may have contributed to higher observed prevalence estimates compared with population-based cohorts.

Importantly, while tertiary recruitment may influence prevalence estimates, it is less likely to invalidate the observed associations between frailty, sensory dysfunction, and clinical outcomes. Internal comparisons within the cohort remain methodologically robust, as all participants were assessed using standardised instruments under uniform conditions. The direction and strength of associations between olfactory dysfunction, neuropsychiatric symptoms, quality of life, and multidomain frailty are therefore likely to reflect true relationships within Lewy body disease, even if absolute prevalence estimates differ in other care settings.

Future studies incorporating population-based or multi-centre recruitment would help to determine whether the magnitude of frailty and sensory impairment observed here is consistent across healthcare contexts. Such work would clarify the external validity of these findings and inform their applicability to routine clinical practice.

6.6.2 Diagnostic Classification

Diagnosis was based on established DLB Consortium and MDS Task Force criteria, supported by clinical consensus. Not all participants underwent biomarker confirmation, reflecting real-world diagnostic practice but limiting pathological specificity. The pragmatic grouping of probable and prodromal DLB in the DLB-spectrum group and PDD

with PD-MCI in the PDD-spectrum group facilitated analysis but inevitably simplified a continuous disease trajectory encompassing overlapping stages.

6.6.3 Measurement and Instrumentation

All sensory assessments were applied using objective, standardised protocols, although each measure has inherent limitations. UPSIT performance can be influenced by nasal pathology, medication, or smoking status [233]. The Peek Acuity test quantifies central vision but not contrast sensitivity or visuoperceptual processing, which may be more relevant to hallucinations and misperceptions [226].
HearCheck evaluates a restricted frequency range and may underestimate mild hearing loss relative to full audiometry [231].

Visual assessment was limited to high-contrast binocular visual acuity testing using the Peek Acuity application, with acuity expressed in logMAR units. While clinically relevant, visual acuity alone does not capture the higher order visuoperceptual and visuospatial disturbances that are characteristic of LBD, closely associated with visual hallucinations and perceptual misinterpretation. In LBD, visual dysfunction frequently reflects cortical processing abnormalities affecting spatial integration, object recognition and visual attention, rather than primary ocular impairment alone. Assessment restricted to acuity therefore likely underestimates the complexity of visual system involvement in this disorder.

The absence of strong associations between logMAR acuity and frailty or clinical outcomes should consequently be interpreted in the context of this measurement constraint. Future studies incorporating more comprehensive visuoperceptual assessments would better characterise the contribution of visual processing deficits to multidomain vulnerability in LBD. The present study therefore reflects primary acuity impairment rather than the broader spectrum of cortical visual dysfunction observed in LBD.

Despite these limitations, the use of unaided, standardised measures minimised subjectivity and ensured consistency across sites. The cumulative deficit frailty

methodology balanced inclusivity with interpretability; conceptual overlap between some frailty components and outcome variables was mitigated by excluding direct duplicates during index construction.

Medication exposure represents an additional potential source of measurement variability. Participants with LBD frequently receive complex pharmacotherapy, including dopaminergic agents, cholinesterase inhibitors, antidepressants, antipsychotics and medications with significant anticholinergic properties. These treatments may influence sensory performance independently of underlying neurodegenerative pathology. In particular, anticholinergic burden has been associated with impaired olfactory and cognitive function, and centrally acting or sedative agents may affect attention-dependent sensory testing such as the UPSIT olfactory assessment. Although polypharmacy was incorporated within the frailty index, specific pharmacodynamic effects on individual sensory modalities were not modelled separately. Residual confounding related to medication exposure therefore cannot be excluded.

6.6.4 Statistical and Analytical Issues

Analyses were exploratory and hypothesis driven. Non-parametric methods were used appropriately given non-normal distributions and ordinal data structures. No correction for multiple comparisons was applied, reflecting the study's exploratory nature. Interpretation therefore emphasised effect sizes, consistency across domains and biological plausibility rather than isolated significance values.

The sample size limited the ability to perform multivariable models including multiple covariates such as comorbidity or education, leaving potential residual confounding. However, the strong internal consistency of associations across independent domains supports the robustness of the findings.

6.6.5 Clinical Implications

External validity is constrained by the single country setting and tertiary recruitment base. Ethnic diversity was limited, and although cultural or linguistic influences on cognitive and sensory testing were minimal, they were not formally evaluated.

Nonetheless, the methodological rigour, diagnostic verification and standardised assessments enhance reproducibility.

The design and analytical strategy provide internally consistent cross-sectional evidence of multidomain associations but cannot establish longitudinal causality.
Measurement and sampling constraints should guide cautious interpretation and guide future prospective replication.

6.7 Strengths of the Study

This thesis presents a detailed characterisation of frailty and sensory function in LBD, integrating objective multimodal assessment with the development of a disease-specific frailty construct.

Key strengths include:

- Comprehensive multidomain assessment: The combined evaluation of sensory, cognitive, motor, autonomic and neuropsychiatric measures provides a multidimensional profile of LBD vulnerability rarely achieved in prior studies.
- Objective sensory testing: Use of validated, unaided measures (UPSIT, Peek Acuity, HearCheck) minimised bias associated in self-reported or informant led ratings.
- Novel frailty index tailored to LBD: The LBD-FI was constructed systematically following established methodological standards, ensuring comprehensive coverage and strong conceptual validity.
- Clinically anchored co-participant data: Informant based measures (BADLS, ZBI) enhanced real world validity and captured functional and psychosocial impact.
- Diagnostic precision: Recruitment through specialist movement disorder and memory clinics maximised diagnostic accuracy and phenotypic specificity.
- Ethical and governance rigour: Full adherence to GDPR, GCP and ethics committee oversight ensured data integrity and replicability.
- Transparent analytic framework: Clear documentation of data processing and analysis enhances credibility and provides a replicable model for multidomain research in neurodegenerative disease.

- Methodological integration, diagnostic precision and the creation of a validated disease specific frailty index represent the principal innovations and enduring strengths of this work.

6.8 Implications for Clinical Practice, Research and Policy

6.8.1 Clinical Implications

The findings underscore the clinical utility of incorporating frailty and sensory assessments into routine LBD evaluation. Frailty screening could inform prognosis, guide care planning and support risk stratification for adverse outcomes. Sensory testing identifies potentially modifiable contributors to functional decline and reduced quality of life. Correction of hearing or vision deficits may mitigate hallucinations and communication difficulties. Another practical implication is the feasibility of embedding simple sensory tools, such as UPSIT or bedside hearing screening, into cognitive clinics. Frailty assessment using a brief index could similarly guide personalised care and multidisciplinary interventions targeting nutrition, mobility and polypharmacy.

6.8.2 Research Implications

Future research should pursue three main directions:

- Longitudinal validation of the LBD-FI and sensory-frailty associations to determine predictive value for decline and mortality.
- Biomarker integration: Linking frailty and sensory profiles with imaging or CSF markers of α-synuclein, tau and neuroinflammation to delineate biological mechanisms.
- Interventional studies: Testing whether targeted management of frailty components (e.g. exercise, deprescribing, nutritional support) or sensory restoration, such as hearing aids or cataract surgery, improves clinical outcomes.

The conceptual model emerging from this work suggests that multisystem frailty is both a manifestation and a modifiable mediator of disease impact in LBD. Translating this into trial design could improve participant stratification, outcome sensitivity and translational relevance.

6.8.3 Policy and Service Implications

At a service level, these findings advocate for integration of both geriatric and neurological approaches within dementia care. Specialist LBD clinics could incorporate frailty and sensory screening into multidisciplinary pathways, enabling anticipatory management.

From a policy perspective, recognising LBD as a multisystem disorder of ageing aligns with broader public health initiatives to reduce dementia-related disability rather than focusing solely on disease modification. Health service planning should account for the dual burden of neurodegeneration and frailty when allocating community supports and caregiver resources.

Clinically, the study supports integrating frailty and sensory measures into diagnostic and management pathways. Scientifically, it provides a platform for longitudinal and interventional research linking neurobiology to multidomain outcomes.

6.9 Discussion Summary

This thesis provides new empirical evidence that frailty and sensory impairment are fundamental, interrelated dimensions of vulnerability in LBD. Through systematic measurement and analysis, the study developed and validated an LBD-FI capturing multisystem decline specific to LBD.

The study also demonstrated high rates of olfactory, auditory, and visual impairment, extending beyond age-related norms and showed that frailty and sensory burden correlate strongly with cognitive, functional and quality of life outcomes. Finally, the study highlighted that these constructs bridge the artificial diagnostic divide between DLB and PDD, supporting the spectrum model of Lewy body disease.

Together, these findings reposition LBD as a disorder of multidomain system failure, in which cognitive and motor symptoms are accompanied, and potentially modulated, by frailty and sensory dysfunction. Recognising and addressing these domains can improve diagnostic accuracy, enhance patient centred care and research translation.

By integrating geriatric and neurological frameworks, this doctoral thesis extends the understanding of LBD and provides a foundation for multidimensional assessment and intervention. The LBD-FI and sensory profiling approach offer practical tools for refining prognosis, guiding interventions and informing future clinical trials.

Ultimately, this thesis advances a unifying model of LBD that reflects its full clinical complexity, one that acknowledges frailty and sensory decline not as peripheral comorbidities, but as core expressions of disease biology and ageing interaction.

Chapter 7. Conclusion

7.1 Overview and Conceptual Integration

This thesis examined frailty and sensory impairment as interconnected dimensions of vulnerability in Lewy Body Dementia (LBD). Within the framework of the SENSE-Cog Lewy study, it developed and applied a multidomain Lewy Body Dementia Frailty Index (LBD-FI), quantified objective sensory impairments, and explored how these domains relate to cognitive, functional, neuropsychiatric, and quality-of-life outcomes. Through this approach, it addressed a major gap in current knowledge: the absence of an integrated model that captures the multisystem nature of LBD, in which neurological, geriatric, and sensory processes converge.

By embedding gerontological methodology within a neurodegenerative framework, the work reconceptualised LBD as a disorder of multisystem dysregulation rather than a purely neurocognitive entity. It demonstrated that frailty and sensory loss are measurable, clinically meaningful, and theoretically unifying constructs with direct implications for diagnosis, prognosis, and management.

A principal conceptual advance of this research lies in establishing frailty as intrinsic to the LBD phenotype. The LBD-FI translated the cumulative-deficit framework into a disease-specific instrument that captured multidimensional vulnerability across motor, cognitive, autonomic, mood, and sensory domains. In doing so, it positioned frailty as a system-level marker of disease burden and adaptability, extending beyond the traditional focus on motor and cognitive decline. Equally important was the integration of sensory function into the understanding of LBD. Objective assessment of olfactory, auditory, and visual performance demonstrated that sensory dysfunction is not a peripheral consequence of ageing but a core expression of disease biology.

Together, frailty and sensory loss define a state of sensory frailty, reflecting the cumulative erosion of physiological and sensory reserve that accompanies neurodegenerative disease. This framework shifts the interpretive focus from isolated

neuropathology to systemic vulnerability and more closely reflects the lived clinical reality of those affected.

7.2 Clinical and Translational Implications

The findings also have practical significance for clinical care. Frailty and sensory assessments are feasible and informative additions to existing diagnostic procedures. Incorporating brief frailty and sensory screening into specialist LBD clinics could improve diagnostic sensitivity, enable earlier identification of risk, and support multidisciplinary management.

Addressing modifiable vulnerability domains provides a pragmatic therapeutic avenue: interventions such as physical reconditioning, nutritional optimisation, medication review, and correction of hearing or visual impairment have potential to improve quality of life, lessen neuropsychiatric symptoms, and delay institutionalisation. These strategies exemplify a proactive and person-centred approach consistent with contemporary dementia care.

More broadly, the work supports greater integration of geriatric and neurological expertise, recognising LBD as both an ageing-related and neurodegenerative disorder that benefits from collaborative models linking movement-disorder neurology, old-age psychiatry, and geriatric medicine.

7.3 Methodological and Theoretical Contributions

Methodologically, this thesis contributes to multidomain dementia research by demonstrating how frailty science can be applied within disease-specific datasets. The systematic development of the LBD-FI, including transparent variable selection, reproducible scoring, and validation across multiple outcomes, provides a template for future application in related conditions. The use of objective, unaided sensory testing across olfactory, auditory, and visual modalities improved accuracy and reduced bias compared with self-report instruments. Combining participant and co-participant data offered a multidimensional perspective on functional and psychosocial burden,

enhancing real-world validity. Collectively, these methodological features highlight the value of integrating neurocognitive and gerontological research approaches to generate clinically interpretable and reproducible data.

Theoretically, the results support a unifying model in which frailty and sensory impairment represent parallel manifestations of system failure in LBD. Both reflect reduced physiological and neural reserve, diminished adaptability to stressors, and progressive loss of resilience. This interpretation aligns with contemporary views of neurodegeneration as a multisystem process rather than a focal pathology. By conceptualising frailty and sensory loss as measurable outcomes of distributed network dysfunction, the thesis links biological, clinical, and functional dimensions of disease. It also establishes a bridge between clinical phenotype and molecular mechanisms such as neuroinflammation, mitochondrial dysfunction, and α-synuclein propagation, providing a foundation for translational research that connects cellular pathology with lived experience.

7.4 Future Directions and Conclusion

Future studies could extend these findings through longitudinal and mechanistic investigation. Prospective studies are needed to establish whether baseline frailty and sensory profiles predict functional decline, hospitalisations or mortality. Integration of frailty and sensory data with imaging and biomarkers could clarify shared mechanisms and identify early indicators of heterogeneity. Interventional studies exploring exercise, nutritional support, sensory rehabilitation and medication optimisation may determine whether modification of these domains can meaningfully alter disease trajectory and improve patient-centred outcomes. Such research would strengthen the construct validity of frailty and sensory measures and identify practical targets for therapy.

Beyond LBD, the conceptual and methodological framework developed in this thesis has wider application across neurodegenerative disorders. Frailty and sensory impairment may represent convergent phenotypes of biological ageing that complement molecular and imaging biomarkers, offering a unifying lens through which to interpret disease

vulnerability. Recognising the intersection of neurodegeneration and frailty also has implications for policy and service design. Embedding multidimensional assessment within national dementia strategies could facilitate earlier detection, anticipatory care, and better integration of community and specialist services. Health-service planning should account for the dual management of neurological disease and systemic vulnerability, addressing the needs of both patients and carers.

This doctoral thesis provides detailed empirical evidence that Lewy body dementia is a condition of multisystem vulnerability rather than isolated cognitive decline. By integrating frailty assessment and sensory measurement into its evaluation, it redefines how LBD disease severity and progression are conceptualised. The LBD-FI developed through this work functions as both a research instrument and a clinical framework for personalised assessment. Together, these findings advocate for the reframing of dementia research towards multidomain, person-centred approaches that integrate neurodegeneration, ageing and resilience.

In conclusion, the integration of both frailty and sensory perspectives advances a more comprehensive and human understanding of LBD. This doctoral research aims to provide a foundation for potential future interventions that seek to preserve function as well as mitigate disease burden. For those who so generously participated in this study, and for all individuals living with Lewy body dementia, the ultimate hope is for a model of care that truly recognises frailty as measurable, modifiable and central to the lived experience of the disease.

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Appendices

Appendix 1: Ethical and Regulatory Documentation

1.1. Study Ethics Approval Letter

1.2. Participant Information Leaflet

1.3. Study Consent Forms

Appendix 2: Recruitment Documentation

2.1. Study Recruitment Standard Operating Procedure

2.2. Study Recruitment Leaflet

2.3. Study Inclusion and Exclusion Criteria

Appendix 3: Case Research Forms: Forms A to F

Appendix 4: Lewy Body Dementia Frailty Index (LBD-FI)

Appendix 1: Ethical and Regulatory Documentation

1.1. Study Ethics Approval Letter

Project ID: 3366

Dr Adam Roche,

St James's Hospital/Trinity College Dublin

Approval Date: 14 November 2023

Submission Number: 3138

Submission Title: SENSE-Cog Lewy
Submission Date: 18.Oct.2023 12:16

Dear Dr Roche,

On behalf of the Chair and members of the SJH/TUH Joint Research Ethics Committee I wish to inform you that your study has received **FULL APPROVAL.** Your study can now proceed.

The following documents were reviewed and approved:

Document Type	File Name	Date	Version
Participant Information Leaflet	SCog_Lewy_PIL Information For Participants_Updated_	11.Oct.2023	2
Participant Information Leaflet	SCog_Lewy_Information_StudyPartner_Updated_For participants	11.Oct.2023	2
Participant Consent Form	Sense-Cog Lewy_Consent Forms_Updated	11.Oct.2023	2
Amended Documents	Sense-Cog Lewy Protocol Updated 16-10-2023	16.Oct.2023	1.1

Please note that ethical approval for this study is only active under the following conditions:

1. *Applicants must submit an annual report for ongoing projects.*

2. *Applicants must submit an end of study declaration/end of study report upon completion of the study.*
3. *All adverse events must be reported to the JREC.*
4. *All changes (minor and substantial) to documentation/study must be submitted to the JREC using the amendment request form and the changes must be tracked/highlighted clearly. Approval from the JREC is required before implementation of the changes.*

It is the responsibility of the researcher/research team to ensure all aspects of the study are executed in compliance with the General Data Protection regulation (GDPR), Health Research Regulations and the Data Protection Act 2018.

Yours sincerely,

Dr Sadhbh O'Neill

Research Ethics & Clinical Trials Manager,

SJH/TUH Joint Research Ethics Committee

The SJH/TUH Joint Research and Ethics Committee operates in compliance with and is constituted in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004 & ICH GCP guidelines.

1.2. Participant Information Leaflet

Tallaght University Hospital
Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

ST. JAMES'S HOSPITAL

SENSE Cog Promoting health for eyes, ears and mind.

SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment

Principal investigator's name: Iracema Leroi
Principal investigator's title: Associate Professor of Geriatric Psychiatry
Telephone number of principal investigator: 01896 8546

Consultant co-investigator's name: _____

Consultant co-investigator's title: _____

Data Controllers' Identity: Dr. Leroi (St. James's Hospital and Trinity College Dublin)
Drs. S. O'Dowd and S. Kennelly (Tallaght University Hospital and Trinity College Dublin)
Dr. J. Kane (Queen's University)
Dr. Irina Kinchin (Trinity College Dublin)

Data Controller's Contact Details:
Dr. Leroi (Iracema.leroi@tcd.ie)
Dr. S. O'Dowd (sean.ODowd@tuh.ie)
Dr. S. Kennelly (Sean.Kennelly@tuh.ie)
Dr. J. Kane (Joseph.Kane@qub.ac.uk
Dr. Irina Kinchin (KINCHINI@tcd.ie)

Data Protection Officer's Identity: _____

Data Protection Officer's Contact Details: _____
TUH = DPO@tuh.ie
SJH = dataprotection@stjames.ie

Tallaght University Hospital
Ospidéal Ollscoile Thamhlachta
An Academic Partner of Trinity College Dublin

ST. JAMES'S HOSPITAL

SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment

Older adult Information Leaflet

We would like to invite you to take part in a research study aimed at shedding light on the frequency of age-related hearing, vision and smell loss in individuals with difficulties in memory and other cognitive functions (e.g. concentration, attention) and on how sensory loss relates to cognitive difficulties, the way the person thinks, feels and acts, and on how such loss pertains to difficulties in activities of everyday life, quality of life and needs for care and support. As we age, the likelihood of developing problems with hearing, vision, smell increases. These problems affect the quality of life of older adults, impair communication with family members and friends and may worsen the impact of cognitive difficulties on activities of daily living. We are interested in studying sensory loss in older adults with cognitive impairment and its relationships with their cognitive difficulties, the way they think, feel and act, as well as with their support- and care needs and quality of life. Before deciding on whether or not you wish to take part, you should understand the risks and benefits of the study. This is called 'informed consent'. If you choose not to take part, this will have no effect on your medical care or treatment.

This information sheet explains what taking part involves. Please read it carefully, discuss it with others if you wish, and ask us if anything is unclear or if you would like more details.

This study is led by Drs I. Leroi (St. James's Hospital/Trinity College Dublin), S. O 'Dowd (Tallaght University Hospital), S. Kennelly (Tallaght University Hospital and Trinity College Dublin) and J. Kane, Queen's University Belfast. Three clinics for cognitive impairment in Dublin and Belfast are involved in it.

PART 1 – THE STUDY

What is the purpose of the study?

The purpose of the study is to assess hearing, vision and smell problems in older adults with cognitive difficulties, as well as to investigate whether and how sensory loss relates to their cognitive difficulties (e.g. difficulties with memory, concentration), the way they think, feel and act (e.g. presence of anxiety symptoms or sleep difficulties), their social functioning, their difficulties with activities of everyday life (e.g. cooking, shopping), their quality of life and the support they need from their care partners. We are hoping that by collecting data on the co-existence of sensory loss and the difficulties which people with cognitive impairment due to different diseases (e.g. Alzheimer's disease, Lewy bodies, Parkinson's disease) and their care partners face the importance of sensory loss assessment and treatment in people with cognitive difficulties will become evident.

Why have I been invited?

You have been invited to participate because you are over 60 and have cognitive difficulties and therefore form part of the population of people that could benefit from sensory loss assessment and treatment. In addition, the person who supports and helps you with everyday activities is also invited to participate in the study.
We need 60 adults over 60 with cognitive difficulties and their study partners to take part in our Ireland sample.

What will I be required to do?

You will undergo a series of tests/questionnaires for hearing, vision, smell and cognitive function (e.g., memory, attention, concentration) as well as tests/questionnaires which assess the way you think, feel and act (e.g. presence of anxiety symptoms or sleep difficulties). The tests will also assess any difficulties you may have with activities of everyday life (e.g. cooking, shopping), your quality of life and the support you need from your relatives and/or friends.

The assessments will be carried out at memory clinics at St. James's Hospital or Tallaght University Hospital in Dublin.

You will need a study partner to take part. We will ask your study partner to answer some questions about you. We will ask your permission for this in the consent form. We will be able to provide you with feedback on your study results once we have analysed the data from the session. We anticipate that each visit

will last around two to three hours. You will be entitled to as many breaks as needed, and coffee will be provided to you.

As the assessments require face-to-face contact all necessary measures of protection will be taken, such as the use of personal protective equipment if necessary. Measures to reduce the face-to-face contact time as much as possible have been put in place.

Do I need to inform my GP and my hospital consultant physician I am involved?
We will send your G.P. a letter and contact your hospital consultant physician to let them know you are taking part in the study, with your permission.

Can I choose whether or not to take part?
Yes, you can decide whether you want to take part. You or your study partner are free to withdraw at any time without giving a reason; this will not affect any of the care you receive. Your withdrawal will be recorded, and no more information will be collected and recorded about you. If you give us permission, we will use the data that we have collected up until that point. Otherwise, your data will be removed from the study.

How will the study benefit me?
Taking part in this study may reveal sensory difficulties which may be corrected (e.g., use of glasses, or hearing aids) leading to an improvement in your communication with family members and friends.

Are there any risks to me taking part?
There are no anticipated risks associated with the assessments.

Data Privacy: Your personal data will be accessed by the study team at the hospital at which you will be assessed. Please refer to Section 2 (Data Protection) for information on how we protect your identity.

What will happen to the results of the study?
Once the study is complete, we will present the findings at conferences and publish them in scientific journals. You will not be identified personally in any publications. We will also write to you (if you choose) and let you personally know the outcome of the study. If you would like this information or would like more information about future studies, please leave us your name and address (which we will keep confidentially). Also, you can take a look at our website: www.sense-cog.eu.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (contact details at the end of this leaflet).

Who has reviewed the study?

This research has been looked at by an independent group of people, called the St James's Hospital/Tallaght University Hospital Joint Research Ethics Committee to protect your safety, rights, well-being and dignity.

PART 2 – DATA PROTECTION

The study team will make every effort to protect your privacy on this study and will do so in accordance with European and Irish laws. The following sections will explain how your data is being used.

According to Art. 6(1)(e) and Art. 9(2)(j) of GDPR, your data is being used in this study for the purpose of scientific research in the public interest, while the right to data protection will be respected and your rights and interests will be safeguarded through the necessary measures being described in the following lines.

St James's Hospital, Tallaght University Hospital, Trinity College Dublin and Queen's University Belfast are independent data controllers for the study data. St James's Hospital and Tallaght University Hospital are the data controllers for your personal data which includes your medical records. Data controllers determine what information to collect, how it is used and how long to keep it. The data for this project will be kept up to a maximum of seven years after data analysis is complete.

What will happen to my personal data?

All of your study information will be labelled with a unique study ID number instead of your name. This is called 'coded' data.

The study teams either at St James's Hospital or at the Tallaght University Hospital, depending on the hospital at which you will be assessed, will have access to your identifiable personal information and the link between your name and the study ID number. Regulatory authorities may need access to your identifiable data to ensure that the study is being carried out properly.

Data collected will include information on your demographic data, care related data, your relationship with your study partner as well as on his/her quality of life.

'Coded' data from assessments will be held separately to your personal information so that you cannot be identified from your responses.

Your 'coded' study data will be sent electronically to the Mercer's Institute for Successful Ageing (MISA) at St. James's Hospital and to Trinity College Dublin to be analysed. 'Coded' electronic data will be stored on a secure database in St. James Hospital or in Tallaght University Hospital until it is transferred to MISA and Trinity College Dublin to be analysed.

How will my privacy be protected?
We will only collect the minimum information required for this study. Anyone accessing your personal information will be trained in data privacy and will be required to protect your privacy.

What are my rights to data?
Under GDPR, you have the following rights (unless the request would make it impossible or very difficult to conduct the research):

a. To access and receive a copy of your data
b. To restrict or object to the use of your data
c. To object to any further processing of the information we hold about you (except where it is de-identified)
d. To have inaccurate information about you corrected or deleted
e. To receive your data in a portable format and to have it transferred to another data controller
f. To request deletion of your data

If you wish to request any of the above or have any questions about your data on this study, you can do so by contacting the research assistant (contact details at the end of this leaflet) or the hospital data protection officer (*dataprotection@stjames.ie or DPO@tuh.ie*).

If you are not satisfied with the response, you can also lodge a complaint with the Irish Data Protection Commissioner (www.dataprotection.ie) or by post to: Data Protection Commission, 21 Fitzwilliam Square South, Dublin 2.

Future research:

This study forms the first wave of longitudinal study, in which you will be invited to return to complete a second and third round of similar assessments.

The 'coded' data collected in this study might be useful for other research related to diseases which affect thinking and movement which will take place in the future, and which will have been approved by a Research and Ethics Committee.

We would like to ask you to consent to future use of your coded data by researchers collaborating with the principal investigator and/or consultant co-investigators' of the present study. Any researchers accessing this data will make sure that your data is protected to the same standard as this study. You may decide if you wish to have your data used in future research or not.

PART 3 – CONTACT DETAILS

Who can I contact for further information on this study?

Please feel free to contact our research team at:

Email: emerald@tcd.ie
Phone: 01 4162082

Professor Iracema Leroi, Principle Investigator
Consultant Psychiatrist and Professor of Geriatric Psychiatry
St. James's University Hospital, James' St, Dublin 8
Global Brain Health Institute and School of Medicine, Trinity College Dublin

Dr Ciara Gibbons, Study Coordinator
Clinical Research Fellow and Specialist Registrar in Geriatrics, St. James's University Hospital, James' St, Dublin 8
Email: cigibbon@tcd.ie

Dr Adam Roche, Study Co-Investigator
Registrar in Geriatrics, St. James's University Hospital, James' St, Dublin 8
Lecturer Registrar, Global Brain Health Institute, Trinity College Dublin
Email: adroche@tcd.ie

Thank you for reading this information leaflet and for considering taking part in this research study.

Appendix 1.3. Study Consent Forms

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in participants with cognitive impairment

Consent Forms booklet

This Consent Form Booklet contains the following:

- *Capacity Checklist*
- *Contact details sheet (can be filled in ahead of visit)*
- *x2 Participant consent forms (one for participant, one for researcher)*
- *x2 Study Partner consent forms (one for participant, one for researcher)*

Guidelines for completing and storing the consent forms:

- ✓ Must be completed in participant's own handwriting
- ✓ Study Partner cannot sign on behalf of the older adult
- ✓ Boxes must be initialled, not ticked
- ✓ If the older adult cannot physically write, they can make a mark in the appropriate box and the researcher can countersign and date. Note a mark doesn't have to be made if the item is optional.
- ✓ Ensure that the signed documents are stored securely with the participant information sheet in a locked cabinet separate from the anonymised CRFs
- ✓ Do not write any participant identifiable information on the anonymised CRFs

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

Capacity Checklist

DEMONSTRATION OF CAPACITY

CHECKLIST FOR RESEARCHER TAKING CONSENT FROM PARTICIPANTS WITH EARLY-STAGE DEMENTIA OR MILD COGNITIVE IMPAIRMENT
Version 1 03/04/2013

The Mental Capacity Act 2005 proposes that people should be assumed to have capacity unless otherwise indicated. People with early-stage dementia or mild cognitive impairment are normally expected to have capacity to give informed consent to research participation. Capacity in this sense is demonstrated by the ability to understand the information given about the research, retain it for long enough to weigh up that information in order to reach a decision, and to state a decision clearly. The following checklist should be used when seeking informed consent from such individuals to ensure that these aspects are evaluated and that the criteria for capacity are met. If there is any doubt about capacity then consent must not be taken.

Study: **Participant ID:**

Ability	**Examples of how ability may be demonstrated**	**Ability demonstrated? (yes/no)**	**Comments and notes**
Understanding the information given about the research	Describing what the study involves. Asking appropriate questions. Seeking clarification.		
Retaining the information given about the research	Referring back to information given earlier in the meeting. Referring to the information sheet.		
Weighing up the information to reach a decision	Identifying advantages of participating or concerns about participating. Asking relevant questions. Discussing the information with a third party e.g. a family member.		
Communicating a clear decision	Giving a clear and unambiguous indication of willingness to take part		

Researcher name: **Signature:** **Date:**

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

Contact details sheet

Name of study participant _____

Address _____

_____

Telephone _____

Mobile _____

Email _____

Name of Study Partner _____

Address (if different) _____

_____

Telephone (if different) _____

Mobile (if different) _____

Email (if different) _____

Name of General Practitioner _____

Address _____

_____

Telephone _____

Email _____

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

Details to enable optimal contact between the research site and the participants during the study:

What is the relationship between the participants? How often do they see each other, where and when?

What is the preferred method of contact? Are there any days or times when it is best to call?

We intend to contact a small number of participants about their experiences. Would you be willing to be contacted for an interview?

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

SENSE-Cog Lewy: Investigating Sensory Function in older adults with cognitive impairment

Tick box

Study Participant Consent Form (researcher copy)

1.	I have read and understood the information sheet for the "SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment" study and have had the opportunity to ask questions.	**Yes** ☐ **No** ☐
2.	I understand that my participation in this study is voluntary and that, if I take part, I may withdraw at any time, without giving reasons, and without the standard of my medical or social care, or legal rights being affected.	**Yes** ☐ **No** ☐
3.	I consent to coded information about me, being sent in confidence to the study coordinators at the St. James's Hospital for analyses.	**Yes** ☐ **No** ☐
4.	I consent to copies of this form being made, the original will be kept in the "SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment" study file, one copy will be given to each participant and one copy placed in the medical records.	**Yes** ☐ **No** ☐
5.	I understand that my GP will be contacted about my participation in this study. I consent to a copy of this consent form being shared with my GP.	**Yes** ☐ **No** ☐
6.	I consent for my study partner to be asked questions about me.	**Yes** ☐ **No** ☐
7.	I agree that the study researchers may contact me by letter, telephone, or email to let me know about progress and results of the "SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment" study.	**Yes** ☐ **No** ☐

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

	Yes	No
8. I understand that all information collected will be held securely, in strict confidence, and used for medical research only and that I will not be identified in any way in the analysis and reporting of the results.	☐	☐
9. I consent to pseudonymised data collected during this study being used to support future research in dementia and may be shared with the other researchers.	☐	☐
10. I understand that data collected during the study may be looked at by St. James's Hospital, Tallaght University Hospital or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to the data.	☐	☐
11. I agree to take part in the "SENSE-Cog Lewy: Investigating sensory function and its relationships with symptoms, support needs and quality of life in older adults with cognitive impairment" study.	☐	☐

Name of Participant _____

Signature _____

Date _____

*Researcher countersignature (if required):*_____

Date: _____

Name of researcher taking consent: _____

Signature: _____

Date: _____

Copy to be placed in trial master file.

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

SENSE-Cog Lewy: Investigating Sensory Function in participants with cognitive impairment.

Tick box

Study Partner Consent Form (researcher copy)

1.	I have read and understood the information sheet for the "SENSE-Cog Lewy: Investigating Sensory Function in older adults with cognitive impairment" and have had the opportunity to ask questions.	**Yes** ☐ **No** ☐
2.	I understand that my participation in this study is voluntary and that, if I take part, I may withdraw at any time, without giving reasons, and without my legal rights being affected.	**Yes** ☐ **No** ☐
3.	I consent to coded information about me, being sent in confidence to the study coordinators at the St. James's Hospital for analyses.	**Yes** ☐ **No** ☐
4.	I consent to copies of this form being made, the original will be kept in the "SENSE-Cog Lewy: Investigating Sensory Function in older adults with cognitive impairment" study file, one copy will be given to each participant and one copy placed in the medical records.	**Yes** ☐ **No** ☐
5.	I agree that the study researchers may contact me by letter, telephone, or email to let me know about progress and results of the "SENSE-Cog Lewy: Investigating Sensory Function in older adults with cognitive impairment" study.	**Yes** ☐ **No** ☐
6.	I understand that all information collected will be held securely, in strict confidence, and used for medical research only and that I will not be identified in any way in the analysis and reporting of the results.	**Yes** ☐ **No** ☐
7.	I consent to pseudonymised data collected during this study being used to support future research and may be shared with the other researchers.	**Yes** ☐ **No** ☐

Participant ID: __ __ __ / __ __ __
Study Partner ID: __ __ __ / __ __ __

	Yes	No
8. I understand that data collected during the study may be looked at by individuals from St. James's Hospital, Tallaght University Hospital or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to the data.	☐	☐
9. I agree that my GP may be contacted about my participation in this study.	☐	☐
10. I agree to take part in the "SENSE-Cog Lewy: Investigating Sensory Function in older adults with cognitive impairment" study.	☐	☐

Name of Participant _____

Signature _____

Date _____

*Researcher countersignature (if required):*_____

Date: _____

Name of researcher taking consent:_____

Signature: _____

Date: _____

Copy to be placed in trial master file

Appendix 2. Recruitment Documentation

2.1. Participant Recruitment Standard Operating Procedure

SENSE-Cog Lewy Participant Recruitment SOP

Patients identified via two pathways:

1. **SJH Pathway**
   - **i.** Interested Participants identified in Clinic
   - **ii.** Details taken by clinician (Adam) reviewing participant and uploaded into locked document on designated research computer, floor 2 SJH (See Appendix 1)
   - **iii.** Participant contacted by researcher the following week and booked in for assessment
   - **iv.** Contact should be initially by phone call (See Appendix 2) with a follow-up email on the 'Emerald@tcd.ie' email address to clarify time, date and location of assessment (See Appendix 3)
   - **v.** Manage calendar to ensure assessing clinician (Adam) and co-participant assessor available to complete assessment on that date and room available & booked
   - **vi.** Room to be booked is the assessment room beside the Dementia Trials Ireland Research Office
   - **vii.** Participants to be contacted at 6 months to be followed up for the potential longitudinal aspect of data collection – this should be done at their clinical follow-up, if at all possible, to ensure they still meet eligibility criteria and wish to continue with the study
   - **viii.** Steps **ii-vii** then repeated

2. **Outside SJH**
   - **i.** Interested participants details forwarded to 'Emerald@tcd.ie' email from other hospital sites
   - **ii.** Details uploaded by individual monitoring email address into locked document on designated research office computer, floor 2 SJH (See Appendix 1)
   - **iii.** Participant contacted by and booked in for assessment
   - **iv.** Contact should be initially by phone call (See Appendix 2)with a follow-up email on the 'Emerald@tcd.ie' email address to clarify time, date and location of assessment (See Appendix 3)
   - **v.** Manage calendar to ensure assessing clinician and co-participant assessor available to complete assessment on that date and room available & booked
   - **vi.** Participants to be contacted at 6 months to be followed up for the potential longitudinal aspect of data collection, depending on ongoing eligibility
   - **vii.** Steps **ii-vi** then repeated

Appendix 1: Interested Participant Document

No. Referral Source	Participant Name	DOB	MRN	Phone Number Email	Co-Participant Name	Phone Number Email	Date Contacted	1st Assessment	2nd Date Contacted	2nd Assessment
1. SJH	Joe Bloggs	21/08/24	12345	123456 joebloggs@gmail.com	Mary Bloggs	45678 marybloggs@gmail.com	20/02/24	01/03/24	21/08/24	

Appendix 2: Phone Call Script

Hello,
I am looking to speak to Mr./Mrs. ____. My name is _____ and I am part of the research team in St. James's Hospital. I believe you were speaking with (clinician's name) about potentially being involved in our study at your last clinic appointment. Firstly, thank you so much for agreeing to be part of our study. We are hugely appreciative.

I am calling to try and arrange a time that would suit you to come in for your research assessment. The assessment takes about 2 hours in total. Please do not feel any pressure though if it no longer suits you to participate.

Are you available on _____ at _____?

Great! I will book you in for that time. On the day, we will meet you at the Leopold Cafe in the MISA building in St. James's Hospital. I will send you an e-mail with all of these details following our phone call so you have them to refer to. Can I confirm your email address please?

We look forward to seeing you on ___ at_____. You will receive our contact details in the email I'm about to send. Please do not hesitate to contact us if you have any further questions or it no longer suits you to be part of the study. Thanks again!

Appendix 3: Draft Email to Participants

Dear Mr/Mrs _____,

Thank you very much for taking my call today and agreeing to participate in our study. Your input is highly appreciated and valued.

As discussed, we will meet you at ___ on ____ at the Leopold Café in the MISA Building, Ground Floor, St. James' Hospital in order to complete our assessment. Our assessment should take a total of 1.5-2 hours.

I have attached to copy of our information leaflet to this email which may answer any further questions that you have. If not, please do not hesitate to contact us on this email address.

We look forward to seeing you!

Warmest regards,

_____

2.2. Inclusion and Exclusion Criteria

Inclusion Criteria

Participants were eligible if they met established diagnostic criteria for Lewy body disease, encompassing:

- Probable Dementia with Lewy Bodies according to the 2017 DLB Consortium criteria [18]
- Prodromal DLB as defined by emerging research consensus for prodromal Lewy body syndromes [41, 127]
- Parkinson's Disease Dementia (PDD) meeting Movement Disorder Society (MDS) Task Force guidelines [35]
- Parkinson's Disease with Mild Cognitive Impairment (PD-MCI) fulfilling MDS Level II (Comprehensive Assessment) criteria [224].

Additional inclusion requirements were:

- Age ≥ 50 years;
- Capacity to provide informed consent, formally verified by trained research personnel;
- Availability of an adult (≥ 18 years) co-participant familiar with the participant's health and daily function; and
- Ability to attend the study site and complete assessments conducted in English.

Exclusion Criteria

Participants were excluded if they met the following criteria:

- Primary neurodegenerative diagnosis other than LBD (e.g. Alzheimer's disease, frontotemporal dementia);
- Acute delirium or had an unstable medical or psychiatric condition likely to interfere with testing;
- Severe uncorrected hearing or visual impairment that precluded valid sensory testing; or
- Unable to complete validated instruments because of language, comprehension, or motor limitations.

EMERALD LEWY STUDY

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Improving the diagnosis, management, and lived experience of overlooked Dementias in Ireland.

Who can get involved?

Inclusion criteria:

All participants must have

- Diagnosis of probable DLB, PDD or PD with Mild Cognitive Impairment
- Mild to Moderate cognitive impairment.
- Spouse, close relative or well-established care partner to act as an informant and research participant.

Exclusion criteria:

- Diagnosis of dementia due to a cause other than DLB/PDD.
- Diagnosis of significant chronic mental disorder other than dementia (e.g. schizophrenia).
- Unstable significant medical comorbidity likely to interfere with cognitive function and/or compliance in the study protocol over 12-month period.

Participation:

The study involves non-invasive sensory, cognitive and autonomic evaluations, including visual acuity, hearing, olfactory and autonomic function tests. Procedures are designed with patient sensitivity as a priority, ensuring comfort and safety and will take place over one or two short visits to Mercer's Institute for Successful Ageing (MISA) in St. James's Hospital Dublin, performed by experienced members of our research team.

Full ethics approval for this study has been granted by SJH/TUH Joint Research Ethics Committee.

Collaboration Invitation:

We invite clinicians to refer potential patients to our study.

2.3. Participant Referral Form

Appendix 3: Case Research Forms

The SENSE-Cog Lewy Case Report Forms (CRFs) supported standardised data collection across demographic, clinical, cognitive, functional, quality-of-life, caregiver burden, and sensory domains. Forms were designed by the author for this study. Only blank or abridged versions are presented. Proprietary instruments are described but not reproduced.

Summary of Report Forms:

- **Form A: Participant and Co-Participant Demographics:** Age, sex, diagnosis, education, marital and living status, accommodation, socioeconomic measures, co-participant relationship and contact frequency.
- **Form B: Medical and Health History:** Medical comorbidities, including cardiovascular, neurological, psychiatric and other comorbidities. Substance and alcohol history. Medication list and class summaries. Anticholinergic burden. Parkinson's therapy summary.
- **Form C: Cognitive and Neuropsychiatric Assessments:** MoCA total score, CDR, NPI-Q, HADS and additional study fields.
- **Form D: Motor and Autonomic Assessments:** UPDRS II and III, Hoen and Yahr stage, Bristol Activities of Daily Living Scale, Non motor symptom scale, Mayo Sleep Scale, Mayo Fluctuation Scale
- **Form E: Quality of Life and Caregiver Burden:** QOL-AD totals. EQ-5D-5L utility and visual analogue scale. Zarit Burden Interview total.
- **Form F: Sensory Assessments:** Hearing, Vision and Olfactory History. Hearing (HearCheck), Vision (PEEK Acuity), Olfaction (UPSIT 40)

All licenced questionnaires and scales were administered under institutional or individual permissions. Full instruments are not reproduced. Derived variables and study-specific fields are shown for transparency.

Form A1. Study Participant Demographics

1. **Participant ID:**
   E L ☐☐☐

2. **Participant Age:**

   _____

3. **Participant Sex:**
Study participant sex*

- 1 = Male ☐
- 2 = Female ☐
- 8 = Prefer not to answer ☐
- 999 = Unknown ☐
- Other: Please specify ☐

*May not need to ask BOTH sex and gender directly
If necessary, can clarify by asking participant: "What is your gender/gender identity?"/"What sex were you assigned at birth, on your original birth certificate?"

4. **Participant Diagnosis:**
   Study participant probable dementia diagnosis
- 0 = Normal cognition ☐

Lewy Body Dementias:
- 1 = Probable Dementia with Lewy bodies (DLB) ☐
- 2 = Prodromal DLB ☐
- 3 = Parkinson's disease with dementia (PDD) ☐
- 4 = Parkinson's disease with mild cognitive impairment (PD MCI) ☐

Other dementia sub-types:
- 5 = Alzheimer's dementia (AD) ☐
- 6 = Alzheimer's dementia with MCI ☐
- 7 = Fronto Temporal dementia ☐
- 8 = Vascular dementia ☐
- 9 = Huntington's Disease ☐
- 10 = Mixed Dementia Diagnosis ☐
- Other: Please specify _____ ☐
- 999 = Unknown ☐

5. **Time since symptom onset:**

   _____ (Time to nearest month)

6. **Time since probable diagnosis (if known):**

   _____ (Time to nearest month)

7. **Participant Referral Source:**
- 0 = Emergency Department ☐
- 1 = Parkinson's Disease Service ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

- 2 = Memory Clinic ☐
- 3 = Falls Unit ☐
- 4 = GP Referral ☐
- 5 = Geriatrics service (excluding Memory clinic) ☐
- 6 = Psychiatry service (excluding Memory clinic) ☐
- 7 = Other Outpatients Clinic ☐
- 8 = Inpatient Unit Referral ☐
- 9 = Self-Referral ☐
- 10 = ICPOP/Community PT/OT/PHN ☐
- 999 = Unknown ☐

8. Participant Handedness:

Hand dominance: Is the subject left- or right-handed or ambidextrous (i.e. which hand would they normally use to write with or throw a ball)?

- 1 = Right-handed ☐
- 2 = Left-handed ☐
- 3 = Ambidextrous ☐
- 999 = Unknown ☐

9. Participant Education:

Study participant's highest level of education completed
(Note: if an attempted level is not completed, enter the number of years completed)

Years in education:

_____

- 8 = Primary School
- 11 = Secondary School (**Lower Level: completed Junior Certificate or equivalent)**
- 13 = Secondary School **(Upper Level: Completed Leaving Certificate or equivalent**)
- 15 = Post Secondary School course or Apprenticeship
- 16 = Primary University or Undergraduate Degree
- 20 = Master's Degree or equivalent
- 22 = Doctorate or equivalent
- 999 = Unknown

10. Participant Marital Status:

Study participant's current marital status should be coded as:

- 1 = Married ☐
- 2 = Widowed ☐
- 3 = Divorced ☐
- 4 = Separated ☐
- 5 = Never married (or marriage was annulled) ☐
- 6 = Living as married/domestic partner ☐
- 999 = Unknown ☐

11. Participant Living Situation:

- 1 = Lives alone ☐
- 2 = Lives with one other person: a spouse or partner ☐
- 3 = Lives with one other person: a relative, friend, or roommate ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

- 4 = Lives with caregiver (not spouse/partner, relative, or friend) ☐
- 5 = Lives with group (related or not related) in private residence ☐
- 6 = Lives in group home (e.g. assisted living, nursing home or convent) ☐
- 999 = Unknown ☐

12. Participant Accommodation Type:

- 1 = Detached, Semi-detached or Terraced House ☐
- 2 = Apartment or Flat ☐
- 3 = Nursing home or long term care ☐
- 4 = Convent or religious order shared accommodation ☐
- 5 = Mobile home or temporary structure ☐
- 6 = Sheltered housing ☐
- 999 = Unknown ☐

13. Participant Ethnicity and Cultural Background:

- 1 = White Irish ☐
- 2 = Any other White background ☐
- 3 = Asian or Asian Irish - Indian/Pakistani/Bangladeshi ☐
- 4 = Asian or Asian Irish - Chinese/other Asian background ☐
- 5 = Black or Black Irish - African/Caribbean/other Black background ☐
- 6 = Arab / Middle Eastern ☐
- 7 = Other including mixed background ☐
- 8 = White Irish Traveller ☐
- 0 = Rather not say ☐
- 999 = Unknown ☐

14. Participant Employment:

Participant's current employment status

- 0 = Retired ☐
- 1 = Person at work / Currently working ☐
- 2 = Unemployed - seeking job ☐
- 3 = Student or pupil ☐
- 4 = Looking after home/family ☐
- 5 = Unable to work due permanent sickness or disability ☐
- 999 = Unknown ☐

15. Participant Occupation: What is or was participant's main occupation or job?

_____ (can use participant's own words)

16. Participant Socioeconomic Group:

Participant Occupational / Socio-Economic Group (as per Census 2022 classification of occupational categories).

The socio-economic groups used in the census are as follows:

- A Employers and managers = 0 ☐
- B Higher professional = 1 ☐
- C Lower professional = 2 ☐
- D Non-manual = 3 ☐
- E Manual skilled = 4 ☐
- F Semi-skilled = 5 ☐
- G Unskilled = 6 ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

- H Own account workers = 7 ☐
- I Farmers = 8 ☐
- J Agricultural workers = 9 ☐
- Z All others gainfully occupied and unknown = 999 ☐

17. Participant Social Deprivation Index:

- 1 = Extremely Disadvantaged ☐
- 2 = Very Disadvantaged ☐
- 3 = Disadvantaged ☐
- 4 = Marginally Below Average ☐
- 5 = Marginally Above Average ☐
- 6 = Affluent ☐
- 7 = Very Affluent ☐
- 8 = Extremely Affluent ☐
- 999 = Unknown ☐

Please note: HP Pobal Deprivation Index *is categorised by home address/Eircode.*
For more information see: https://www.pobal.ie/pobal-hp-deprivation-index

18. Participant Medical or GP Visit Card:

- 0 = No medical or GP visit card ☐
- 1 = Medical card only ☐
- 2= GP visit card only ☐
- 3 = Both GP visit card and medical card ☐
- 999 = Unknown ☐

19. Participant Home Support Service:
Participant has Home Support Service
(i.e. Home Care Package or other home support) in place:

- 0 = No ☐

Form A2. Study Co-Participant Demographics

- 1 = Yes ☐
- 999 = Unknown ☐

20. Co-Participant Age: Age in years

_____

21. Co-Participant Sex:
Study participant sex*

- 1 = Male ☐
- 2 = Female ☐
- 8 = Prefer not to answer ☐
- 999 = Unknown ☐

22. Co-Participant Education:

_____

Study participant's highest level of education completed
(Note: if an attempted level is not completed, enter the number of years completed)

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

Years in education:

- 8 = Primary School
- 11 = Secondary School **(Lower Level: completed Junior Certificate or equivalent)**
- 13 = Secondary School **(Upper Level: Completed Leaving Certificate or equivalent)**
- 15 = Post Secondary School course or Apprenticeship
- 16 = Primary University or Undergraduate Degree
- 20 = Master's Degree or equivalent
- 22 = Doctorate or equivalent
- 999 = Unknown

23. Co-Participant Relationship:

Co-participant's relationship to the participant:

- 1 = Spouse, partner or companion (incl. ex-spouse, fiancé, boyfriend, girlfriend) ☐
- 2 = Child (by blood or through marriage or adoption) ☐
- 3 = Sibling (by blood or through marriage or adoption) ☐
- 4 = Other relative (by blood or through marriage or adoption) ☐
- 5 = Friend, neighbour or know through family, friends, work or community ☐
- 6 = Paid caregiver, health care provider, or clinician ☐
- 999 = Unknown ☐

24. Co-Participant Years known

_____

25. Is the Co-Participant living with the Study Participant?

- 0 = No ☐
- 1 = Yes ☐
- 999 = Unknown ☐

26. Co-Participant Visit Frequency

If answered "no" to above (i.e. co-participant does not live with participant):
what is the approximate frequency of in-person visits?

- 1 = Daily ☐
- 2 = At least three times per week ☐
- 3 = Weekly ☐
- 4 = At least three times per month ☐
- 5 = Monthly ☐
- 6 = Less than once a month ☐
- 999 = Unknown ☐

27. Co-Participant Contact Frequency

If answered "no" to above (i.e. co-participant does not live with participant):
what is the approximate frequency of non in-person contact
(phone call, text, email or social media)?

- 1 = Daily ☐
- 2 = At least three times per week ☐
- 3 = Weekly ☐
- 4 = At least three times per month ☐
- 5 = Monthly ☐
- 6 = Less than once a month ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

- 999 = Unknown ☐

Form B1: Study Participant Health History

Key Health History Categories:

- **Form B1.1. Smoking, Alcohol and Substance History**
- **Form B1.2. Psychiatric History**
- **Form B1.3. Cardiovascular and Cerebrovascular History**
- **Form B1.4. Neurological History**
- **Form B1.5. Other Medical Disease History**
- **Form B1.6. Dementia Family History**

Categories for individual medical conditions coded as:

- 0 = Absent - It has never been present
- 1 = Recent/Active - It happened in the last year or still requires active management
- 2 = Remote/Inactive - It existed or occurred in the past (more than one year ago) but was resolved or there is currently no treatment currently underway
- 999 = Unknown - There is insufficient information available to assess this condition

Form B1.1: Smoking, Alcohol and Substance History

A. Smoking History

1. Smoking Status

- 0 = Never Smoker ☐
- 1 = Ex-Smoker ☐
- 2 = Current Smoker (i.e. Smoked in last 30 days) ☐
- 3 = E-Cigarette/Vape User ☐
- 999 = Unknown ☐

2. Total Pack Years

No. of cigarettes per day DIVIDED by 20 MULTIPLIED by no. of years smoking

_____

0 = Never smoked
999 = Unknown
Pack year online calculator: https://www.smokingpackyears.com/

3. E-Cigarette Use

- 0 = Never ☐
- 1 = Current User (last 30 days) ☐
- 999 = Unknown ☐

4. E-Cigarette Frequency

- 0 = Never ☐
- 1 = Some days (last 30 days) ☐
- 2 = Everyday/most days (last 30 days) ☐
- 999 = Unknown ☐

B. Alcohol History

1. Current Drinker

- 0 = Never Drinker/No alcohol last 30 days ☐
- 1 = Yes (i.e. drank in last 30 days) ☐
- 999 = Unknown ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

2. Alcohol Frequency

During the past three months:
How often did the subject have at least one drink of any alcohol?

- 0 = Less than once a month ☐
- 1 = About once a month ☐
- 2 = About once a week ☐
- 3 = A few times a week ☐
- 4 = Daily or almost daily ☐
- 999 = Unknown ☐

3. Alcohol Volume

On days when the participant drink alcoholic beverages, how many standard drinks would they consume?
(A standard drink is a half pint of beer (4.5% lager), a small glass of wine (100ml of 12.5% strength) or a measure of spirits (40%). One unit equals 10ml alcohol.)

- 0 = No alcohol / Never drinks ☐
- 1 = 1 to 2 ☐
- 2 = 3 to 4 ☐
- 3 = 5 to 6 ☐
- 4 = 7 to 9 ☐
- 5 = 10 or more ☐
- 999 = Unknown ☐

C. Substance Use

1. Recent Substance Use

Has the participant used substances including prescription or recreational drugs WITHIN the last 12 months that caused significant impairment in:
Work, driving, legal, social or other activities?

- 0 = No ☐
- 1 = Yes ☐
- 999 = Don't know ☐

2. Previous Substance Use

Has the participant used substances including prescription or recreational drugs prior to the last 12 months that caused significant impairment in: Work, driving, legal, social or other activities?

- 0 = No ☐
- 1 = Yes ☐
- 999 = Don't know ☐

3. Substance Use Category

What is main substance used by the participant, if substance abuse present?

- 0 = No substance abuse ☐
- 1 = Opioids ☐
- 2 = Stimulants ☐
- 3 = Cannabis ☐
- 4 = Benzodiazepine ☐
- 999 = Unknown ☐
- Other substances (Please specify): _____ ☐

4. Substance Use Frequency

Substance use frequency If the participant engages in substance abuse, in the past 12 months, how often has the participant consumed the substance in question?

- 0 = No substance abuse / Never ☐

Form Authors: Dr Adam Roche (adroche@tcd.ie) and Dr Ciara Gibbons (cigibbon@tcd.ie)

- 1 = Monthly or less ☐
- 2 = 2 - 4 times a month ☐
- 3 = 2 - 4 times a week ☐
- 4 = 4 or more times a week ☐
- 999 = Unknown ☐

Form B1.2. Psychiatric History:

0 = Absent / 1 = Recent or Active / 2 = Remote or Inactive / 999 = Unknown

• Post-traumatic stress disorder (PTSD)	0 ☐	1 ☐	2 ☐	999 ☐
• Bipolar disorder	0 ☐	1 ☐	2 ☐	999 ☐
• Schizophrenia	0 ☐	1 ☐	2 ☐	999 ☐
• Depression/Anxiety	0 ☐	1 ☐	2 ☐	999 ☐
• Obsessive-compulsive disorder	0 ☐	1 ☐	2 ☐	999 ☐
• Neurodevelopmental disorders	0 ☐	1 ☐	2 ☐	999 ☐

Form B1.3. Cardiovascular and Cerebrovascular History:

0 = Absent / 1 = Recent or Active / 2 = Remote or Inactive / 999 = Unknown

• Atrial Fibrillation/Arrhythmias	0 ☐	1 ☐	2 ☐	999 ☐
• Pacemaker and/or defibrillator	0 ☐	1 ☐	2 ☐	999 ☐
• Cardiac Arrest	0 ☐	1 ☐	2 ☐	999 ☐
• IHD/Angina/MI treated medically	0 ☐	1 ☐	2 ☐	999 ☐
• IHD/MI treated with PCI	0 ☐	1 ☐	2 ☐	999 ☐
• IHD/MI treated with CABG	0 ☐	1 ☐	2 ☐	999 ☐
• Congestive heart failure	0 ☐	1 ☐	2 ☐	999 ☐
• Heart valve disease or surgery	0 ☐	1 ☐	2 ☐	999 ☐
• Hypertension	0 ☐	1 ☐	2 ☐	999 ☐
• Hypercholesterolaemia	0 ☐	1 ☐	2 ☐	999 ☐
• Stroke	0 ☐	1 ☐	2 ☐	999 ☐
• TIA	0 ☐	1 ☐	2 ☐	999 ☐
• Carotid artery surgery or stents / significant stenosis (≥50% or symptomatic)	0 ☐	1 ☐	2 ☐	999 ☐
• Peripheral vascular disease	0 ☐	1 ☐	2 ☐	999 ☐
• AAA/Aneurysm surveillance	0 ☐	1 ☐	2 ☐	999 ☐

Form B1.4. Neurological Disease History:

0 = Absent / 1 = Recent or Active / 2 = Remote or Inactive / 999 = Unknown

• Epilepsy or history of seizures	0 ☐	1 ☐	2 ☐	999 ☐
• Chronic headaches	0 ☐	1 ☐	2 ☐	999 ☐
• Multiple sclerosis	0 ☐	1 ☐	2 ☐	999 ☐
• Normal pressure hydrocephalus	0 ☐	1 ☐	2 ☐	999 ☐
• Traumatic brain injury (TBI) or repetitive head trauma	0 ☐	1 ☐	2 ☐	999 ☐

Form B1.5. Other Medical Condition History:

0 = Absent / 1 = Recent or Active / 2 = Remote or Inactive / 999 = Unknown

• Diabetes Mellitus	0 ☐	1 ☐	2 ☐	999 ☐
• Vitamin B12 Deficiency	0 ☐	1 ☐	2 ☐	999 ☐
• Thyroid Disease	0 ☐	1 ☐	2 ☐	999 ☐
• Arthritis/Joint or Back Pain	0 ☐	1 ☐	2 ☐	999 ☐

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• Osteoporosis/Osteopaenia	0 ☐	1 ☐	2 ☐	999 ☐
• Malignancy (Primary or Secondary)	0 ☐	1 ☐	2 ☐	999 ☐
• Chronic Kidney Disease	0 ☐	1 ☐	2 ☐	999 ☐
• Asthma/COPD/Pulmonary Disease	0 ☐	1 ☐	2 ☐	999 ☐
• Liver Disease	0 ☐	1 ☐	2 ☐	999 ☐
• Peripheral Vascular Disease	0 ☐	1 ☐	2 ☐	999 ☐
• HIV	0 ☐	1 ☐	2 ☐	999 ☐
• Recent Covid infection	0 ☐	1 ☐	2 ☐	999 ☐

Form B1.6. Family History of Dementia

Is there a first degree family history of dementia/neurological/psychiatric conditions?

Family history = Are there affected first-degree relatives?
(i.e. biological parents, full siblings, or biological children)

- 0 = No ☐
- 1 = Yes ☐
- 999 = Don't know ☐

If yes, please select which disease there a family history of:

- Alzheimer's Disease ☐
- Lewy body dementia (DLB and PDD) ☐
- Parkinson's disease (with no known dementia) ☐
- Vascular dementia ☐
- Stroke ☐
- Frontotemporal dementia ☐
- Primary progressive aphasia ☐
- Corticobasal syndrome ☐
- Supranuclear palsy ☐
- Multiple systems atrophy ☐
- Huntington's disease ☐
- Dementia of unknown aetiology ☐
- Amyotrophic lateral sclerosis/MND ☐
- Multiple Sclerosis ☐
- Psychiatric condition ☐
  (e.g. schizophrenia, bipolar disorder or depression)

Form B2: Participant Medication

Form B2.1. Current Medication List:

Current Medications:
1.
2.
3.
4.
5. etc.

B2.2. Specific Medications: Cognitive

1. **Is the participant taking dementia specific medications?**

- 0 = No dementia specific medications ☐
- 1 = Donepezil ☐
- 2 = Rivastigmine ☐

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- 3 = Galantamine ☐
- 4 = Memantine ☐
- 999 = Unknown ☐

2. Anticholinergic cognitive burden (ACB) score

Anticholinergic burden is the cumulative effect on an individual of taking one or more medications with anticholinergic activity.
See: https://www.acbcalc.com/ to calculate score.

ACB Score: _____

B2.3. Other Relevant Medications:

A. Neuropsychiatric Treatment

- **Mood or Anxiety medications: SSRIs/SNRIs e.g. Duloxetine/Mirtazapine** ☐
- **Antipsychotics: e.g. Quetiapine and Clozapine** ☐
- **Sedatives (for anxiety or agitation) e.g. Benzodiazepines** ☐

B. Sleep Disorders Management:

- **Melatonin** ☐
- **Hypnotic (e.g. Z drugs: Zolpidem or Zopiclone)** ☐
- **Sedative (if used primarily as sleep aid) e.g. Clonazepam or other benzodiazepines** ☐

C. Motor Symptom Treatment:

- **Levodopa** ☐
- **Dopamine agonists (pramipexole, ropinirole)** ☐
- **MAO-B inhibitors (rasagiline, selegiline, safinamide)** ☐
- **COMT inhibitors (entacapone, opicapone)** ☐
- **Other Motor Symptom Treatment** ☐

Levodopa Equivalent Dose: _____

Levodopa Equivalent Dose Calculator:
https://www.parkinsonsmeasurement.org/toolBox/levodopaEquivalentDose.htm

D. Autonomic Management

Management or treatment of any of following;
(***Please clarify which medication used)***

- **Orthostatic Hypotension:** Medication _____ ☐
- **Drooling:** Medication _____ ☐
- **Urinary dysfunction:** Medication _____ ☐
- **Erectile dysfunction:** Medication _____ ☐
- **GI dysfunction:** Medication _____ ☐
- **Pain (due to PD/DLB):** Medication _____ ☐

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Form C. Cognitive and Neuropsychiatric Assessments

Purpose is to capture global cognition and neuropsychiatric symptoms relevant to Lewy body disorders. Licenced content not reproduced. CDR. HADS. NPI-Q and NPI. Present only the derived and study-specific fields below.

Form C1: Cognitive Assessments

C1.1. Montreal Cognitive Assessment (MoCA)

- Visuospatial/Executive [/5]
- Language [/ 8]
- Attention [/ 6]
- Memory/Recall [/ 5]
- Orientation [/ 6]

MoCA Total Score **[_____ / 30]**

C1.2. Verbal Fluency [/ 14]

C1.3. Degraded letter test [/ 4]

C1.4. Clinical Dementia Rating (CDR): [_____]

Scored 0 / 0.5 / 1 / 2 / 3

Form C2: Neuropsychiatric Assessments

C2.1: Hospital Anxiety and Depression Score (HADS)

Depression Score: [_____ / 21]

Anxiety Score: [_____ / 21]

Total Score: **[_____ / 42]**

C2.2: Neuropsychiatric Inventory (NPI)

Total Severity Score: [/ 36]

Total Distress Score: [/ 60]

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Form D. Motor and Non-Motor Assessments

Form D1: Motor Assessments

D1.1. UPDRS Part II: Motor Aspects of Experiences of Daily Living (M-EDL)

1. Speech
2. Saliva and Drooling
3. Chewing and Swallowing
4. Eating Tasks
5. Dressing
6. Hygiene
7. Handwriting
8. Hobbies and Activities
9. Turning in Bed
10. Tremor
11. Getting out of Deep Seating Position
12. Walking and Balance
13. Freezing

Rated 0 – 4: Normal / Slight / Mild / Moderate or Severe Impairments

Total Score: / 52

D1.2. UPDRS Part III: Motor Examination

1. Speech
2. Facial Expression
3. Rigidity (Neck / RUE / LUE / RLE / LLE)
4. Finger Tapping (R / L)
5. Hand Movement (R / L)
6. Pronation-Supination of Hands (R / L)
7. Toe Tapping (R / L)
8. Leg Agility (R / L)
9. Arising from Chair
10. Gait
11. Freezing of Gait
12. Postural Stability
13. Posture
14. Global Spontaneity of Movement (Body Bradykinesia)
15. Postural Tremor of the Hands (R / L)

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16. Kinetic Tremor of the Hands (R / L)
17. Rest Tremor Amplitude (R+LUE/R+LLE/Lip and Jaw)
18. Constancy of Rest Tremor

Rated 0 – 4: Normal / Slight / Mild / Moderate or Severe Impairments

Total Score: / 132

Dyskinesia Impact on Score: Yes / No

D1.3. Hoehn and Yahr Scale:

Rated 0 – 5 (Score / 5)

D1.4. Bristol Activities of Daily Living

- 20 Activities of Daily Living
- Rated 0 – 4:
- Normal / Mild / Moderate / Complete Dependence or N/A

Total Score: / 60

Form D2: Non-Motor Assessments

D2.1. Non-Motor Symptom Scale for Parkinson's Disease

- Comprises 30 items across 9 domains:
- Cardiovascular
- Sleep/fatigue
- Mood/cognition
- Perceptual problems/hallucinations
- Attention/memory
- Gastrointestinal tract
- Urinary
- Sexual function
- Miscellaneous

- Scoring system: Each symptom is rated for Severity (0–3) and Frequency (1–4).
- Total Severity Score: / 90
- Total Frequency Score: / 120
- A domain score is derived as: Severity × Frequency for each item, summed across that domain.
- The Total NMSS score equals the sum of all domain scores, ranging from 0 to 360.
- Higher scores indicate greater non-motor symptom burden.

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D2.2. Mayo Sleep Questionnaire

Core domains assessed:

- Acting out dreams (REM sleep behaviour disorder).
- Repetitive leg jerks or twitching (periodic limb movements).
- Restless legs sensations disrupting sleep.
- Sleepwalking or nocturnal wandering.
- Snorting, choking, or apnoea episodes during sleep.
- Nocturnal leg cramps.
- Daytime alertness rating (0–10 scale).

..

D2.3. Mayo Fluctuations Scale

Mayo Fluctuations Scale	Yes	No	Don't Know
1. How often is the participant drowsy and lethargic during the day, despite getting enough sleep the night before?			
2. Does the participant sleep two or more hours during the day (before 7:00 p.m.)?			
3. Are there times when the patient's flow of ideas seem disorganised, unclear or not logical?			
4. Does the participant stare into space for long periods of time?			

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Form E. Quality of Life and Caregiver Burden

Purpose. To record participant quality of life and caregiver burden.

Form E1: Quality of Life Assessments

E1.1 and E1.2. Quality of Life in Alzheimer's Disease (QOL-AD)

Participant / Co-participant

1. Physical Health
2. Energy Level
3. Mood
4. Living Situation
5. Memory
6. Family
7. Marriage
8. Friends
9. Self as a whole
10. Ability to do chores around the house
11. Ability to do things for fun
12. Money
13. Life as a whole

Rated 1 – 4: 1 = Poor/ 2 = Fair / 3 = Good / 4 = Excellent / 999 = Unknown

E1.3. EQ-5D-5L

1. Mobility
2. Self-Care
3. Usual Activity
4. Pain and Discomfort
5. Anxiety and Depression

Rated 0 – 4: Normal / Slight / Moderate / Severe Impairments
Health Rating: 0 – 100

Form E2.1: Zarit Caregiver Burden Assessment (12 Item)

Domains assessed:

- Emotional strain (e.g. frustration, guilt, resentment).
- Physical fatigue and health impact.
- Social and family role disruption.
- Financial and time demands.
- Perceived loss of control or overload.

Scoring: 5-point Likert scale per item (0 = Never to 4 = Nearly always).
Total score = sum of all items (range 0–48).
Higher scores indicate greater perceived caregiver burden.
Interpretation (approximate categories):

- 0–10 = Little or no burden
- 10–20 = Mild–moderate burden
- 21–30 = Moderate–high burden
- 30 = High burden

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Form F. Sensory Assessments

1. **Hearing Health History:**
   Current or previous medical or surgical history of issues with ears or hearing?

   - 0 = No ☐
   - 1 = Yes ☐

2. **Hearing Aids:**
   Current or previous use of hearing aids?

   - 0 = No ☐
   - 1 = Yes ☐

3. **Tinnitus:**
   Current or previous issues with hyperacusis, tinnitus or sensitivity to noise?

   - 0 = No ☐
   - 1 = Yes ☐

4. **Wax and Infections:**
   Current or previous issues with wax build up
   (+/- requiring syringing of ears) or recurrent ear infections?

   - 0 = No ☐
   - 1 = Yes ☐

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Form F1.2. Hearing Assessments: Hear Check Screening

1. **STEP 1.**
   - Gently place the cup of the device over the ear. It's important that the edges of the cup are in contact with the patient's head.
   - Move any hair out of the way, remove glasses, earrings and hair bands or anything that may prevent achieving adequate contact around the ear.
2. **STEP 2.**
   - Press the start button once to initiate the functional test sequence. If it is working correctly, you will see all 3 lights flash in sequence 3 times.
   - This indicates that the device is ready to use.
   - The test sequence will begin in 3 seconds with three signals at 1000 Hz:
     55dBHL → 35dBHL → 20dBHL.
   - A light will appear when a tone is being played: first left, then middle, then right.
   - The subject should indicate when a tone is heard to the tester by a suitable method such as raising a finger
3. **STEP 3.** Count and record the number of times indicated for the first sequence.
4. **STEP 4.** The start button must be pushed within 20 seconds of the end of the first sequence (after the third light has appeared) to start the second sequence.
5. **STEP 5.**
   - You will see all 3 lights flash in sequence 3x3 times.
   - The test sequence will begin in 3 seconds with three signals at 3000 Hz:
   - 75dBHL → 55dBHL → 35dBHL
6. **STEP 6.** Count and record the number of times the subject has indicated that a tone was heard.
7. **STEP 7.** Repeat steps 2 through 6 on the other ear

	0	1	2	3
Right Ear: No. of Tones heard in **1000 Hz test**				
Right Ear: No. of Tones heard in **3000 Hz test**				
Left Ear: No. of Tones heard in **1000 Hz test**				
Left Ear: No. of Tones heard in **3000 Hz test**				

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Form F2.1. Visual Health History

1. **Vision Health History**:
   Current or previous medical or surgical history of issues with eyes or vision?

   - 0 = No ☐
   - 1 = Yes ☐

2. **Glasses:**
   Current or previous use of glasses or visual aids?

   - 0 = No ☐
   - 1 = Yes ☐

3. **Glasses Type:**
   Type of glasses used?

   - 0 = No glasses ☐
   - 1 = Bifocals ☐
   - 2 = Varifocals ☐

4. **Cataracts/Glaucoma/Macular Degeneration:**
   Current or previous issues with Cataracts, glaucoma or macular degeneration?

   - 0 = No ☐
   - 1 = Yes ☐

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Form F2.2. Visual Acuity Assessment: PEEK Acuity Assessment

Peek Acuity instructions:

1. Explain test to the participant.
2. Measure two meters from the participant to the smartphone (e.g. use pre-cut length of string)
3. One eye is tested at a time: **Right Eye** then **Left Eye**.
   Eye not being tested is covered by patient's palm and checked by the tester to ensure sufficient occlusion.
4. Tester displays the smartphone screen to participant, but does not observe screen.
5. Smart phone displays single optotype **(E in one of 4 orientations: 90, 180, 270, 360)** in a bounding box.
   Participant points in the **direction the arms of the E points**
   Tester swipes the surface of smartphone screen in direction indicated (whether correct or incorrect).
6. If participant indicates they cannot see optotype. the phone is shaken
   (shake detected by device accelerometer – records "not seen")
7. Test algorithm concludes (for each eye) automatically.
   Result is stored on device and displayed on screen
8. Same sequence is repeated for the other eye.
9. If participant cannot see largest optotype at two metres, app instructs tester to move to one meter (then 30 centimetres and so on)

Peek Acuity Results:

LogMAR Score:	
Both Eyes	
Right Eye	
Left Eye:	

Snellen	LogMAR	Visual Category
NPL	4.0	Blindness
PL	3.0	
HM	2.5	
CF	1.8	
6/120	1.3	Severe Visual Impairment
6/60	1.0	Moderate Visual Impairment
6/36	0.8	
6/24	0.6	
6/18	0.5	Mild Visual Impairment
6/12	0.3	Normal
6/9	0.2	
6/6	0.0	
6/5	-0.1	

LogMAR: Logarithm of the Minimal Angle of Resolution
NPL: No perception of light, PL: Perception of light, HM: Hand Movements, CF: Counts Fingers

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Form F3.1. Olfactory History

1. Does the participant report any changes in their sense of smell (or taste)

   - No = 0 ☐
   - Yes = 1 ☐
   - Unknown = 999 ☐

2. If answers yes to impaired smell or taste - how long as this been going on for?

3. If answers yes to impaired smell or taste – has there been a recent Covid infection?

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Form F3.2. Olfactory Assessment: University of Pennsylvania Smell Identification Test (UPSIT)

UPSIT Total Score: _____ / 40

What is the olfactory diagnosis?
(categorise for age and gender percentile values)

Test score:

- 00 - 05: Probable malingering
- 06 -18: Total anosmia
- 19 -25: Severe Microsmia
- 26 -29: Moderate Microsmia (Males)
- 26 - 30: Moderate Microsmia (Females)
- 30 - 33: Mild Microsmia (Males)
- 31 - 34: Mild Microsmia (Females)
- 34 - 40: Normosmia (Males)
- 35 - 40: Normosmia (Females)

Score as:

0 = Normosmia ☐
1 = Mild Microsmia ☐
2 = Moderate Microsmia ☐
3 = Severe Microsmia ☐
4 = Total Anosmia ☐
888 = Probable Participant Misidentification ☐

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Appendix 4

Lewy Body Dementia Frailty Index Variable Composition

The Lewy Body Dementia Frailty Index (LBD-FI) was developed using a Rockwood's cumulative-deficit framework to quantify multidimensional vulnerability in Lewy body disorders. The index comprised 34 binary variables representing comorbidity, medication use, mood, motor impairment, autonomic and non-motor symptoms, and sleep or fluctuation features.

Each item was coded as 0 (absent) or 1 (present). The participant's frailty index equalled the number of deficits present divided by the number of items assessed to yield a continuous frailty score between 0 and 1.
Participants with fewer than 80 percent of valid items were excluded from analysis.

Frailty scores were analysed as continuous variables.
Higher scores correlated with greater caregiver burden and neuropsychiatric symptom severity, supporting construct validity.

Associations with sensory impairment, particularly olfactory loss, reinforced the multidimensional nature of the frailty construct in Lewy body disease.

This appendix lists the 34 variables used in constructing the Lewy Body Dementia Frailty Index (LBD-FI).

Variables were selected following standard cumulative-deficit principles (Rockwood et al., 2005), representing multiple clinical and psychosocial domains relevant to Lewy body disease. The methodological process is described further in Section 3.6.

Domain	Variables Included	SPSS Variable Name
Comorbidities and Medical History (10 items)	• Hypertension • Diabetes Mellitus • Stroke or TIA • Atrial Fibrillation or Arrhythmia • History of IHD/Angina/MI • Congestive Heart Failure • Peripheral Vascular Disease • Chronic Kidney Disease • Asthma or COPD • Cancer (Primary or Secondary)	• fi_history_hypertension • fi_history_diabetes • fi_history_stroke_tia • fi_history_afib • fi_history_ihd • fi_history_ccf • fi_history_pvd • fi_history_ckd • fi_history_asthma_copd • fi_history_cancer
Medication Use (1item)	• Polypharmacy (≥ 5 concurrent medications)	• fi_polypharmacy_5
Mood Symptoms (2 items)	• Anxiety (HADS Anxiety score ≥ 11) • Depression (HADS Depression score ≥ 11)	• fi_hads_anxiety_11 • fi_hads_depression_11
Motor Symptoms (7 items)	**UPDRS Part II:**	
	• Speech Difficulties ≥3 • Swallowing Difficulties ≥3 • Tremor Impact ≥3 • Turning in Bed Difficulties ≥3	• fi_updrs_ii_speech_3 • fi_updrs_ii_swallowing_3 • fi_updrs_ii_tremor_3 • fi_updrs_ii_turning_3
	UPDRS Part III:	
	• Rigidity ≥3 • Bradykinesia ≥3 • Gait Difficulties ≥3	• fi_updrs_iii_rigidity_3 • fi_updrs_iii_bradykinesia_3 • fi_updrs_iii_gait_3
Autonomic and Non-Motor Symptoms: MDS Non-Motor Symptoms Scale **(6 items)**	• NMSS Urinary (Severity x Frequency) • NMSS Constipation (Severity x Frequency) • NMSS Light-headedness (Severity x Frequency) • NMSS Fainting (Severity x Frequency) • NMSS Sleep Difficulty (Severity x Frequency) • NMSS Fatigue (Severity x Frequency)	• fi_nmss_urinary • fi_nmss_constipation • fi_nmss_cv_lightheadedness • fi_nmss_cv_fainting • fi_nmss_sleep_difficulty • fi_nmss_fatigue
Sleep and Fluctuation-Related Features (8 items)	**Mayo Sleep Questionnaire (5 items):**	
	• REM Sleep Behaviour Disorder (Acting out dreams) • Leg jerks or Restless legs during sleep • Breathing Pauses During Sleep • Snorting or Choking Themselves Awake • Sleepwalking or Unusual Nocturnal Behaviours	• fi_nmss_fatigue • fi_mayo_rbd • fi_mayo_legs • fi_mayo_apnoea • fi_mayo_snorting • fi_mayo_sleepwalking
	Mayo Fluctuation Scale (3 items)	
	• Daytime Drowsiness or Lethargy • Disorganised Flow of Ideas (Cognitive fluctuations) • Staring Spells	• fi_mfs_drowsiness • fi_mfs_disorganised_thoughts • fi_mfs_staring_spells

Scoring Procedure:

The final LBD-FI was computed as the number of deficits present divided by the total number of valid variables for each participant. Participants with < 80 % complete data were excluded from FI calculation. Higher scores indicate greater frailty burden.