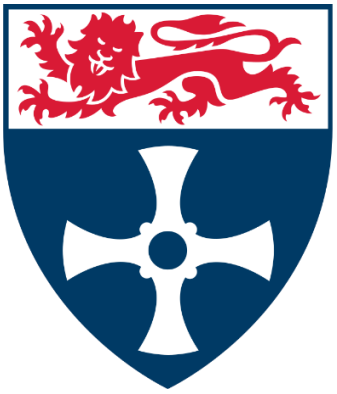

THE CONTRIBUTION OF MIXED AND CONCOMITANT PATHOLOGY TO DEMENTIA

LONGITUDINAL DATA ANALYSIS OF THE BRAINS FOR DEMENTIA RESEARCH COHORT

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Abstract

Dementia is a leading cause of dependence and disability in older adults. Currently, there are over 55 million people living with dementia globally and, due to increasing life expectancy resulting in an ageing population, this is expected to triple by 2050. Neurodegenerative pathologies, such as Alzheimer's disease, Lewy body disease and TDP-43 inclusions, and cerebrovascular disease are frequently associated with different clinical presentations of dementia. However, individuals often exhibit a combination of these pathologies, resulting in heterogenous and overlapping clinical phenotypes, complicating diagnosis, prognosis, and treatment. Examining these clinicopathological correlations may provide useful insights into how mixed and concomitant pathology contribute to the clinical manifestation of dementia. Longitudinal statistical methods, including latent class and multistate models, were used to analyse clinicopathological data from the Brains for Dementia Research programme, aiming to examine how co-existing pathologies contribute to cognitive decline and disease trajectory in dementia in comparison to cognitively healthy controls. A preliminary analysis indicated a high prevalence of mixed and concomitant pathology across the entire cohort, with poor concordance between study diagnosis and postmortem neuropathology. Mixed pathology was consistently associated with more severe cognitive impairment and faster decline in cognitive function, and greater risk of transition between cognitive states of dementia. Concomitant Alzheimer's disease neuropathology, specifically neurofibrillary tangle pathology, appears to drive cognitive decline in other age-related neurodegenerative diseases, including Lewy body disease and limbic-predominant age-related TDP-43 encephalopathy (LATE), frequently associated with dementia. These findings highlight the importance of considering and accounting for mixed and concomitant pathology in dementia research and clinical management, providing supporting evidence for the application of comprehensive biomarker screening and personalised treatment strategies tailored to individual pathological profiles. The consistent association between mixed and concomitant pathology and more severe cognitive trajectories suggests that there may be shared pathways and processes underlying cognitive decline across the dementia spectrum.

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COVID-19 Impact Statement

Although this was a computer-based project, the first 2 years of the PhD were remote due to Covid. I was not able to meet my supervisors in person or work on campus for the first 18 months. This meant I did not have any opportunities to meet and collaborate with other PhD students or post-docs and had to learn all the statistical methods remotely without any in-person support. While my project was not altered or delayed due to lockdowns, it was incredibly isolating and difficult to undertake most of a PhD entirely alone.

Presentations

Transitions between cognitive states in dementia with mixed pathology (Chapter 7)

Dementias Platform UK Translation 2023, London [Poster]

Clinical under recognition of Lewy body disease (Chapter 4)

Alzheimer's Research UK Conference 2023, Aberdeen [Poster]

Alzheimer's Disease/Parkinson's Disease 2023, Gothenburg [Poster & Presentation]

Neuropathological correlates of neuropsychiatric symptoms of dementia (Not in thesis)

Alzheimer's Association International Conference 2023, Amsterdam [Poster]

LATE-NC and cognitive decline. (Chapter 5)

Alzheimer's Research UK Northern Network Meeting December 2023 [Presentation & First Prize Abstract]

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List of Abbreviations

ACE	Addenbrookes cognitive examination
AD	Alzheimer's disease
ADNC	Alzheimer's disease neuropathological change
AGD	Argyrophilic grain disease
ALS	Amyotrophic lateral sclerosis
APOE	Apolipoprotein E
ARTAG	Age-related tau astrogliopathy
Aβ	Amyloid beta
BDR	Brains for Dementia Research
CBD	Corticobasal degeneration
CDR	Clinical dementia rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CR	Cognitive reserve
CTE	Chronic traumatic encephalopathy
CVD	Cerebrovascular disease
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
IMD	Index of multiple deprivation
LATE	Limbic-predominant age-related TDP-43 encephalopathy
LB	Lewy body
LBD	Lewy body disease
LBP	Lewy body pathology
LCA	Latent class analysis
LCMM	Latent class mixture modelling
LME	Linear mixed effects models
LN	Lewy neurite

logLik	Log-likelihood
LPC	Low pathology controls
MCI	Mild cognitive impairment
MMSE	Mini mental state examination
MoCA	Montreal cognitive assessment
MSM	Multistate modelling
NFT	Neurofibrillary tangles
NIA-AA	National Institute on Ageing – Alzheimer's Association
NPI	Neuropsychiatric inventory
NT	Neuropil threads
PART	Primary age-related tauopathy
PCA	Posterior cortical atrophy
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PiD	Pick's disease
PSP	Progressive supranuclear palsy
TDP-43	Transactive response DNA binding protein 43 kDa
TTD	Time to death
VaD	Vascular dementia
VCI	Vascular cognitive impairment
VCING	Vascular cognitive impairment neuropathology guidelines
αSyn	alpha-synuclein

Thesis: The Contribution of Mixed and Concomitant Pathology to Dementia

Chapter 1. Background

Over 55 million individuals are currently living with dementia. This is expected to triple by 2050 to approximately 150 million (Patterson, 2018, Nichols et al., 2022). Despite the increasing prevalence of dementia and magnitude of the global burden associated with dementia-related costs, the precise underlying mechanisms and pathways that lead to clinical dementia lack conclusive explanation (Zhang et al., 2024). For disease-modifying therapies to be successful, the specific mechanisms leading to neurodegeneration and cognitive impairment need to be clearly defined first (Cummings and Fox, 2017, Gadhave et al., 2024). Numerous distinct pathologies are reported postmortem in dementia and the ageing brain, and the correlations between these hallmark pathologies and the biological processes responsible for cognitive decline remain unclear (Qiu et al., 2018, Nelson et al., 2012). A deeper understanding of the changes in the ageing brain, in both cognitively impaired and healthy individuals, is needed to effectively assess potential causes of age-related dementia (Nichols *et al.*, 2023).

Dementia itself is not a disease; it is an umbrella term that refers to a range of debilitating clinical conditions characterised by a decline in cognitive function across multiple domains severe enough to interfere with daily life that can develop as a symptom of a number of underlying causes, including neurodegeneration (Peng, 2003, Gale, Acar and Daffner, 2018, Cipriani et al., 2020). Dementia most commonly affects the elderly population but is not a normal part of ageing (Graham et al., 1997, Savva et al., 2009, Lisko et al., 2021). A number of modifiable risk factors that occur during midlife are associated with increased risk of dementia during later life (Livingston et al., 2020). These include alcohol misuse, traumatic brain injury, hearing loss and metabolic factors, such as diabetes, hypertension, obesity and low levels of high-density lipoprotein cholesterol (Livingston et al., 2020). Factors in later life that are associated with increased risk of dementia include air pollution, diabetes, social isolation, depression, smoking and physical inactivity (Knopman et al., 2021). Several of these factors may be part of the prodromal phase of or have a bi-directional link with dementia (Knopman et al., 2021, Teipel et al., 2025).

1.1 Clinical Dementia

All-cause dementia, or major neurocognitive disorder (DSM-5), is defined as sufficient cognitive or neuropsychiatric symptoms that interfere with the ability to perform normal activities and

represent a decline from previous levels of functioning that cannot be explained by delirium or major psychiatric disorders (McKhann et al., 2011). Cognitive impairment is usually detected and diagnosed from patient histories through the patient and a reliable informant, and an independent mental status examination, such as the MMSE or MoCA (McKhann et al., 2011). Neuropsychological testing is used if the combined history and mental status examination cannot provide a confident diagnosis (McKhann et al., 2011).

A symptomatic, transitional stage between normal cognition and dementia is referred to as mild cognitive impairment (MCI), or mild neurocognitive disorder (Sachs-Ericsson and and Blazer, 2015, Langa and Levine, 2014, Bermejo-Pareja et al., 2021). MCI is characterised by greater cognitive impairment than expected relative to age and education that is not significant enough to interfere with activities of daily living (Knopman and Petersen, 2014, Eshkoor et al., 2015). Diagnostic criteria for mild cognitive impairment are outlined in the NIA-AA consensus published in 2011 (Albert et al., 2011, McKhann et al., 2011). Briefly, criteria for diagnosis of MCI include concern regarding a change in cognition, impairment in one or more cognitive domain, preservation of independence in functional abilities, and absence of dementia (Albert et al., 2011).

There are a number of neurodegenerative diseases commonly associated with clinical dementia in the over 65s, including Alzheimer's disease, Lewy body disease, cerebrovascular disease, and frontotemporal lobar degeneration (Matej, Tesar and Rusina, 2019, Das, Zhang and Ang, 2020). Dementia can also occur after repetitive traumatic brain injury (Nordström and Nordström, 2018), exposure to prion diseases or infections, alcoholism, epilepsy, and metabolic diseases (Almeida and Lautenschlager, 2005). Although there are many causes of dementia, most age-related dementias are grouped into four major categories: Alzheimer's disease, Lewy body, vascular and frontotemporal dementias (Salardini, 2019, Matej, Tesar and Rusina, 2019). Although underlying neurodegenerative diseases can be broadly classified by their clinical symptoms, it is often not possible to reliably distinguish between subtypes of dementia clinically due to heterogenous and overlapping clinical profiles (Dugger and Dickson, 2017).

Cognitive trajectories in dementia encompass the patterns of cognitive change over time, which can vary significantly between individuals (Payton et al., 2023). Several distinct trajectories have been identified including stable, slow decline, fast decline, and improvement (Cohen, Reisberg and Yaffee, 2024, Li et al., 2022). One study found three primary cognitive trajectory classes: rapid cognitive decline, moderate progression, and optimal cognitive ageing (Walsh et al., 2022, Wu et

al., 2022). Each of these trajectories were associated with varying risks of dementia and mortality, highlighting the heterogeneity of cognitive ageing (Walsh et al., 2022). An additional study observed that individuals exhibiting fast decline across multiple cognitive domains had a significantly higher risk of developing dementia in the subsequent years. A study utilising data from the UK Biobank found that participants approaching dementia diagnosis exhibited worsening functional assessments and an increased prevalence of health conditions, highlighting the gradual nature of cognitive decline leading up to dementia (You et al., 2024). These findings underscore the importance of identifying and monitoring cognitive trajectories in older adults as early indicators for dementia risk. Understanding these patterns of cognitive decline and considering the individual variability in cognitive ageing allows for more nuanced approaches to dementia prevention and management.

1.1.1 Alzheimer's disease dementia

Alzheimer's disease is the most common cause of age-related dementia, accounting for 50-80% of cases, and is characterised by an insidious onset of progressive amnestic dysfunction, followed by a significant and gradual increase in disability throughout the course of disease (Long and Holtzman, 2019, Arvanitakis, Shah and Bennett, 2019). Alzheimer's disease typically presents with pronounced amnestic cognitive impairment but in some cases as non-amnestic impairments may be more prominent, affecting language, visuospatial processing, and executive function (Liampas et al., 2023, Vos et al., 2013). Typical symptoms of early Alzheimer's disease include apathy, anxiety, and depression (Johansson et al., 2020, Leung et al., 2021). Middle stages are defined by impaired communication, disorientation, confusion, and poor judgement (Arvanitakis, Shah and Bennett, 2019). Late-stage Alzheimer's disease is defined by difficulty speaking, swallowing, and walking. The progressive deterioration to immobility and eventual death lasts between 5-12 years (Vermunt et al., 2019).

The prevalence of dementia due to Alzheimer's disease in 60-74 year olds is estimated to be 5.3%, increasing to 13.8% in 75-84 year olds and 34.6% in over 85s (Rajan et al., 2021). Recent large autopsy studies have shown that, although Alzheimer's disease is the most common cause of dementia, more than 50% of cases have more than one underlying neuropathology (Nichols et al., 2023). Advancing age remains the biggest risk factor for Alzheimer's disease. In addition to the ten modifiable risk factors outlined by Livingston et al. (2020), risk factors for Alzheimer's disease

include the presence of specific variants of the APOE4 gene, and less common pathogenic variants (e.g. in *APP*, *PSEN1*, *PSEN2*) that cause familial AD (Knopman et al., 2021).

In terms of neuropathology, Alzheimer's disease is a neurodegenerative disease associated with the accumulation of misfolded β-amyloid and tau aggregates in the brain (Deture and Dickson, 2019). The accumulation of pathological protein aggregates and neurodegeneration begins many years before symptoms occur clinically (Kovacs, 2019b, Golde, 2022). Macroscopically, AD characterised by gross atrophy of gyri in the frontal, parietal, and temporal lobes, particularly the entorhinal cortex and hippocampus, and ventricular enlargement (Schneider, 2022, Serrano-Pozo et al., 2011). Brain weight and volume are usually significantly reduced (Serrano-Pozo et al., 2011, Deture and Dickson, 2019). Microscopically, the main pathological hallmarks of Alzheimer's disease are the accumulation of extracellular Aβ plaques and intracellular neurofibrillary tangles (Schneider, 2022, Serrano-Pozo et al., 2011). Aβ plaques can be classified into diffuse plaques, which lack significant neuritic components and are often found in cognitively normal individuals, and neuritic plaques, which are composed of a dense core of aggregated amyloid-β protein surrounded by tau-positive dystrophic neurites (Nelson et al., 2011, Deture and Dickson, 2019). Neuritic plaques are distributed throughout cortical and limbic regions as well as the basal forebrain (Serrano-Pozo et al., 2011). Neurofibrillary tangles (NFT) are intracellular accumulations composed of hyperphosphorylated microtubule associated protein tau and ubiquitin and are distributed throughout cortical and limbic regions, particularly the hippocampus (Deture and Dickson, 2019). These pathologies are accompanied by widespread cortical and hippocampal neuronal loss, in addition to degeneration of subcortical structures, such as the cholinergic basal forebrain (Deture and Dickson, 2019).

The presence and distribution of Aβ plaques and neurofibrillary tangles are used to stage disease severity (Deture and Dickson, 2019). Thal phasing is used to describe the topographical progression of Aβ deposition from the neocortex to the cerebellum (Thal et al., 2002), while Braak NFT staging characterises the spread of tau pathology, beginning in the transentorhinal cortex and progressing to the neocortex (Braak et al., 2006). An additional CERAD score is used to categorise cases based on the abundance of amyloid pathology (Mirra et al., 1991). The NIA-AA classification system uses a combination of Thal phase, Braak NFT stage, and CERAD score to assign a likelihood that Alzheimer's disease neuropathology is responsible for cognitive impairment (Montine et al., 2012). The ATN classification extends this model for in vivo diagnosis by using biomarkers to

define Alzheimer's disease pathophysiological changes: amyloid PET or CSF $A\beta_{42}$, tau PET or CSF phosphorylated-tau, and markers of neurodegeneration (e.g. MRI atrophy or FDG-PET) (Jack et al., 2018). This model facilitates earlier and more accurate diagnosis of Alzheimer's disease, including in preclinical stages (Jack et al., 2018).

Clinically, the original criteria for Alzheimer's disease, NINCDS-ADRDA, was established by a working group from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 1984 (McKhann et al., 1984). The NINCDS-ADRDA defined one state of dementia and focused on memory loss as the central feature of Alzheimer's disease. The National Institute on Aging – Alzheimer Association (NIA-AA) criteria updated clinical criteria for dementia and AD in 2011 (Albert et al., 2011, McKhann et al., 2011, Montine et al., 2012), and revised these again in 2018 (Jack et al., 2018). Major changes included dividing the Alzheimer's disease spectrum into three major stages reflecting disease progression: preclinical, mild cognitive impairment and Alzheimer's disease (Tahami Monfared et al., 2022). The update expanded the criteria to include other aspects of cognition, such as language or judgement, that may become impaired first and included information on the distinctions and associations between Alzheimer's disease and other non-Alzheimer's dementias (McKhann et al., 2011). The 2018 updated NIA-AA framework defines a numerical clinical staging system for individuals on the Alzheimer's continuum using biomarker for Aβ, pathologic tau, and neurodegeneration or neuronal injury (Jack et al., 2018). Clinical diagnostic criteria for Alzheimer's disease is outlined in **Figure 1.1**.

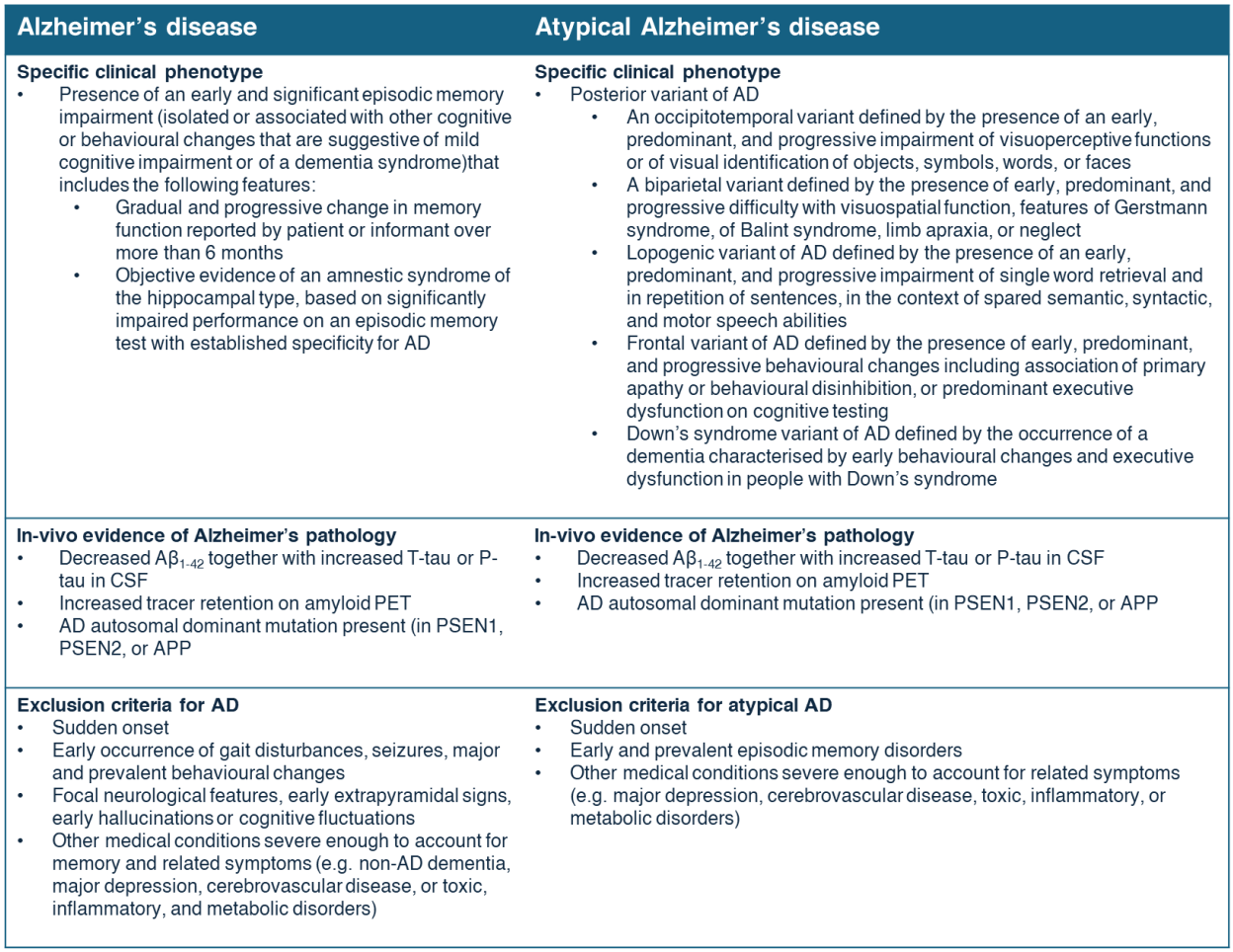

Figure 1.1. **Diagnostic Criteria for Clinical Alzheimer's Disease**: Clinical criteria for the diagnosis of Alzheimer's disease, including both classical and atypical phenotypes, are outlined along with in-vivo evidence and exclusion criteria. The figure highlights the distinguishing features of Alzheimer's disease, including cognitive and neuroimaging markers, and the specific criteria used for diagnosis. Adapted from Dubois *et al.* (2014).

The NIA-AA criteria is commonly used in research settings, while other clinical criteria, such the DSM-V or ICD-11, are used in regular clinical settings (Sachdev et al., 2014). A diagnosis of probable Alzheimer's disease dementia depends on an insidious onset of symptoms with distinct decline in cognition (McKhann et al., 2011). The amnesic presentation of Alzheimer's disease dementia is most common but non-amnesic presentations, including language, visuospatial and executive dysfunction are also included in the diagnostic criteria (McKhann et al., 2011). Evidence of substantial cerebrovascular disease, core features of dementia with Lewy bodies or prominent features of frontotemporal dementias exclude probable AD from diagnosis (McKhann et al., 2011).

The use of biomarkers as indicators of underlying brain pathology is almost exclusive to research and is not yet regularly implemented in clinical settings (Hayes-Larson et al., 2024, Andersen et al.,

2021, Weinhofer, Rommer and Berger, 2025). Current biomarkers for Alzheimer's disease are imaging and fluid based, and include cerebral amyloid markers, such as positron emission tomography (PET) and cerebrospinal fluid (Breijyeh and Karaman, 2020), markers of neuronal injury (e.g. cerebrospinal fluid tau), fluorodeoxyglucose (FDG) for metabolic injury, and magnetic resonance imaging (MRI) of cortical atrophy (Breijyeh and Karaman, 2020).

Symptomatic treatment of Alzheimer's disease is generally palliative and mainly consists of cholinesterase inhibitors, such as donepezil, rivastigmine, galantamine and memantine, to increase cholinergic levels and improve cognitive and neural cell function (Breijyeh and Karaman, 2020). In addition to cholinesterase inhibitors, other medications such as anti-psychotics and selective serotonin reuptake inhibitors, may also be used to treat neuropsychiatric symptoms (Masterman, 2004). Research has primarily focused on interventions to inhibit the onset and progression of cognitive impairment, modifiable risk factors, and improving quality-of-life (Kamatham et al., 2024, Logsdon, McCurry and Teri, 2007, Rosenberg et al., 2020, Ornish et al., 2024).

Recently, significant advancements in disease modifying therapies (DMT) that aim to alter disease progression by targeting the underlying pathological mechanisms of the disease has led to the approval of several therapies for use in Alzheimer's disease. The majority of these are monoclonal antibodies targeting β-amyloid, including aducanumab (Rahman et al., 2023), lecanemab (van Dyck et al., 2023), and donanemab (Sims et al., 2023), and have shown modest clinical benefits in slowing cognitive decline in early-stage AD (Breijyeh and Karaman, 2020). However, concerns remain about associated adverse effects, particularly amyloid-related imaging abnormalities (ARIA), including vasogenic oedema and microhaemorrhages. Beyond anti-amyloid approaches, tau-targeting therapies (Congdon et al., 2023) and BACE1 inhibitors (Bazzari and Bazzari, 2022), which block Aβ production, have been investigated. Most of these have failed due to safety concerns or lack of efficacy in late-phase trials. Accurate diagnosis at an early stage of disease progression and combination therapies will be crucial in improving the efficacy of these new treatments (Khan, Barve and Kumar, 2020).

1.1.2 Lewy body dementias

Lewy body disease is the second most common cause of neurodegenerative dementia and is characterised by fluctuating cognition, visual hallucinations, parkinsonism and REM sleep behaviour disorder (Walker et al., 2015). Lewy body dementia is characterised by a fast onset and

progression of disease, with fluctuations in alertness and cognition (Arvanitakis, Shah and Bennett, 2019, McKeith et al., 2017). The three core symptoms associated with DLB include fluctuating cognition, recurrent visual hallucinations, and parkinsonism (Morra and Donovick, 2014, Matar et al., 2020a). Cognitive fluctuations are sudden changes in attention or cognition and characteristic of Lewy body dementias (Matar et al., 2020b). Recurrent visual hallucinations are estimated to be present in 70 to 85% of patients with DLB (Prasad et al., 2023), while spontaneous parkinsonism is estimated to occur in between 60 and 92% of cases (Walker, Stefanis and Attems, 2019). In Lewy body dementia, REM sleep behaviour disorder typically precedes cognitive impairment occurring as an initial or early symptom (Chan et al., 2018). Well-formed visual hallucinations and visuospatial impairment also occur early (Hamilton et al., 2012). Problems with motor functions, similar to those seen in Parkinson's disease, are also common (Prasad et al., 2023).

Lewy body dementia is an umbrella term that includes both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) (Walker et al., 2015). This spectrum of dementia syndromes are thought to share the same underlying pathobiological mechanism of neurodegeneration resulting from Lewy body disease, but clinical syndrome is determined by the order of and time between specific symptom onset (Walker et al., 2015, Walker, Stefanis and Attems, 2019). DLB and PDD differ in the sequence of onset of dementia and parkinsonism but as progression of disease and underlying pathological changes are similar, the two syndromes can be viewed as a continuum rather than separate entities (Lippa et al., 2007, Jellinger, 2018, Borghammer, Okkels and Weintraub, 2024). In dementia with Lewy bodies, dementia occurs prior to or concurrently with parkinsonism (McKeith et al., 2017, Walker, Stefanis and Attems, 2019). In Parkinson's disease dementia, parkinsonism precedes the onset of dementia by at least one year (Walker, Stefanis and Attems, 2019). Up to 80% of patients with Parkinson's disease eventually develop dementia (Jellinger and Korczyn, 2018, Walker, Stefanis and Attems, 2019). The similarities and subtle difference between PDD and DLB are outlined in **Figure *1.2***.

Dementia with Lewy bodies	Overlap	Parkinson's disease dementia
• Some cognitive dysfunctions: deficiencies of attention greater, episodic verbal memory tasks lower in DLB • Tremor less frequent in DLB • Motor performance: slower walk and poorer balance in DLB • Hallucinations (visual) more frequent in DLB • Relative timing of dementia and parkinsonism (one year rule) • Orthostatic hypertension more frequent in DLB • Frontal/temporal-associated cognitive subsets more severe in DLB, cognitive decline is faster in DLB/DLB+AD • Delusions, visual hallucinations, and attentional fluctuation more frequent in DLB • Spontaneous visual hallucinations in DLB	• Rigidity • Akinesia • Cognitive impairments • Frontal executive dysfunction • Visual-constructive impairment • Mild language impairment • Mood disturbances (depression, anxiety) • REM sleep behaviour disorder (RBD) • Neuroleptic sensitivity	• Onset of dementia earlier in PDD • Visual hallucinations after L-dopa therapy in PDD, but also in drug-naïve cases

Figure 1.2. Clinical Presentation of Lewy Body Dementias: Comparison of the clinical features of Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), highlighting both their similarities and key differences. While both disorders are characterised by Lewy body pathology, the timing and nature of cognitive decline relative to motor symptoms distinguish PDD from DLB. Adapted from Jellinger , and Korczyn (2018).

Dementia with Lewy bodies is the second most common neurodegenerative dementia but is often under-represented in clinical settings (Kane *et al.*, 2018). Although many consider vascular dementia to be the second most common cause of clinical dementia (O'Brien and Thomas, 2015), Lewy body disease is the second most common neuropathology in dementia, suggesting there is discordance between clinical and neuropathological prevalences (Prasad et al., 2023, Heidebrink, 2002). Current estimates of prevalence vary widely, ranging from 0 to 30% of all dementia cases (Lebouvier et al., 2013, Zaccai, McCracken and Brayne, 2005). Lewy body disease affects 1-2% of the population over the age of 65 (Kane et al., 2018). In clinical studies, DLB accounts for around 4% of dementia cases in the community, increasing to around 7.5% in secondary care (Vann Jones and O'Brien, 2014). This is likely to be an underestimate as DLB diagnoses are often missed, with the prevalence of Lewy body disease being significantly higher in autopsy series (Jellinger and Attems, 2011). The majority of DLB cases also have brain changes associated with one or more other causes of dementia, including Alzheimer's disease and TDP-43 inclusions (Toledo et al., 2023). Advancing age remains the biggest risk factor for Lewy body dementia. In addition to the ten modifiable risk factors outlined by Livingston et al. (2020), risk factors for Lewy body dementia include maleness, the *APOE* ε4 variant, and mutations in *GBA* and *SNCA* genes (Rongve *et al.*, 2019).

Lewy body dementia is thought to be caused by Lewy body disease, part of the synucleinopathy spectrum of neurodegenerative disorders (Irwin and Hurtig, 2018, Jellinger, 2003, Outeiro et al., 2019). Macroscopically, Lewy body dementia is characterised by generalised bilaterally symmetrical atrophy of frontal, parietal, temporal and occipital lobes, usually accompanied by

decreased gross brain weight (Arvanitakis, Shah and Bennett, 2019). Microscopically, the hallmark pathological features of Lewy body dementia is the presence of abnormal intracellular aggregates of α-synuclein, such as Lewy bodies or Lewy neurites, accompanied by neuronal loss (Walker et al., 2015). Lewy bodies are most often found in the brainstem, specifically in the substantia nigra and the locus coeruleus, in individuals with DLB and PDD (McKeith et al., 2005, Arvanitakis, Shah and Bennett, 2019). In DLB, Lewy bodies can also be found in the limbic system, neocortical regions and occasionally in the peripheral nervous system (Outeiro et al., 2019). The majority of DLB cases also show loss of pigmented, dopaminergic neurons in the substantia nigra, similar to the loss seen in PD (Outeiro et al., 2019). The presence of cortical Lewy bodies is necessary at autopsy to confirm a diagnosis of Lewy body dementia (McKeith et al., 2017). It is unclear whether Lewy bodies and neurites have a neuroprotective or neurotoxic role and to what extent they contribute to the clinical picture because some individuals with severe α-synuclein pathology do not have clinical symptoms of Lewy body dementia (Walker et al., 2015).

Dementia with Lewy bodies
Essential • Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. • Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. • Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.
Core clinical features • Fluctuating cognition with pronounced variations in attention and alterness. • Recurrent visual hallucinations that are typically well formed and detailed • REM sleep behaviour disorder, which may precede cognitive decline. • One or more spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, or rigidity)
Supportive clinical features • Severe sensitivity to antipsychotic agents • Postural instability or repeated falls • Syncope or other transient episodes of unresponsiveness • Severe autonomic dysfunction (e.g., constipation, orthostatic hypotension, urinary incontinence) • Hypersomnia or hyposmia • Other neuropsychiatric symptoms, including delusions, hallucinations in other modalities, apathy, anxiety, and depression
Indicative biomarkers • Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET • Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy • Polysomnographic confirmation of REM sleep without atonia.
Supportive biomarkers • Relative preservation of medial temporal lobe structures on CT/MRI scan • Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging • Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.
Probable DLB can be diagnosed if: a. Two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers, or b. Only one core clinical feature is present, but with one or more indicative biomarkers Probable DLB should not be diagnosed on the basis of biomarkers alone.
Possible DLB can be diagnosed if: a. Only one core clinical feature of DLB is present, with no indicative biomarker evidence, or b. One or more indicative biomarker is present but there are no core clinical features.
DLB is less likely: a. In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation, or b. If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. Parkinson's disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson's disease. In a practice setting, the term that is most appropriate to the clinical situation should be used and generic terms such as Lewy body disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism continues to be recommended.

Figure 1.3. **Clinical Criteria for Diagnosing Lewy Body Dementia:** Overview of the clinical criteria used for diagnosing Lewy body dementia (LBD), including key features such as cognitive fluctuations, visual hallucinations, parkinsonism, and REM sleep behaviour disorder, based on the guidelines outlined by McKeith *et al.* (2017).

Diagnostic criteria for DLB (**Figure 1.3**) was originally outlined by the Dementia with Lewy bodies Consortium and most recently updated in 2017 (McKeith *et al.*, 2017). Clinical signs and symptoms are weighted as core or supportive and biomarkers as indicative or supportive, based on their diagnostic specificity (Cousins et al., 2022, del Campo et al., 2018). Neuropsychological assessment includes tests covering the full range of cognitive domains (McKeith *et al.*, 2017). A diagnosis of probable DLB can be made when at least two core features or one core feature and one indicative biomarker, are present (McKeith *et al.*, 2005). The core clinical features of Lewy body dementia include fluctuating cognition with pronounced variation in attention and alertness, recurrent visual hallucinations that are typically well formed and detailed, REM sleep behaviour disorder which may occur in the prodromal phase prior to cognitive decline, and at least one spontaneous

cardinal feature of parkinsonism (bradykinesia, rest tremor or rigidity) (McKeith *et al.*, 2017). Further core and supportive clinical features, such as REM sleep behaviour disorder and autonomic dysfunction, are outlined in **Figure 1.3**. Typically DLB is characterised by marked visuospatial problems with relative preservation of memory, occurring alongside parkinsonism (Arvanitakis, Shah and Bennett, 2019).

Diagnosis of DLB can be difficult due to the heterogenous and overlapping clinical presentations of dementia syndromes (Huang and Halliday, 2013). Accurate diagnosis of dementia with Lewy bodies is necessary in order to more accurately predict the progression of the disease and negative side effects from pharmacological treatment (Morra and Donovick, 2014, Jellinger and Korczyn, 2018). The development of effective biomarkers to be used in combination with existing diagnostic criteria has improved the accuracy of diagnosis, particularly in specialist centres (Bousiges and Blanc, 2022, Armstrong et al., 2021). Indicative biomarkers for DLB are reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET, abnormal ^{123}I-MIBG myocardial scintigraphy and polysomnographic confirmation of REM sleep without atonia (McKeith et al., 2020). Supportive biomarkers are outlined in **Figure 1.3**.

1.1.3 Frontotemporal dementias

Frontotemporal dementia (FTD) is an umbrella term that encompasses a group of clinically heterogenous subtypes of dementia broadly characterised by progressive changes in behaviour, executive function, or language (Boeve et al., 2022, Rabinovici and Miller, 2010, Onyike and Diehl-Schmid, 2013). Frontotemporal dementias typically have an insidious onset with gradual progression (Arvanitakis, Shah and Bennett, 2019, Boeve et al., 2022, Rabinovici and Miller, 2010, Onyike and Diehl-Schmid, 2013). The median survival time of FTD is estimated to be 6-11 years from symptom onset and 3-4 years from diagnosis (Rabinovici and Miller, 2010). The most predominant clinical features of FTDs tend to be marked changes in behaviour and personality, such as disinhibition (Arvanitakis, Shah and Bennett, 2019).

Major clinical subtypes of frontotemporal dementia include the behavioural variant (bvFTD) and two forms of primary progressive aphasia (PPA); the non-fluent (nfvPPA) and semantic (svPPA) variants (Boeve et al., 2022). Symptoms of frontotemporal dementias may mimic primary psychiatric disorders such as schizophrenia or bipolar disorder (Onyike, Shinagawa and Ellajosyula, 2021). Behavioural variant frontotemporal dementia (bvFTD) is the most common frontotemporal dementia and is characterised by dissocial and compulsive behaviour with either impulsive and

disinhibited, or an apathetic demeanour (Lanata and Miller, 2016, Pąchalska et al., 2011). The semantic variant of primary progressive aphasia (svPPA) is characterised by the loss of semantic understanding with anomia and agnosia, resulting in fluent speech lacking in substance (Onyike, Shinagawa and Ellajosyula, 2021). In contrast, the non-fluent variant of PPA is characterised by progressive difficulties in speech production, resulting in effortful, non-grammatical speech and difficulty understanding sentences (Onyike, Shinagawa and Ellajosyula, 2021).

Frontotemporal dementia accounts for 2.6% of all-cause dementia compared to 3 to 16% in studies of the under 65s (Hogan et al., 2016, Rabinovici and Miller, 2010, Zhang et al., 2022). Although FTD is often regarded as an early onset form of dementia, 20-25% of all FTD cases occur in the over 65s (Rabinovici and Miller, 2010). The incidence of FTD increases with age, peaking between ages 75-79, with the majority of all FTD cases are diagnosed after the age of 65 years (Nilsson et al., 2014). The primary risk factor for frontotemporal dementias is pathogenic variants of genes such as *GRN* or *C9orf72* (Steele et al., 2018). As a result, the condition is often hereditary, with onset occurring during midlife (Onyike and Diehl-Schmid, 2013).

FTD tends to be associated with underlying neurodegenerative disease defined by the progressive deterioration of cortical grey matter in the frontal and temporal lobes and, at the pathological level, the accumulation of protein aggregates (Boeve et al., 2022, Zetterberg et al., 2019). Frontotemporal lobar degeneration (FTLD) is characterised by neuronal loss, gliosis and microvacuolar changes in frontal lobes, anterior temporal lobes, anterior cingulate and insular cortex (Bang, Spina and Miller, 2015). Atrophy can be either bilateral or asymmetric (Snowden, Neary and Mann, 2002). The features of the behavioural and language phenotypes of FTD reflect the pattern of frontal and temporal cortical degeneration (Onyike, Shinagawa and Ellajosyula, 2021). Two prevalent proteins observed in FTLD at the pathological level include hyperphosphorylated tau protein, as described previously, and TDP-43 inclusions (Zhang et al., 2020).

Subtypes of FTLD are associated with characteristic patterns of abnormal protein deposition (Bang, Spina and Miller, 2015). There are three main molecular subgroups of frontotemporal lobar degeneration: FTLD-tau, FTLD-TDP and FTLD-FUS (Zhang et al., 2020, Mackenzie and Neumann, 2016). FTLD-tau accounts for 36-50% of cases and is typically associated with specific pathological phenotypes including Pick's disease (PiD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (De Boer et al., 2021). FTLD-TDP accounts for approximately 50% of FTD

cases and is subdivided into groups based on the patterns of cytoplasmic or intranuclear pathological and cortical association (Burrell *et al.*, 2016). FTLD-FUS represents approximately 10% of FTD cases and typically manifests as bvFTD with severe disinhibition and other psychiatric features (Burrell *et al.*, 2016). Rare cases of FTLD have ubiquitin only or p62-positive inclusions, or no inclusions at all (Bang, Spina and Miller, 2015).

Subtype	Criteria
bvFTD	Progressive deterioration of behaviour and/or cognition that is not better accounted for by another neurological, psychiatric, or medical disorder. **Possible** At least three of the following: - Early behavioural disinhibition - Early apathy or inertia - Early loss of sympathy or empathy - Hyperorality or dietary change - Neuropsychological profile showing executive deficits with relative sparing of memory and visuospatial function **Probable**. All of the following: - Meets criteria for possible bvFTD - Significant functional decline - Neuroimaging showing frontal and/or temporal atrophy, hypoperfusion or hypometabolism
Non-fluent variant PPA	At least one of: - Agrammatism in language production - Effortful, halting speech +/- speech apraxia And, at least two of: - Impaired comprehension of complex sentences - Spared single word comprehension - Spared object naming Supportive imaging: left posterior, frontoinsular atrophy, hypoperfusion or hypometabolism
Semantic variant PPA	Both: - Impaired naming - Impaired single word comprehension And, at least three of: - Impaired object knowledge - Surface dyslexia or dysgraphia - Spared repetition - Spared speech production Supportive imaging: predominant anterior temporal atrophy, hypoperfusion, or hypometabolism

Figure 1.4. Diagnostic Criteria for Frontotemporal Dementia Subtypes: Clinical criteria for diagnosing subtypes of frontotemporal dementia, as defined by Tartaglia , and Mackenzie (2023). The figure outlines the key diagnostic features distinguishing each subtype, including behavioural, language, and motor symptoms, along with their respective neuroimaging and neuropathological characteristics.

Clinical criteria for FTD subtypes are outlined in **Figure 1.4**. Typically diagnosis involves an assessment of significant changes in behaviour, e.g. disinhibition, or language, with relative preservation of memory (Arvanitakis, Shah and Bennett, 2019). Briefly, a clinical diagnosis of bvFTD is based on the presence of at least three of five behavioural and one cognitive criterion. Diagnostic criteria for variants of primary progressive aphasia (PPA) are outlined in **Figure 1.4**. As FTD phenotypes often converge over the course of disease progression, diagnostic criteria tend to focus on symptoms that present early in the disease course to allow clear delineation between the

variants (Bang, Spina and Miller, 2015, Mackenzie and Neumann, 2016). Structural MRI, PET scans and biomarkers are used to confirm frontal and temporal atrophy to support diagnosis (Swift et al., 2021). Due to the overlapping nature of clinical phenotypes in FTDs, classifying cases by underlying molecular pathology during life can be difficult, making the development of accurate biomarkers in FTD particularly important (Zetterberg et al., 2019).

1.1.4 Vascular dementia

Vascular dementia is also a common form of dementia in older individuals and is characterised by cognitive decline due to reduced blood flow to the brain, often resulting in deficits in executive dysfunction, attention, and memory (Kapasi and Schneider, 2016, Gorelick, Counts and Nyenhuis, 2016). Vascular dementia is generally not considered a neurodegenerative dementia as there is no specific underlying protein accumulation involved (Vinters et al., 2018, Korczyn, Vakhapova and Grinberg, 2012). Vascular dementia is considered the second most common subtype of clinical dementia, accounting for approximately 15-20% of dementia cases in Europe (Rizzi, Rosset and Roriz-Cruz, 2014). The incidence of dementia ranges from 5% at 1-year post-transient ischaemic attack to 34% at 1-year post-stroke (Pendlebury and Rothwell, 2019). There are several subtypes of vascular dementia, including multi-infarct dementia, small vessel disease, strategic infarct dementia, hypoperfusion, haemorrhagic dementia, and hereditary vascular dementia (O'Brien and Thomas, 2015). All subtypes are defined by different pathological changes as outlined in **Figure 1.5**.

Subtype	Imaging and pathological changes
Multi-infarct dementia (cortical vascular dementia)	Multiple cortical infarcts
Small vessel disease (subcortical vascular dementia)	Lacunes, extensive white matter lesions; Pathologically, infarcts, demyelination, and gliosis
Strategic infarct dementia	Infarct in strategic location (e.g. thalamus)
Hypoperfusion	Watershed infarcts, white matter lesions; Pathologically, incomplete infarcts in white matter
Haemorrhagic dementia	Haemorrhagic changes, may be association with amyloid angiopathy
Hereditary vascular dementia (CADASIL)	Multiple lacunes and white matter lesions, temporal lobe white matter affected
Alzheimer's disease with cardiovascular disease	Combination of vascular changes and atrophy, especially medial temporal lobe; pathologically, mixture of vascular and degenerative (plaque and tangle) pathology

***Figure 1.5*. Subtypes of Vascular Dementia:** Imaging and pathological features associated with the different subtypes of vascular dementia. The diagram highlights the distinct neuroimaging patterns and underlying neuropathological changes characteristic of each subtype, as outlined by O'Brien , and Thomas (2015)

Cognitive changes in vascular dementia are more variable than in Alzheimer's disease and are highly dependent on the location and form of vascular pathology (Agrawal and Schneider, 2022). As subcortical vascular pathology is frequently present, vascular dementia is often associated with deficits in attention, information processing and executive function (Kalaria and Erkinjuntti, 2006, O'Brien and Thomas, 2015). Cognitive decline in vascular dementia is typically characterised by a fluctuating, stepwise progression. Risk factors for vascular dementia include age, diabetes, hypertension, metabolic disorders, stroke and genetic factors (Rönnemaa et al., 2011). Lifestyle factors increasing risk of vascular dementia include smoking, diet, and obesity (Livingston et al., 2020).

The National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria is the most frequently used diagnostic criteria for vascular dementia (Román, 2002). The NINDS-AIREN criteria for probable vascular dementia requires a combination of dementia, cerebrovascular disease, and a temporal relationship between the two (Román, 2002). As outlined in **Figure 1.6**, evidence of cerebrovascular disease includes a history of cerebrovascular disease, focal signs on examination, or CT/MRI scans showing lesions that confirm vascular pathology. The temporal relationship between dementia and cerebrovascular disease could be demonstrated by the onset of dementia within 3 months following stroke, abrupt deterioration in cognitive functions, or fluctuating, stepwise progression of cognitive deficits (McVeigh and Passmore, 2006, Kling et al., 2013).

Clinical Diagnosis of Vascular Dementia

1. Dementia
2. Cerebrovascular disease, defined by one of:
   a. History of cerebrovascular disease
   b. Focal signs on examination (with or without history)
   c. CT/MRI showing lesions that confirm cerebrovascular disease
3. Temporal relationship between 1 and 2, demonstrated by one of:
   a. Onset of dementia within 3 months following stroke
   b. Abrupt deterioration in cognitive functions
   c. Fluctuating, stepwise progression of cognitive deficits

Figure 1.6. **Clinical Diagnosis of Vascular Dementia:** Diagnostic criteria for vascular dementia as defined by the NINDS-AIREN criteria. This figure outlines the key clinical features, including cognitive impairment, evidence of cerebrovascular disease, and the temporal relationship between vascular changes and cognitive decline.

Large vessel atherosclerosis, small vessel arteriosclerosis, and other vascular diseases, such as cerebral amyloid angiopathy, can lead to subcortical infarcts, microinfarcts in the grey matter, white matter lesions and cerebral haemorrhages (O'Brien and Thomas, 2015) and contribute to vascular dementia. Abnormalities in vascular brain pathologies are almost universal in people aged over 75 years (Wolters and Ikram, 2019). A large burden of vascular disease pathology is needed to produce dementia in the absence of Alzheimer's disease or other neurodegenerative pathologies (Vinters et al., 2018). As a result, the prevalence of pure vascular dementia is significantly lower than previously accepted, accounting for approximately 10% of cases (Silva et al., 2022). The majority of which have large subcortical infarcts. The burden of cerebrovascular disease increases with age (Bir et al., 2021). As cerebral amyloid angiopathy exists at the interface between cerebrovascular pathology and Alzheimer's disease, the two conditions often co-occur, particularly in the ageing brain (Greenberg and Charidimou, 2018, Greenberg et al., 2020).

1.2 Dementia-related neuropathology

Neuropathology is considered the gold standard of determining neurodegenerative disease presence and severity (Jack et al., 2018). As a result, the disease that is responsible for the neurodegeneration that causes clinical dementia cannot be confirmed without *postmortem* neuropathological assessment (Jellinger, 2020). Neurodegenerative diseases are generally characterised by progressive loss of selectively vulnerable populations of neurons and often the accumulation of abnormal protein inclusions in the brain (Dugger and Dickson, 2017, Hyman et al., 2012). Subclinical pathology may be present decades before the onset of cognitive impairment (Schneider, 2022). Evidence exists for cognitive resilience for accumulating brain pathologies in ageing, which is thought to be related to a myriad of pathologic, genetic and environmental factors (Schneider, 2022). There are a number of different and overlapping underlying pathologies that are frequently observed *post-mortem* in clinical dementia cases (**Figure 1.7**). These can be grouped into neurodegenerative pathology, such as amyloid, tau, a-synuclein and TDP-43 proteinopathies, and vascular features, such as infarcts and small vessel disease (Schneider, 2022). The accumulation of pathogenic forms of misfolded proteins in neurodegenerative disease can result in both loss- and gain-of-function. Although there are is variability in the pathways involved, the end result is shared: neurotoxicity and synaptic loss presenting clinically as dementia. (Raz, Knoefel and Bhaskar, 2016).

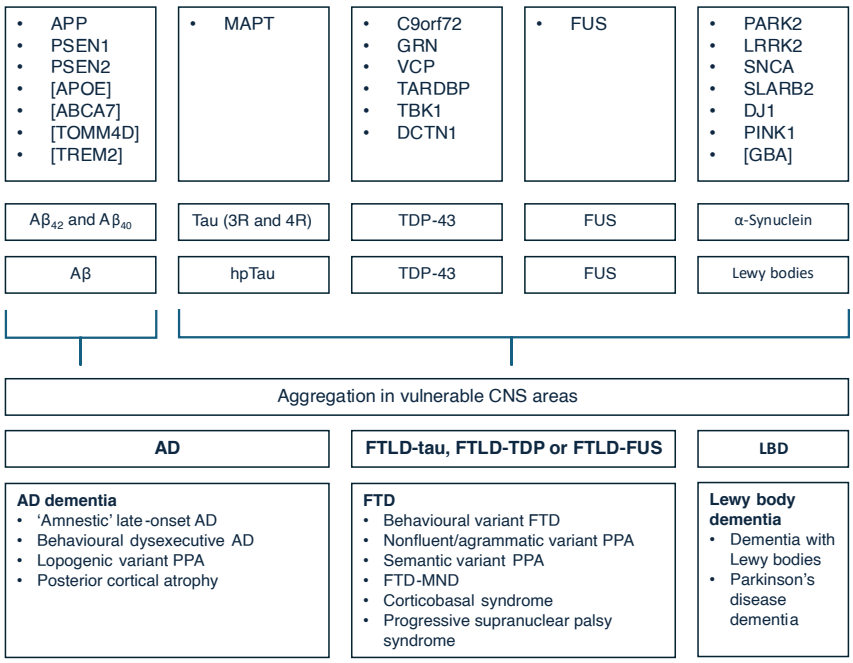

Figure 1.7. **Neuropathologies of Age-Related Dementia**: Overview of clinical dementia subtypes, their associated neuropathologies, and relevant genetic variants. Causative genes are listed without brackets, while genetic risk factors are indicated in square brackets.

1.2.1 Amyloid pathologies

Amyloid beta (Aβ) is a small 4 kDa protein fragment composed of 39-43 amino acids that derives from the amyloid precursor protein (APP). APP is a large transmembrane precursor molecule present in neurons, vascular and blood cells, and astrocytes. APP plays a role in synaptic formation and repair. APP is upregulated in neuronal differentiation and after neuronal injury. Aβ is a by-product of sequential proteolytic cleavages of APP by β- and γ-secretase (Hampel et al., 2021, Kent, Spires-Jones and Durrant, 2020). Aβ is expressed in a number of tissues throughout the body, including the brain, pancreas, appendix and gastrointestinal tract (Kent, Spires-Jones and Durrant, 2020). Most intracellular Aβ in neurons is localised to the cytosol but can also be associated with mitochondria and organelles involved in the secretory pathway. Familial Alzheimer's disease typically arises from mutations in the amyloid precursor protein (*APP)*, presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*). Of these, *PSEN1* mutations are the most common, followed by *APP*. These mutations alter γ-secretase activity, promoting the production of longer, aggregation-prone Aβ isoforms, particularly $Aβ_{42}$.

There are two major isoforms of Aβ produced by the sequential cleavage of APP: soluble $Aβ_{40}$ and insoluble $Aβ_{42}$ (Hampel et al., 2021). These isoforms are of varying length, primarily $Aβ_{40}$ and the

more aggregation prone $A\beta_{42}$. Aβ monomers can aggregate into soluble oligomers, protofibrils, and eventually insoluble fibrils that form the core of plaques (Tolar et al., 2021). Among these, soluble Aβ oligomers are considered the most neurotoxic species, disrupting synaptic function and contributing to cognitive decline, even in the absence of overt plaque deposition (Hampel et al., 2021).

The role of Aβ under homeostatic conditions remains unclear and poorly defined (Sun, Chen and Wang, 2015). The absence of amyloid does not appear to lead to any obvious cytotoxic loss of function. Potential roles of amyloid include the activation of kinases, regulation of cholesterol transportation, functioning as a transcription factor, and possible pro-inflammatory antimicrobial activity (Li et al., 2018). Aβ is also thought to play a role in the regulation of vasculature and myelination (Kent, Spires-Jones and Durrant, 2020). Levels of Aβ increase following stroke, spinal cord injury and traumatic brain injury suggesting that it may have a protective role within neurons (Kent, Spires-Jones and Durrant, 2020).

Despite investigation over several decades, the mechanisms involved in the pathogenesis of Alzheimer's disease remain unclear and widely debated. The most widely accepted theory is the amyloid cascade hypothesis in which Aβ is the initiator of a series of events that eventually leads to Alzheimer's disease (Sun, Chen and Wang, 2015). The amyloid cascade hypothesis proposes that Aβ is the main cause of Alzheimer's disease and postulates that the misfolding of extracellular Aβ protein found in neuritic plaques and the intracellular deposition of misfolded tau protein as neurofibrillary tangles results in memory loss and changes in cognition mood and behaviour over time (Chen et al., 2017). The amyloid cascade hypothesis, originally proposed by Hardy , and Higgins (1992), postulates that the aggregation of Aβ as neuritic plaques leads to neurotoxicity and dementia by pathogenic mechanisms that contribute to the pathogenesis of Alzheimer's disease and other amyloidopathies (Chen et al., 2017). Although Aβ does aggregate to form the fibrils found in amyloid plaques associated with Alzheimer's disease, many studies have suggested that there is no direct correlation between amyloid plaque burden and the synaptic and neuronal loss seen in Alzheimer's disease (Chen et al., 2017). Generally, a linear pathway that begins with Aβ formation and ends with Alzheimer's disease dementia (Herrup, 2015). The imbalance in production and clearance leads to the aggregation of Aβ in the brain, initiating a neurotoxic cascade (Herrup, 2015). The presence of misfolded Aβ is thought to accelerate the formation of neurofibrillary tangles that eventually cause synaptic failure and neuronal death (Herrup, 2015).

Increased production of insoluble and aggregation prone $A\beta_{42}$, and a corresponding reduction in soluble $A\beta_{40}$, is a common feature of both familial and sporadic Alzheimer's disease and is thought to be the catalyst for the aggregation of hyperphosphorylated tau and neurotoxicity (Sun, Chen and Wang, 2015, Kent, Spires-Jones and Durrant, 2020).

The main strength of the amyloid cascade hypothesis is the increased frequency of amyloid plaques in Alzheimer's disease affected brains. The presence of plaques as seen with biomarker studies is also associated with an increased risk of Alzheimer's disease. Furthermore, some subject with amyloid burdens and early dementia do experience improved cognition with anti-amyloid therapies (Herrup, 2015). There are however several weaknesses of the amyloid cascade hypothesis. In terms of pathology, neurofibrillary tangles have a stronger correlation with neurodegeneration than amyloid plaques and individuals with substantial amyloid plaque burdens can have normal cognition. Clinically, after Alzheimer's disease begins, immunoclearance of plaques does not improve cognition. Until recently, no phase 3 clinical trials based on the hypothesis had been successful (Walsh and Selkoe, 2020). Inhibition of gamma-secretase increased AD symptoms. Furthermore, there is some circularity within research based on findings from over 100 years ago. By definition, there is no Alzheimer's disease without amyloid pathology and the presence of amyloid pathology without clinical dementia is "preclinical Alzheimer's disease" (Jicha et al., 2012). This only makes sense if there is complete certainty that Aβ directly causes AD. Notably, substantial Aβ plaque burden can be present in cognitively normal older individuals, with the prevalence of Aβ plaques continuing to increase with age, suggesting a degree of cognitive resilience or preclinical AD (Sperling, Mormino and Johnson, 2014, Davis et al., 1999). This highlights the complexity of AD pathology and the potential role of compensatory mechanisms or protective factors (Stern, 2012, Walker and Richardson, 2023).

Aβ plaques accumulate extracellularly from the aggregation and fibrillation of Aβ peptides that are released from neurons into the extracellular space (Arnsten et al., 2021) . The pathological accumulation of misfolded amyloid is most frequently associated with Alzheimer's disease as it is a hallmark pathology. However, the accumulation of amyloid, at least to some extent, is seen in the majority of age-related neurodegenerative diseases. Deposits of amyloid are mainly observed as plaques in the neocortex and hippocampus, and as CAA in the cerebral vasculature (Chen et al., 2017). Amyloid deposition in the brain occurs in a number of forms, including diffuse or dense amyloid plaques and cerebral amyloid angiopathy (**Figure 1.8**).

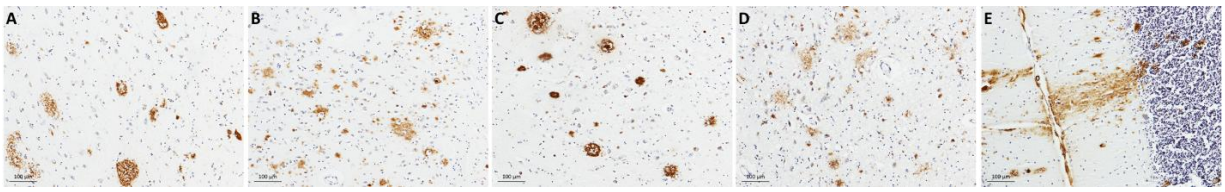

Figure 1.8. **Amyloid-β Histology:** Histological images of β-amyloid, diffuse amyloid deposits, neuritic plaques, and cerebral amyloid angiopathy (CAA), across different brain regions. Own images produced on a Nikon Eclipse 90i using immunohistochemistry from *postmortem* brain tissue from the Brains for Dementia Research programme stored in the Newcastle Brain Tissue Resource.

Amyloid plaques are aggregations of Aβ found in the extracellular space between neurons in the brain and can be in diffuse or neuritic form. Diffuse pre-amyloid plaques are poorly delineated extracellular accumulations of non-fibrillary misfolded Aβ that are not associated with dystrophic neurites. Diffuse plaques are amorphous and irregular. It is thought that diffuse plaques may later form into classical senile neuritic plaques. Mature amyloid plaques are spherical and consist of a central Aβ core with fibrillary outward extensions encompassing surrounding dystrophic neurites. Alzheimer's disease is characterised, in part, by the accumulation of the Aβ protein in specific brain regions in the form of diffuse and neuritic plaques (Chen et al., 2017). Dense Aβ aggregates comprise the main constituent of the neuritic plaques found in ageing brains that are a hallmark feature of Alzheimer's disease, together with neurofibrillary tau tangles. Diffuse plaques are common in the caudate nucleus and putamen of the basal ganglia and the cerebellum. Neuritic plaques are more commonly found in the neocortex, particularly in association areas.

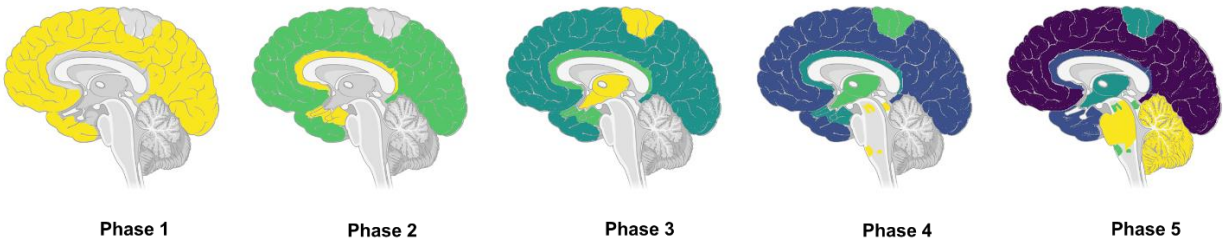

Figure 1.9 **Thal Phases of β-amyloid Deposition**: Representation of the Thal staging system for amyloid deposition, which classifies the progression of amyloid plaques in the brain across distinct phases. These phases reflect the regional spread of amyloid pathology, starting in the neocortex and advancing to subcortical structures. Adapted from Hampel et al. (2021) and Thal et al. (2002).

A staging system of Aβ pathology, proposed by Thal et al. (2002), sequences the formation of plaques in the brains of Alzheimer's disease patients (Wharton et al., 2019) and is illustrated in **Figure 1.9**. Diffuse plaques appear earlier in the disease course than neuritic plaques. In Phase 1, plaques are present in the neocortex. In Phase 2, plaques are observed in the allocortex,

hippocampus and amygdala. In Phase 3, the basal ganglia and diencephalon are affected. In Phase 4, plaques are present in the midbrain and medulla. By Phase 5, the pons and cerebellum are also affected (Thal et al., 2002). The CERAD neuritic plaque scoring system was developed to assess burden. Scores include sparse, moderate, and frequent burden of neuritic plaques.

Cerebral amyloid angiopathy is a type of blood vessel disease in which Aβ deposits are found in the walls of cerebral and meningeal blood vessels. Although technically a disease of the vasculature, CAA is associated with risk factors for Alzheimer's disease, rather than vascular disease, including the accumulation of Aβ protein (Schneider, 2022). Although associated with AD, not all AD cases have CAA and vice versa. CAA is also associated with infarcts, haemorrhages, and cognitive impairment (Schneider, 2022). Increased production and abnormal clearance of Aβ are thought to be responsible for the deposition in blood vessels seen in CAA. CAA can be classified as one of two types. Type 1 is characterised by detectable amyloid deposits within cortical capillaries, and within leptomeningeal and cortical arteries and arterioles (Greenberg and Charidimou, 2018). Type 2 is more prevalent and characterised by amyloid deposits in leptomeningeal and cortical arteries and arterioles but not capillaries.

The most prevalent cooccurring pathology in brains with neuritic Aβ plaques is neurofibrillary tangles, the second hallmark pathology of Alzheimer's disease. Aβ plaques are thought to accelerate the spread of tau and cognitive decline in Alzheimer's disease (Busche and Hyman, 2020). As Alzheimer's disease is the most common pathology observed post-mortem in dementia cases, neuritic Aβ plaques are an abundant pathology type in the ageing brain. However, further concomitant pathology in Alzheimer's disease is also common, with pure AD accounting for a minority of cases in autopsy series (Robinson et al., 2018b). Robinson et al. (2018b) found Aβ pathology in 80% of neocortical Lewy body disease cases and over 50% of non-neocortical cases. In addition, concomitant CAA was common, reported in 64% of AD cases in the same autopsy series (Robinson et al., 2018b). Over 50% of AD cases had sufficient pathology to meet neuropathological criteria for multiple neurodegenerative diseases.

1.2.2 Tauopathies

Tau is a 55-62 kDa soluble, unfolded, microtubule-associated protein (MAP) encoded by the *MAPT* gene on chromosome 17 (Forrest and Kovacs, 2022, Kent, Spires-Jones and Durrant, 2020). Tau is a vital component of the neuronal skeleton that is responsible for numerous essential functions within cells, including the maintenance of the cellular architecture (Tabeshmehr and Eftekharpour,

2023). Tau is expressed in a range of tissues throughout the body, including cardiac cells, skeletal muscle, the pancreas and the kidneys (Kent, Spires-Jones and Durrant, 2020). In healthy adult brains, tau is expressed in neurons of cortical and hippocampal regions and, in trace amounts, in astrocytes and oligodendroglia (Tabeshmehr and Eftekharpour, 2023). Six isoforms of tau are expressed in the adult human brain as a result of alternative splicing: three isoforms with three microtubule repeat domains (3-repeat tau) and three isoforms with four microtubule repeat domains (4-repeat tau) (Kametani and Hasegawa, 2018). Healthy adult brains contain balanced levels of 3R and 4R tau isoforms (Chung et al., 2021).

Under normal conditions, tau is involved in the maintenance of microtubule stability through interaction with tubulin and the promotion of axon assembly (Tabeshmehr and Eftekharpour, 2023). Additional roles include the regulation of critical cell processes, synaptic function, maintenance of cell shape, proper cell division and healthy transport of organelles. Within neurons, tau is predominantly found in the axon, where it binds to tubulin, promoting polymerisation, regulating stability and microtubule spacing (Arendt, Stieler and Holzer, 2016). Microtubular organisation is critical for axon stability and the trafficking of material and organelles to and from the cell body and tau is essential in preventing microtubule disintegration (Kent, Spires-Jones and Durrant, 2020).

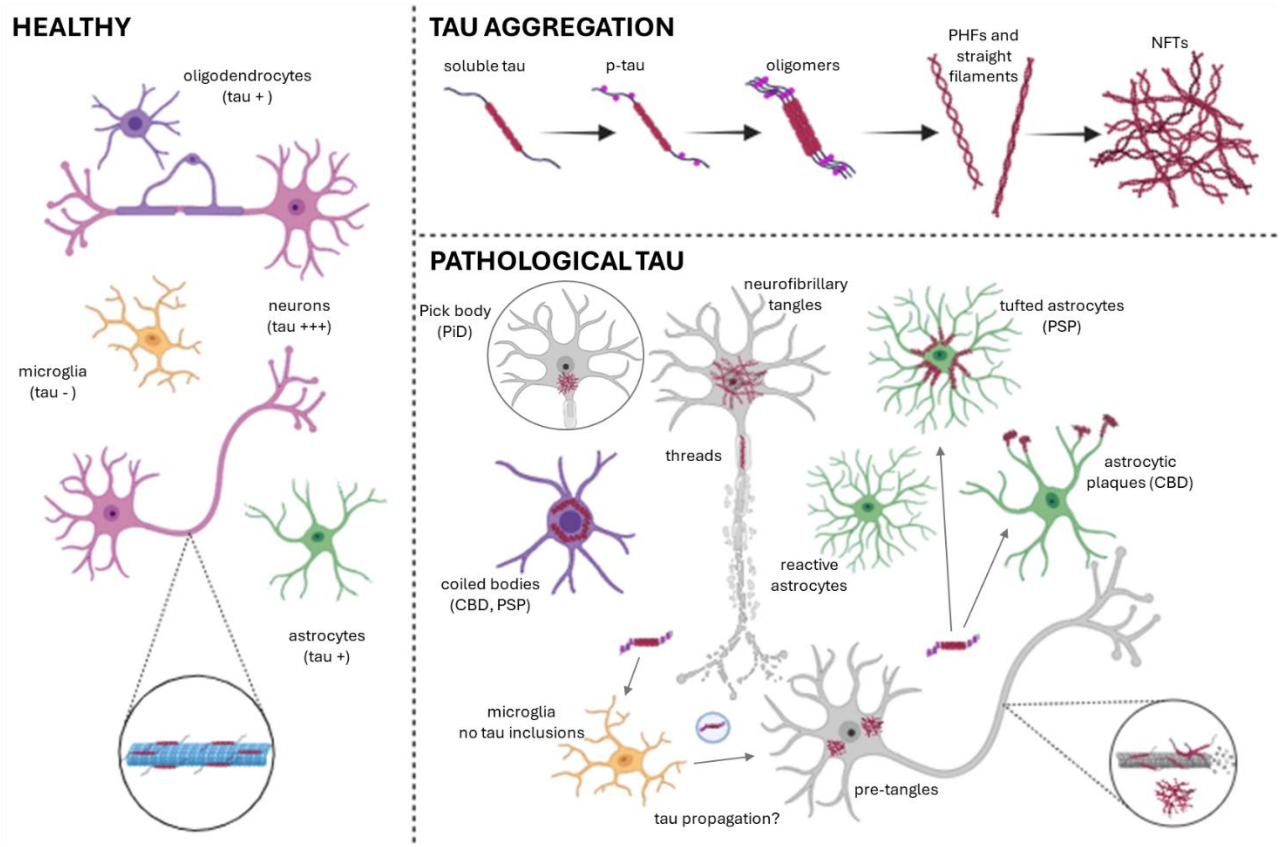

Figure 1.10. **Tau Pathology:** Normal Function, Accumulation, and Pathological Forms. Illustration depicting the normal function of tau in microtubule stabilization, its pathological accumulation, and the different types of tau aggregates that lead to tauopathies. The figure also distinguishes between various tau species, including those associated with neurofibrillary tangles, paired helical filaments, and other tau inclusions. Adapted from Zhang et al. (2022) and Chung et al. (2021)

Under pathological conditions, the ratio of 3R and 4R tau isoform shifts, leading to the accumulation of misfolded intracellular tau. In contrast to the amyloid cascade hypothesis, the tau hypothesis proposes that tau is the principle causative substance of neurodegeneration in Alzheimer's disease, rather than Aβ (Arnsten et al., 2021, Braak and Del Tredici, 2014). It states that neurofibrillary tangle pathology precedes the formation of Aβ plaques and that the hyperphosphorylation and subsequent aggregation of tau is the primary cause of neurodegeneration (**Figure 1.10**). In this theory, tau becomes abnormally phosphorylated and dissociates from microtubules (Pooler et al., 2013). Hyperphosphorylated tau aggregates intracellularly first into oligomers, then as paired helical filaments (PHF) and eventually as filamentous brain inclusions referred to as NFTs neurofibrillary tangles (NFT) (Pooler et al., 2013, Arnsten et al., 2021). The dissociation of tau from microtubules leads to destabilisation and prevention of microtubule assembly, causing neurodegeneration through synaptic dysfunction (Di et al., 2016). Neurons with intracellular neurofibrillary tangles are characterised by loss of

cytoskeletal stability. Under pathologic conditions, the balance of 3R and 4R isoforms is disrupted. The spread of both 3-repeat (3R) and 4-repeat (4R) tau isoforms can induce neurodegeneration and propagation of tau pathology (Stamelou et al., 2021).

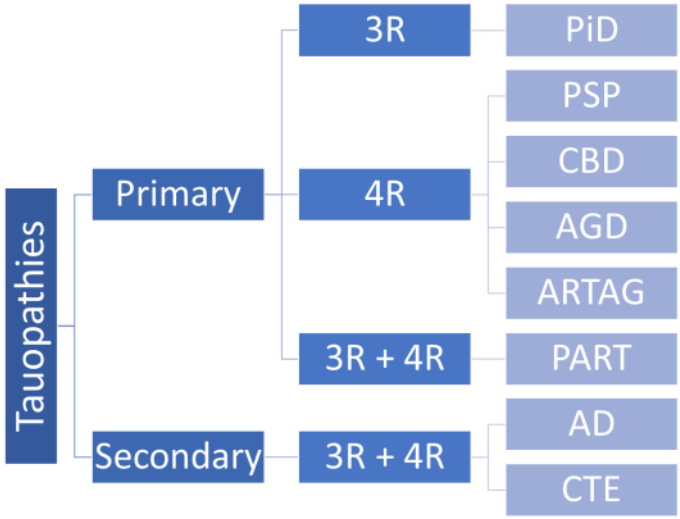

Figure 1.11. **Classification of Tauopathies**: Primary and Secondary Tauopathies and Tau Isoforms. Tauopathies are divided into primary tauopathies where tau aggregation is the central feature, and secondary tauopathies which result from external factors. The figure also illustrates the two main tau isoforms: those with 3 microtubule-binding repeats (3R) and those with 4 repeats (4R), whose distribution and aggregation patterns are linked to specific tauopathies. Abbreviations: PiD, Pick's disease; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; AGD, argyrophilic grain disease; ARTAG, age-related tau astrogliopathy; PART, primary age-related tauopathy; AD, Alzheimer's disease; CTE, chronic traumatic encephalopathy.

As outlined in **Figure 1.11**, tauopathies are classified based on the most prevalent tau isoform that accumulates and whether the accumulation of tau is considered to be the primary or secondary pathology present in each specific neurodegenerative disease (Zhang et al., 2022). The majority of primary tauopathies present clinically as frontotemporal dementias and predominantly result in atrophy restricted to the frontal and temporal cortices. Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE) are considered to be secondary tauopathies to Aβ and trauma respectively, which are considered to be the principle causative agents, whereas primary age-related tauopathy (PART) is classified a primary tauopathy, despite being characterised by the same neurofibrillary tangle pathology present in AD, due to the absence of any significant Aβ deposition (Chung et al., 2021). Tau isoform groups include 3-repeat, 4-repeat and both 3- and 4-repeat inclusions. Both 3R and 4R tau isoforms are present in Alzheimer's disease, primary age-related tauopathy, and chronic traumatic encephalopathy. The main tauopathy characterised by the accumulation of 3-repeat tau immunopositive intracellular inclusions is Pick's disease

(Stamelou et al., 2021). There are a number of tauopathies characterised by the accumulation of 4-repeat tau immunopositive inclusions in neurons and glia, which include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and age-related tau astrogliopathy (ARTAG). Primary tauopathies include PART, PiD, PSP, CBD, AGD and ARTAG (Chung et al., 2021).

The most common tau pathology seen in dementia is neurofibrillary tangles in Alzheimer's disease. Neurofibrillary tangles are not specific and in some neuropathological studies have been reported in almost every brain (Robinson et al., 2018b). Neurofibrillary tau tangles are insoluble and protease resistant aggregates and a fundamental neuropathological hallmark of Alzheimer's disease, along with diffuse and neuritic Aβ plaques (Nelson et al., 2012). Alzheimer's disease neuropathological change (ADNC) is classified as a secondary tauopathy as neuropathological diagnosis requires both amyloid deposition and tau aggregation (Chung et al., 2021). Tau lesions in Alzheimer's disease include neurofibrillary tangles (NFTs) and neuropil threads (NT) composed of paired helical filaments (PHFs) and straight filaments (SFs) that are immunoreactive for both 3R and 4R tau (Chung et al., 2021).

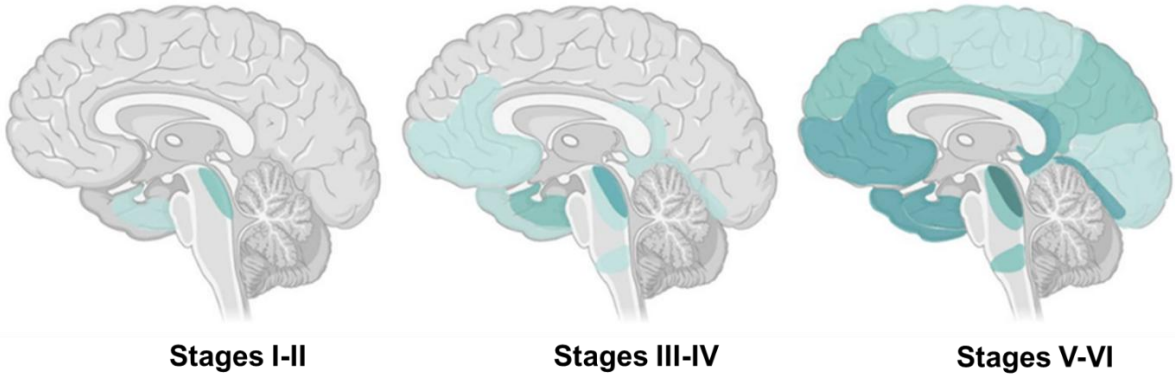

Figure 1.12. **Topographical Distribution of Neurofibrillary Tangles:** Illustration of the topographical distribution of neurofibrillary tangles (NFTs) across Braak stages, with emphasis on the brain regions typically affected at each stage of the disease. Adapted from Oostveen , and Lange (2021).

In Alzheimer's disease, the accumulation of neurofibrillary tangles follows a typical pattern of progression first described by Braak , and Braak (1991) as illustrated in ***Figure 1.12***. In Braak stages I and II, neurofibrillary tangles are confined to the transentorhinal region of the brain (Braak et al., 2006). In Braak stages III and IV, there is involvement of the limbic regions, including the hippocampus (Braak et al., 2006). In stages V and VI, there is extensive neocortical involvement (Braak et al., 2006).

Neurofibrillary tangle pathology has the strongest correlation with cognitive decline (Nelson et al., 2012). One of the strengths of the tau hypothesis is that neuropathological data has shown that tau pathology precedes Aβ deposition by ~10 years and the stronger correlation between the clinical progression of AD and tau pathology compared to Aβ (Alafuzoff et al., 2008). Hippocampal neurofibrillary tangles have been associated with a number of neuropsychiatric symptoms in dementia including aggregation and depression. Pure Alzheimer's disease accounts for a minority of cases (approximately 35%), with the majority having concomitant αSyn or TDP-43 pathology (Robinson et al., 2018b). Both Robinson et al. (2018b) and Visanji, Kovacs , and Lang (2021) reported Lewy pathology in at least 40% of all AD cases (Visanji, Kovacs and Lang, 2021). TDP-43 co-pathology was also present in 33% of intermediate ADNC cases and 40% of high ADNC cases (Robinson et al., 2018b). The majority of TDP-43 co-pathology reported in Alzheimer's disease is confined to limbic regions (Robinson et al., 2018b). In other neurodegenerative diseases, tau is a highly prevalent co-pathology, present in 100% of limbic and neocortical Lewy body disease cases (Robinson et al., 2018b). Distinguishing features of primary and secondary tauopathies are illustrated in ***Figure 1.13***.

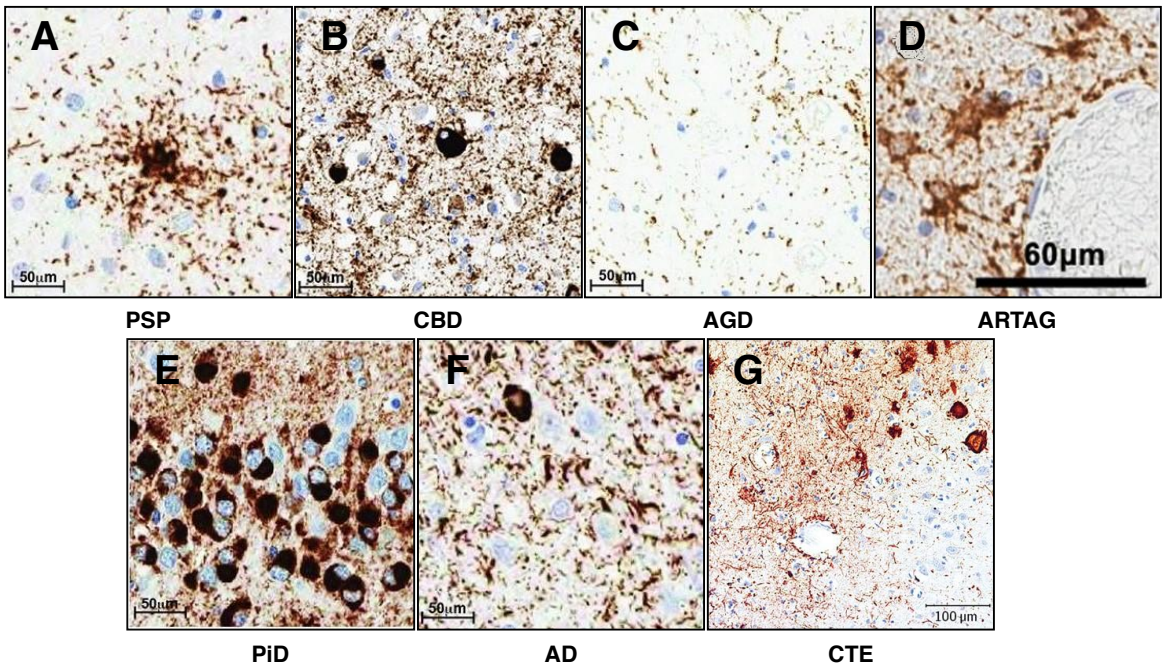

Figure 1.13. **Distinguishing Features of Primary and Secondary Tauopathies:** Key pathological features distinguishing primary and secondary tauopathies, including PSP (progressive supranuclear palsy), CBD (corticobasal degeneration), AGD (argyrophilic grain disease), ARTAG (age-related tau astrogliopathy), PiD (Pick's disease), AD (Alzheimer's disease), and CTE (chronic traumatic encephalopathy). Adapted from Chung et al. (2021) and Forrest , and Kovacs (2022).

Chronic traumatic encephalopathy (CTE) is a sporadic tauopathy, secondary to repetitive traumatic brain injuries and concussions (Chung et al., 2021). Neuronal inclusions in CTE are neurofibrillary tangles that are immunopositive for both 3R and 4R tau, similar to those seen in Alzheimer's disease (Chung et al., 2021). Unlike AD, tau pathology in CTE does not follow the typical topographical spread but is thought to initiate in the depths of the sulci, usually in the form of perivascular neuronal and glial tau lesions (Chung et al., 2021). CTE is relatively rare in the general population and the majority of CTE observed at autopsy occurs as a concomitant pathology in Alzheimer's disease or Lewy body disease (McCann et al., 2022).

Primary age-related tauopathy (PART) is a primary tauopathy characterised by Alzheimer's disease-like neurofibrillary tangles in the absence of amyloid co-pathology (Crary *et al.*, 2014). Duyckaerts et al. (2015) suggest that PART is be an atypical form of Alzheimer's disease whereas Jellinger et al. (2015) propose that it is a distinct tauopathy. Definite PART is defined by NFTs in the limbic system (Braak NFT stage II-III) with no amyloid pathology (Thal phase 0). Possible PART indicates cases with similar levels of NFT pathology but also mild amyloid co-pathology. Clinically, PART is sometimes associated with amnestic cognitive decline but does not always result in cognitive impairment (Crary *et al.*, 2014).

Pick's disease (PiD) is a 3R tauopathy characterised by Pick cells and Pick bodies. An additional neuropathological feature of Pick's disease is circumscribed "knife-edge" cortical atrophy observed in the frontal and temporal lobes, associated with severe neuronal loss and gliosis (Chung et al., 2021). Astrogliosis and spongiosis of the cortical ribbon with secondary axonal loss in the white matter is also present. The striatum, subthalamic nucleus and the substantia nigra are often affected (Chung et al. 2021). Pick bodies are 3R immunopositive neuronal cytoplasmic inclusions that are distinct spherical forms with a well-defined border (Chung et al., 2021). The anatomic distribution of Pick bodies mirrors brain atrophy. Pick cells are prominent neuronal lesions in the form of ballooned neurons and are not specific to PiD and are also seen in other tauopathies such as CBD and AGD. Glial lesions are less prevalent than neuronal lesions in PiD but Pick body-like inclusions can be detected in oligodendrocytes in affected white matter (Chung et al., 2021). Clinically, PiD presents with a feature of frontotemporal dementia including deterioration of language, personality, and memory. The mean survival time for Pick's disease is 10 years (Choudhury et al., 2020). Pure PiD is common, representing approximately 73% of cases in one study. The remaining 27% of cases had just one co-pathology (Robinson et al., 2018b).

ADNC was present in 20-30% of cases and αSyn pathology was reported in 5-7% of cases (Choudhury et al., 2020, Robinson et al., 2018b). TDP-43 inclusions were not present in any cases in this study (Robinson et al., 2018b).

Progressive supranuclear palsy (PSP) is a 4R tauopathy, characterised by tufted astrocytes, globose tangles, and neuronal loss in the substantia nigra (Forrest et al., 2020). Tufted astrocytes are most prevalent in the primary motor cortex and globose tangles in the substantia nigra (Forrest et al., 2020). Neurofibrillary tangles and threads are also present in subcortical nuclei (Zhang et al., 2022). Clinically, PSP is characterised by postural instability and oculomotor dysfunction, including vertical saccades and supranuclear gaze palsy (Chung et al., 2021). Behavioural and personality changes, and non-dopaminergic parkinsonism are common clinical features. The mean survival time for PSP is 6-8.5 years. ADNC is reported in 25% of cases and αSyn pathology is reported in 20% of cases (Robinson et al., 2018b). TDP-43 inclusions are reported in 6% up to 16% of PSP cases (Kovacs, 2019a).

Similar to PSP, corticobasal degeneration (CBD) is a sporadic 4R tauopathy, characterised by ballooned neurons (Zhang et al., 2022). Other features of CBD include widespread deposition of hyperphosphorylated 4R tau in neurons and as astrocytic plaques in glia in specific topographic areas, threads in the white and grey matter (Forrest et al., 2020). Pathology is most prevalent in the superior frontal cortex (Forrest et al., 2020). Clinically, CBD shows a wide range of symptoms, including impaired execution of skilled movements (apraxia), parkinsonism, executive dysfunctions, language impairments, and symptoms also seen in PSP such as postural instability and gaze palsy (Armstrong et al., 2013). Similar to PSP, ADNC is reported in approximately 25% of cases and αSyn in 20% of cases (Robinson et al., 2018b). TDP-43 inclusions are reported in 45% of cases (Kovacs, 2019a).

Argyrophilic grain disease (AGD) is a late-onset dementia first described by Braak , and Braak (1987). The hallmark feature of this 4R tauopathy is the accumulation of spindle-shaped argyrophilic grains in neuronal processes and coiled bodies in oligodendrocytes which are primarily seen in limbic regions (Ding et al., 2006, Wurm et al., 2020). The frequency of AGD pathology increases with age occurring in more than a third of post-mortem examinations performed on centenarians (Ding et al., 2006), often in combination with other neuropathological findings (Knopman *et al.*, 2003). Clinically, AGD is practically unrecognised (Wurm et al., 2020). The

most frequent symptoms reported in cases with relatively pure AGD pathology were progressive cognitive decline, urinary incontinence, seizures and psychological disorders (Wurm et al., 2020).

Although not a distinct neurodegenerative disease, astrocytic tau lesions are present in many neurodegenerative tauopathies and normal ageing (Chung et al., 2021, Zhang et al., 2022). Age-related tau astrogliopathy (ARTAG) is a defined by the presence of 4R-tau positive thorn-shaped astrocytes in areas near the pial surface of the brain, such as subpial, perivascular and subependymal regions (Kovacs *et al.*, 2016). Another subtype of ARTAG can also be tau-positive granular/fuzzy astrocytes in the grey matter, particularly the amygdala (Kovacs *et al.*, 2016). Unlike CTE, the characteristic pathology of ARTAG follows a specific distribution and progression (Kovacs et al., 2018). ARTAG is rarely observed in individuals younger than 60 and is rarely an isolated finding at autopsy. ARTAG is a common co-pathology found in more than 65% of primary tauopathies (Kovacs et al., 2018).

1.2.3 Synucleinopathies

Synucleinopathies are a group of neurodegenerative diseases linked by the presence of intracellular inclusions containing misfolded α-synuclein (αSyn) that include Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). The form of αSyn aggregation differs between diseases but in both PD and DLB, αSyn aggregates primarily as Lewy bodies (Kim, Kågedal and Halliday, 2014). αSyn is a small 14 kDa soluble protein consisting of 140 amino acids, encoded by the *SNCA* gene located on chromosome 4 (Stefanis, 2012, Burré, Sharma and Südhof, 2018). It is abundantly expressed in the human brain, accounting for approximately 1% of protein content in neuronal cytosol, but is also found in cells in the heart, muscles, and other tissues (Stefanis, 2012, Burré, Sharma and Südhof, 2018, Kim, Kågedal and Halliday, 2014). αSyn is expressed throughout the brain with high levels in the neocortex, hippocampus, substantia nigra, thalamus and cerebellum (Kim, Kågedal and Halliday, 2014). It is primarily expressed in neurons and to a lesser extent in glial cells (Kim, Kågedal and Halliday, 2014). The protein is also highly expressed in neuronal mitochondria, particularly of the olfactory bulb, hippocampus, striatum, and thalamus but not in mitochondria of the cerebral cortex or cerebellum.

The exact function of αSyn under homeostatic conditions is unclear but it is thought to play a role in plasticity, synaptic vesicle trafficking, transcriptional regulation, and the modulation of immune responses (Kasen et al., 2022). In the brain, αSyn is found mainly in the axon terminals of presynaptic neurons as a soluble unfolded protein that adopts an α-helical formation near

membranes with high curvature (Kim, Kågedal and Halliday, 2014). Proposed functions of αSyn under normal conditions include influencing synaptic activity as a molecular chaperone in the formation of presynaptic terminal SNARE complexes which are essential for the release of neurotransmitters, (Meade, Fairlie and Mason, 2019). As a result, αSyn may modulate the release of dopamine in controlling movement or influence memory and cognition (Sulzer and Edwards, 2019). The overexpression of αSyn slows synaptic vesicle exocytosis (Runwal and Edwards, 2021).

Post translational modification are prevalent and altered αSyn proteins impact on a number of pathological processes including the aggregation of αSyn, formation of Lewy bodies and neurotoxicity (Kim, Kågedal and Halliday, 2014). A common posttranslational modification of αSyn in Lewy body disease is phosphorylation (Kim, Kågedal and Halliday, 2014). In DLB brains, 90% of insoluble αSyn is phosphorylated at S129, compared with 4% in soluble cytosolic αSyn implicating phosphorylated αSyn in the process of αSyn aggregation (Kim, Kågedal and Halliday, 2014). Under pathological conditions, αSyn misfolds and interacts with tubulin to undergo a conformational change and aggregates as β-sheet-rich oligomers and fibrils predominantly in neurons (Walker, Stefanis and Attems, 2019, Outeiro et al., 2019). The misfolding of αSyn into aggregates, and loss of αSyn monomers, results in a series of secondary processes leading to neuroinflammation, neurodegeneration and cell death. The trigger for the accumulation of misfolded αSyn in neurons is unclear but several hypotheses have been proposed suggesting it may originate in the gut (gut-brain axis hypothesis) or olfactory system, or result from the upregulation of αSyn in immune activation (Kasen et al., 2022).

Lewy body diseases, such as DLB and PDD, are characterised by significant and preferential neuronal loss in specific regions, such as the substantia nigra, accompanied by the presence of intracellular inclusions containing aggregated vesicles, ubiquitin, and proteins, such as unbranched αSyn filaments, known as Lewy bodies or Lewy neurites (Power, Barnes and Chegini, 2017, Outeiro et al., 2019). Lewy bodies are observed in both cortical and subcortical neurons and are typically spherical, eosinophilic inclusion bodies with αSyn as a major component. In some cases, LBs may be located extracellularly and be multilocular or fusiform. Cortical Lewy bodies are eosinophilic, rounded, angular or reniform structures without a halo and can be seen most frequently in layers V and VI of the neocortex (Outeiro et al., 2019). In subcortical regions, such as the brainstem and limbic system, Lewy bodies often have an acidophilic and argyrophilic hyaline core with a pale-stained halo, and are typically localised to the locus coeruleus and the substantia nigra (Outeiro et

al., 2019). Lewy neurites are precursors of Lewy bodies containing deposits of ubiquitin and αSyn localised to neuronal processes. Lewy body pathology is often accompanied by the loss of dopaminergic neurons. αSyn has also been identified as a minor component of amyloid plaques in Alzheimer's disease (Bendor, Logan and Edwards, 2013). Lewy body pathology is illustrated in **Figure 1.14**.

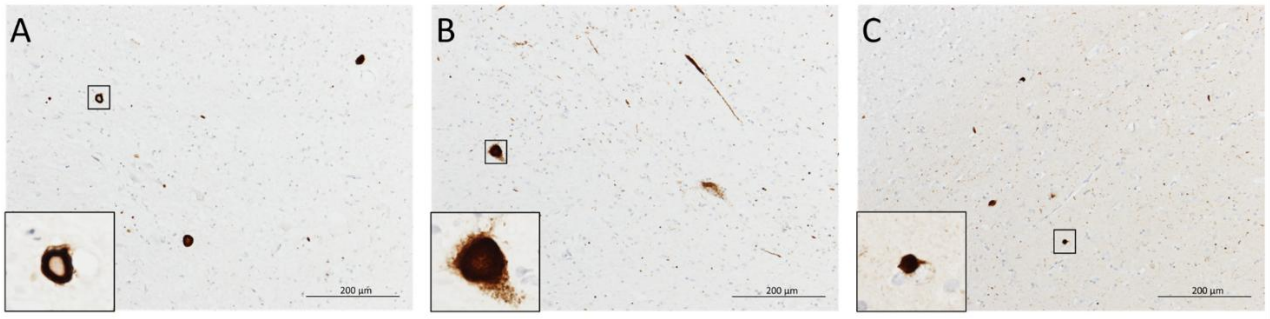

Figure 1.14. **Lewy Body Histology**: Lewy bodies (classical, cortical) and Lewy neurites. Own images produced on a Nikon Eclipse 90i using immunohistochemistry from postmortem brain tissue from the Brains for Dementia Research programme stored in the Newcastle Brain Tissue Resource.

Based only on neuropathology observed postmortem, differentiating between DLB and PDD is a challenge and confounded by the shared hallmark pathology. There are, however, some slight differences. In DLB cases, there is often a higher burden of Lewy pathology in limbic and neocortical regions, particularly the CA2 region of the hippocampus and the temporal lobe, compared to PDD cases (Walker, Stefanis and Attems, 2019). In contrast, dopaminergic cell loss tends to be higher in PDD compared to DLB (Walker, Stefanis and Attems, 2019).

A number of classification systems are used to stage Lewy body disease; the majority of which rely on semi-quantitative scoring of Lewy pathology in defined cortical and subcortical regions (Braak et al., 2003, McKeith et al., 2005, Leverenz et al., 2008, Beach et al., 2009). Braak staging, outlined in **Figure 1.15**, describes a caudo-rostral pattern of disease progression throughout brain regions in Lewy body disease (Braak et al., 2003). Initially, Lewy pathology is limited to the lower brainstem and olfactory system. In particular, the dorsal IX/X motor nucleus of the vagus nerve in the medulla oblongata and the anterior olfactory nucleus are preferentially affected (Walker et al., 2015). In stage 2, additional lesions are present in the raphe nuclei and gigantocellular reticular nucleus of the medulla oblongata and Lewy pathology spreads up the brainstem to the locus coeruleus of the pons. In both stage 1 and 2, Lewy neurites are more prevalent than Lewy bodies. By stage 3, Lewy bodies begin to form in the substantia nigra with Lewy bodies forming in the pars compacta and the basal nucleus of Meynert (Jellinger, 2009, Braak et al., 2003). The amygdala and

the subthalamic nuclei are affected in stage 4 with additional involvement of meso- and allocortical regions. By this stage, there is severe loss of dopaminergic pathways. Lewy body pathology spread to the neocortex in stage 5, affecting structures of the parietal, temporal and frontal lobes. Neurodegeneration is seen in regions affected in earlier stages of disease including the substantia nigra, the dorsal motor nucleus and the locus coeruleus. By stage 6, there is full neocortical involvement, with motor and sensory area involvement. The mechanism of the spread of the disease process is unknown but evidence suggests that α-synuclein pathology can spread from cell to cell. Not all cases follow the caudo-rostral progression (Walker et al., 2015). The majority of staging systems follow a similar structure of disease progression to Braak staging. The Lewy Pathology Consensus Criteria is a simplified dichotomous approach to scoring of Lewy pathology based on the McKeith system that includes amygdala-predominant and olfactory-only stages, allowing classification of all cases into distinct categories (Attems et al., 2021).

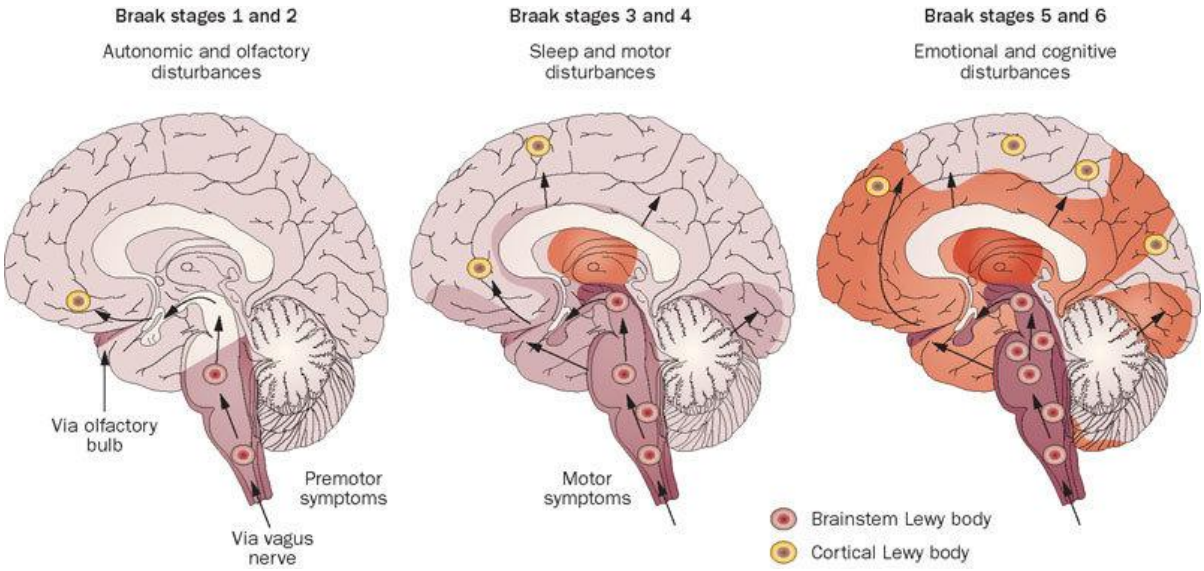

Figure 1.15. **Topographical Spread of Lewy Body Pathology:** Braak staging of Lewy body disease, illustrating the progressive spread of Lewy body pathology across different brain regions. The stages reflect the anatomical progression of Lewy body involvement, as outlined by Petersen (2017), from early involvement in the brainstem to later cortical regions.

The gut-brain axis hypothesis postulates that Lewy pathology may originate in the peripheral and enteric nervous systems, with gastrointestinal problems preceding the onset of neurodegeneration (Klann et al., 2022, Tan, Lim and Lang, 2022, Carabotti et al., 2015). The spread of Lewy body pathology from brainstem, through the limbic structures to the neocortex is the strongest neuropathological correlate of emerging dementia in Lewy body disease (Irwin, Lee and Trojanowski, 2013). Autonomic and olfactory disturbances occur early in the prodromal phase of

Lewy body disease when pathology is limited to the brainstem. Once the brainstem is severely affected and pathology has reached the limbic system, sleep and motor disturbances occur. Brainstem Lewy body disease is most frequently associated with the cardinal triad of extrapyramidal motor symptoms (rigidity, bradykinesia and tremor) known as parkinsonism. Visual hallucinations are often associated with a greater burden of Lewy bodies in limbic structures such as the amygdala and transentorhinal region, and in the temporal and frontal lobes (Ferman et al., 2013). Cognitive impairment occurs in the later stages of disease once Lewy body pathology has spread through the neocortex.

Mixed and concomitant pathology is prevalent in Lewy body disease but is often overlooked as a confounding factor in research. Approximately 5% of dementia cases show evidence of DLB alone (Outeiro et al., 2019). Several studies have characterised the frequency of common co-pathologies in Lewy body disease and determined that, regardless of the criteria applied, cases of pure Lewy body pathology are in the minority (Outeiro et al., 2019, Robinson et al., 2018b). Robinson et al. (2018b) reported pure pathology in only 19% of neocortical Lewy body disease cases. The majority of people with DLB have Alzheimer's disease neuropathological changes with almost half of DLB and PDD cases developing sufficient amyloid and tau pathology to fulfil the criteria for a secondary diagnosis of Alzheimer's disease (Outeiro et al., 2019, Irwin, Lee and Trojanowski, 2013, Visanji, Kovacs and Lang, 2021). Similarly, Lewy bodies are observed in over 50% of Alzheimer's disease cases (Robinson et al., 2018b). Robinson et al. (2018b) reported that concomitant Aβ was present in 80% and tau pathology in 100% of neocortical Lewy body disease cases examined. It is thought that Alzheimer's disease pathology may act synergistically with αSyn pathology resulting in worse clinical prognosis and reduced survival time (Irwin, Lee and Trojanowski, 2013, Lemstra et al., 2017). Concomitant TDP-43 inclusions were observed in 22% of the neocortical LBD cases examined (Robinson et al., 2018b).

1.2.4 TDP-43 proteopathies

Transactive response DNA-binding protein 43 (TDP-43) proteinopathy is a prevalent pathology in aging brains and is often associated with dementia and cognitive impairment (Nelson et al., 2022b). TDP-43 has been identified as the major pathological protein in multiple neurodegenerative diseases, including the TDP variant of frontotemporal dementia (FTLD-TDP), limbic-predominant age-related TDP-43 encephalopathy (LATE), and amyotrophic lateral sclerosis (ALS). As TDP-43 proteinopathies are characterised by the accumulation of intracellular deposits of

TDP-43, albeit in different topographical regions, it is thought that the diseases share common neurodegenerative pathways and are part of a spectrum of diseases (Ferrari et al., 2011). Both FTD-TDP and LATE affect cognitive function whereas ALS affects movement.

TDP-43 is a 43 kDa protein encoded by the *TARDBP* gene on chromosome 1. TARDBP is highly expressed and is critical for normal development of neurons in the early stages of embryogenesis (Suk and Rousseaux, 2020). TDP-43 is a 414 amino acid nuclear RNA/DNA-binding protein belonging to the large heterogeneous nuclear ribonucleoprotein (hnRNP) family (Arseni et al., 2022). It is highly conserved and localised to the nucleus due to its involvement in gene regulation and RNA metabolism, including mRNA transport and splicing. TDP-43 is ubiquitously expressed in many tissue and cell types including neurons and glial cells of the central nervous system. Genetic abnormalities associated with the progranulin gene (*GRN*) and the *C9orf72* gene are also associated with TDP-43 pathology.

TDP-43 is normally expressed in neuronal and glial nuclei in the brain and has significant roles in transcription, splicing, and a number of cellular processes including mRNA stability, regulation of RNA metabolism, mRNA transport, microRNA maturation and stress granule formation (De Boer et al., 2021). TDP-43 is able to move between the nucleus and the cytoplasm but under normal physiological conditions, it is predominantly localised to the nucleus (Jo et al., 2020). TDP-43 is thought to act as a transcription repressor and play a role in mRNA stability, miRNA biogenesis, apoptosis, and cell division. TDP-43 may also act as a neuronal activity response factor involved in the regulation of neuronal plasticity. Under homeostatic conditions, TDP-43 binds to DNA to regulate transcription, and binds to RNA to promote stability. TDP-43 is also involved in alternative splicing of mRNA. TDP-43 influences the functions of a cell through the regulation of protein production.

Under pathological conditions, TDP-43 abnormally redistributes from the nucleus to the cytoplasm and forms intracellular aggregates (Cohen, Lee and Trojanowski, 2011). The mechanism of propagation and subsequent cellular dysfunction and death once TDP-43 pathogenesis has been initiated remains unclear (Chen and Mitchell, 2021). Pathological TDP-43 aggregates are composed of the full-length protein and of abnormally cleaved fragments (Arseni et al., 2022). The aggregates are insoluble, granulofilamentous and unbranched with abnormal post-translational modifications, including ubiquitylation and phosphorylation (Arseni et al., 2022). Hyperphosphorylated and ubiquitinated TDP-43 cytoplasmic inclusions have been identified as a

pathological feature of both amyotrophic lateral sclerosis and frontotemporal lobar degeneration (Gao et al., 2018). The cytoplasmic aggregation of misfolded TDP-43 and loss of function leads to neurotoxicity and neurodegeneration. TDP-43 pathology tends to be bilaterally asymmetrical and localised to a specific region and spreads outwards from the initial site as the disease progresses suggesting that a cell-to-cell mechanism may underly the propagation of pathogenic TDP-43 (Chen and Mitchell, 2021).

Intracellular aggregation of misfolded TDP-43 is associated with a number of neurodegenerative diseases, including FTLD, ALS and LATE. TDP-43 proteinopathy refers to the loss of normal nuclear TDP-43 immunoreactivity, with mislocalised and phosphorylated TDP-43 inclusion bodies seen in the neuronal cytoplasm, as well as abnormal TDP-43 accumulation in the nuclei and neurites of neurons and in oligodendroglia and astrocytes (Nelson *et al.*, 2019). Frontotemporal lobar degeneration is characterised by gross atrophy of the frontal and temporal lobes due to progressive neuronal loss over the disease course, accompanied by the presence of TDP-43 inclusions. There are a number of different inclusion types present in FTLD-TDP. Neuronal cytoplasmic inclusions vary in morphology, ranging from crescent to ring shaped (Lee et al., 2017). Dystrophic neurites of varying lengths are also present across the spectrum of TDP proteinopathies. Other pathologies present include lentiform neuronal intranuclear inclusions, curvilinear oligodendroglial inclusions in the white matter, granulofilamentous neuronal inclusions and fine neuropil aggregates (Lee et al., 2017). Pathology present in LATE-NC includes NFT-like, granular or discrete neuronal cytoplasmic inclusions and processes of glial or neuronal cells (Nelson et al., 2022b).

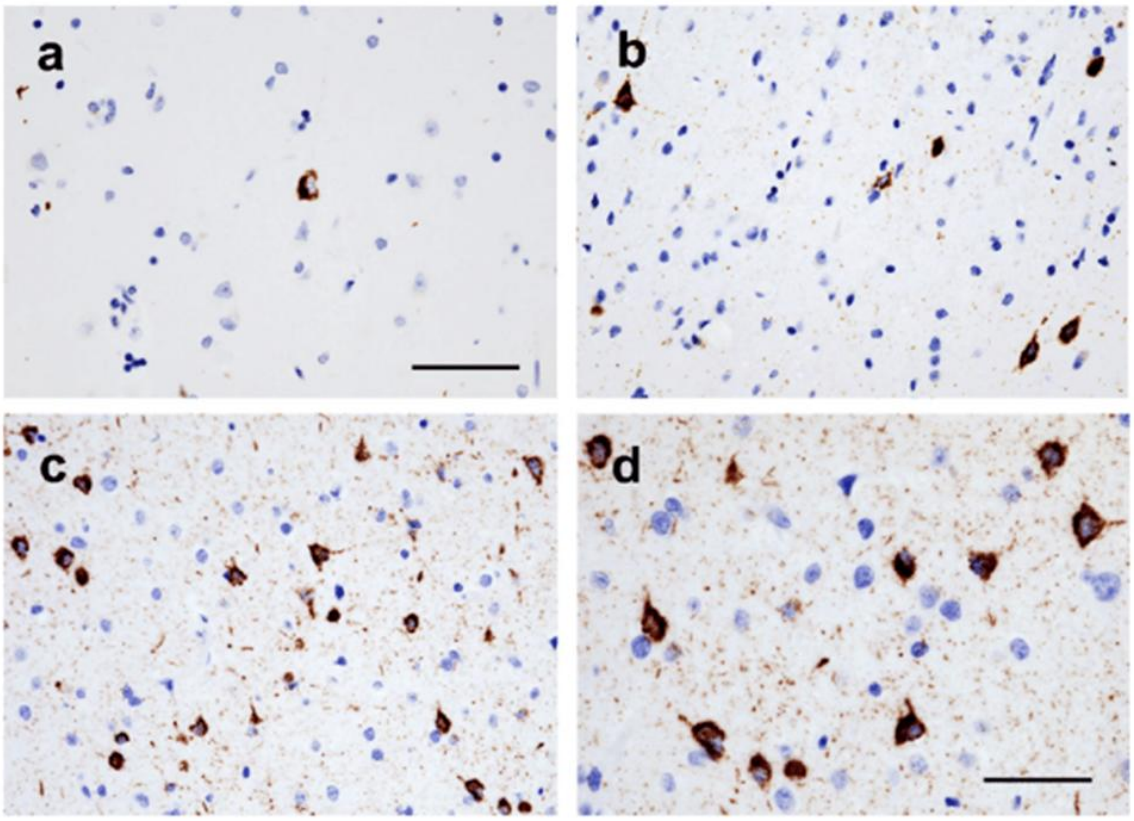

Figure 1.16. LATE-NC Histology: Histological images showing TDP-43 inclusions in limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC). The presence of TDP-43-positive inclusions in specific brain regions is a hallmark of LATE pathology. Images from Nag et al. (2017).

Frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) is characterised by ubiquitin and TDP-43 positive inclusion bodies (**Figure 1.16**) and associated atrophy of the frontal and temporal lobes. A neuropathological diagnosis of FTLD-TDP is given to cases where the predominant neuropathological abnormalities observed at autopsy are frontotemporal neuronal loss and gliosis with ubiquitin-positive, tau-negative inclusion bodies (Cairns et al., 2007). FTLD-TDP cases are classified into five subtypes based on the morphological diversity topographical, location and severity of the TDP-43 pathology seen post-mortem (Lee et al., 2017, Mackenzie et al., 2011). Type A is defined by the presence of a variety of different shaped neuronal cytoplasmic inclusions, including ring inclusions, lentiform neuronal intranuclear inclusions and short dystrophic neurons, affecting superficial neocortical layers II-III (Lee et al., 2017). Common clinical phenotypes of Type A include bvFTD and nfvPPA. Type B is characterised by the presence of neuronal cytoplasmic inclusions affecting superficial to deep neocortical layers II-V (Lee et al., 2017). The most common clinical phenotype of Type B is bvFTD (Neumann, Lee and Mackenzie, 2021). Type C is defined predominantly by the presence of long dystrophic neurons affecting superficial layers II-III of the

neocortex. svPPA and bvFTD are the most common clinical phenotypes associated with Type C (Neumann, Lee and Mackenzie, 2021). Type D is characterised by lentiform neuronal intranuclear inclusions affecting superficial and deep layers (II-V) of the neocortex (Lee et al., 2017). Type E is characterised by granulofilamentous inclusions and small neuropil aggregates affecting all neocortical layers (I-VI). Curvilinear oligodendroglial inclusions in the white matter are also present in Types A, B and E (Lee et al., 2017). In addition to pathognomonic neocortical features, most cases of FTLD-TDP are also found to have significant TDP-43 pathology in limbic and subcortical regions (Neumann, Lee and Mackenzie, 2021). Clinical characteristics of FTLD-TDP overlap significantly with those of other FTLD classes. In general, semantic variant primary progressive aphasia cases tend to have underlying FTLD-TDP and behavioural variant FTD can have either underlying FTLD-TDP or FTLD-tau (Neumann, Lee and Mackenzie, 2021).

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a recently defined, but debated, distinct disease associated with an underlying TDP-43 proteinopathy, known as LATE neuropathological change (LATE-NC), in the absence or presence of co-existing hippocampal sclerosis (Nelson et al., 2019, Zhang et al., 2020). In LATE-NC, mislocalised and phosphorylated TDP-43 is present as inclusion bodies in the olfactory bulb, neocortex, basal ganglia and, occasionally, the brainstem (Josephs et al., 2016). Nelson *et al.* (2019) defined a simplified staging scheme for TDP-43 proteinopathy in LATE-NC combining previously defined more detailed staging systems for TDP-43 pathology in LATE with relatively similar patterns of progression (Josephs et al., 2016, Nag et al., 2017). The general consensus is that in the early stages of LATE, the amygdala is selectively affected, followed by the hippocampus, and by the final stages, TDP-43 inclusions affect the middle frontal gyrus (Nelson *et al.*, 2019). Unlike other neuropathology staging systems, regions are reported as positive if TDP-43 immunoreactivity is reported anywhere in the brain region.

LATE-NC is present in approximately 25% of aging brains and the prevalence of LATE-NC increases substantially with advancing age (Wang et al., 2022, Gauthreaux et al., 2022, Zhang et al., 2020). LATE-NC is correlated clinically, independent of other coexisting pathologies, with an amnestic dementia syndrome that has similar features to Alzheimer's disease dementia which can progress to involve multiple cognitive domains and impair activities of daily living (Nelson et al., 2010, Josephs et al., 2015, Harrison et al., 2021). The neurological features associated with LATE-NC are different from the behavioural or aphasic clinical syndromes seen in FTLD-TDP (Nag et al., 2017).

Although there is some overlap in clinical features, cases of pure LATE-NC tend to have a more gradual clinical decline than pure ADNC.

Although LATE-NC and FTLD-TDP share the same pathologic protein and the clinical and pathological differences have not been fully characterised, the two diseases differ in both epidemiology and clinical phenotype, with LATE-NC being more prevalent than FTLD-TDP and primarily affecting older individuals (Nelson et al., 2019, Katsumata et al., 2020). In addition, a recent study found that the density of TDP-43 pathology in neocortical regions is more severe in FTLD-TDP than in severe LATE-NC cases (Robinson et al., 2020). As pathology in LATE-NC does not appear to progress to severe involvement of the frontal and cingulate cortices, even in the oldest-old, there may be an additive pathogenic mechanism present in FTLD-TDP that is not present in LATE-NC, potentially comparable to the relationship between AD and PART (Robinson et al., 2020).

TDP-43 is a common co-pathology in many neurodegenerative diseases, particularly Alzheimer's disease (Robinson et al., 2018b). Aβ is the most common co-pathology in TDP43 proteinopathies affecting 32-42% of cases. αSyn is less prevalent affecting 11-16% of cases and increases with severity of TDP-43 pathology. Tau pathology observed in 16% of FTLD-TDP cases and 24% of severe cases. Co-pathology prevalence in TDP-43 proteinopathies was of a similar prevalence to controls. In addition, Koga et al. (2021) found that tau co-pathology was relatively common in FTLD-TDP cases. Over 40% of cases had concomitant ARTAG, 34% had PART and 23% had co-occurring AGD (Koga et al., 2021). Cerebral amyloid pathology is also relatively common in FTLD-TDP, affecting 34% of cases in the same study (Koga et al., 2021). LATE-NC is most commonly seen as a concomitant pathology in other neurodegenerative diseases. For example, LATE-NC affects between 29-74% of autopsy confirmed Alzheimer's disease cases (McAleese et al., 2020). LATE-NC with ADNC co-pathology also shows faster decline and more severe cognitive impairment than either in the absence of the other (Nag et al., 2017, Boyle et al., 2017). In another study, LATE-NC with hippocampal sclerosis was associated with greater impairment (Gauthreaux et al., 2022).

1.2.5 Cerebrovascular pathologies

Briefly, cerebrovascular pathology is a critical component in the aetiology and progression of dementia, influencing cognitive decline through various mechanisms (Kalaria, 2016). Cerebrovascular pathology encompasses a range of vascular changes that lead to impaired cerebral perfusion and neuronal injury, contributing to cognitive deficits (Skrobot *et al.*, 2016). Distinct from primary neurodegenerative processes, cerebrovascular alterations can co-exist with

various neuropathological diseases (Kalaria, 2016). The vasculature of the brain serves vital functions in maintaining cerebral blood flow and ensuring optimal neuronal function. Comprising arteries, veins, and capillaries, this intricate network delivers essential nutrients and oxygen while facilitating the removal of metabolic waste products. The integrity of vascular function is paramount for preserving neuronal homeostasis (Kalaria, 2016)..

Cerebrovascular pathology is characterised by several pathophysiological mechanisms, including atherosclerosis, hypertension, and small vessel disease. Atherosclerosis, involving the accumulation of plaques within arterial walls, leads to luminal narrowing and reduced blood flow to brain regions. Concurrently, chronic hypertension induces structural changes in the vasculature, such as arteriolosclerosis, which comprises the integrity of small penetrating arteries. Microangiopathy is another critical mechanism, wherein degenerative changes in small vessels contribute to ischaemia and cognitive dysfunction.

Cerebrovascular pathology manifests in various forms, including ischaemic strokes, haemorrhagic strokes, lacunar infarcts, and white matter hyperintensities (Agrawal and Schneider, 2022). Ischaemic strokes, resulting from occlusions in the cerebral vasculature, lead to focal areas of ischaemia and subsequent neuronal death. In contrast, haemorrhagic strokes arise from the rupture of blood vessels, resulting in haematoma formation and potential secondary brain injury. Lacunar infarcts, often linked to chronic hypertension, represents small, deep-seated lesions that can significantly impact cognitive function. White matter hyperintensities reflect chronic small vessel disease and are associated with cognitive impairment.

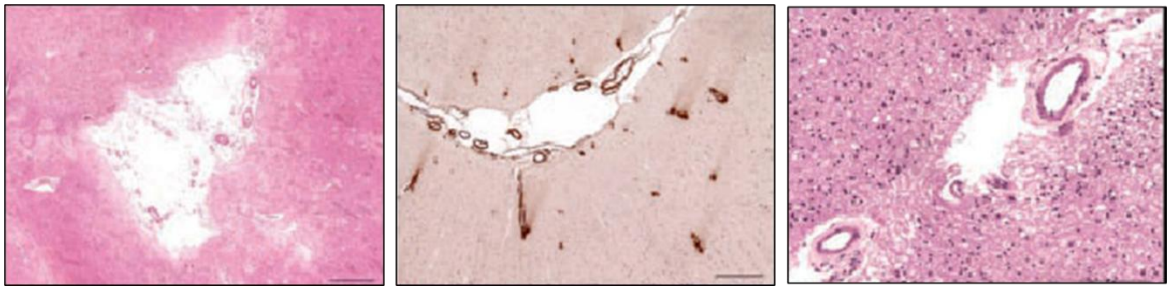

Figure 1.17. Vascular Histology: Histological images illustrating the three key pathologies as outlined in the VCING guidelines for vascular cognitive impairment: large subcortical infarcts, occipital leptomeningeal cerebral amyloid angiopathy (CAA), and occipital white matter arteriosclerosis. These pathologies are frequently implicated in vascular dementia and contribute to cognitive decline. Images from Skrobot et al. (2016).

The Vascular Cognitive Impairment Neuropathology Guideline (VCING) provides a systematic approach for staging cerebrovascular pathology within the dementia spectrum (**Figure *1.17***). This

classification scheme evaluates the severity of vascular lesions, including infarcts and white matter changes, facilitating a nuanced understanding of their impact on cognitive performance. By quantifying cerebrovascular contributions, the VCING rating allows for a more precise correlation between vascular pathology and cognitive decline. Three pathology types are included in the Vascular Cognitive Impairment Neuropathology Guidelines (VCING): large subcortical infarcts, moderate or severe occipital leptomeningeal cerebral amyloid angiopathy, and moderate or severe occipital white matter arteriolosclerosis. Combinations of the three vascular features are used to assign a low, moderate, or high likelihood that cerebrovascular disease contributed to cognitive impairment in each individual case (Skrobot *et al.*, 2016).

1.3 Mixed and concomitant pathology

Mixed pathology in age-related dementia is common (Nichols et al., 2023, Kovacs et al., 2013, Kawas et al., 2015). Many clinicopathological and brain banking studies have reported that the co-occurrence of pathologies in dementia is standard for many, rather than an atypical experience of a few (Coulthard and Love, 2018, Alafuzoff and Libard, 2020). For example, an autopsy series found that the combination of Alzheimer's disease with Lewy body disease or vascular pathology was so widespread that mixed pathology represented the most common cause of dementia (Bennett et al., 2012a). Others suggest that mixed pathology could be considered the end stage of Alzheimer's disease (De Reuck et al., 2016).

Numerous large-scale clinicopathological and autopsy studies have shown that mixed pathologies are present in a substantial proportion of dementia cases, particularly in older populations (Tanskanen et al., 2017, Wharton et al., 2023, Matthews et al., 2009, Brayne et al., 2009, Kovacs et al., 2013, Wakisaka et al., 2003, White et al., 2005, Snowdon et al., 1997, Bennett et al., 2012a, Bennett et al., 2012b). Despite 50-60% of age-related dementia cases having multiple neuropathological diagnoses at autopsy, interactions between pathologies and the influence on clinical presentation, mixed pathology is frequently overlooked as a factor influencing the clinical presentation of dementia in both translational research and clinical trials (Liyanage, Santos and Weaver, 2018).

Despite advances in understanding the independent contributions of Alzheimer's disease, cerebrovascular disease, and Lewy body disease, the role of mixed and concomitant pathologies in dementia remains under-investigated (Keage et al., 2012, Wharton et al., 2023). The relationship between mixed pathology and cognitive decline is not yet fully defined. However, accumulating

evidence suggests that mixed and concomitant pathologies often interact synergistically, accelerating cognitive decline in other neurodegenerative diseases. The high prevalence of mixed pathologies complicates both clinical diagnosis and the interpretation of disease trajectories (Nichols et al., 2023, Kovacs et al., 2013, Kawas et al., 2015). This complexity is particularly evidence in advanced stages of cognitive impairment or in the oldest-old, where multiple overlapping pathologies may obscure the contributions of individual disease processes. Clarifying these interactions is critical for refining diagnostic frameworks and better characterising the clinical course of dementia.

1.4 Clinicopathological Studies of Dementia

Neuropathological and epidemiological studies, such as large-scale brain banking and population-based studies, have provided crucial findings for interpreting clinicopathological correlations in dementia (Hokkanen et al., 2020, Nelson et al., 2022a). Brain banking studies provide detailed postmortem data from often well-characterised clinical research cohorts that expose the complexity of neuropathology (Wharton et al., 2023). At present, postmortem studies are critical for validating diagnostic criteria, identifying co-existing pathologies, and understanding disease heterogeneity (Brayne and Wu, 2022). In contrast, population-based clinicopathological studies offer insights into dementia burden and clinical impact in the general population in a more representative sample. Together, these approaches provide evidence to advance the understanding the variability in both clinical presentation and neuropathological profiles.

1.4.1 Brain banking studies

Brain banking refers to the systematic collection, preservation, and distribution of postmortem human brain tissue for research. In the context of dementia, access to well-characterised brain tissue is essential for studying disease mechanisms, validating clinical findings, and identifying neuropathological subtypes (Alafuzoff and Winblad, 1993). The impact of brain banking relies not only on the quality of tissue but also on the scale and coordination of collections, which has led to the development of large, collaborative brain banking networks. Brain banking plays a critical role in advancing dementia research by providing access to postmortem human brain tissue, which remains the gold standard for confirming neuropathological diagnoses (Francis et al., 2019). While clinical assessments and imaging can indicate the presence of dementia, they cannot confirm underlying pathology burden or the combination of pathologies (Sarris et al., 2002). Brain tissue donation allows researchers to identify the true prevalence of underlying pathologies and identify

atypical presentations of disease that contribute to the heterogeneity seen in clinical populations (Kretzschmar, 2009). Brain banks support the development and validation of biomarkers by offering well-characterised samples linked to clinical data (Danner et al., 2024). This integration of clinical and pathological information is essential for improving diagnostic accuracy, refining disease classification, and informing the development of targeted therapies. As such, brain banking remains a cornerstone of translational dementia research.

There are a number of existing well-established brain bank networks which have been established with the aim of harmonising data, collecting gold-standard or high-quality neuropathological data, and creating tissue resources to support dementia research (Palmer-Aronsten et al., 2016). In the United Kingdom, the UK Brain Banks Network (UKBBN) consists of 10 brain banks (Edinburgh, Newcastle, Manchester, Sheffield, Cambridge, Oxford, Bristol and three London sites) and aims to improve the supply of healthy tissue that can be used as a control or comparison (Francis, Costello and Hayes, 2018). BrainNet Europe is a consortium of 19 brain banks based in academic or health institutions across 11 different European countries (Bell et al., 2008, Kovacs et al., 2008). In the USA, there are two main brain banking networks for dementia research: The NIH NeuroBioBank, which consists of 6 brain banks, and a network of 36 Alzheimer's Disease Research Centres (ADRCs) across 25 states is coordinated by the National Alzheimer's Coordinating Centre (NACC).

Brain banking studies typically offer detailed clinical, genetic, and imaging data, enabling high-resolution exploration of disease mechanisms. Brain bank networks share common standards and protocols. Postmortem diagnosis is the current gold standard in dementia research. Brain banking is typically non-specific and complete neuropathological assessments are undertaken which can be useful for calculating the prevalences of mixed and concomitant pathology. Additionally, donated brain tissue generally has associated longitudinal clinical data to maximise the value of donations.

There are several limitations to brain banking for dementia research. Occasionally brain tissue is donated with no useful clinical data and frequently donations are made without repeated clinical measures. While this can be useful for simple cross-sectional studies, the longitudinal applications are somewhat limited (Ravid and Park, 2014, Kretzschmar, 2009, Rush et al., 2024). Participants are often highly selected, resulting in issues with generalisability. Similarly, those willing to donate brain tissue are often unrepresentative of the general population (Striley et al., 2019). While two-thirds of people living with dementia live in low- or middle-income countries (LMICs), most well-established brain banks are located in high income countries (HICs) and as, a consequence,

dementia research is skewed towards these populations (Kalaria et al., 2024). The prevalence of dementia in LMICs is expected to more than double.

To combat this issue, new brain banking studies and networks have been established in countries on continents previously disproportionately underrepresented in the field (Akinyemi et al., 2023, Akinyemi et al., 2019, Grinberg et al., 2007). For example, The Ibadan Brain Ageing, Dementia, and Neurodegeneration Brain Bank (IBADAN) based in Nigeria is the first organised brain tissue biorepository in sub-Saharan Africa (Akinyemi et al., 2019). Additionally, a multinational collaboration between Nigeria, Ghana, Benin, Cameroon, Kenya, Uganda, Tanzania, Mozambique and Ethiopia called the African Dementia Consortium (AfDC) has been set up to address the underrepresentation of African populations in dementia research through prospective clinical follow up and the establishment of biobanking (Akinyemi et al., 2023). Although the Brain Bank of the Brazilian Ageing Brain Study Group (BBBABSG) does not collect prospective longitudinal clinical data from subjects, the study can provide other insightful information about the cross-sectional prevalence of postmortem neuropathology associated with severity of dementia in a representative sample (Grinberg et al., 2007).

1.4.2 Population-based studies

While brain banking studies have their strengths, population-based clinicopathological studies provide longitudinal clinical data in combination with postmortem neuropathological data in a sample representative of the population. The majority of population-based clinicopathological studies of dementia are based in Europe, the USA, and Asia. A key strength of population-based studies is the ability to reduce selection bias. Unlike studies recruiting from memory clinics or specialist centres, population-based cohorts are typically drawn from defined geographical regions or demographic registries, ensuring a more inclusive and representative sample of the population. This enhances the generalisability of findings, allowing conclusions to be applied to the wider population rather than to selected subgroups.

The **Cognitive Function Ageing Study (United Kingdom)** is a longitudinal, population-based study of cognitive impairment and frailty in the United Kingdom (Cambridgeshire, Gwynedd, Newcastle upon Tyne, Nottingham, Oxford, and Liverpool). Approximately 3% (N > 550) of the full cohort donated brain tissue and, although dementia is overrepresented, the neuropathology subgroup remains representative of the population (CFAS, 2001, Matthews et al., 2009, Wharton et al., 2011). Findings from CFAS indicate a high prevalence of mixed pathologies, even in those without

clinical dementia (Brayne, McCracken and Matthews, 2006). Alzheimer's disease pathology is common but not always clinically expressed suggesting resilience or cognitive reserve. Similarly, Lewy body pathology was observed across the cognitive spectrum suggesting that pathology alone does not always equate to clinical symptoms. CFAS found that vascular pathology was highly prevalent and contributed significantly to cognitive decline (Wharton et al., 2023).

The **Cambridge City over 75 Cohort Study (United Kingdom)** is a longitudinal study of people aged 75 and above registered at general practices (Xuereb et al., 2000). Findings from CC75C include the high prevalence of amyloid and tau pathologies, even in the absence of clinical dementia (Brayne et al., 2009). This suggests that neuropathology can precede or occur without overt cognitive symptoms. Additional findings indicate variable patterns of pathology in the elderly and highlight the co-existence of multiple pathologies (Fleming et al., 2007). Some individuals showed significant brain pathology but retained cognitive function, supporting the idea of cognitive reserve or protective factors.

Vantaa 85+ (Finland) is an unselected prospective population-based study investigating the prevalence, incidence, and risk factors of dementia, and neuropathological correlates of dementia and cognitive impairment among individuals aged 85 years and over living in the city of Vantaa, Finland. Key findings from the study include the high prevalence of mixed pathologies in the oldest-old and that neuropathological burden does not fully account for cognitive impairment (Tanskanen et al., 2017, Hall et al., 2019).

The Religious Orders Study (Illinois, USA) is a longitudinal, clinicopathological study to examine the neuropathological and psychosocial determinants of ageing and Alzheimer's disease (Bennett et al., 2013). The cohort study comprises older Catholic clergy members across the United States who had completed annual clinical evaluations and consented to brain donation upon death. Key findings include evidence of cognitive resilience, with some participants exhibiting extensive neuropathology without corresponding clinical symptoms, supporting the concept of cognitive reserve (Bennett et al., 2018). The study also identified psychosocial factors, such as purpose in life, social engagement, and early life experiences, as significant modifiers of cognitive decline (Negash et al., 2011).

The RUSH Memory and Ageing Project (Illinois, USA) is an ongoing longitudinal cohort study designed to investigate risk factors for cognitive decline and Alzheimer's disease in community-

dwelling older adults (Bennett et al., 2005). Participants are recruited from retirement communities and subsidised housing facilities in the Chicago area (Bennett et al., 2012b). Participants undergo detailed annual clinical and neuropsychological evaluations with a commitment to brain donation upon death. The Memory and Ageing Project includes a more socioeconomically and ethnically diverse population (Bennett et al., 2013). Findings from the study have contributed to the understanding the complexity of interactions between neuropathology and cognitive outcomes, reinforcing evidence that Alzheimer's disease does not invariably lead to dementia and the frequent co-occurrence of mixed brain pathologies (Bennett et al., 2018). The study has also highlighted that modifiable lifestyle, and psychosocial factors influence cognitive trajectories and may confer resilience against neuropathology (Bennett et al., 2018).

The Honolulu-Asia Ageing Study (Hawaii, USA) is a longitudinal epidemiological investigation of rates, risk factors, and neuropathological abnormalities associated with cognitive decline and dementia in Japanese-American men that ran from 1991 to 2012 (Gelber, Launer and White, 2012). The autopsy component of HAAS has indicated five important lesion types linked independently to cognitive impairment (Gelber, Launer and White, 2012). White et al. (2016) reported that neuropathological comorbidity was common and very strongly associated with cognitive impairment. The findings indicated that it was total burden of comorbid neuropathological abnormalities, rather than any single lesion type, that was the most relevant determinant of cognitive impairment (White et al., 2016).

The Cache County Study on Memory in Ageing (Utah, USA) is a large population-based study investigating the epidemiology of Alzheimer's disease and other dementias in later life (Fearing et al., 2007). Key findings include the confirmation of APOE ε4 allele as a strong risk factor for Alzheimer's disease and evidence that its impact diminishes with advancing age. (Tschanz et al., 2013). The study also identified modifiable protective factors, including social engagement and physical activity. The study has contributed to understanding the relationship between genetic risk, environmental exposures, and lifestyle factors and cognitive trajectories in ageing

The Hisayama Study (Japan) is a population-based cohort study initiated in 1985 (1988 to 2003) to investigate the epidemiology of dementia and risk factors among the Japanese elderly population (Kiyohara, 2011). The study has provided valuable insights into the prevalence, incidence, and risk factors associated with various types of dementia, including Alzheimer's disease and vascular dementia (Hamasaki et al., 2017, Hamasaki et al., 2019, Ninomiya, 2018). The study found that the

incidence of dementia subtypes rose with advancing age, particularly after 85 years (Matsui et al., 2009). The study has also provided neuropathological insights indicating that tauopathies, including all-cause dementia and Alzheimer's disease, have become more prevalent over time, whereas the prevalence of vascular dementia has decreased (Honda et al., 2016, Yagita et al., 2022).

Population-based clinicopathological studies of dementia provide representative samples, reduce selection bias and increase generalisability. These studies capture the full spectrum of disease and support the identification of risk factors and characterisation of clinical profiles in relation to specific neuropathological subtypes, strengthening the basis for targeted prevention and treatment strategies. Population based clinicopathological studies of dementia have several limitations. These studies are resource intensive and require long term follow up and brain donation which can limit sample size and introduce bias. Autopsy rates may be low which can lead to underrepresentation of certain groups. Clinical assessment can vary in quality or frequency. Neuropathological criteria and definitions of disease also evolve over time which can complicate comparisons across cohorts or studies and create inconsistencies in the quality of data within the same study depending on the timepoint at which neuropathological assessments were completed.

1.4.3 Emerging Themes

Findings from clinicopathological studies across diverse cohorts consistently demonstrate several key themes that highlight the complexity of dementia pathophysiology and its relationship with cognitive decline. These findings challenge traditional models in dementia research and underscore the need for multidimensional approaches to studying cognitive decline in ageing populations.

The coexistence of multiple neuropathological processes is increasingly recognised as a common feature in dementia (Kovacs et al., 2008). Rahimi , and Kovacs (2014) reported that mixed pathologies were prevalent in up to 74% of participants in community-based cohorts. This included combinations of Alzheimer's disease, Lewy body, TDP-43, and vascular pathologies. A study by McAleese et al. (2021) found that only 22.7% of cases exhibited pure Alzheimer's disease pathology, with the majority exhibiting additional low-level pathologies. These findings suggest that dementia is often multifactorial with combinations of overlapping pathologies contributing to clinical manifestations. This pathological heterogeneity complicates attribution of clinical

symptoms to a single disease process and suggests that a multifactorial framework is required to capture the complexity of late-life cognitive decline.

There is a notable discrepancy between neuropathological findings and clinical symptoms. For example, a study by Kapasi, Decarli , and Schneider (2017) indicated that the presence of concomitant cerebrovascular pathologies in individuals with Alzheimer's disease can lower the threshold for a clinical diagnosis of dementia. Numerous studies report a poor correspondence between severity or extent of neuropathological change and clinical dementia status. Some individuals with substantial pathologies remain cognitively intact, while others exhibit marked impairment with comparatively modest pathological findings. These discrepancies point to the influence of modifying factors such as cognitive reserve, comorbidity, genetic variation, and life-course exposures, which modulate the impact of neuropathology on clinical expression.

Ageing is associated not only with higher prevalence of neurodegenerative pathology but also with an increased likelihood of multiple overlapping pathologies. The oldest old (85+) are particularly likely to exhibit mixed pathological profiles (Rahimi and Kovacs, 2014), which can contribute additively or synergistically to cognitive impairment. The accumulation of diverse neuropathological processes in older age groups further underscores the challenge of drawing simple causal links between single pathologies and clinical outcomes.

These themes collectively reinforce the view that dementia is a heterogeneous condition, shaped by an interplay of multiple neuropathological and non-neuropathological factors (Wharton et al., 2023). A deeper understanding of this complexity is essential for improving diagnostic accuracy, prognostication, and the development of effective interventions.

1.4.4 Implications for Research

Findings from large-scale clinicopathological studies have established a consistently high prevalence of mixed neuropathologies, particularly in the elderly, and these neuropathologies are frequently observed even among individuals with minimal or no decline in cognition. These observations complicate traditional linear models of disease progression and highlight the inadequacy of attributing cognitive decline to single pathological entities in isolation. In particular, Alzheimer's disease pathology often co-exists with Lewy body disease and cerebrovascular pathology and the relative contribution of each pathology to clinical outcomes varies between individuals.

Evidence from population-based cohorts also indicates that the relationship between neuropathological burden and cognitive impairment is neither uniform nor direct. Variability in clinical presentation despite comparable pathology suggests that additional factors, such as resilience, reserve, and comorbidity, may influence symptom emergence. As a result, approaches that examine not only the presence of pathology but also its interaction with demographic, clinical, and contextual variables are increasingly necessary.

Together, these findings underscore the complexity of clinicopathological relationships in dementia, the importance of moving beyond single-diagnosis frameworks in dementia research, and support analytical strategies that accommodate heterogeneity, multifactorial pathology, and variable clinical expression. The integration of neuropathological and clinical data, particularly from representative population-based samples, remains essential for refining diagnostic frameworks and improving understanding of disease mechanisms in late-life cognitive decline.

1.5 Research Aims

This study primarily aimed to investigate the extent of the impact and contribution of mixed and concomitant neuropathology to the clinical presentation of dementia in the Brains for Dementia Research programme. Any relationship, if present, may provide insights into the complexities and interactions between common neuropathologies of age-related dementia in a large neuropathology cohort.

The overarching hypothesis for the study was that any combination of mixed pathology (Alzheimer's disease, Lewy body disease, cerebrovascular disease, LATE-NC) would result in more severe clinical dementia and worse clinical prognosis than a single pathology in isolation. It was also hypothesised that concomitant pathology, particularly Alzheimer's disease pathology, in a neurodegenerative disease would result in worse clinical prognosis than a single pathology in isolation.

The study aimed to:

- Assess clinicopathological concordance and accuracy of study diagnosis in dementia cases, specifically in neocortical Lewy body disease, a clinically under-recognised neurodegenerative pathology.
- Examine the contribution of different neuropathology burdens to longitudinal decline in the Brains for Dementia Research cohort.
- Identify the contribution of mixed and concomitant pathology in Alzheimer's disease, Lewy body disease and LATE-NC to latent profiles of cognitive decline in the final years of life.
- Calculate the contribution of mixed and concomitant neuropathology to the risk of clinical conversion to, and severity of, dementia over time.

Chapter 2. Methods

2.1 Study Background: Brains for Dementia Research

Brains for Dementia Research (BDR) is a programme of planned brain donation based in the United Kingdom. The specialised dementia brain banking study was set up in 2008 with the intention of collecting high-quality neuropathological data together with associated longitudinal clinical data (Hayes et al., 2018). The study aims to provide full neuropathological characterisation from post-mortem brain tissue, together with clinical data, from both dementia cases and cognitively healthy controls for research. The study has been directed and managed by Newcastle, the current coordinating centre, since 2018.

Data collection is conducted across six dementia research centres (Bristol, Cardiff, King's College London, Manchester, Newcastle, and Oxford) and five associated brain banks (London Neurodegenerative Diseases Brain Bank, Oxford Brain Bank, Manchester Brain Bank, Newcastle Brain Tissue Resource, and South West Dementia Brain Bank). Participants complete repeated assessments of cognition, behaviour, and mood and, upon death, donate their brains for detailed neuropathological assessment (Costello et al., 2017). The same clinical and neuropathology measures are used across all sites, allowing comparison across sites in a large clinicopathological cohort.

The study is funded by Alzheimer's Research UK (ARUK) and the Alzheimer's Society (AS). There have been four funding phases to date: BDR-1 (2008-2013), BDR-2 (2013-2018), BDR-3 (2018-2021) and, currently, BDR-4 (2021-2026). The study was originally established for members of the public with dementia and carers requesting to donate brain tissue (Francis, Costello and Hayes, 2018, Hayes et al., 2018). An additional objective of BDR was to establish a network of brain bank facilities across England and Wales, with standardised neuropathological assessments to enable easy integration of data.

2.1.1 Recruitment

Brains for Dementia Research was established as a Research Tissue Bank following ethical approval covering the recruitment of participants for longitudinal assessment and brain donation for research upon death (Francis, Costello and Hayes, 2018, Hayes et al., 2018). All participants with capacity gave written informed consent, identified a nominated representative to facilitate brain donation and a study partner to attend interviews and provide additional study data. Where the

participant lacked capacity, a consultee provided advice on ongoing participation and consent to donation on death. Further checks of mental capacity and consent were carried out at every follow-up assessment.

King's College London, the original co-ordinating centre, recruited the majority of participants for the study through advertisements in the media and talks in relevant settings, such as support groups and memory clinics (Hayes et al., 2018). Almost all participants were self-referring or referred by a family member acting as a study partner (Hayes et al., 2018), with a small percentage of participants recruited by clinicians (Francis, Costello and Hayes, 2018). Of the 4000 enquiries received, over 3200 brain donors registered for the study (Costello et al., 2017). At registration, approximately 70% of the cohort were enrolled as controls. Over 1000 brain donations have been made so far.

Study design has been previously outlined by Francis, Costello , and Hayes (2018). Inclusion criteria for participant selection included a willingness to register for brain donation and participate annually in clinical and psychometric assessments until death. Volunteers with a diagnosis of dementia or mild cognitive impairment were able to register at any age and those without any diagnoses of memory impairment could register from age 65. Other inclusion criteria included living in the UK and a sufficient level of English language skills in order to complete assessments. Each participant was also required to have a study partner willing to attend interviews with them. Exclusion criteria for cohort were largely practical and primarily related to the suitability of the donated brain tissue for research. As a result, clinical diagnoses that indicated an alternative brain bank might be more appropriate, including conditions such as neurological disorders (e.g., multiple sclerosis), pre-existing psychiatric conditions (e.g., schizophrenia and bipolar disorder), brain tumours (specifically previous radiotherapy treatment to the head), and significant cerebrovascular incidents (i.e., major strokes or aneurysms), were excluded. Participants with infections (e.g., meningitis, encephalitis, HIV, prion disease) were also excluded as the use of donated brain tissue would pose an infection risk.

2.1.2 Baseline and Follow-Up Interviews

Initially, all participants completed a face-to-face interview, either at home or in a BDR centre. A detailed medical history of each participant was recorded at baseline, with any changes noted during follow-up assessments. This included demographic, socioeconomic, and relevant medical information (Palmer-Aronsten et al., 2016), hearing and eyesight impairment and any known

family history of dementia. Sections F and H (Medical History) of the Cambridge Examination for Mental Disorders of the Elderly were also administered at every appointment (Roth et al., 1986). Other assessments used included the Bristol Activities of Daily Living Scale (Bucks et al., 1996), the Hachinski Ischaemic Score (Hachinski et al., 1975) and a lifestyle questionnaire covering additional information of interest (e.g., social contacts, diet).

After baseline assessment, follow up assessments were intended to be undertaken annually and primarily conducted face-to-face. Briefly, interviews followed the following structure. Participants without any memory or hearing problems (controls) underwent brief annual reviews between visits consisting of a general health enquiry and brief assessments of cognition and mood. The Clinical Dementia Rating (CDR) was used to assign a dementia rating to all participants. If the interview indicated a change in cognition from the previous visit, a further face-to-face interview was scheduled. Participants with mild cognitive impairment (MCI) or mild to moderate dementia underwent annual face-to-face assessments. Participants with no cognitive impairment also completed face-to-face assessments every third year. For participants with severe dementia, a study partner or carer completed either a face-to-face or telephone interview on behalf of the participant. These followed a similar structure but with all participant sections removed. A range of neuropsychological measures were available at baseline and follow up to provide a comprehensive clinical profile from minimal measures. The clinical assessments selected for BDR were frequently used measures, based on the protocol was based on that of the European AddNeuroMed consortium, to enable dataset integration with other studies (Lovestone et al., 2009).

Briefly, the Mini-Mental State Examination (MMSE) (Braekhus, Laake and Engedal, 1992) was the primary measure of cognitive function and was aimed to be completed by every participant at every face-to-face assessment. In cases where an MMSE score of 24 or above was recorded, the Montreal Cognitive Assessment (MoCA) was also completed. In addition to this, Clinical Dementia Rating (CDR) was used to assess dementia severity. Where participants were unable to complete all assessments, the priority was to determine cognitive status from at least one measure. Once severe cognitive impairment had been identified, only assessments that could be completed by the study partner were used. The Neuropsychiatric Inventory with Caregiver Distress Scale was used as measures of mood and behaviour. The Neuropsychiatric Inventory (NPI) was administered

to all participants as the primary measure of mood and behaviour commonly associated with dementia (Cummings et al., 1994).

2.1.3 Brain Donation and Neuropathological Assessment

Upon death, brains were donated and underwent assessment, unless consent had been withdrawn or the window for donation was missed. While ante mortem withdrawals in BDR are relatively low (3%), lost or failed donations are more common with approximately 15% of brain donations being lost in cases where the project was not informed of death by the family or the donation could not be made within a reasonable time frame for logistical regions (Francis et al 2019) (Francis, Costello and Hayes, 2018). Donated brain tissue is then transferred to the appropriate brain bank (Francis, Costello and Hayes, 2018).

A full neuropathological dissection, sampling, and characterisation of brain tissue was undertaken for all cases by neuropathologists in each of the five brain banks according to a standardised BDR protocol, as outlined in Francis, Costello , and Hayes (2018). The standardised neuropathological assessments used in BDR provide a detailed narrative description of the severity and spread of regional pathology within the brain of participants with and without cognitive impairment during life. Standardised scoring measures of neuropathology included the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Jack et al., 2018) for Alzheimer type pathology, Thal phases of amyloid β deposition (Thal et al., 2002), Braak staging of neurofibrillary tangle pathology (Alafuzoff et al., 2008), Consortium to Establish a Registry of Alzheimer's Disease scoring of the density of neuritic plaques (Mirra et al., 1991), Braak staging of Lewy bodies (Braak et al., 2003), McKeith staging of Lewy body predominance (McKeith *et al.*, 2017), presence of TDP-43 inclusions (Josephs et al., 2016, Nelson et al., 2022b) and the classification, extent, location of vascular pathology (including categorisation using the Vascular Cognitive Impairment Neuropathology Guidelines (Skrobot *et al.*, 2016). Antibodies used for staining were 4G8 for amyloid-β, AT8 for tau, KM51 for α-synuclein and pTDP for TDP-43 inclusions. Additional data, including post-mortem delay, brain weight, and region pH levels, were also reported.

2.1.4 Neuropathology Cohort

Using data from the BDR programme, a sub-cohort was created containing all deceased participants who had made successful brain donations at the time of data locking (October 2020). Further criteria for inclusion were that each participant had completed at least one clinical assessment prior to death and that a detailed neuropathological assessment had been completed

and digitised. Exclusion criteria from this sub-cohort were being under age 65 at baseline and the presence of any non-age associated neurological disease (e.g., Creutzfeldt-Jacob Disease).

Eight hundred and thirteen cases were included. The cohort was 47.4% female, with a mean age of 81.6 years (SD = 7.83) at baseline. The cohort was predominantly white, with less than 1% (N = 8) reporting non-British heritage. The original full BDR cohort at baseline was predominantly controls with only 30% of participants having clinical dementia. As this sub-cohort consists of the first participants to come to autopsy, the composition of the cohort differs from that of the full BDR cohort. At baseline, the neuropathology sub-cohort was 50.7% cases and 49.3% controls. By final assessment, this had shifted further with 57.7% having dementia and 42.3% remaining as controls. Participants had a mean follow up time of 3.03 years (SD = 2.68) with a median of three visits per participant. Demographics of the cohort are outlined in **Table 2.1**.

Table 2.1. Cohort Characteristics by Centre at Final Assessment: Summary of demographic, clinical, and neuropathological features across six BDR centres. Continuous variables are shown as mean (SD) and median [range]; categorical variables as counts (%). Education indicates years of full-time education. Index of Multiple Deprivation (IMD) is in quintiles (Q1 = least deprived, Q5 = most deprived). Time refers to years of clinical follow-up. Clinical scores include CDR (Clinical Dementia Rating), MMSE (Mini-Mental State Examination), and NPI (Neuropsychiatric Inventory) at final assessment. Primary pathology reflects the main diagnosis at autopsy. Mixed pathology includes cases with multiple primary diagnoses. Low to moderate pathology only refers to cases lacking a defined primary pathology but with limited pathological burden.

	Bristol (N=109)	**Cardiff (N=94)**	**London (N=147)**	**Manchester (N=110)**	**Newcastle (N=123)**	**Oxford (N=230)**	**Overall (N=813)**
Age	85.9 (8.10)	86.1 (7.95)	85.9 (7.83)	84.5 (8.69)	85.3 (8.17)	85.6 (7.00)	85.6 (7.82)
	87.1 [68.5, 99.0]	85.9 [68.7, 103]	85.6 [68.8, 102]	85.2 [68.7, 103]	85.4 [65.5, 102]	86.2 [65.9, 104]	86.0 [65.5, 104]
Sex	49 (45.0%)	60 (63.8%)	68 (46.3%)	50 (45.5%)	51 (41.5%)	105 (45.7%)	383 (47.1%)
	60 (55.0%)	34 (36.2%)	79 (53.7%)	60 (54.5%)	72 (58.5%)	125 (54.3%)	430 (52.9%)
Education	12.4 (2.93)	12.4 (2.76)	13.4 (3.73)	13.1 (3.12)	12.2 (3.21)	12.1 (3.16)	12.6 (3.22)
	12.0 [5.00, 21.0]	11.0 [7.00, 18.0]	13.0 [0, 25.0]	13.0 [9.00, 21.0]	11.0 [9.00, 21.0]	11.0 [7.00, 24.0]	12.0 [0, 25.0]
Missing	*2 (1.8%)*	*2 (2.1%)*	*19 (12.9%)*	*3 (2.7%)*	*5 (4.1%)*	*51 (22.2%)*	*82 (10.1%)*
Index of Multiple Deprivation	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	1.00 [1.00, 5.00]	2.00 [1.00, 5.00]
IMD 1	39 (35.8%)	15 (16.0%)	56 (38.1%)	38 (34.5%)	31 (25.2%)	105 (45.7%)	284 (34.9%)
IMD 2	29 (26.6%)	35 (37.2%)	30 (20.4%)	24 (21.8%)	31 (25.2%)	52 (22.6%)	201 (24.7%)
IMD 3	22 (20.2%)	17 (18.1%)	33 (22.4%)	17 (15.5%)	22 (17.9%)	22 (9.6%)	133 (16.4%)

IMD 4	12 (11.0%)	12 (12.8%)	12 (8.2%)	12 (10.9%)	16 (13.0%)	10 (4.3%)	74 (9.1%)
IMD 5	7 (6.4%)	8 (8.5%)	11 (7.5%)	19 (17.3%)	14 (11.4%)	6 (2.6%)	65 (8.0%)
Missing	*0 (0%)*	*7 (7.4%)*	*5 (3.4%)*	*0 (0%)*	*9 (7.3%)*	*35 (15.2%)*	*56 (6.9%)*
Time	3.11 (2.36)	3.95 (3.70)	3.02 (3.01)	2.47 (2.01)	3.21 (2.65)	2.83 (2.31)	3.04 (2.68)
	3.02 [0, 8.88]	2.97 [0, 16.0]	2.40 [0, 17.3]	2.14 [0, 8.14]	2.61 [0, 9.50]	2.47 [0, 8.90]	2.66 [0, 17.3]
CDR	0.50 [0, 3.00]	2.00 [0, 3.00]	0.50 [0, 3.00]	3.00 [0, 3.00]	1.00 [0, 3.00]	3.00 [0, 3.00]	2.00 [0, 3.00]
MMSE	28.0 [8.00, 30.0]	23.5 [0, 30.0]	26.0 [0, 30.0]	27.5 [0, 30.0]	25.0 [0, 30.0]	23.0 [0, 30.0]	26.0 [0, 30.0]
NPI	4.00 [0, 84.0]	18.0 [0, 75.0]	12.0 [0, 110]	30.0 [0, 88.0]	4.00 [0, 84.0]	3.50 [0, 91.0]	9.00 [0, 110]
Primary pathology							
Alzheimer's disease	10 (9.2%)	13 (13.8%)	10 (6.8%)	22 (20.0%)	21 (17.1%)	37 (16.1%)	113 (13.9%)
Lewy body disease	7 (6.4%)	4 (4.3%)	7 (4.8%)	5 (4.5%)	6 (4.9%)	17 (7.4%)	46 (5.7%)
Cerebrovascular disease	6 (5.5%)	2 (2.1%)	3 (2.0%)	2 (1.8%)	5 (4.1%)	9 (3.9%)	27 (3.3%)
Frontotemporal lobar degeneration	2 (1.8%)	6 (6.4%)	6 (4.1%)	1 (0.9%)	6 (4.9%)	3 (1.3%)	24 (3.0%)
Argyrophilic grain disease	5 (4.6%)	5 (5.3%)	9 (6.1%)	2 (1.8%)	1 (0.8%)	3 (1.3%)	25 (3.1%)

LATE-NC	13 (11.9%)	4 (4.3%)	10 (6.8%)	6 (5.5%)	2 (1.6%)	20 (8.7%)	55 (6.8%)
Mixed pathology	20 (18.3%)	25 (26.6%)	35 (23.8%)	29 (26.4%)	34 (27.6%)	88 (38.3%)	231 (28.4%)
Low to moderate pathology only	46 (42.2%)	35 (37.2%)	67 (45.6%)	43 (39.1%)	48 (39.0%)	53 (23.0%)	292 (35.9%)

2.2 Clinical Variables

The clinical variables selected for statistical analyses fall into three categories: demographic variables (e.g., age, sex, education, and deprivation), non-time-varying variables (e.g., study diagnosis) and time-varying variables (e.g., CDR-GS, CDR-SB, MMSE, NPI). Demographic variables selected for clinical relevance included age, sex, education, and deprivation, and were typically included in analyses as adjustment covariates. Non-time-varying clinical variables, such as reported study diagnoses, were generally used for basic statistical methods and cross-sectional analyses of clinicopathological concordance in the neuropathology cohort. The main clinical measures selected as outcomes were time-varying measures of cognitive function, such as clinical dementia rating, MMSE scores, and NPI scores. Time-varying measures of cognitive function were used as dependent outcome variables in the majority of the longitudinal statistical models selected and are outlined in

Table 2.2.

***Table 2.2*. Clinical Variables at Final Assessment:** Sex-stratified summary of clinical measures at final assessment. Continuous variables are presented as mean (SD) and median [range]. Missing data are reported as counts (%). BADLS refers to the Bristol Activities of Daily Living Scale. CDR (Clinical Dementia Rating) global and domain-specific scores assess cognitive and functional impairment across multiple areas. CDR-SUM is the sum of domain scores. MMSE (Mini-Mental State Examination) and MoCA (Montreal Cognitive Assessment) are global cognitive screening tools. NPI total reflects the total score on the Neuropsychiatric Inventory.

	Female (N=383)	**Male (N=430)**	**Overall (N=813)**
Age (at death)	87.3 (7.86)	84.0 (7.47)	85.6 (7.82)
	87.9 [65.5, 104]	83.9 [67.4, 104]	86.0 [65.5, 104]
BADLS	30.7 (23.0)	33.4 (21.3)	32.2 (22.1)
Median	34.0 [0, 60.0]	38.0 [0, 60.0]	37.0 [0, 60.0]
Missing	109 (28.5%)	109 (25.3%)	218 (26.8%)
CDR global score	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Missing	52 (13.6%)	63 (14.7%)	115 (14.1%)
Memory	1.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Orientation	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Judgement & Problem Solving	1.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Community	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Home & Hobbies	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Personal Care	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]
Missing	56 (14.6%)	63 (14.7%)	119 (14.6%)
CDR-SUM	6.49 (6.77)	7.22 (6.59)	6.87 (6.68)
Median	2.50 [0, 15.0]	6.50 [0, 15.0]	5.00 [0, 15.0]
MMSE	23.3 (8.27)	20.3 (9.72)	21.8 (9.16)
Median	27.0 [0, 30.0]	24.0 [0, 30.0]	26.0 [0, 30.0]
Missing	189 (49.3%)	220 (51.2%)	409 (50.3%)
MoCA	23.9 (4.49)	23.1 (4.91)	23.6 (4.70)
Median	25.0 [11.0, 30.0]	24.0 [7.00, 30.0]	24.0 [7.00, 30.0]
Missing	278 (72.6%)	334 (77.7%)	612 (75.3%)
NPI total	14.7 (19.0)	18.6 (22.7)	16.8 (21.2)
Median	6.00 [0, 88.0]	10.0 [0, 110]	9.00 [0, 110]
Missing	103 (26.9%)	102 (23.7%)	205 (25.2%)

2.2.1 Demographic Variables

A wide range of background information was available for each participant. Relevant demographic variables, such as age and sex, were included covariates in all analyses. More detailed sociodemographic data including education, index of multiple deprivation, and family history of dementia were also available.

Age was included as one of two different variables depending on the analysis: time-varying age at time of assessment and non-time-varying age at death. For some analyses, age was transformed to a categorical variable (65-69, 70-79, 80-89, and 90+) to enable group comparisons, and not assume exponential growth with year of age. Mean age at baseline was 81.6 years (SD = 7.83) with no significant difference between visit centres. Mean age at death was 85.5 (SD = 7.88) with little evidence of a difference between visit centres. Sex at birth was included as a binary variable and selected as a covariate in all analyses to adjust for any differences in development, density, structure, and function between male and female brains. The majority of the cohort was male (52.6%), with similar proportions seen at all centres except Cardiff where females made up almost two-thirds of participants (64.2%).

Years in Education was selected as a non-time-varying continuous covariate and adjusted for in all analyses regarding cognition. Education was measured as the number of self-reported years a participant had spent in full-time education. If the participant had given the age they were when they left formal education, the number reported was reduced by 5 to give years in education. In some analyses, education was transformed to a categorical variable to enable group comparisons (<= 9, 10-11, 12+) and reduce the linearity assumption that each year of additional education (e.g. 8 to 9 years and 14 to 15 years) would have the same effect. The mean number of years spent in full-education was 12.6 years – much higher than the national average for comparable populations – indicating that the BDR cohort, as with most neuropathological studies, spent more time in formal education than the general population of the same age. This is most likely a result of higher socioeconomic status and greater access to education during childhood.

The Index of Multiple Deprivation (IMD) was selected as a non-time-varying measure of relative deprivation. The IMD rates geographical deprivation based on seven domains including income, employment, education, health, crime, barriers to housing and services and living environment based on participant's home postcodes which provides a rank for

England, this is then converted to quintiles (Abel, Barclay and Payne, 2016). In this study, lower IMD scores indicate lower deprivation (i.e., an IMD of 1 indicates the lowest deprivation quintile and an IMD of 5 represents the highest deprivation quintile). The median quintile for the cohort was 2.0 suggesting that, on average, the cohort were not residing in areas of the UK with a high level of deprivation at the time of enrolment.

2.2.2 Cognitive State: Clinical Dementia Rating

The Clinical Dementia Rating scale was selected as a global measure of dementia severity, and used as cognitive state in the exploration of pathological factors influencing transitions between disease states in dementia across the follow up period. Clinical Dementia Rating (CDR) is a clinical assessment used to quantify the severity, or stage, of dementia (Hughes et al., 1982). The CDR global score (CDR-GS) is a five-point scale, ranging from cognitively healthy (CDR 0) to severe dementia (CDR 3). There are six domains covered by the CDR including memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Scores across the six domains can be summed to give a CDR Sum of Boxes (CDR-SB), with a maximum of 18.

The CDR-SB was selected as a time-varying continuous measure of cognitive decline for each participant at each interview. The CDR-GS was used as a time-varying categorical measure of cognitive state for each participant at every clinical assessment. In some analyses, CDR scores representing dementia (CDR-GS 1-3) are amalgamated into one category to improve group size. This amalgamation also allowed the cohort to be split into groups of individuals with (CDR 1-3) and without (CDR 0 or 0.5) dementia for descriptive analyses.

The median CDR-GS across the whole cohort at final assessment was 2 in both males and females, indicating moderate dementia. All CDR subdomain scores also had a median of 2 at final assessment. Median CDR-SB at final assessment was 5.5 and was higher in males (7.0) than females (3.0). All subdomain scores of the CDR scale were significantly higher in males than females at baseline and final assessment. At baseline, all median subdomain scores were 0.5 for females, indicating questionable dementia, and 1.0 for males, indicating mild dementia. By final assessment, the median rating for all subdomains in males was 2.0, indicating moderate dementia. In females, median ratings were lower for memory, orientation, and judgement subdomains.

2.2.3 Cognitive Function: Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) was selected as a measure of cognitive function. The MMSE is a 30-point test examining cognitive impairment in dementia or head injury developed by Folstein, Folstein , and McHugh (1975). The test contains 11 items divided into two sections and covers problems with thinking, communication, understanding, and memory. MMSE scores of less than 23 indicated clinical dementia.

At baseline, females had a higher MMSE score (24.2 (8.03)) than males (22.4 (8.76)) on average. Males had a slightly faster rate of decline than females over the follow up period. In cognitively healthy control subjects, there was no significant difference in the pattern of decline over the follow up period. In the dementia group, males appeared have to a very steep trajectory of decline in MMSE scores whereas women appeared to remain relatively stable but starting with a very low MMSE score.

2.2.4 Behavioural and Psychological Symptoms of Dementia: Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) was selected as a measure of common neuropsychiatric features of dementia. The NPI is an assessment tool originally developed by Cummings et al. (1994) that is frequently used in clinical assessments to evaluate and quantify neuropsychiatric symptoms often seen in dementia and other related neurological disorders. The NPI with caregiver distress scale (NPI-D) assesses overall neuropsychiatric symptomatology in terms of frequency, severity, and associated distress, across twelve behavioural domains *(Cummings et al., 1994, Cummings, 1997)*.

The NPI is an assessment used to quantify and evaluate neuropsychiatric symptoms across 12 areas (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, sleep disturbances, and appetite and eating disorders) and is administered as a brief structured interview with a caregiver, family member, or study partner. Each of the twelve domains is scored on frequency (1-4), severity (1-3) and associated caregiver distress (0-5). The score for each domain is calculated as a multiplication of frequency and severity scores (F x S). Total NPI score is a sum of all domains, with a maximum score of 144.

Mean NPI score at baseline was 15.7 (SD = 21.6), with higher median score reported in males (7, [0,110]) than females (1, [0, 86]). Similarly, mean NPI score at final assessment was

16.9 (SD = 21.3), with a higher median score reported in males (10.0, [0, 110]) than females (6, [0, 88]). Apathy was the most common neuropsychiatric symptom at baseline (28.2%) and final assessment (31.5%) in both males and females. Agitation/aggression was the relatively common seen in 21.8% of participants at baseline and 25.3% of participants at final assessment and was more frequently reported in males than females.

2.2.5 Study Clinical Diagnosis

Each participant within the neuropathology cohort was assigned a Clinical Study Diagnosis based on self-reported dementia diagnosis from interview question and clinical notes and ICD-10 codes included in the neuropathology records available from the UK Brain Bank Network. The majority of participants fell into one of four categories: Alzheimer's disease, Lewy body disease, vascular dementia and frontotemporal dementia. Some cases with multiple clinical diagnoses were assigned to a fifth group: mixed dementia. In cases where no clinical diagnosis had been reported but dementia was present, participants were allocated a clinical diagnosis of "unspecified dementia". Data for clinical study diagnosis was aggregated and compared across three variables available in the BDR database to ensure the most comprehensive study diagnosis was included.

Frequencies of study diagnoses in the cohort are summarised in

Table 2.3. Alzheimer's disease was the most common study diagnosis reported in both males (33.5%) and females (31.9%). Mixed dementia was the second most common study diagnosis reported in both males (13.3%) and females (11.2%). A study diagnosis of Lewy body dementia was more common in males (3.5%) than females (1.8%). No study diagnosis was significantly more common in females (40.7%) than males (29.5%).

Table 2.3. Study diagnosis: Distribution of clinical dementia diagnoses reported within the cohort, stratified by sex. Values represent absolute counts and corresponding percentages. Diagnoses include specific dementia subtypes, mild cognitive impairment, unspecified dementia, and cases with no clinical diagnosis recorded.

Study Diagnosis	Female (N=383)		Male (N=430)		Overall (N=813)	
Alzheimer's disease	122	(31.9%)	144	(33.5%)	266	(32.7%)
Lewy body dementia	7	(1.8%)	15	(3.5%)	22	(2.7%)
Vascular dementia	15	(3.9%)	36	(8.4%)	51	(6.3%)
Frontotemporal dementia	8	(2.1%)	19	(4.4%)	27	(3.3%)
Unspecified dementia	13	(3.4%)	17	(4.0%)	30	(3.7%)
Mixed dementia	43	(11.2%)	57	(13.3%)	100	(12.3%)
Mild cognitive impairment	19	(5.0%)	15	(3.5%)	34	(4.2%)
No clinical diagnosis	156	(40.7%)	127	(29.5%)	283	(34.8%)

Although the study diagnoses included here are not comparable to true clinical diagnoses given in other studies of dementia as full clinical diagnostics were not part of the interview schedule in BDR, it is likely that these study diagnoses reflect an experience that is marginally more representative of the general population living with dementia than those enrolled in studies. There are obviously many limitations to the use of these diagnoses, but it is important to include them to show the differences between clinical presentation and neuropathological findings in dementia.

2.3 Neuropathology Variables

A number of variables were used in the following analyses to characterise the composition and severity of pathology present at neuropathological assessment. The neuropathology variables used were all non-time varying providing a cross-sectional summary of the brain at time of death. The majority were ordinal variables derived from staging criteria. Others were binary presence/absence variables. Few were continuous (e.g., age at death, brain weight at autopsy, and post-mortem delay).

The general benefits of the variables selected was the standardisation of neuropathological assessment across the cohort. The main limitations of the majority of the variables used is the lack of temporal and spatial information. The majority of the categorical or ordinal variables are also limited by a ceiling effect, where once the threshold for the stage denoting highest severity is reached there is no differentiation between cases despite potentially significant variation in the pathology observed. Other variables suffer from their binary nature. For example, TDP-43 is reported as being present if a singular inclusion is observed during neuropathological assessments. This case would be treated the same as a case with numerous and widespread TDP-43 inclusions.

Mean age at death for all participants was 85.6 years (SD = 7.82). On average, age at death was higher in females (87.3 years ± 7.86) than males (84.0 years ± 7.47). The mean brain weight at autopsy was 1200g (SD = 155). Postmortem brain weight was higher in males (1260g) than in females (1130g). The mean post-mortem delay (i.e., time between death and autopsy) was 56 hours (SD = 35.8) and did not differ between males and females. Further neuropathology variables for the full cohort are outlined in **Table 2.4**

High Alzheimer's disease neuropathological change was reported in 30.1% of the cohort, with no significant difference between males (30.9%) and females (29.3%). There was a significant difference in Braak Lewy body score between males and females. A low VCING rating was reported in the majority of the cohort (60.3%), with no significant difference between males (58.0%) and females (63.0%). Limbic-predominant age-related TDP-43 encephalopathy (LATE) neuropathological change was reported in 28.5% of the cohort, with no significant difference in prevalence between males (31.1%) and females (25.6%). Frontotemporal lobar degeneration with TDP-43 and tau were uncommon, reported in 2.0% and 1.6% of the cohort respectively. There was no significant difference between males and females. Argyrophilic grain disease was slightly more common (3.1%), with no significant difference between males and females. Hippocampal sclerosis was reported in 7.6% of the cohort, with no significant difference between males and females. Age-related tau astrogliopathy (ARTAG) was reported in 4.9% of the cohort and was almost twice as common in males (6.3%) than females (3.4%).

Table 2.4. **Neuropathological Variables**: Summary of neuropathological characteristics, stratified by sex. Continuous variables are presented as mean (SD) and median [range]; categorical data are presented as counts and percentages. Group differences were assessed using the Kruskal–Wallis test for continuous variables and the Chi-squared test for categorical variables.

	Female (N=383)	**Male (N=430)**	**Overall (N=813)**	**p-value**
Age at death	87.3 (7.86)	84.0 (7.47)	85.6 (7.82)	**<.001**
	87.9 [65.5, 104]	83.9 [67.4, 104]	86.0 [65.5, 104]	
Brain weight	1130 (143)	1260 (139)	1200 (155)	**<.001**
Postmortem delay	55.2 (33.4)	57.2 (37.9)	56.2 (35.8)	0.814
Thal AB phase	4.00 [0, 5.00]	4.00 [0, 5.00]	4.00 [0, 5.00]	0.247
Braak NFT stage	3.00 [0, 6.00]	4.00 [0, 6.00]	4.00 [0, 6.00]	0.315
CERAD score	2.00 [0, 3.00]	2.00 [0, 3.00]	2.00 [0, 3.00]	0.371
Braak LB	0 [0, 6.00]	0 [0, 6.00]	0 [0, 6.00]	**0.011**
NIA-AA Rating				0.223
High	113 (29.5%)	133 (30.9%)	246 (30.3%)	
Intermediate	77 (20.1%)	107 (24.9%)	184 (22.6%)	
Low	103 (26.9%)	102 (23.7%)	205 (25.2%)	
VCING rating				0.063
High	27 (7.0%)	28 (6.5%)	55 (6.8%)	
Moderate	34 (8.9%)	60 (14.0%)	94 (11.6%)	
Low	244 (63.7%)	249 (57.9%)	493 (60.6%)	
FTLD				
with Tau	6 (1.6%)	6 (1.4%)	12 (1.5%)	0.841
with TDP-43	6 (1.6%)	10 (2.3%)	16 (2.0%)	0.592
LATE-NC	98 (25.6%)	133 (30.9%)	231 (28.4%)	0.101
AGD	8 (2.1%)	8 (1.9%)	16 (2.0%)	0.779
ARTAG	13 (3.4%)	27 (6.3%)	40 (4.9%)	0.080
HpSc	25 (6.5%)	36 (8.4%)	61 (7.5%)	0.460

2.3.1 Amyloid: Thal Aβ phase

Thal phase staging is used to quantify Alzheimer's disease pathology in accordance with international consensus guidelines and was selected as a measure of diffuse amyloid pathology (Thal et al., 2002). Thal Aβ phase categorises the extent and severity of amyloid pathology into ordinal stages (0-5), with higher stages indicating a more advanced and widespread deposition of amyloid and is outlined in **Table 2.5**.

***Table 2.5*. Thal phases of *Aβ* deposition**: Brain regions affected at each Thal phase of β-amyloid (*Aβ)* deposition, reflecting the progressive anatomical spread of Aβ pathology.

Phase	Region
1	Sparse, small groups of diffuse neocortical plaques
2	Allocortex, hippocampus, and entorhinal cortex
3	Striatum, post cingulate gyrus
4	Midbrain, substantia nigra, medulla oblongata
5	Cerebellum, reticular formation of the pons

2.3.2 Neurofibrillary Tangles: Braak NFT stage

Braak neurofibrillary tangle stage is a core component of Alzheimer's disease neuropathological assessment and was selected as a measure of tau pathology (Braak and Braak, 1991). Braak staging categories tau pathology into stages (0-VI) based on the progression and topographical distribution of neurofibrillary tangles and is outlined in **Table 2.6**.

***Table 2.6*. Braak Neurofibrillary Tangle (NFT) Stages**: Anatomical progression of tau pathology as defined by Braak staging. Higher stages indicate more widespread involvement.

Stage	Region
I-II	Transentorhinal cortex
III-IV	Limbic regions, including hippocampus
V-VI	Neocortex

2.3.3 Neuritic Plaques: CERAD score

CERAD scores were selected as a measure of neuritic plaque pathology (Mirra et al., 1991) CERAD score reflects the density of neuritic plaques (i.e., dystrophic neurites with and

without amyloid cores) in specific neocortical regions including midfrontal, superior middle temporal and inferior parietal areas of the neocortex, and is outlined in **Table 2.7**.

Table 2.7. **CERAD score**: Semi-quantitative assessment of neuritic plaque burden used to estimate the likelihood of Alzheimer's disease pathology. The CERAD scoring system categorizes neuritic plaque density based on standardized histopathological criteria, informing the probability of AD diagnosis in postmortem brain tissue.

		Density	Neuritic plaques / mm^2	Likelihood of Alzheimer's disease
	0	None	Zero	Normal brain
A	1	Sparse	5 or fewer	Possible AD
B	2	Moderate	More than 5 but fewer than 20	Probable AD
C	3	Frequent	20 or more	Definite AD

2.3.4 Alzheimer's disease Neuropathological Change: NIA-AA ABC scores

The overall level of Alzheimer's disease neuropathological change present at autopsy was defined using the NIA-AA criteria (Montine et al., 2012). This scoring system reflects the combined burden of amyloid-β deposition, neurofibrillary tangles, and neuritic plaques according to the National Institute on Aging–Alzheimer's Association (NIA-AA) guidelines, providing a standardized framework for AD neuropathologic diagnosis. A numeric value (0-3) is assigned to each of these three categories, with higher scored indicating more extensive and severe pathology. These three scores are then combined to assign one of four overall Alzheimer's disease neuropathological change (ADNC) ratings (Not, Low, Intermediate, or High) as outlined in

Table *2.8*.

Table 2.8.NIA-AA ABC score: Composite neuropathological assessment integrating Thal Aβ phase (A), Braak neurofibrillary tangle stage (B), and CERAD neuritic plaque score (C) to estimate the likelihood of Alzheimer's disease pathology. This scoring system reflects the combined burden of amyloid-β deposition (Thal phase), neurofibrillary tangles (Braak NFT stage), and neuritic plaques (CERAD score).

			Braak NFT stage					
			0 or I-II	III-IV	V-VI			
			B0 or B1	**B2**	**B3**			
Thal AB phase	0	**A0**	Not	Not	Not	**C0**	None	**CERAD score**
	1 or 2	**A1**	**Low**	**Low**	**Low**	**C0 or C1**	None to Sparse	
			Low	**Intermediate**	**Intermediate**	**C2 or C3**	Moderate to Frequent	
	3	**A2**	**Low**	**Intermediate**	**Intermediate**	**Any C**	None to Frequent	
	4 or 5	**A3**	**Low**	**Intermediate**	**Intermediate**	**C0 or C1**	None to Sparse	
			Low	**Intermediate**	**High**	**C2 or C3**	Moderate to Frequent	

As NIA-AA ABC scores combine the hallmark pathologies found in Alzheimer's disease, a NIA-AA High score was used to indicate the presence of Alzheimer's disease and an NIA-AA Intermediate score was used to indicate the presence of concomitant or additional Alzheimer's disease pathology in non-AD cases (

*Table **2.8***).

2.3.5 Lewy body pathology: Braak LB score and McKeith Region

One of two measures of Lewy body pathology was selected depending on availability of data: Braak Lewy body stage and McKeith criteria for Lewy body disease. The Braak LB staging system uses six stages to describe the distribution and progression of Lewy bodies in the brains of individuals with Parkinson's disease. Lewy body McKeith criteria categorises cases based on the presence of Lewy body pathology in specific brain regions. The six stages of Braak LB staging and estimated equivalence to McKeith categories are outlined in ***Table 2.9***.

Table 2.9. Lewy Body Staging: Anatomical progression of Lewy body pathology classified by Braak Lewy body (LB) stages, detailing affected brain regions at each stage. Corresponding McKeith classifications are provided, distinguishing brainstem, limbic (amygdala), and neocortical involvement. Increasing Braak LB stage reflects more widespread Lewy body deposition across brain regions.

Braak LB stage	Region	McKeith
1	Brainstem and olfactory system	Brainstem
2	Pons	
3	Substantia nigra, pars compacta, basal nucleus of Meynert, basal forebrain	
4	Mesocortex, allocortex, amygdala, thalamus	Limbic | Amygdala
5	Neocortex – temporal, parietal, and frontal	Neocortical
6	Neocortex – motor and sensory regions	

2.3.6 Vascular pathology: VCING Rating

The variables selected as measures of vascular disease were the three components used in the Vascular Cognitive Impairment Neuropathology Guidelines (VCING): one or more large subcortical infarcts, moderate or severe occipital leptomeningeal cerebral amyloid angiopathy, and moderate or severe occipital white matter arteriolosclerosis. Combinations of the three vascular features are used to assign a low, moderate, or high likelihood that cerebrovascular disease contributed to cognitive impairment in each individual case

(Skrobot *et al.*, 2016). The combination of the selected vascular features is then used to assign a rating using the VCING scoring matrix outlined in

Table 2.10.

Table 2.10. **VCING Rating**: Vascular Cognitive Impairment Neuropathology Guidelines (VCING) rating system used to assess the likelihood that vascular pathology contributed to cognitive impairment. Columns indicate combinations of vascular pathology and their corresponding VCING rating categories (Low, Moderate, High), based on the extent and severity of pathology.

	Low (< 50%)			**Moderate (50-80%)**		**High (> 80%)**		
One or more large subcortical cerebral infarcts (> 10 mm)	-	-	+	+	-	+	+	+
Moderate or severe occipital leptomeningeal CAA	-	+	-	-	+	+	-	+
Moderate or severe occipital white matter arteriolosclerosis	+	-	-	-	+	-	+	+

As this is the primary vascular variable available in the database, a high VCING was used to indicate the presence of cerebrovascular disease and a moderate VCING rating indicated concomitant vascular pathology (

Table 2.11).

2.3.7 Other Pathologies as Binary Variables

Frontotemporal lobar degeneration (FTLD) was primarily defined as a binary variable denoting the presence, or absence, of atrophy in the frontal and temporal lobes. Cases with frontotemporal lobar degeneration were then assigned an additional categorical variable indicating the primary inclusions present (i.e., TDP-43 or tau inclusions). Argyrophilic grain disease, another tauopathy, was also defined as a binary variable indicating the presence of argyrophilic grains in the limbic system.

Limbic-predominant age-related TDP-43 encephalopathy (LATE) was defined as a binary variable based on the staging system outlined by Nelson et al. (2022b) in the most up-to-date consensus on staging criteria. LATE was defined as any TDP-43 inclusions in the amygdala, hippocampus, or middle frontal gyrus, by combining LATE-NC stages 1-3 to create a binary variable indicating the presence or absence of the pathology due to availability of data.

A number of additional pathologies were selected for inclusion as binary variables for some analyses. Age-related tau astrogliopathy (ARTAG) was defined as the presence of tau positive astrocytes in limbic structures. Hippocampal sclerosis was defined as a binary variable. Primary age-related tauopathy (PART) was defined as a binary variable based on the Crary staging system (Crary et al., 2014).

2.3.8 Neuropathological Diagnosis

Each participant was assigned a neuropathological diagnosis as outlined in

Table 2.11. Dementia-related pathologies were categorised as high level (sufficient for neuropathological diagnosis) or moderate level (below required threshold but higher than would be expected in normal, healthy ageing). Then neuropathological entities selected were loosely based on the classification system outlined by (McAleese *et al.*, 2021) using data from the same cohort. Other studies such as Robinson et al. (2023) have used similar methods.

Participants that met the relevant criteria were assigned a neuropathological diagnosis. If multiple criteria were met, multiple neuropathological diagnoses were assigned. Assigned neuropathological diagnoses were then compared with pathology notes to prevent misclassification as some neuropathological assessments were completed prior to the introduction of relevant staging criteria used and not all records had been updated to reflect the changes at the time of data locking.

Diagnoses included AD, LBD, CVD, FTLD, AGD, LATE and low pathology only controls (LPC). Alzheimer's disease pathology was categorised using the NIA-AA ADNC likelihood system. Alzheimer's disease was equivalent to a "High" NIA-AA score, and moderate AD pathology was equivalent to an "Intermediate" NIA-AA score. Low NIA-AA score was considered negligible due to the high occurrence of low-level Alzheimer's disease pathology in ageing brains, regardless of cognitive status.

Lewy body disease was split into two levels. Full LBD was equivalent to Braak LB stages 4-6 or McKeith limbic or neocortical, whereas moderate LBD was equivalent to Braak LB stages 1-3 or McKeith brainstem or McKeith amygdala. These are roughly equivalent to previously outlined categories of clinical and subclinical Lewy body disease.

Cerebrovascular disease was defined, according to the Vascular Cognitive Impairment Neuropathology Guidelines (VCING), as the presence of one or more large (>10mm) subcortical infarcts and at least one of moderate to severe occipital leptomeningeal cerebral amyloid angiopathy and moderate to severe occipital white matter arteriolosclerosis. Moderate cerebrovascular pathology was defined, according to VCING, as the presence of either one or more large (>10mm) subcortical infarcts or both moderate to severe occipital leptomeningeal cerebral amyloid angiopathy and moderate to severe occipital white matter

arteriolosclerosis. A low VCING rating was considered a normal level of cerebrovascular impairment in ageing due to the construction of the VCING scoring system.

Frontotemporal lobar degeneration (FTLD) was defined as the presence of frontal or temporal lobe degeneration accompanied by pathological tau or TDP-43 inclusions. Argyrophilic grain disease (AGD) and limbic-predominant age-related TDP-43 encephalopathy (LATE) were also included as neuropathological diagnoses.

As the primary focus of the thesis is around the relationship between mixed and concomitant pathology on clinical dementia, the definitions of pure, mixed and concomitant pathology are outlined as follows. In cases with pure pathology, the criteria for one neuropathological diagnosis is met with no substantial additional pathologies present. In cases with mixed pathology, criteria for multiple neuropathological diagnoses are met (e.g., Alzheimer's disease and Lewy body disease). Concomitant pathology refers to additional pathology in cases where the criteria for a neuropathological diagnosis has been met but there are additional distinct pathological lesions are present that do not meet the associated criteria but are still present at a substantial level out of the norm from healthy brain ageing. Low pathology controls were cases that did not meet the criteria for any neuropathological diagnosis.

***Table 2.11*. Operationalisation of Neuropathology**: Classification framework for neuropathological diagnoses and subclinical pathology applied in this study, adapted from McAleese et al. (2021). Diagnostic categories are defined by specific pathological features, established staging criteria, and additional pathology markers where applicable. Abbreviations for staging systems and pathological features are provided for clarity.

Neuropathological Diagnosis	Description	Criteria and stages	Additional Pathology
Alzheimer's disease neuropathological change (ADNC)	Presence of Aβ plaques, neurofibrillary tangles/neuropil threads and neuritic plaques in topographically distinct regions	NIA-AA High Thal Aβ: 4-5 Braak NFT: V-VI CERAD: B-C	NIA-AA Intermediate Thal Aβ: 1-5 Braak NFT: III-VI CERAD: Any
Lewy body disease (LBD)	Presence of α-synuclein aggregations in the form of LB and Lewy neurites in topographically distinct regions	McKeith: Limbic or Neocortical Lewy bodies Braak LB 4-6	McKeith: Brainstem or Amygdala LBs Braak LB 1-3
Cerebrovascular disease (CVD)	Presence of large (> 10mm) subcortical cerebral infarction(s) and/or white matter arteriolosclerosis or leptomeningeal cerebral amyloid angiopathy of the occipital lobe	VCING High	VCING Moderate
Frontotemporal lobar degeneration (FTLD) with TDP-43	Presence of TDP-43 inclusions in neurons accompanied by degeneration of the frontal and temporal lobes	TDP-43 (not LATE-NC)	--
Frontotemporal lobar degeneration (FTLD) with tau	Presence of specific 3R/4R hyperphosphorylated tau inclusions in neurons and/or glial cells accompanied by degeneration of the frontal and temporal lobes	PiD: neuronal inclusions (3R) PSP: globose NFT, tufted astrocytes (4R) CBD: astrocytic plaques (4R) AGD: neuronal processes (4R)	--
Limbic-predominant age-related TDP-43 encephalopathy (LATE-NC)	Presence of TDP-43 inclusions in topographically distinct regions	TDP-43 inclusion(s) present in limbic regions	--
Age-related tau astrogliopathy (ARTAG)		--	ARTAG: present
Hippocampal sclerosis (HpSc)	Presence of severe pyramidal cell loss in CA1 and subiculum of the hippocampal formation, that is out of proportion to ADNC	--	Hippocampal sclerosis: present
Primary age-related tauopathy (PART)		Definite PART	Braak NFT: I-IV Thal Aβ: 0-II

Cases that did not fulfil neuropathological criteria for Alzheimer's disease, Lewy body disease, cerebrovascular disease, LATE-NC, or frontotemporal lobar degeneration were classified as "low pathology controls". Many of these cases did have low level pathologies, including ARTAG, hippocampal sclerosis and primary age-related tauopathy (PART), to expand sample size for the comparison group.

Figure 2.1 shows the frequency of neuropathology groups and intersections between neuropathological diagnoses in the cohort and **Figure 2.2** shows the frequency of and intersections between individual pathologies across the cohort.

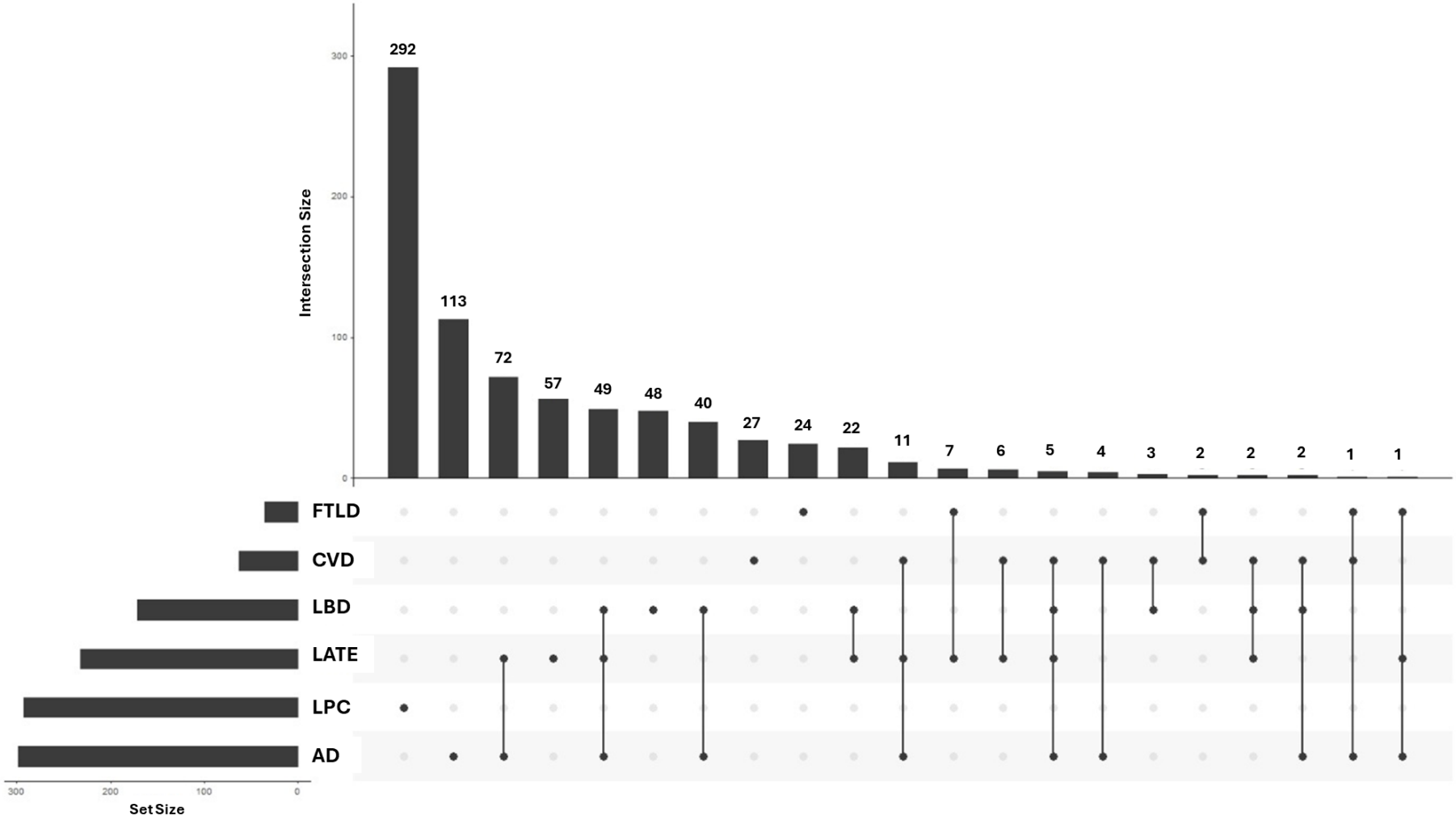

***Figure 2.1*. Frequency of, and intersections between, neuropathology groups:** Alzheimer's disease (AD), low pathology controls (LPC), limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy body disease (LBD); cerebrovascular disease (CVD), frontotemporal lobar degeneration (FTLD).

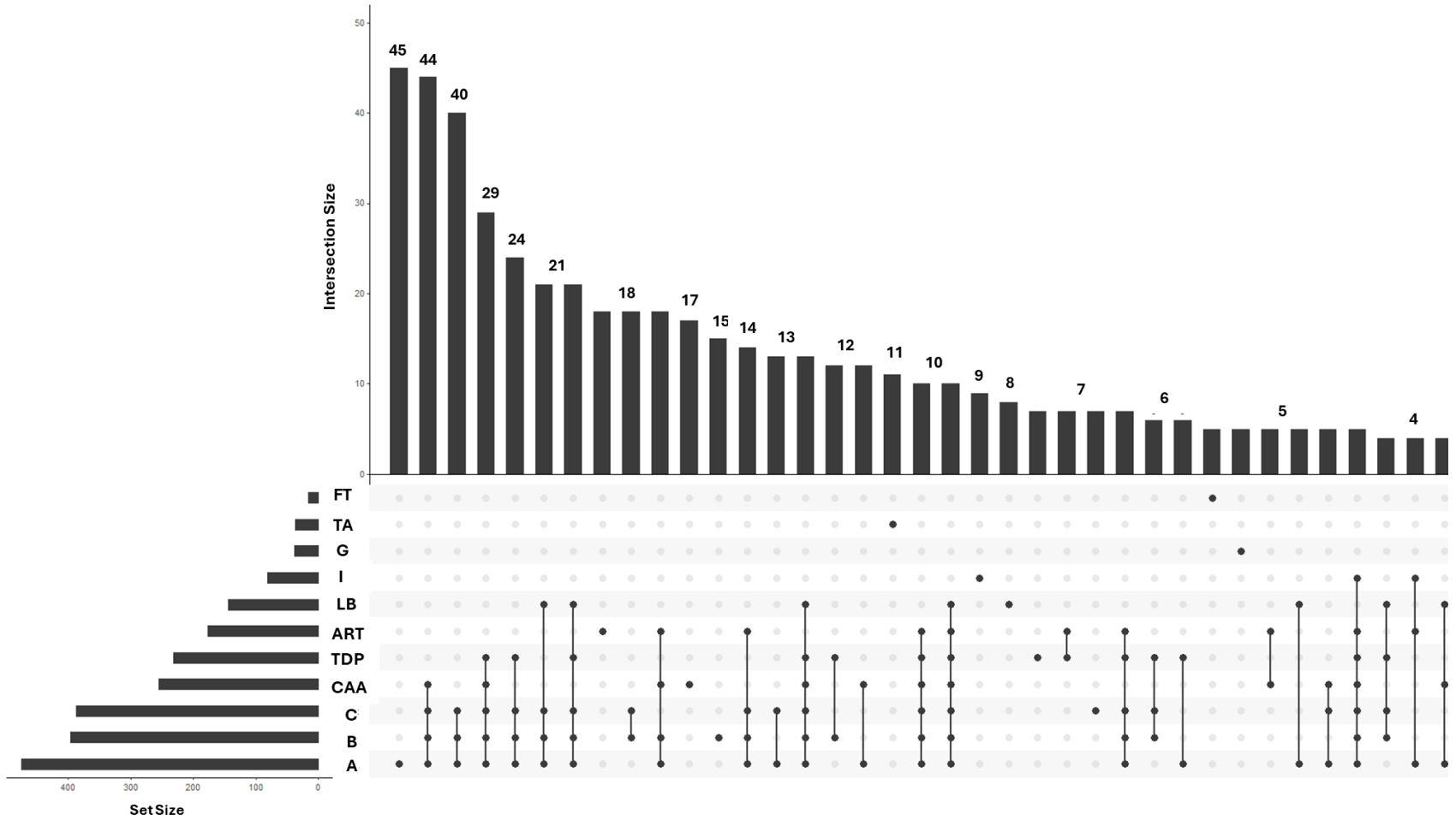

Figure 2.2. Frequency of intersection between eleven different pathology types: Pathologies included: A, Thal AB phase 3-5; B, Braak NFT stage 4-6; C, CERAD stage 2-3; LB, Braak LB stage 4-6; I, presence of large subcortical infarcts (>10mm); CAA, presence of cerebral amyloid angiopathy; ART, arteriolosclerosis; TDP, presence of limbic TDP-43 pathology; G, presence of ARTAG pathology; TA, primary tauopathy present; FT, FTLD-TDP-43 present. There were 159 different combinations of the 11 pathologies (including cases with absence of all included pathologies). Note: not all possible combination are shown in this figure.

2.4 Data Analysis

This study relied on secondary data from the Brains for Dementia Research cohort, which provided access to longitudinally collected cognitive and neuropathological data. The use of existing data allowed for the investigation of long-term cognitive trajectories, clinicopathological concordance, and neuropathological outcomes across a large sample that would not have been feasible to collect prospectively.

While secondary data analysis offers substantial advantages in terms of sample size, follow-up duration, and linkage to postmortem pathology, it also imposes limitations. Variables were constrained to those already collected, and definitions may vary slightly from contemporary standards. The timing and frequency of cognitive assessments were not uniform across all participants, which may affect the precision of transition modelling. However, the data source was selected for its high quality, depth, and clinical relevance, and appropriate statistical methods were applied to address its structure and limitations.

2.4.1 Dataset

Data obtained from longitudinal clinical assessments are available through the Dementias Platform UK (DPUK) data repository (Bauermeister et al., 2020). Brain tissue samples are stored at one of five established Brain Banks in the BDR network (Francis, Costello and Hayes, 2018). Neuropathological data obtained from neuropathological assessments are stored and accessible through a central searchable database of brain bank samples, the MRC UK Brain Bank Network (Francis, Costello and Hayes, 2018). All data used in the following analyses are available through these platforms following application approval. Data from repeated clinical assessments and comprehensive neuropathological assessments for each participant was integrated using subject ID codes.

2.4.2 Data Preparation

Data preparation and cleaning was conducted using OpenRefine (Ham, 2013). Relevant demographic variables with missing values were cross checked with clinical notes available in the database to ensure minimal missing data. All data was routinely checked for anomalies and inconsistencies, and suspected errors were checked against original records and notes included in the database. All statistical analyses were conducted in R Studio version 4.3.2.

2.4.3 Missing Data

For the majority of analyses, complete case analysis was used, and the number of participants in each model is reported in the relevant chapters and illustrated in **Figure 2.3**. The linear mixed models utilised missing at random methodology.

2.4.4 Model Building

Covariate selection was based on prior literature, theoretical plausibility, and availability in the dataset. In most models, a pre-specified set of variables, including age, sex, education, and index of multiple deprivation, were included as core covariates. Interaction terms were included if biologically or clinically meaningful. In exploratory analyses, progressive model comparison using Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), and/or log-likelihood testing was used to determine the inclusion of additional terms and assess model fit.

2.4.5 Statistical Methods

A range of statistical methods were employed to address the complexity of cognitive decline and dementia progression using longitudinal observational data (**Table *2.12***). Logistic regression was used to identify factors associated with missed diagnosis. Linear mixed effects models captured the continuous, person-specific trajectories of cognitive decline over time. Latent class models allowed for the identification of discrete subgroups with shared patterns of cognitive change, independent of diagnostic labels. Multistate models quantified the probability of transitions across ordered cognitive states and death. These complementary approaches provided a comprehensive framework to evaluate both cross-sectional diagnostic patterns and dynamic longitudinal processes related to cognitive decline.

Table 2.12. Data Analysis Overview: Summary of statistical models used, including their objectives, data structure, and R packages applied.

Model	Purpose	Data Structure	Package
Logistic regression	Identify factors associated with missed diagnosis	Cross-sectional; binary outcome	*glm*; *logistf*
Mixed effects modelling	Model trajectory of cognitive decline in neuropathology groups	Longitudinal cognitive data	*lme4*; *lmerTest*
Latent class modelling	Identify subgroups with distinct cognitive trajectories	Longitudinal cognitive data	*lcmm*

Multistate modelling	Model transitions across cognitive states and death	Panel data with discrete states	*msm*

Logistic Regression

Multivariable logistic, or binomial, regression was used to examine whether characteristics were associated with an increased likelihood of a missed diagnosis. The outcome variable was binary, with "1" representing individuals who met neuropathological criteria but were not identified as such during life, and "0" representing individuals who neither met neuropathological criteria nor received a clinical diagnosis of the condition during life. Logistic regression was selected due to its appropriateness for binary outcome modelling and its capacity to estimate adjusted odds ratios, facilitating the interpretation of effect sizes for individual predictors while controlling for potential confounding variables.

Given the imbalance in outcome frequency and the potential for small-sample bias or separation, logistic regression models were fitted using Firth's penalised maximum likelihood estimation. Firth's method applies a penalty term to the likelihood function to reduce the bias of maximum likelihood estimates, particularly in settings with rare outcomes or quasi-complete separation. This approach provides finite, stable estimates even when standard logistic regression would fail to converge or yield inflated effect sizes.

Firth's correction retains most assumptions of logistic regression: linearity of the logit for continuous predictors, independence of observations, and low multicollinearity between predictors. The linearity assumption was tested using Box-Tidwell tests and visual inspection of smoothed residual plots. Where non-linearity was detected, predictors were transformed or categorised. Multicollinearity was evaluated using Variance Inflation Factors. Models were fitted using penalised likelihood estimation, as implemented in the *logistf* package in R. Penalised likelihood ratio tests were used to assess predictor significance, and profile likelihood confidence intervals were reported. All p-values were two-sided, and FDR correction was applied where multiple comparisons were made.

While Firth's method reduces small-sample bias, it does not eliminate all limitations of logistic regression (Puhr et al., 2017). The assumption of linearity in the logit still applies and can bias estimates if unmet. Although penalisation helps to address separation, it can also lead to more conservative estimates, especially in well-powered samples. The

interpretability of penalised coefficients is the same as standard odds ratios but may differ in magnitude from traditional maximum likelihood estimates. Despite these considerations, Firth's logistic regression was chosen as the most appropriate method given the observed data characteristics and model convergence issues in preliminary analyses.

Mixed Effects Modelling

Linear mixed-effects models were utilised to examine cognitive decline over time in participants stratified by neuropathology group. This approach accommodates the repeated measures nature of cognitive assessments collected at multiple time points per individual, while accounting for inter-subject variability and potential differences in baseline cognition and rate of decline. Mixed effects models provided a flexible and robust framework to study longitudinal cognitive decline in relation to neuropathology.

The assumptions underlying the model include normally distributed random effects with constant variance, normally distributed and homoscedastic residuals, and independence of residuals conditional on the random effects. The linearity of the time effect on cognitive decline was assessed by comparing models with polynomial or spline terms, confirming that a linear specification was appropriate. Model diagnostics involved examining Q-Q plots of the random effects and residuals to evaluate normality, as well as residual versus fitted value plots to assess homoscedasticity. The random effects structure was selected based on theoretical considerations and likelihood ratio test comparing nested models.

Inference for fixed effects and their interactions was performed using t-tests with Satterthwaite approximation for degrees of freedom, implemented via the *lmerTest* package in R. Statistical significance was evaluated at $\alpha = 0.05$. Estimated marginal means and slopes by neuropathological groups were computed to aid interpretation. Limitations of this modelling approach include the assumption of linear cognitive decline which may not fully capture more complex trajectories, potential bias due to missing data assumed missing at random, and reliance on correctly specified random effects. Sensitivity analyses were performed to explore these limitations.

Latent Class Modelling

Latent class modelling was employed to identify distinct subgroups of participants exhibiting different trajectories of cognitive decline over time, while accounting for individual

variability within classes. This method extends traditional latent class growth analysis by incorporating random effects within each latent class, allowing for both discrete latent heterogeneity and continuous subject-specific deviations. This approach assumes that the population is composed of a finite number of unobserved (latent) classes, each characterised by its own pattern of change in cognitive function.

Models were fitted using the *lcmm* package in R. Mini-Mental State Examination (MMSE) scores, as a measure of cognition were measured longitudinally and served as the outcome variable. Time to death was treated as a continuous predictor, and the model estimated class-specific intercepts and slopes. Random intercepts and slopes were included to capture individual variation within each latent class. The number of latent classes was determined by comparing models with increasing class numbers using log-likelihood, Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC). Posterior class membership probabilities were reviewed to assess classification certainty and model adequacy.

Neuropathological diagnosis was not included as a covariate in the model itself. Instead, once class membership was estimated, neuropathological groups were compared across latent classes in post hoc analyses to explore how cognitive decline patterns mapped onto underlying neuropathology.

The latent class mixed model assumes conditional independence of observations given latent class and random effects, normality of random effects and residuals, and a valid specification of the functional form of time. Model diagnostics included visual inspection of class-specific trajectories and assessment of residual patterns. Limitations of this approach include potential misclassification of individuals, sensitivity to the number of classes selected, and assumptions regarding the linearity and normality of decline within classes. Latent class mixed modelling provided a flexible and data driven method to identify naturally occurring subgroups of cognitive decline, independent of diagnostic labels, offering complementary insights to other analytical methods used.

Multistate Modelling

Multistate models were selected to investigate transitions between cognitive states over time, incorporating death as an absorbing state to enable realistic modelling of disease that

would be easily interpretable in a clinical setting. Two related but distinct models were specified to capture different levels of diagnostic resolution and to evaluate the effect of model granularity on observed transition dynamics.

Model A included six states. This model allowed for bidirectional transitions between adjacent cognitive states, as well as transitions from any cognitive state to death. The bidirectional structure enabled the modelling of temporary fluctuations or diagnostic uncertainty, such as reversion from mild dementia to MCI. Transitions skipping intermediate states were not permitted in the base model, maintaining clinically plausible stepwise progression. Model B used a simplified three state illness-death structure. This model was more parsimonious, focusing on the core clinical transition from preclinical stages to dementia and death, and did not distinguish dementia severity. It was used to examine cumulative risk of dementia conversion in a form more comparable to clinical diagnostic pathways.

Both models were implemented using the *msm* package in R, which fits continuous-time Markov models to panel data. The transition intensity matrix Q was estimated, where each element represents the instantaneous transition rate from state to state. Covariates were incorporated as linear predictors of these transitions. Transition probabilities over time were derived from the matrix exponential of Q providing estimates of the likelihood of occupying a given state at any future time point, expected time spent in each state and competing risk-adjusted cumulative incidence. Model assumptions included the Markov assumption that future transitions depend only on the current state, time homogeneity of transition rates between observed time points, and no misclassification of cognitive state.

Model selection and diagnostics included comparison of observed versus expected transition frequencies, examination of individual state sequences, and sensitivity analyses using restricted transition structures (e.g. unidirectional progression only). Limitations of the multistate modelling framework include the possibility of biased transition estimates due to irregular or infrequent cognitive assessments (though missing states are interpolated using missing at random assumption), the assumption of time-invariant transition intensities, and potential overfitting in more complex state structures. Multistate modelling provided a flexible and interpretable framework to describe the progression of cognitive decline and quantify risks of transitioning to dementia in relation to neuropathology burden.

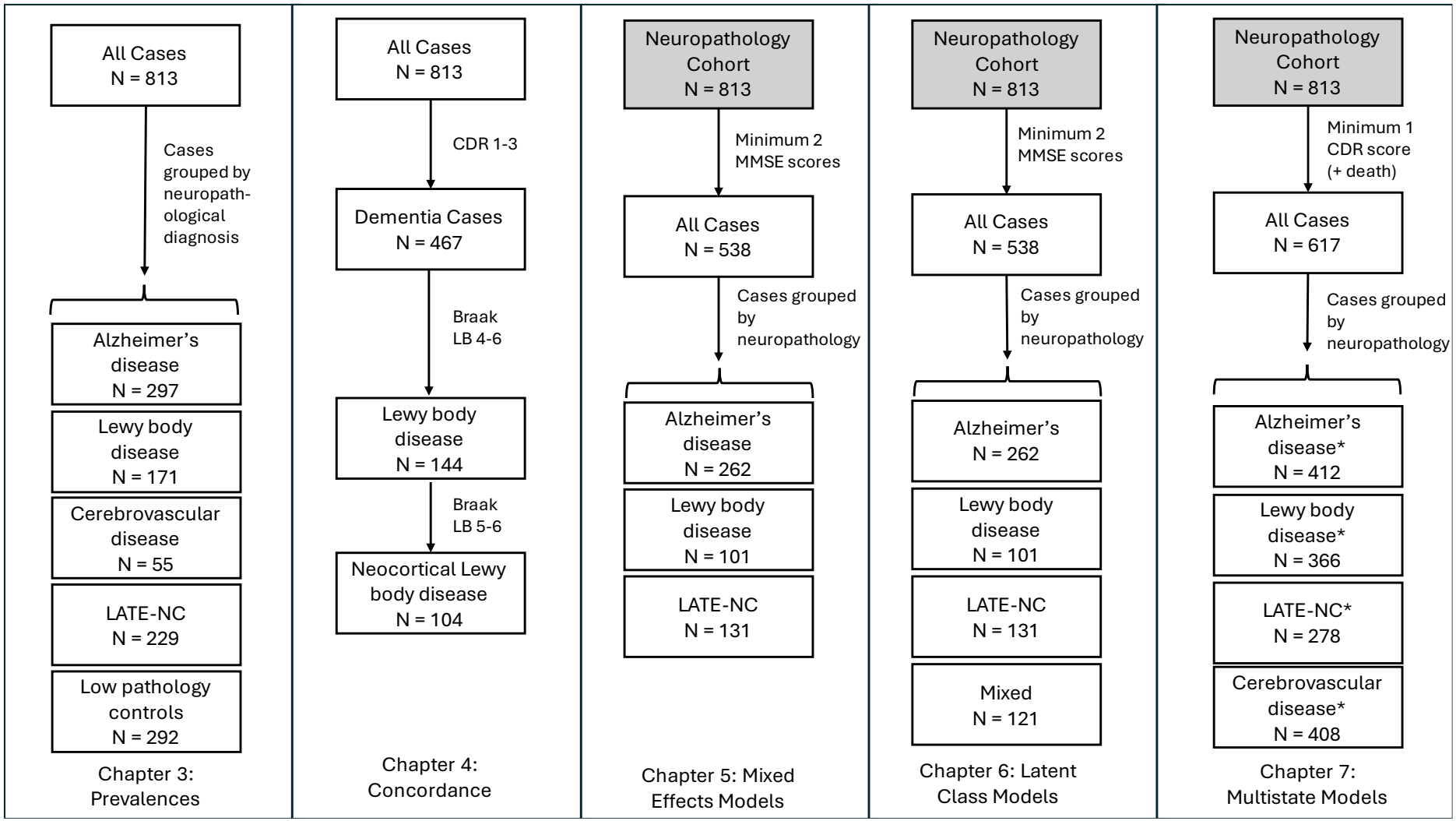

***Figure 2.3*. Sample Selection:** Flow diagram illustrating the number of participants included in each analysis from the original neuropathology cohort (N = 813). Groups with an asterisk include a comparison group of low pathology controls. Further details are provided in each chapter.

Chapter 3. The Prevalence of Mixed and Concomitant Neuropathology in the Brains for Dementia Research Cohort

3.1 Background

Autopsy studies allow for detailed characterisation of a wider range of neuropathologies than possible with in vivo measures such as scans or biomarkers, providing important insights into the biological processes occurring in the brain (Beach et al., 2012, Serrano-Pozo et al., 2013). Typically, neuropathology cohorts are highly selective clinical samples, with small cohort size and limited controls for comparisons (Robinson et al., 2018b, Nelson et al., 2012). Due to the narrow focus of many neuropathology studies on a single neurodegenerative disease, the prevalence of mixed and concomitant pathology is frequently overlooked or occasionally excluded as an atypical presentation of disease (Schneider et al., 2007, Rahimi and Kovacs, 2014). These limitations of small, restrictive autopsy studies can limit both statistical power and the generalisability of results. As a result, many prevalence figures are based on small, non-representative samples. Ideally, neuropathology data would be routinely collected from population-based studies (Bennett et al., 2012b). However, it is uncommon for donated brain tissue to have longitudinal clinical assessments to fully characterise temporal clinicopathological associations.

While BDR is not population-based, the cohort provides longitudinal data accompanied with full neuropathological assessment covering a wide range of neuropathological features associated with age-related dementia. Characterising the prevalence of pathology in both dementia cases and controls in crucial for understanding how neuropathological changes relate to dementia rather than normal ageing. Post-mortem classification of cases also provides validation of the diagnostic criteria and potential biomarkers used to ensure accurate differentiation between dementia subtypes. As the Brains for Dementia Research programme contains both dementia cases and controls, characterisation of the prevalence of key age-related neuropathologies in this neuropathology cohort can provide further insights into differences between cases and controls and the concomitance of neuropathologies in a large sample.

3.1.1 Aims and Hypotheses

Using post-mortem neuropathological assessment of donated brain tissue from longitudinally followed-up individuals in the Brains for Dementia Research cohort with and without clinical dementia, this study aimed to:

1. Calculate the prevalence of age-related neuropathologies in individuals with and without clinical dementia.
2. Quantify the prevalence of concomitant pathologies in Alzheimer's disease, Lewy body disease, cerebrovascular disease, frontotemporal lobar degeneration and LATE-NC.
3. Examine the frequency of different combinations of mixed neuropathology.

The primary aim of this chapter was cohort characterisation in terms of neuropathology, rather than identification of clinicopathological relationships. Based on previous studies, it was hypothesised that age-related neuropathologies would be more common in cases with clinical dementia, and that of these age-related neuropathologies, Alzheimer's disease would be the most common pathology and be present, to some extent, in almost all cases of dementia (Ott et al., 1995). Further to this, it was hypothesised that age-related neuropathology and normal cognition would not be mutually exclusive (Bennett et al., 2006).

3.2 Methods

All 813 cases aged 65 years or older with neuropathology data were included in this summary of mixed and concomitant pathology in the cohort. Demographic variables included age, sex, years in full time education, index of multiple deprivation, *APOE4* presence, dementia status, and study diagnosis. As previously outlined in *Section 2.3*, pathology variables included Alzheimer's disease, Lewy body disease, cerebrovascular disease, LATE-NC, hippocampal sclerosis, and ARTAG. Neuropathological diagnoses included Alzheimer's disease, Lewy body disease, frontotemporal lobar degeneration, argyrophilic grain disease, cerebrovascular disease, LATE-NC, mixed pathology and low pathology controls. Concomitant pathology included intermediate Alzheimer's disease neuropathological change, incidental Lewy bodies, moderate cerebrovascular disease, and the presence of hippocampal sclerosis or ARTAG. Dementia status was determined based on the final clinical assessment prior to death. Group comparisons were performed between

individuals with and without clinical dementia to examine differences in demographic and neuropathological variables

3.2.1 Statistical Tests

Basic descriptive statistics were used to summarise demographic and clinical characteristics of the cohort. Continuous variables were either reported as means and standard deviations (SD) or medians and ranges, depending on the distribution. Categorical variables were summarised as counts and percentages. Group comparisons were performed using Kruskal-Wallis tests for non-normally distributed continuous variables, and χ^2 or Fisher's exact tests for categorical variables, as appropriate. A p-value of < 0.05 was considered statistically significant. All analyses were conducted using R. Missing data were reported but not imputed unless otherwise specified.

3.3 Descriptive Epidemiology

Table 3.1 presents demographic and clinical characteristics of individuals in the cohort, stratified by clinical dementia status at final assessment (N = 813). The average age at death was 84.7 years (S.D. = 7.87; range 65.2 – 104) with males representing 52.9% of the cohort. The proportion of *APOE4* carriers was 40.3% and the proportion of individuals with dementia at final assessment was 57.4%.

Participants with clinical dementia (N = 467) were younger on average (mean age at death 84.0 vs 85.6 years; p = 0.002), and more likely to be male (58% vs 46%; p < 0.001). The dementia group had spent fewer years in full-time education (mean 12.1 vs 13.2 year; p < 0.001). Index of Multiple Deprivation (IMD) scores did not differ significantly between groups (p = 0.120), although the dementia group had slightly higher representation in the most deprived quintile (Q5). APOE ε4 allele presence was markedly higher among those with dementia (54.0% vs 22.0%; p < 0.001).

Table 3.1. Cohort Demographics and Clinical Characteristics: Summary statistics for age, sex, education, index of multiple deprivation (IMD), and APOE ε4 status in participants with and without clinical dementia at final assessment. Continuous variables are presented as mean (standard deviation) and median [range]; categorical variables as counts (percentages). IMD is categorized into quintiles (Q1 = least deprived, Q5 = most deprived). APOE ε4 presence indicates at least one ε4 allele. P-values correspond to group comparisons using Kruskal-Wallis or χ^2 tests. Missing data are reported where applicable.

	Dementia (N = 467)	**No Dementia (N = 346)**	**All (N = 813)**	**p-value**
Age (at death)				
Mean (SD)	84.0 (8.12)	85.6 (7.44)	84.7 (7.87)	**0.002**
Median [Min, Max]	84.0 [65.2, 104]	86.2 [67.4, 104]	85.1 [65.2, 104]	
Sex				
Female	196 (42.0%)	187 (54.0%)	383 (47.1%)	**< 0.001**
Male	271 (58.0%)	159 (46.0%)	430 (52.9%)	
Education				
Mean (SD)	12.1 (3.14)	13.2 (3.21)	12.6 (3.22)	**< 0.001**
Median [Min, Max]	11.0 [0, 24.0]	12.0 [9.00, 25.0]	12.0 [0, 25.0]	
Missing	*49 (10.5%)*	*33 (9.5%)*	*82 (10.1%)*	
IMD				
Median [Min, Max]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.120
Quintile 1	154 (33.0%)	130 (37.6%)	284 (34.9%)	
Quintile 2	120 (25.7%)	81 (23.4%)	201 (24.7%)	
Quintile 3	70 (15.0%)	63 (18.2%)	133 (16.4%)	
Quintile 4	38 (8.1%)	36 (10.4%)	74 (9.1%)	
Quintile 5	45 (9.6%)	20 (5.8%)	65 (8.0%)	
Missing	*40 (8.6%)*	*16 (4.6%)*	*56 (6.9%)*	
APOE4				
Present	252 (54.0%)	76 (22.0%)	328 (40.3%)	**< 0.001**

Absent	135	(28.9%)	158	(45.7%)	293	(36.0%)
Missing	*80*	*(17.1%)*	*112*	*(32.4%)*	*192*	*(23.6%)*

3.3.1 Neuropathology groups

Cases with low pathology only (i.e. no neuropathological diagnosis) were used as the comparison group (low pathology controls). These are not true controls as almost all individuals had some level of neuropathology, albeit below the threshold required for a neuropathological diagnosis. Low pathology was the most common pathology type across the whole cohort (35.9%; N = 292), and in individuals without dementia (66.5%; N = 230). As expected, low pathology was significantly more common in those without dementia ($p < 0.001$).

The most common pathology in dementia cases was mixed pathology, accounting for 44.5% of the group (N = 208). Mixed pathology was significantly more common in individuals with dementia than without ($p < 0.001$). Alzheimer's disease was the second most common neuropathology group in dementia cases, present in 20.6% of cases. Alzheimer's disease as an assigned neuropathology group was significantly more common in those with dementia than those without ($p < 0.001$).

Table 3.2 Prevalence of Primary Neuropathology Groups: Counts and percentages of individuals classified by primary neuropathological diagnosis, stratified by clinical dementia status at final assessment. Diagnoses were assigned according to established criteria. Mixed pathology indicates the presence of two or more primary pathologies meeting diagnostic thresholds. Low pathology comparison group comprises individuals with minimal or no neuropathological findings below the threshold for diagnosis. P-values represent group comparisons using χ^2 or Fisher's exact tests as appropriate.

	Dementia (N = 467)		**No Dementia (N = 346)**		**Overall (N = 813)**		**p-value**
Alzheimer's disease	96	(20.6%)	17	(4.9%)	113	(13.9%)	***< 0.001***
Lewy body disease	32	(6.9%)	14	(4.0%)	46	(5.7%)	*0.119*
Cerebrovascular disease	9	(1.9%)	18	(5.2%)	27	(3.3%)	***0.017***
Frontotemporal lobar degeneration	22	(4.7%)	2	(0.6%)	24	(3.0%)	***< 0.001***
Argyrophilic grain disease	10	(2.1%)	15	(4.3%)	25	(3.1%)	*0.073*
LATE-NC	28	(6.0%)	27	(7.8%)	55	(6.8%)	*0.310*
Mixed pathology	208	(44.5%)	23	(6.6%)	231	(28.4%)	***< 0.001***
Low pathology controls	62	(13.3%)	230	(66.5%)	292	(35.9%)	***< 0.001***

Lewy body disease and LATE-NC were less common, accounting for 5.7% and 6.8% of the cohort respectively, with no significant difference between those with and without dementia (LBD, p = 0.119; LATE-NC, p = 0.310). Cerebrovascular disease was the assigned neuropathology group of 5.2% of individuals without dementia and 1.9% of those with dementia, with a small but significant difference in prevalence between the two groups (p = 0.017). Frontotemporal lobar degeneration was significantly more common in cases (4.7%) than controls (0.6%) but relatively uncommon across the whole cohort, assigned to only 3% of participants. Argyrophilic grain disease was equally rare (3.1%) and there was no significant difference in prevalence between cases and controls (p = 0.073). All prevalences are reported in **Table 3.2**.

3.3.2 Mixed pathology

Mixed pathology, one of the most common pathology groups, was present in 231 donors. Mixed pathology refers to cases fulfilling diagnostic criteria for more than one neuropathological disease. There was no limit to the number of co-occurring pathologies, but the highest number of co-occurring neuropathological diseases observed in this sample was four (Alzheimer's disease, Lewy body disease, cerebrovascular disease and LATE-NC). The combinations of different neuropathological diagnoses in the 231 mixed pathology cases are reported in **Table 3.3** in order of frequency.

Of these, 208 (90.0%) mixed pathology cases in the cohort had clinical dementia proximal to death. There were 18 different combinations of mixed pathology in this Brains for Dementia Research cohort. Although mixed pathology was reported in cognitively healthy controls, all combinations of mixed pathology were more frequently observed in dementia cases. The majority of mixed pathology cases had Alzheimer's disease as a constituent part (79.7%). The most common combination observed in the cohort was AD/LATE, accounting for 31.2% of mixed pathology cases. AD/DLB/LATE and AD/DLB were also relatively common, accounting for 21.2% and 17.3% of mixed pathology cases respectively. DLB/LATE represented 9.5% of mixed pathology cases. LATE was a constituent part of the mixed pathology reported in 87.0% of cognitively healthy controls with mixed pathology.

Figure 3.1 shows the frequency of neuropathology groups and intersections between neuropathological diagnoses in the cohort and **Figure 3.2** shows the frequency of and intersections between individual pathologies across the cohort.

Table 3.3. Mixed Pathology Combinations: Frequencies and percentages of participants with two or more co-occurring neuropathological diagnoses at autopsy, stratified by dementia status. Diagnoses include Alzheimer's disease (AD), Lewy body disease (DLB), limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebrovascular disease (CVD), frontotemporal lobar degeneration (FTLD), and argyrophilic grain disease (AGD). Hyphens indicate no observed cases in the respective group.

	Dementia (N = 208)		No Dementia (N = 23)		Overall (N = 231)	
AD/LATE	65	(31.3%)	7	(2.0%)	72	(31.2%)
AD/DLB/LATE	44	(21.2%)	5	(1.4%)	49	(21.2%)
AD/DLB	38	(18.3%)	2	(0.6%)	40	(17.3%)
DLB/LATE	18	(8.7%)	4	(1.2%)	22	(9.5%)
AD/CVD/LATE	10	(4.8%)	1	(0.3%)	11	(4.8%)
FTLD/LATE	7	(3.4%)		-	7	(3.0%)
CVD/LATE	4	(1.9%)	2	(0.6%)	6	(2.6%)
AD/DLB/CVD/LATE	5	(2.4%)		-	5	(2.2%)
AD/CVD	4	(1.9%)		-	4	(1.7%)
AD/DLB/CVD	1	(0.5%)	1	(0.3%)	2	(0.9%)
AGD/LATE	2	(1.0%)		-	2	(0.9%)
CVD/FTLD	2	(1.0%)		-	2	(0.9%)
DLB/CVD	2	(1.0%)		-	2	(0.9%)
DLB/CVD/LATE	1	(0.5%)	1	(0.3%)	2	(0.9%)
DLB/FTLD	2	(1.0%)		-	2	(0.9%)
AD/CVD/FTLD	1	(0.5%)		-	1	(0.4%)
AD/FTLD/LATE	1	(0.5%)		-	1	(0.4%)
DLB/CVD/AGD	1	(0.5%)		-	1	(0.4%)

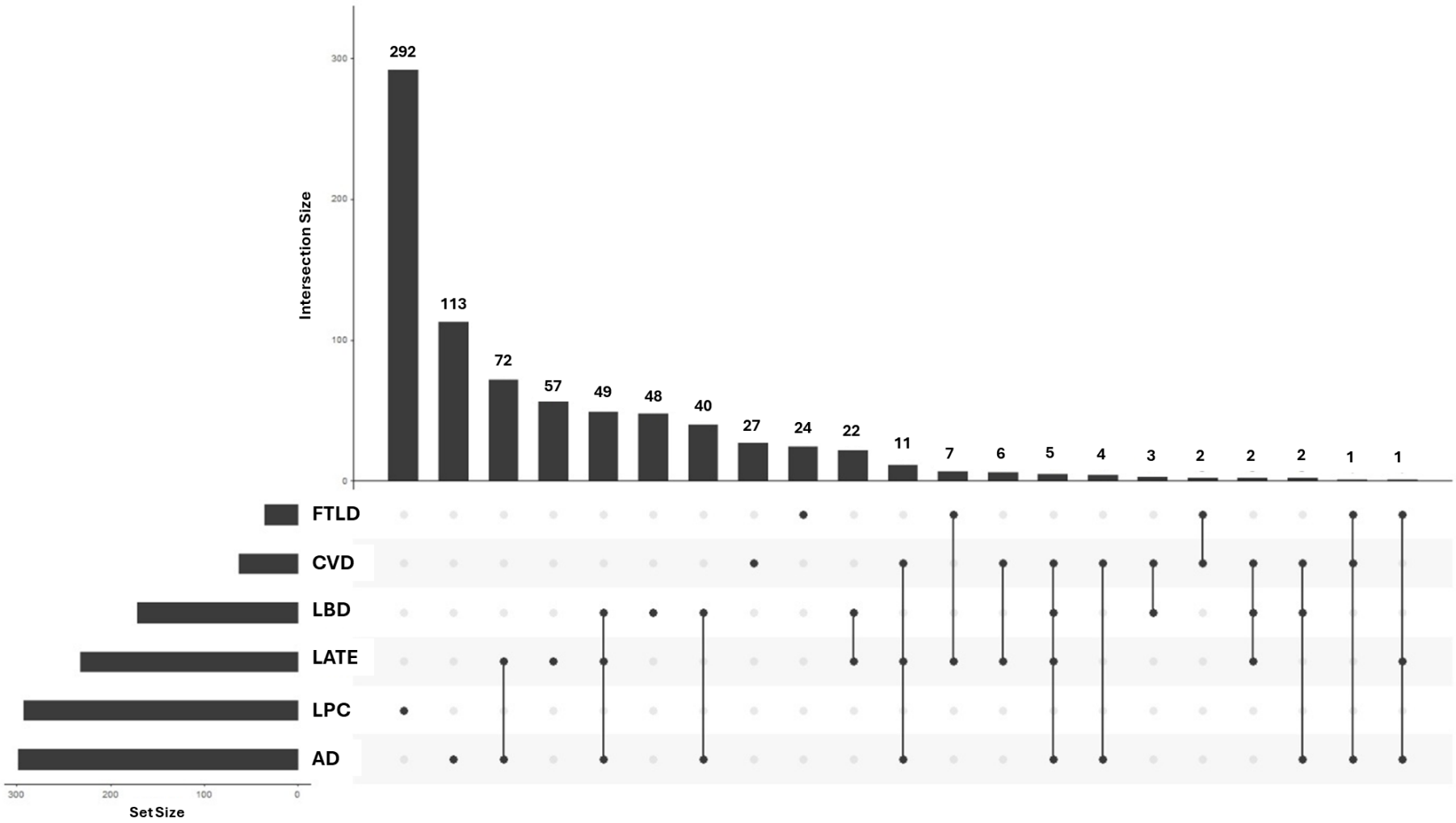

***Figure 3.1*. Frequency of, and intersections between, neuropathology groups:** Alzheimer's disease (AD), low pathology controls (LPC), limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy body disease (LBD); cerebrovascular disease (CVD), frontotemporal lobar degeneration (FTLD).

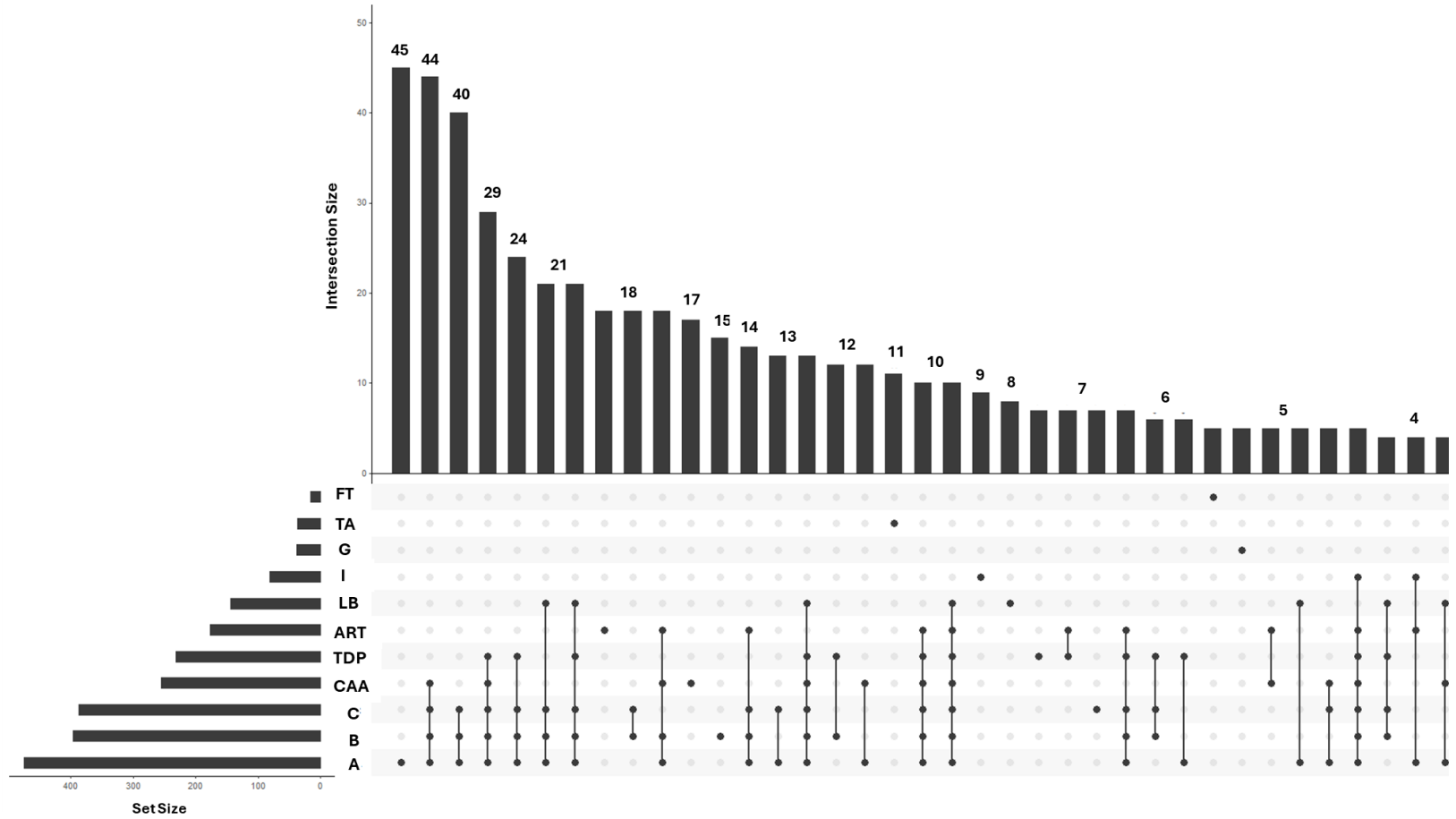

Figure 3.2. Frequency of intersection between eleven different pathology types: Pathologies included: A, Thal AB phase 3-5; B, Braak NFT stage 4-6; C, CERAD stage 2-3; LB, Braak LB stage 4-6; I, presence of large subcortical infarcts (>10mm); CAA, presence of cerebral amyloid angiopathy; ART, arteriolosclerosis; TDP, presence of limbic TDP-43 pathology; G, presence of ARTAG pathology; TA, primary tauopathy present; FT, FTLD-TDP-43 present. There were 159 different combinations of the 11 pathologies (including cases with absence of all included pathologies). Note: not all possible combination are shown in this figure.

3.3.3 Alzheimer's disease

Demographic variables and clinical characteristics of individuals with Alzheimer's disease are outlined in **Table 3.4**. Of the 297 donors with Alzheimer's disease, 184 (62.0%) exhibited mixed neuropathological diagnoses, while 113 (38.0%) had Alzheimer's disease as the sole primary pathology. The mean age at death was significantly higher in the mixed AD group (85.7 ± 7.23 years) compared to the non-mixed AD group (82.6 ± 8.18 years; $p = 0.001$). Mixed AD cases demonstrated a significantly longer follow-up duration (mean 3.44 ± 2.73 years versus 1.99 ± 2.04 years; $p < 0.001$) and increased number of clinical visits (median 4.00 [range 1–10] vs. 2.00 [range 1–7]; $p < 0.001$).

Table 3.4. Demographic and Clinical Characteristics of Individuals with Alzheimer's Disease Pathology: Summary statistics for participants with non-mixed Alzheimer's disease (AD) and mixed Alzheimer's disease (mixed AD) in the Brains for Dementia Research cohort. Continuous variables are presented as mean (SD) and median [range]. Categorical variables are reported as counts (%). Index of Multiple Deprivation (IMD) is presented in quintiles (Q1 = least deprived, Q5 = most deprived). APOE4 presence indicated at least one ε4 allele. Group comparisons were conducted using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Significant p-values (< 0.05) indicate differences between non-mixed and mixed AD groups.

	AD (N = 113)	**Mixed AD (N = 184)**	**All (N = 297)**	**p-value**
Age (at death)	82.6 (8.18)	85.7 (7.23)	84.5 (7.74)	**0.001**
	82.6 [65.9, 103]	85.4 [67.8, 104]	84.3 [65.9, 104]	
Sex (Female)	51 (45.1%)	88 (47.8%)	139 (46.8%)	0.740
	62 (54.9%)	96 (52.2%)	158 (53.2%)	
Education	12.5 (3.11)	12.1 (3.37)	12.2 (3.27)	0.190
	12.0 [5.00, 20.0]	11.0 [0, 24.0]	11.0 [0, 24.0]	
IMD	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.706
IMD Q1	32 (28.3%)	61 (33.2%)	93 (31.3%)	
IMD Q2	29 (25.7%)	49 (26.6%)	78 (26.3%)	
IMD Q3	18 (15.9%)	26 (14.1%)	44 (14.8%)	
IMD Q4	11 (9.7%)	14 (7.6%)	25 (8.4%)	
IMD Q5	8 (7.1%)	21 (11.4%)	29 (9.8%)	

Missing	*15 (13.3%)*	*13 (7.1%)*	*28 (9.4%)*	
APOE4 Present	65 (57.5%)	105 (57.1%)	170 (57.2%)	0.125
Follow up time	1.99 (2.04)	3.44 (2.73)	2.89 (2.58)	**< 0.001**
	1.20 [0, 8.14]	3.13 [0, 12.6]	2.21 [0, 12.6]	
Time to death	0.633 (0.646)	0.902 (1.09)	0.800 (0.955)	**0.010**
	0.498 [0, 3.64]	0.687 [0, 9.10]	0.583 [0, 9.10]	
Visits	2.00 [1.00, 7.00]	4.00 [1.00, 10.0]	3.00 [1.00, 10.0]	**< 0.001**
Dementia	96 (85.0%)	168 (91.3%)	264 (88.9%)	0.134
MMSE	16.9 (9.46)	11.5 (7.97)	14.0 (9.07)	**0.008**
	18.0 [0, 30.0]	11.0 [0, 28.0]	14.0 [0, 30.0]	
NPI total	21.7 (22.8)	19.5 (20.1)	20.4 (21.1)	0.764
	17.0 [0, 88.0]	12.0 [0, 84.0]	14.5 [0, 88.0]	

Cognitive function, assessed via MMSE, was significantly lower in mixed AD cases (mean 11.5 ± 7.97) relative to non-mixed cases (mean 16.9 ± 9.46; p = 0.008), indicating greater cognitive impairment (**Figure 3.3**). Time to death was also prolonged in mixed AD cases (mean 0.902 ± 1.09 years) compared to AD-only cases (mean 0.633 ± 0.646 years; p = 0.010). There were no significant differences in sex distribution (p = 0.740), or neuropsychiatric symptoms measured by NPI total scores (p = 0.764) between groups (**Table 3.4; Figure 3.3**). The prevalence of neuropsychiatric symptoms at final assessment was relatively similar between Alzheimer's disease and mixed Alzheimer's disease across all NPI subdomains (**Figure 3.3**). Dementia was reported in 91.3% of mixed AD cases and 85.0% of non-mixed AD cases (p = 0.134).

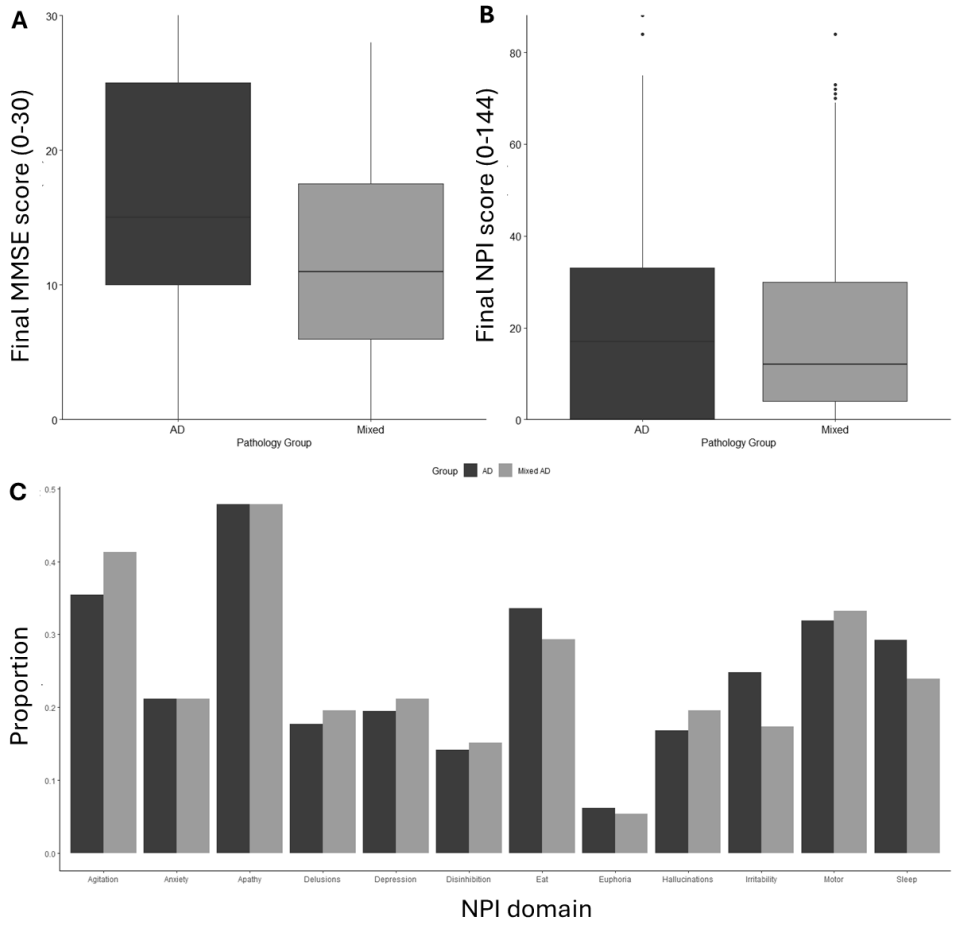

***Figure 3.3*. Clinical Profile of Alzheimer's disease (AD):** Comparison of (A) Mini-Mental State Examination (MMSE) scores (0-30), (B) total Neuropsychiatric Inventory (NPI) scores (0-144), and (C) presence of neuropsychiatric symptoms across the twelve subdomains at final clinical assessment in mixed and non-mixed Alzheimer's disease.

Table 3.5 summarises the prevalence of concomitant pathologies in mixed and non-mixed Alzheimer's disease. Of the 297 Alzheimer's disease cases, 184 had at least one additional neuropathological diagnosis. Of these 184 mixed AD cases, 137 (74.5%) also had LATE-NC as a component of the mixed pathology. Lewy body disease was reported in 96 mixed AD cases (52.2%), while cerebrovascular disease was present in 23 mixed AD cases (12.5%). The most common mixed pathology combinations were AD/LATE, observed in 71 cases (38.6%), AD/DLB/LATE in 49 cases (26.6%), and AD/DLB in 40 cases (21.7%).

Among the remaining 113 Alzheimer's disease cases without additional neuropathological diagnoses, 44 (38.9%) exhibited concomitant pathology, including incidental Lewy body disease in 7 cases (6.2%) and moderate cerebrovascular disease in 20 cases (17.7%). In the mixed AD group, concomitant pathology was present in 68 of 184 cases (37.0%), with

moderate cerebrovascular disease observed in 28 cases (15.2%) and incidental Lewy body disease in 8 cases (4.3%). Both hippocampal sclerosis (N = 32, 17.4%) and ARTAG (N = 12, 6.5%) were more common in mixed AD cases than non-mixed cases (N=3, 2.7%).

Table 3.5. Mixed and concomitant pathology in Alzheimer's disease (AD): Frequencies and percentages of additional neuropathological and concomitant pathologies in individuals with pure AD and mixed AD. Mixed AD cases exhibit multiple primary neuropathological diagnoses, whereas pure AD cases have AD as the sole primary pathology. Additional neuropathological diagnoses include Lewy body disease, cerebrovascular disease, and LATE-NC. Concomitant pathologies comprise incidental Lewy body disease, moderate cerebrovascular disease, hippocampal sclerosis, and ARTAG. "Any concomitant pathology" denotes the presence of one or more of these pathologies. Percentages are calculated within each subgroup.

	AD (N = 113)		Mixed AD (N = 184)		All (N = 297)	
Lewy body disease	0	(0.0%)	88	(47.8%)	88	(29.6%)
Incidental LBD	7	(6.2%)	8	(4.3%)	15	(5.1%)
Cerebrovascular disease	0	(0.0%)	19	(10.3%)	19	(6.4%)
Moderate CVD	20	(17.7%)	28	(15.2%)	48	(16.2%)
LATE-NC	0	(0.0%)	134	(72.8%)	134	(45.1%)
Hippocampal sclerosis	3	(2.7%)	32	(17.4%)	35	(11.8%)
ARTAG	3	(2.7%)	12	(6.5%)	15	(5.1%)
Any concomitant pathology	31	(27.4%)	68	(37.0%)	99	(33.3%)

3.3.4 Lewy body disease

Demographic and clinical characteristics of individuals with Lewy body disease are outlined in **Table 3.6**. Of the 171 participants classified with LBD, 46 (26.9%) exhibited LBD as the sole primary neuropathological diagnosis, while 125 (73.1%) had LBD in conjunction with at least one additional primary pathology (mixed LBD). There were no statistically significant differences in age at death between non-mixed and mixed LBD groups (mean 83.9 ± 7.38 vs. 84.6 ± 7.51 years; p = 0.607), nor in sex distribution (female: 37.0% vs. 38.4%; p = 1.000),

years spent in full-time education (mean 12.4 ± 3.26 vs. 12.3 ± 3.64 years; p = 0.717), APOE ε4 allele presence (45.7% vs. 52.0%; p = 0.514), or Index of Multiple Deprivation (IMD) quintile distributions (p = 0.125).

Mixed LBD cases were associated with a significantly longer time to death from final clinical assessment (mean −0.911 ± 0.878 years) compared to non-mixed LBD cases (mean −0.648 ± 0.659 years; p = 0.018). Mixed cases also had a greater number of clinical follow-up visits (median 4.00 [range 1–15] vs. 3.00 [range 1–7]; p = 0.045). The proportion of participants with clinical dementia at final assessment was significantly higher in the mixed LBD group (89.6%) than in the non-mixed group (69.6%; p = 0.003).

Table 3.6 Demographic and Clinical Characteristics of Individuals with Lewy Body Disease Pathology: Summary statistics for participants with non-mixed Lewy body disease (LBD) and mixed Lewy body disease (mixed LBD). Continuous variables are presented as mean (SD) and median [range]. Categorical variables are reported as counts (%). Index of Multiple Deprivation (IMD) is presented in quintiles (Q1 = least deprived, Q5 = most deprived). APOE4 presence indicates at least one ε4 allele. Group comparisons were conducted using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Significant p-values (< 0.05) indicate differences between non-mixed and mixed LBD groups.

	LBD (N = 46)	**Mixed LBD (N = 125)**	**All (N = 171)**	**p-value**
Age (at death)	83.9 (7.38)	84.6 (7.51)	84.4 (7.46)	0.607
	83.1 [68.8, 98.8]	84.3 [67.8, 101]	83.6 [67.8, 101]	
Sex (Female)	17 (37.0%)	48 (38.4%)	65 (38.0%)	1.000
	29 (63.0%)	77 (61.6%)	106 (62.0%)	
Education	12.4 (3.26)	12.3 (3.64)	12.3 (3.54)	0.717
	12.0 [8.00, 22.0]	11.0 [0, 24.0]	11.0 [0, 24.0]	
IMD.N	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.125
Q1	18 (39.2%)	43 (34.4%)	61 (35.7%)	
Q2	14 (30.4%)	32 (25.6%)	46 (26.9%)	
Q3	2 (4.3%)	17 (13.65)	19 (11.1%)	
Q4	5 (10.9%)	9 (7.2%)	14 (8.2%)	

Q5	1 (2.2%)	15 (12.0%)	16 (9.4%)	
Missing	6 (13.0%)	9 (7.2%)	15 (8.8%)	
APOE4 Present	21 (45.7%)	65 (52.0%)	86 (50.3%)	0.514
Follow up time	3.00 (2.81)	3.55 (2.89)	3.40 (2.87)	0.217
	2.15 [0, 14.7]	3.31 [0, 17.3]	3.06 [0, 17.3]	
Time to death	-0.648 (0.659)	-0.911 (0.878)	-0.840 (0.831)	**0.018**
	-0.457 [-2.53, 0]	-0.778 [-5.49, 0]	-0.674 [-5.49, 0]	
Visits	3.00 [1.00, 7.00]	4.00 [1.00, 15.0]	4.00 [1.00, 15.0]	**0.045**
Dementia	32 (69.6%)	112 (89.6%)	144 (84.2%)	**0.003**
MMSE	19.6 (8.95)	13.7 (8.03)	16.2 (8.87)	**0.005**
	22.0 [0, 30.0]	13.0 [0, 28.0]	16.0 [0, 30.0]	
NPI total	17.6 (18.3)	23.9 (23.8)	22.3 (22.7)	0.177
	13.0 [0, 73.0]	15.0 [0, 110]	14.0 [0, 110]	

Cognitive performance, as measured by the Mini-Mental State Examination (MMSE), was significantly lower in mixed LBD cases (mean 13.7 ± 8.03) than in non-mixed LBD cases (mean 19.6 ± 8.95; p = 0.005). Neuropsychiatric symptom burden, assessed by the Neuropsychiatric Inventory (NPI) total score, was higher in mixed LBD (mean 23.9 ± 23.8) than in non-mixed LBD (mean 17.6 ± 18.3), though this difference did not reach statistical significance (p = 0.177).

Further analysis of neuropsychiatric features revealed distinct symptom profiles between groups (**Figure 3.4**). Mixed LBD cases exhibited a higher prevalence of most neuropsychiatric symptoms at final assessment, including agitation, anxiety, apathy, delusions, disinhibition, irritability, aberrant motor behaviour, and sleep disturbances. In contrast, hallucinations and depression were more frequently reported in individuals with non-mixed LBD. The prevalence of euphoria and appetite or eating disturbances was relatively similar across

both groups. These symptom patterns are consistent with the higher overall NPI total scores observed in mixed LBD cases, although the difference was not statistically significant.

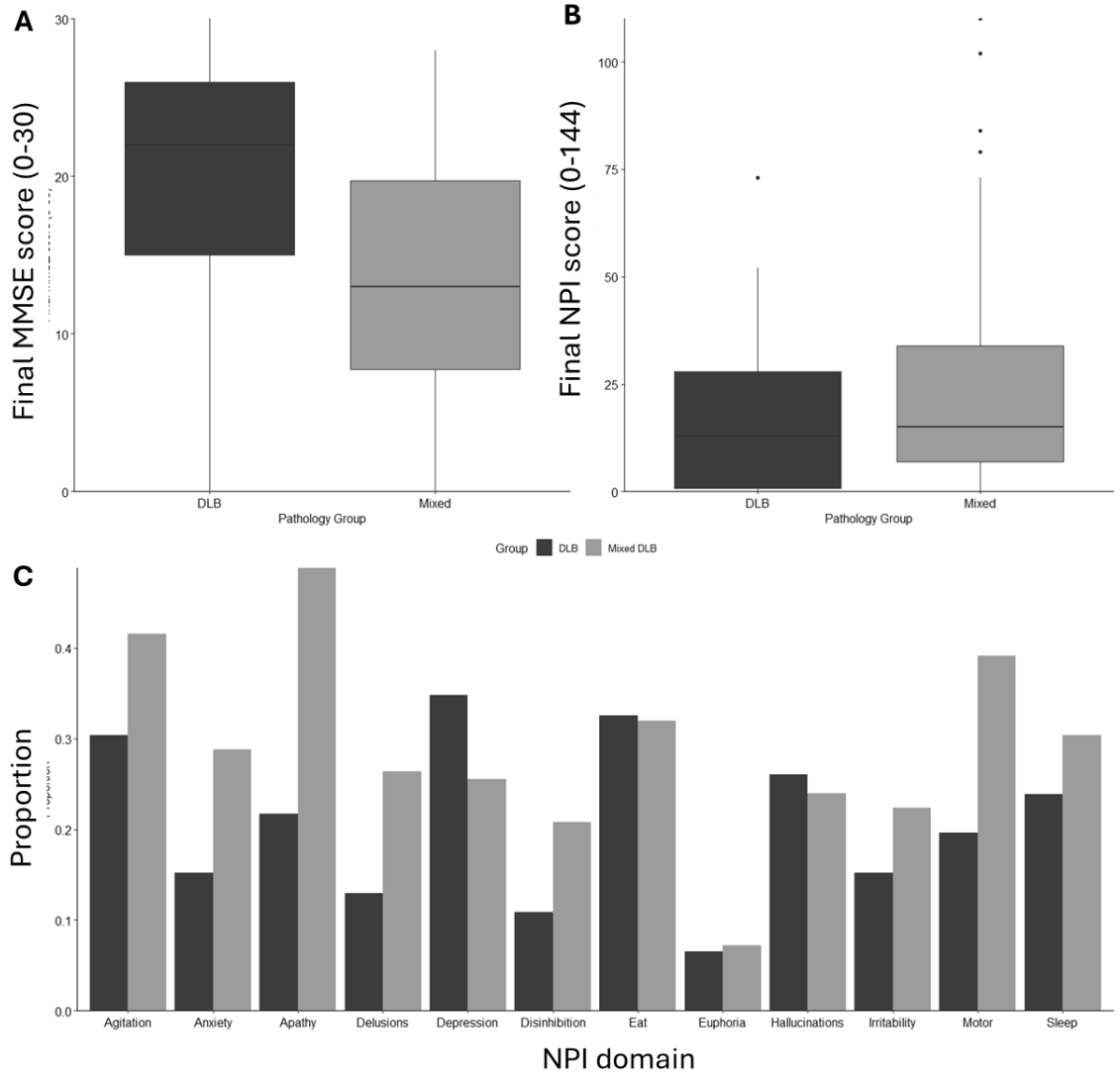

***Figure 3.4*. Clinical Profile of Lewy Body Disease (LBD):** Comparison of (A) Mini-Mental State Examination (MMSE) scores (0–30), (B) total Neuropsychiatric Inventory (NPI) scores (0–144), and (C) presence of neuropsychiatric symptoms across the twelve subdomains at final clinical assessment in mixed and non-mixed Lewy body disease.

Table 3.7 summarises the prevalence of concomitant pathologies in mixed and non-mixed Lewy body disease. Of the 171 cases with Lewy body disease (LBD), 125 (73.1%) had at least one additional primary neuropathological diagnosis (**Table 3.7**). Among these mixed LBD cases, Alzheimer's disease (AD) was the most frequent co-occurring pathology, present in 90 individuals (72.0%). LATE-NC was also relatively common, reported in 78 individuals (62.4%) mixed LBD cases. Cerebrovascular disease (CVD) was less frequently observed, reported in

13 cases (10.4%). The most prevalent combinations of co-primary pathologies in mixed LBD were AD/DLB/LATE (n = 49, 39.2%), AD/DLB (n = 40, 32.0%), and DLB/LATE (n = 22, 17.6%).

Concomitant pathology was present in 27 of 46 non-mixed LBD cases (58.7%) and 51 of 125 mixed LBD cases (40.8%). Intermediate AD neuropathological change (ADNC) was more common in non-mixed LBD (n = 23, 50.0%) than in mixed LBD (n = 21, 16.8%). Conversely, hippocampal sclerosis (17 cases, 13.6%) and ARTAG (6 cases, 4.8%) were more frequently observed in mixed LBD than in non-mixed LBD (1 case each, 2.2%).

Table 3.7. Mixed and Concomitant Pathology in Lewy Body Disease (LBD): Frequencies and percentages of additional neuropathological and concomitant pathologies in individuals with pure LBD and mixed LBD. Mixed LBD cases have multiple primary neuropathological diagnoses, while pure LBD cases present LBD as the sole primary pathology. Additional neuropathological diagnoses include Alzheimer's disease, cerebrovascular disease, and LATE-NC. Concomitant pathologies comprise incidental Lewy body disease, moderate cerebrovascular disease, hippocampal sclerosis, and ARTAG. "Any concomitant pathology" indicates the presence of one or more of these additional pathologies. Percentages are calculated within each subgroup.

	LBD (N = 46)		**Mixed LBD (N = 125)**		**All (N = 171)**	
Alzheimer's disease	0	(0.0%)	90	(72.0%)	90	(52.6%)
Intermediate AD	23	(50.0%)	21	(16.8%)	44	(25.7%)
Cerebrovascular disease	0	(0.0%)	13	(10.4%)	13	(7.6%)
Moderate CVD	4	(8.7%)	19	(15.2%)	23	(13.5%)
LATE	0	(0.0%)	78	(62.4%)	78	(45.6%)
Hippocampal sclerosis	1	(2.2%)	17	(13.6%)	18	(10.5%)
ARTAG	1	(2.2%)	6	(4.8%)	7	(4.1%)
Any concomitant pathology	27	(58.7%)	51	(40.8%)	78	(45.6%)

3.3.5 Cerebrovascular disease

Demographic variables for cerebrovascular disease are outlined in **Table 3.8**. Among the 55 individuals diagnosed with cerebrovascular disease (CVD), 25 had pure CVD pathology, and 30 exhibited mixed CVD pathology with additional neuropathologies. No significant differences were observed between pure and mixed CVD groups regarding age at death (mean 88.7 vs. 87.5 years; p = 0.360), sex distribution (female: 56.0% vs. 43.3%; p = 0.506), years of education (mean 13.3 vs. 12.0; p = 0.131), or socioeconomic status measured by the Index of Multiple Deprivation (median IMD 1.50 vs. 2.00; p = 0.855). APOE ε4 allele presence was also similar between groups (24.0% vs. 36.7%; p = 0.192). Dementia was significantly more prevalent in the mixed CVD group (83.3%) compared to pure CVD cases (28.0%; p < 0.001). Follow-up duration (mean 2.77 vs. 3.89 years; p = 0.147), time to death (mean -1.30 vs. -1.00 years; p = 0.787), and number of clinical visits (median 3.00 for both groups; p = 0.456) did not differ significantly.

Table 3.8. Demographic and Clinical Characteristics of Individuals with Cerebrovascular Disease (CVD): Summary statistics for participants with non-mixed cerebrovascular disease (CVD) and mixed cerebrovascular disease (mixed CVD). Continuous variables are presented as mean (SD) and median [range]. Categorical variables are reported as counts (%). Index of Multiple Deprivation (IMD) is presented in quintiles (Q1 = least deprived, Q5 = most deprived). APOE4 presence indicates at least one ε4 allele. Group comparisons were conducted using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Significant p-values (< 0.05) indicate differences between non-mixed and mixed CVD groups.

	CVD (N = 25)	**Mixed CVD (N = 30)**	**All (N = 55)**	**p-value**
Age (at death)	88.7 (6.28)	87.5 (6.62)	88.0 (6.44)	0.360
	88.7 [77.1, 99.8]	86.4 [71.1, 103]	87.0 [71.1, 103]	
Sex (Female)	14 (56.0%)	13 (43.3%)	27 (49.1%)	0.506
	11 (44.0%)	17 (56.7%)	28 (50.9%)	
Education	13.3 (3.87)	12.0 (3.48)	12.6 (3.68)	0.131
	12.0 [9.00, 25.0]	11.0 [9.00, 24.0]	11.0 [9.00, 25.0]	
IMD.N	1.50 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.855
Q1	12 (48.0%)	12 (40.0%)	24 (43.6%)	

Q2	4	(16.0%)	6	(20.0%)	10	(18.2%)	
Q3	5	(20.0%)	4	(13.3%)	9	(16.4%)	
Q4	2	(8.0%)	2	(6.7%)	4	(7.3%)	
Q5	1	(4.0%)	3	(10.0%)	4	(7.3%)	
Missing	1	(4.0%)	3	(10.0%)	4	(7.3%)	
APOE4	6	(24.0%)	11	(36.7%)	17	(30.9%)	0.192
Follow up time	3.89 (2.66)		2.77 (2.39)		3.28 (2.55)		0.147
	3.93 [0, 9.50]		2.50 [0, 8.44]		3.00 [0, 9.50]		
Time to death	-1.00 (0.761)		-1.30 (1.89)		-1.16 (1.48)		0.787
	-0.778 [-2.52, -0.0958]		-0.700 [-9.10, 0]		-0.731 [-9.10, 0]		
Visits	3.00 [1.00, 10.0]		3.00 [1.00, 7.00]		3.00 [1.00, 10.0]		0.456
Dementia	7	(28.0%)	25	(83.3%)	32	(58.2%)	**< 0.001**
MMSE	25.0 (6.89)		20.3 (5.75)		23.5 (6.82)		**0.022**
	28.0 [3.00, 30.0]		19.5 [11.0, 27.0]		26.0 [3.00, 30.0]		
NPI total	3.41 (5.37)		22.0 (25.4)		14.5 (21.8)		**< 0.001**
	0 [0, 17.0]		10.0 [0, 84.0]		4.50 [0, 84.0]		

Cognitive performance, assessed via Mini-Mental State Examination (MMSE), was significantly lower in mixed CVD cases (mean 20.3) than in pure CVD cases (mean 25.0; $p = 0.022$). Likewise, neuropsychiatric symptoms, measured by the total Neuropsychiatric Inventory (NPI) score, were markedly higher in mixed CVD cases (mean 22.0) compared to pure CVD cases (mean 3.41; $p < 0.001$). All neuropsychiatric domains, except for depression and euphoria, were more frequently reported in mixed CVD than pure CVD cases (**Figure 3.5**).

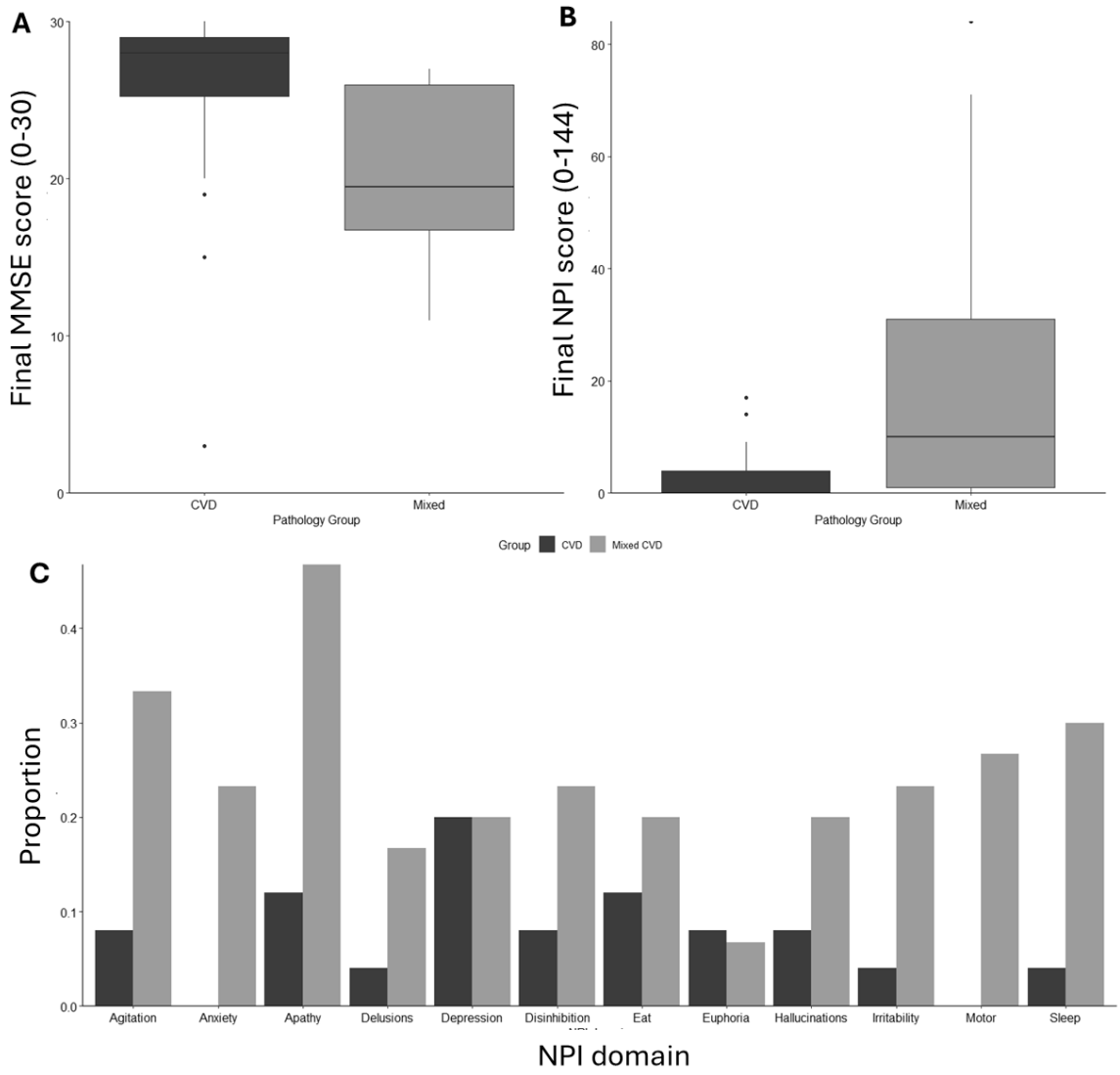

***Figure 3.5*. Clinical profile of cerebrovascular disease (CVD):** Comparison of (A) Mini-Mental State Examination (MMSE) scores (0–30), (B) total Neuropsychiatric Inventory (NPI) scores (0–144), and (C) presence of neuropsychiatric symptoms across the twelve subdomains at final clinical assessment in mixed and non-mixed cerebrovascular disease.

Table 3.9 summarises the prevalence of concomitant pathologies in mixed and non-mixed Alzheimer's disease. Of the 55 cases with cerebrovascular disease (CVD), 30 had at least one additional neuropathological diagnosis. Among these mixed CVD cases, 21 (70.0%) included LATE-NC as part of the mixed pathology. Alzheimer's disease was also frequently observed, present in 19 (63.3%) mixed CVD cases. Lewy body disease was less common but still identified in 43.3% (N = 13) of mixed CVD cases.

Concomitant pathology was reported in 53.3% of mixed CVD cases and 48.0% of non-mixed CVD cases. Intermediate ADNC was observed in 32.0% of non-mixed CVD and 26.7% of

mixed CVD cases. Incidental Lewy bodies were present in 6.7% of mixed CVD and 4.0% of non-mixed CVD cases. Both hippocampal sclerosis and ARTAG were more prevalent in mixed CVD, reported in 20.0% and 16.7% of cases respectively, compared to 4.0% and 12.0% in non-mixed CVD cases.

Table 3.9. Mixed and Concomitant Pathology in Cerebrovascular Disease (CVD): Frequencies and percentages of additional neuropathological and concomitant pathologies in individuals with pure CVD and mixed CVD. Mixed CVD cases have multiple primary neuropathological diagnoses, while pure CVD cases present CVD as the sole primary pathology. Additional neuropathological diagnoses include Alzheimer's disease, Lewy body disease, and LATE-NC. Concomitant pathologies comprise intermediate Alzheimer's disease, incidental Lewy body disease, hippocampal sclerosis, and ARTAG. "Any concomitant pathology" indicates the presence of one or more of these additional pathologies. Percentages are calculated within each subgroup.

	CVD (N = 25)		Mixed CVD (N = 30)		All (N = 55)	
Alzheimer's disease	0	(0.0%)	17	(56.7%)	17	(30.9%)
Intermediate AD	8	(32.0%)	8	(26.7%)	16	(29.1%)
Lewy body disease	0	(0.0%)	13	(43.3%)	13	(23.6%)
Incidental LBD	1	(4.0%)	2	(6.7%)	3	(5.5%)
LATE	0	(0.0%)	20	(66.7%)	20	(36.3%)
Hippocampal sclerosis	1	(4.0%)	6	(20.0%)	7	(12.7%)
ARTAG	3	(12.0%)	5	(16.7%)	8	(15.4%)
Any concomitant pathology	12	(48.0%)	16	(53.3%)	28	(50.9%)

3.3.6 LATE-NC

Demographic and clinical characteristics of individuals with non-mixed (N = 55) and mixed (N = 174) LATE-NC are summarised in **Table 3.10**. The mean age at death was significantly greater in non-mixed LATE-NC cases (89.9 ± 6.27 years) compared to mixed cases (86.7 ± 7.13 years; p = 0.002). Sex distribution did not differ significantly, with females representing 38.2% of non-mixed and 44.3% of mixed cases (p = 0.524). Years spent in full-time education and Index of Multiple Deprivation (IMD) scores were comparable between groups (p > 0.05). APOE ε4 allele frequency was 41.8% in non-mixed and 51.7% in mixed LATE-NC cases, with no statistically significant difference (p = 0.242). Follow-up duration and time to death were also similar across groups. Median clinical visit count was higher in mixed LATE-NC cases (4.0 vs. 3.0; p = 0.011). Clinically, dementia prevalence was significantly elevated in mixed LATE-NC (89.1%) relative to non-mixed cases (50.9%; p < 0.001).

Table 3.10. Demographic and Clinical Characteristics of Individuals with LATE-NC: Summary statistics for participants with non-mixed LATE-NC and mixed LATE-NC. Continuous variables are presented as mean (SD) and median [range]. Categorical variables are reported as counts (%). Index of Multiple Deprivation (IMD) is presented in quintiles (Q1 = least deprived, Q5 = most deprived). APOE4 presence indicates at least one ε4 allele. Group comparisons were conducted using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Significant p-values (< 0.05) indicate differences between non-mixed and mixed LATE-NC groups.

	LATE (N=55)	**Mixed (N=174)**	**All (N=229)**	**p-value**
Age (at death)	89.9 (6.27)	86.7 (7.13)	87.5 (7.05)	**0.002**
	90.8 [70.3, 98.5]	86.3 [67.8, 104]	87.1 [67.8, 104]	
Sex (Female)	21 (38.2%)	77 (44.3%)	98 (42.8%)	0.524
	34 (61.8%)	97 (55.7%)	131 (57.2%)	
Education	12.8 (3.55)	12.0 (3.03)	12.2 (3.17)	0.247
	11.0 [9.00, 21.0]	11.0 [6.00, 24.0]	11.0 [6.00, 24.0]	
IMD.N	1.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.071
Q1	27 (49.1%)	65 (37.4%)	92 (40.2%)	
Q2	4 (7.3%)	45 (25.9%)	49 (21.4%)	
Q3	9 (16.4%)	24 (13.8%)	33 (14.4%)	

Q4	5	(9.1%)	14	(8.0%)	19	(8.3%)	
Q5	5	(9.1%)	13	(7.5%)	18	(7.9%)	
Missing	5	(9.1%)	13	(7.5%)	18	(7.9%)	
APOE4	23	(41.8%)	90	(51.7%)	113	(49.3%)	0.242
Follow up time	2.96 (2.19)		3.38 (2.66)		3.28 (2.57)		0.399
	2.75 [0, 7.26]		3.13 [0, 17.3]		3.08 [0, 17.3]		
Time to death	-0.678 (0.589)		-0.800 (0.812)		-0.771 (0.765)		0.393
	-0.591 [-2.78, 0]		-0.698 [-5.49, 0]		-0.668 [-5.49, 0]		
Visits	3.00 [1.00, 6.00]		4.00 [1.00, 15.0]		3.00 [1.00, 15.0]		**0.011**
Dementia	28	(50.9%)	155	(89.1%)	183	(79.9%)	**< 0.001**
MMSE	21.1 (9.33)		13.0 (8.10)		16.3 (9.46)		**< 0.001**
	25.0 [0, 30.0]		12.0 [0, 27.0]		16.0 [0, 30.0]		
NPI total	21.4 (26.3)		19.4 (21.7)		19.9 (22.7)		0.691
	11.0 [0, 89.0]		12.0 [0, 110]		12.0 [0, 110]		

Final MMSE score was significantly lower in mixed LATE-NC compared to non-mixed LATE-NC (13.0 (8.10) vs. 21.1 (9.33); $p < 0.001$). Total NPI scores did not differ significantly between groups (19.4 (21.7) vs. 21.4 (26.3); $p = 0.691$). Neuropsychiatric symptoms such as agitation, apathy, appetite and eating disorders, aberrant motor behaviour, and sleep disturbances were more frequently observed in mixed LATE-NC compared to non-mixed LATE-NC. Conversely, depression, disinhibition, and irritability were reported more commonly in non-mixed LATE-NC than in mixed cases (**Figure 3.6**).

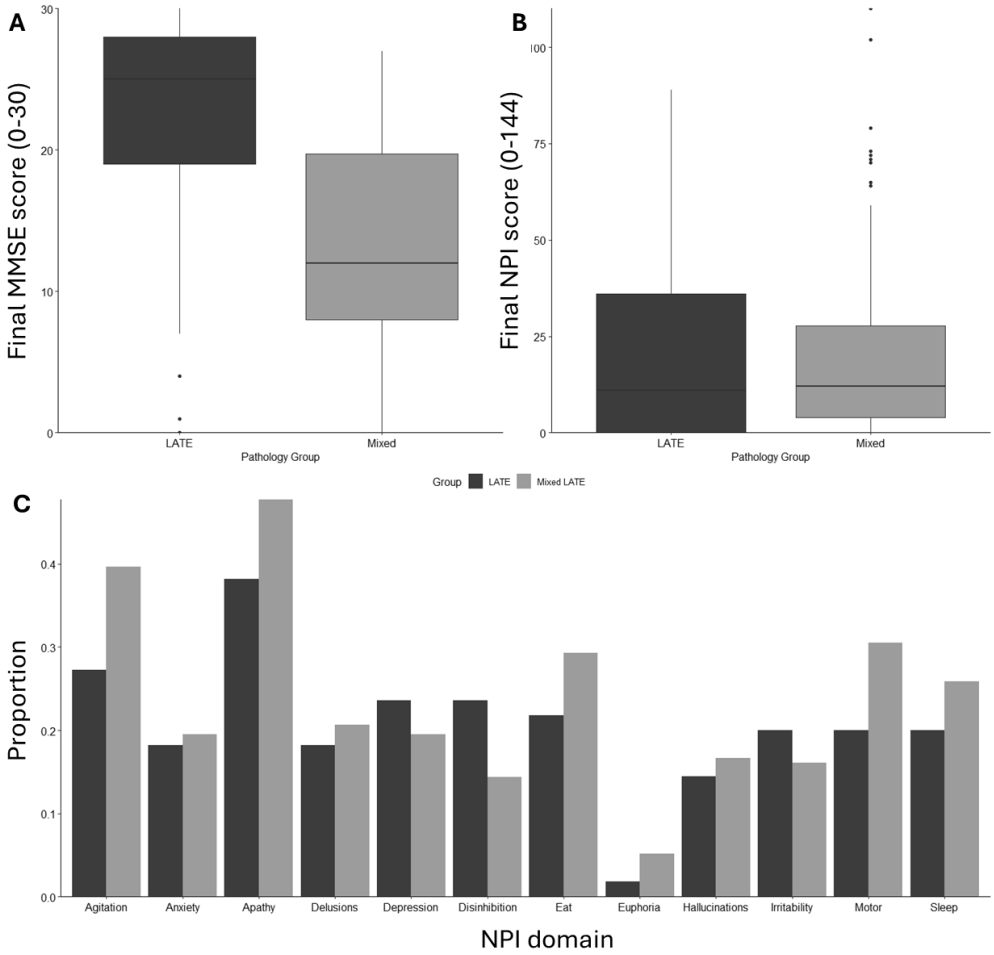

***Figure 3.6*. Clinical profile of LATE-NC:** Comparison of (A) Mini-Mental State Examination (MMSE) scores (0–30), (B) total Neuropsychiatric Inventory (NPI) scores (0–144), and (C) presence of neuropsychiatric symptoms across the twelve subdomains at final clinical assessment in mixed and non-mixed LATE-NC**.**

Table 3.11 summarises the prevalence of concomitant pathologies in mixed and non-mixed LATE-NC. Of the 229 cases with LATE-NC, 174 (75.9%) had at least one additional neuropathological diagnosis. Alzheimer's disease was the most prevalent co-pathology, present in 118 out of 174 mixed cases (67.8%). Lewy body disease was also relatively common, reported in 75 (43.1%) mixed cases. Cerebrovascular disease was less frequent, observed in 20 (11.5%) mixed cases.

Concomitant pathology was identified in 87 of 174 mixed cases (50.0%) and 39 of 55 non-mixed cases (70.9%). Intermediate ADNC was notably more prevalent in non-mixed LATE-NC (N = 33, 60.0%) compared to mixed cases (N = 27, 15.5%). Incidental Lewy body disease

occurred in 9 mixed cases (5.2%) and 2 non-mixed cases (3.6%). Moderate cerebrovascular pathology was similarly distributed, affecting 27 mixed cases (15.5%) and 8 non-mixed cases (14.5%). Hippocampal sclerosis was more frequent in mixed cases (N = 42, 24.1%) than in non-mixed cases (N = 7, 12.7%), whereas ARTAG was slightly more common in non-mixed (N = 4, 7.3%) compared to mixed LATE-NC cases (N = 10, 5.7%).

Table 3.11 Mixed and Concomitant Pathology in LATE-NC: Frequencies and percentages of additional neuropathological and concomitant pathologies in individuals with pure LATE-NC and mixed LATE-NC. Mixed LATE-NC cases have multiple primary neuropathological diagnoses, while pure LATE-NC cases present LATE-NC as the sole primary pathology. Additional neuropathological diagnoses include Alzheimer's disease, Lewy body disease, and cerebrovascular disease. Concomitant pathologies comprise intermediate Alzheimer's disease, incidental Lewy body disease, moderate cerebrovascular disease, hippocampal sclerosis, and ARTAG. "Any concomitant pathology" indicates the presence of one or more of these additional pathologies. Percentages are calculated within each subgroup.

	LATE-NC (N = 55)		**Mixed LATE-NC (N = 174)**		**All (N = 229)**	
Alzheimer's disease	0	(0.0%)	118	(67.8%)	118	(51.5%)
Intermediate AD	33	(60.0%)	27	(15.5%)	60	(26.2%)
Lewy body disease	0	(0.0%)	75	(43.1%)	75	(32.8%)
Incidental LBD	2	(3.6%)	9	(5.2%)	11	(4.8%)
Cerebrovascular disease	0	(0.0%)	20	(11.5%)	20	(8.7%)
Moderate CVD	8	(14.5%)	27	(15.5%)	35	(15.3%)
Hippocampal sclerosis	7	(12.7%)	42	(24.1%)	49	(21.4%)
ARTAG	4	(7.3%)	10	(5.7%)	14	(6.1%)
Any concomitant pathology	39	(70.9%)	87	(50.0%)	126	(55.0%)

3.3.7 Low pathology controls

Demographic and clinical characteristics of low pathology controls are summarised in **Table 3.12**. Of the 292 participants, 21.2% (N = 62) had dementia at the final assessment, while 78.8% (N = 230) did not. There were no significant differences in age at death between dementia and non-dementia groups (mean 85.7 ± 8.93 vs. 85.9 ± 7.46 years; p = 0.738) or sex distribution (female: 40.3% [N = 25] vs. 54.8% [N = 126]; p = 0.060). Education was significantly lower in the dementia group (mean 11.7 ± 2.74 years) compared to controls (mean 13.1 ± 3.08 years; p < 0.001). APOE ε4 allele presence was more frequent in dementia cases at 41.9% (N = 26) compared to 20.9% (N = 48) in controls (p = 0.005). No significant differences were observed in Index of Multiple Deprivation (IMD) quintile distributions (p = 0.582).

Follow-up time did not differ significantly between groups (mean 2.72 ± 2.70 vs. 3.46 ± 2.90 years; p = 0.084). Time from last clinical assessment to death was significantly shorter in dementia cases (mean −0.781 ± 0.904 years) compared to non-dementia controls (mean −0.994 ± 0.826 years; p = 0.008). Median number of clinical visits was comparable at 3.00 [range 1–10] for both groups (p = 0.854). Cognitive performance, measured by MMSE, was significantly lower in dementia cases (mean 14.8 ± 8.79) relative to controls (mean 28.2 ± 2.08; p < 0.001). Similarly, neuropsychiatric symptom severity (NPI total score) was significantly higher in dementia cases (mean 24.8 ± 23.0) compared to non-dementia participants (mean 2.54 ± 8.23; p < 0.001).

Table 3.12. Demographic and Clinical Characteristics of Low Pathology Controls: Low pathology controls stratified by dementia status at final assessment. Continuous variables are presented as mean (SD) and median [range]. Categorical variables are reported as counts (%). Index of Multiple Deprivation (IMD) is shown in quintiles (Q1 = least deprived, Q5 = most deprived). APOE4 presence indicates individuals with at least one ε4 allele. Group comparisons between participants with and without dementia were performed using Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Significant p-values (< 0.05) indicate differences between groups.

	Dementia (N=62)	**No Dementia (N=230)**	**Overall (N=292)**	**p-value**
Age (at death)	85.7 (8.93)	85.9 (7.46)	85.9 (7.78)	0.738
	85.5 [68.7, 104]	86.9 [68.7, 102]	86.7 [68.7, 104]	

Sex (Female)	25 (40.3%)	126 (54.8%)	151 (51.7%)	0.060
	37 (59.7%)	104 (45.2%)	141 (48.3%)	
Education	11.7 (2.74)	13.1 (3.08)	12.8 (3.06)	**< 0.001**
	11.0 [7.00, 18.0]	12.0 [9.00, 23.0]	12.0 [7.00, 23.0]	
IMD.N	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	0.582
Q1	18 (29.0%)	75 (32.6%)	93 (31.8%)	
Q2	15 (24.2%)	65 (28.3%)	80 (27.4%)	
Q3	15 (24.2%)	44 (19.1%)	59 (20.2%)	
Q4	6 (9.7%)	21 (9.1%)	27 (9.2%)	
Q5	7 (11.3%)	14 (6.1%)	21 (7.2%)	
Missing	1 (1.6%)	11 (4.8%)	12 (4.1)	
APOE4	26 (41.9%)	48 (20.9%)	74 (25.3%)	**0.005**
Follow up time	2.72 (2.70)	3.46 (2.90)	3.30 (2.87)	0.084
	2.07 [0, 9.20]	3.66 [0, 16.0]	3.05 [0, 16.0]	
Time to death	-0.781 (0.904)	-0.994 (0.826)	-0.949 (0.846)	**0.008**
	-0.517 [-5.30, -0.0602]	-0.799 [-4.76, 0]	-0.741 [-5.30, 0]	
Visits	3.00 [1.00, 10.0]	3.00 [1.00, 10.0]	3.00 [1.00, 10.0]	0.854
MMSE	14.8 (8.79)	28.2 (2.08)	25.6 (6.84)	**< 0.001**
	14.5 [0, 30.0]	29.0 [19.0, 30.0]	28.0 [0, 30.0]	
NPI – mean	24.8 (23.0)	2.54 (8.23)	9.08 (17.5)	**< 0.001**
Median [range]	24.0 [0, 97.0]	0 [0, 70.0]	0 [0, 97.0]	

3.4 Summary

Results reported in 0 highlight the complexity and heterogeneity of neuropathology in ageing and dementia. The frequent overlap between age-associated neuropathologies and an absence of clear delineation between neuropathological profiles in the Brains for Dementia Research programme, even in cognitively healthy individuals, blurs the distinction between neuropathological profiles and complicates existing theories on the relationship

between neuropathologies and dementia. This lack of clear delineation suggests that the majority of dementia cases may be driven by more than one underlying pathology.

Mixed pathology was the most common neuropathological profile in this cohort, with over 40% of dementia cases having sufficient pathology for two or more neuropathological diagnoses at postmortem. The high prevalence of mixed pathology further suggests that dementia is regularly the result of multiple co-occurring neurodegenerative diseases, rather than a single neuropathological cause. Furthermore, there was significant overlap between all pathologies and variation in the clinical profiles of cases with mixed pathology when compared to isolated pathologies. The presence and co-existence of these neuropathologies was not exclusive to dementia, with approximately 6% of cognitively healthy controls reported to have multiple neuropathological diagnoses. Dementia was associated with the presence of pathology, but the absence of dementia does not indicate the absence of pathology. Similarly, the presence of significant neuropathology did not guarantee the presence of dementia.

In addition, concomitant pathology was present with varying prevalence in all pathology groups, including mixed pathology, in this cohort. Prevalence of concomitant low-level pathology varied between pure (i.e., non-mixed) cases (27-71%) and mixed cases (37-53%) of Alzheimer's disease, Lewy body disease, cerebrovascular disease, and LATE-NC. The widespread prevalence of concomitant pathology, even in cases below the diagnostic threshold, further underscores the pervasive nature of low-level brain changes in both dementia and cognitively healthy individuals. This suggests that even in cases classified as having a single pathology, other co-existing changes may also be contributing to the disease process, indicating a need to view neuropathology holistically rather than as isolated diseases. This further complicates the relationship between pathology and clinical symptoms and suggests that the presence of neuropathology alone does not necessarily result in cognitive impairment, challenging current theories about what triggers the transition from normal ageing to dementia. Additionally, the presence of neuropathological changes in individuals without cognitive impairment suggests that neuropathology alone may not be sufficient to predict clinical outcomes.

While the descriptive cross-sectional methods used in 0 are relatively straightforward and effective for hypothesis formation and assessing prevalences, there are several limitations.

Cross sectional methods cannot establish causality, directionality, or time-based relationships between risk factors and disease outcomes. These methods are also susceptible to multiple forms of bias and can be limited by ecological fallacy, confounding factors, and inaccuracies in data reporting. The primary limitation of this analysis was the availability of neuropathological variables included in the Brains for Dementia Research study protocol.

Overall, these results highlight the heterogeneity of dementia-related neuropathology, suggesting that focusing on individual pathologies may oversimplify the underlying causes of cognitive decline. The dominance of mixed and concomitant pathology in dementia cases underscores the need for a broader approach to diagnosis and treatment, as focusing on single pathologies may overlook important contributing factors. Instead, these findings emphasise the importance of considering the interaction between multiple co-existing pathologies in both dementia and healthy ageing, particularly in the development of biomarkers, diagnostic tools, and targeted therapeutic treatments.

Chapter 4. Discordance Between Clinical Diagnosis and Postmortem Neuropathology

4.1 Background

Although the predominant underlying pathology in a dementia case cannot be confirmed with certainty without autopsy, the most frequently reported age-related neuropathologies are Alzheimer's disease (AD), Lewy body dementia (LBD), and cerebrovascular disease (CVD) (McAleese *et al.*, 2021). Currently, clinical diagnosis of dementia is made by clinical assessment of symptoms, often in combination with neuroimaging, but potential pathologies identified in vivo are considered 'probable' or 'possible' causes rather than a definitive diagnosis (Attems, 2017). Clinicopathological studies of dementia often report a mismatch in prevalences of clinical dementias and their associated neuropathologies (Mehta and Schneider, 2021, Jellinger and Attems, 2010). For example, Lewy body disease typically accounts for 15-20% of cases in autopsy series, whereas only 5% of clinical dementia cases in the United Kingdom are attributed to Lewy body dementia (Kane et al., 2018, Vann Jones and O'Brien, 2014). Discordance between clinical diagnosis and Lewy body disease has also been reported in other countries outside the UK, including France (Lebouvier et al., 2013) and the US (Gauthreaux et al., 2020, Mok et al., 2004). This discrepancy suggests that the majority of LBD cases are missed clinically despite thorough assessments and the existence of specialist centres.

Clinical diagnosis is challenging due to heterogeneity and overlap between symptoms of different dementia subtypes. The presence of multiple underlying pathologies may provide a more complex clinical picture by obscuring distinguishing features used to identify specific dementia subtypes (Coughlin, Hurtig and Irwin, 2020)As reported in 0, neuropathologies frequently overlap and co-occur in the ageing brain and the presence of mixed pathology can result in a different clinical presentation. The clinical heterogeneity arising from complex neuropathological profiles may result in clinical misdiagnosis of dementias. In addition to clinical presentation, other factors, including sex, geographical location, education, and deprivation, may also contribute to atypical clinical presentations and misdiagnosis (Bayram et al., 2021, Bayram, Coughlin and Litvan, 2022). It is therefore important to identify which factors are contributing to missed diagnosis and misdiagnosis of

dementia to identify groups who may be less likely to receive an accurate diagnosis during life.

Accurate and early diagnosis of dementia subtypes is central to the implementation of effective, personalised care and the providing accurate information to both patients and caregivers regarding their prognosis (Kane *et al.*, 2018). Improving the diagnostic accuracy of clinical diagnoses will improve the reliability, stratification, and usefulness of natural history studies and clinical trials. Improved sensitivity for Lewy body dementia in clinical settings, for example, would help clinicians avoid the administration of anti-psychotic treatments for classical psychotic symptoms that can have severe, and sometimes fatal, side effects in Lewy body disease (Taylor et al., 2020). It is likely that future disease-modifying treatments will target specific aggregated proteins (e.g., neurofibrillary tangles, Lewy body pathology) and therefore, the success and efficacy of future targeted therapeutic treatments for neurodegenerative disease will heavily rely on accurate ante-mortem diagnoses provided by clinicians (Rabinovici et al., 2017).

4.1.1 Aims and Hypotheses

Using study diagnoses provided during longitudinal clinical assessments and neuropathological diagnosis obtained after comprehensive post-mortem neuropathological assessment, this study aimed to:

1. Compare self-reported study diagnosis and neuropathological diagnosis neuropathology reported post-mortem across the cohort.
2. Determine accuracy of study diagnosis in predicting neuropathological diagnosis.
3. Determine if missed diagnosis specifically was more common in cases with mixed and concomitant pathology.
4. Investigate the factors influencing missed and misdiagnosis of Lewy body disease in more depth, examining factors such as sex, specific co-occurring pathologies, and the neuropsychiatric symptoms reported over the follow-up period.

It was hypothesised that the presence of mixed and concomitant pathology would reduce the accuracy of study diagnoses in the BDR cohort. In addition, it was hypothesised that the presence of concomitant pathology in Lewy body disease would lead to greater rates of missed study diagnosis of DLB.

4.2 Methods

4.2.1 Case Selection

This study included 467 individuals clinically diagnosed with dementia from the Brains for Dementia Research neuropathology cohort. All participants were aged over 65 years at baseline and had undergone at minimum one ante-mortem clinical assessment, followed by a comprehensive neuropathological examination postmortem. Demographic variables included in the analyses were age at death, sex, years spent in full-time education, Index of Multiple Deprivation (IMD), and BDR study site. Descriptive statistics were used to summarise demographic and clinical features. Clinical variables included the Mini-Mental State Examination (MMSE) and the Neuropsychiatric Inventory (NPI).

Clinical diagnoses were assigned using all available BDR study records, including data from NHS medical records, research nurses and study partners. The final antemortem clinical study diagnosis recorded for each participant was used as the basis for comparison with eventual post-mortem neuropathological findings, which served as the diagnostic gold standard. Missing data was minimal for clinical variables. Listwise deletion was applied for cases with missing outcome data and complete cases analysis was used in regression models. The extent of missing data is reported for each variable. No imputation was performed.

4.2.2 Diagnostic Accuracy

To determine the accuracy of the study diagnosis, final recorded antemortem clinical diagnosis available from each participant's study records was mapped onto a corresponding neuropathological category to facilitate direct comparison. For example, cases clinically diagnosed as Alzheimer's disease were assessed against neuropathological confirmation of Alzheimer's disease, defined as NIA-AA High Alzheimer's disease neuropathological change. **Table *4.1*** outlines the definition of each clinical study diagnosis and their associated pathology group.

Table 4.1. Clinical Diagnosis and Associated Neuropathology: Classification of clinical study diagnoses alongside corresponding neuropathological groups. Neuropathological criteria serve as the reference standard for evaluating the accuracy of clinical diagnoses.

Clinical Study Diagnosis	Subtypes	Pathology Group	Pathological terms
Alzheimer's disease	Alzheimer's disease, posterior cortical atrophy, atypical Alzheimer's disease	Alzheimer's disease	NIA-AA High
Lewy body dementia	Dementia with Lewy bodies; Parkinson's disease dementia; Lewy body dementia	Lewy body disease	McKeith Limbic or neocortical; Braak 4-6
Vascular dementia		Cerebrovascular disease	VCING High
Frontotemporal dementias		Frontotemporal lobar degeneration	Presence of frontotemporal lobar degeneration and tau/TDP-43 inclusions
Mixed dementias	Any combination of the above	Mixed pathology	Any combination of the above

Cases were classified into one of four diagnostic groups, as outlined in **Table 4.2**, for each study diagnosis included. Group A represents correctly identified cases (true positives). Group B represents cases that are misdiagnosed as the disease in question (false positives). Group C represents missed cases (false negatives). Group D represents other dementia controls that do not have the study diagnosis or pathology related to the question (true negatives).

Table 4.2. Diagnostic Groups: Categorisation of cases based on fulfilment of clinical and pathological criteria. True positives (a) represent cases where both clinical and pathological criteria for diagnosis are met; false positives (b) have clinical but not pathological diagnosis; false negatives (c) lack clinical diagnosis but meet pathological criteria; and true negatives (d) meet neither.

	Pathological criteria fulfilled	Pathological criteria not fulfilled
Clinical criteria fulfilled	a. True Positive	b. False Positive
Clinical criteria not fulfilled	c. False Negative	d. True Negative

Sensitivity was defined as the proportion of true positives who were correctly identified as such, e.g., the percentage of patients with Lewy body disease who are clinically identified as having Lewy body dementia. Specificity was defined as the proportion of true negatives that were correctly identified, e.g., the percentage of patients without pathological AD who did not have a study diagnosis of AD. Positive predictive value represented the proportion of clinically diagnosed individuals who were pathologically confirmed, while negative predictive value indicated the proportion of individuals without a clinical diagnosis who also lacked relevant pathology.

Diagnostic accuracy metrics were calculated for each major diagnostic category, with additional subgroup analyses. For Lewy body disease, differences in accuracy according to sex, study site, co-occurring pathology, and presence of mixed versus pure pathology were explored. These analyses were conducted to identify factors that may influence the concordance between clinical and neuropathological diagnoses of Lewy body disease.

4.2.3 Linear Mixed Effects Modelling

Longitudinal cognitive function was assessed using Mini-Mental State Examination (MMSE) scores collected from antemortem clinical assessments. Two models were included with participants were grouped by clinical study diagnosis and postmortem neuropathology group. Linear mixed effects models were employed to estimate trajectories of cognitive decline over time, measured as annual changes in MMSE scores. Fixed effects included diagnosis group, age, education, while random intercepts accounted for individual variability. Differences in both the rate of decline and final MMSE score were compared to

highlight differences in trajectory between antemortem diagnosis and corresponding postmortem neuropathology. As linear mixed effects models are used extensively in Chapter 5, the methods are discussed in greater depth in Section 5.2.3.

4.2.4 Logistic Regression

To identify predictors of clinical misdiagnosis, Firth's penalised binary logistic regression was used. This statistical method was selected due to its suitability for datasets with rare events or small subgroups, as it addresses potential bias in maximum likelihood estimation and facilitates model convergence in situations where standard logistic regression may fail (Heinze and Schemper, 2002, Puhr et al., 2017, Maiti and Pradhan, 2009).

Two sets of regression models were developed to compare true positives to false negatives to investigate factors (e.g. co-occurring pathology and neuropsychiatric symptoms) associated with missed diagnosis specifically in Lewy body dementia. Covariates included in the first model were age at death, sex, education, and neuropathology variables. These included NIA-AA level of Alzheimer's disease neuropathological change, Braak Lewy body stage, presence of large subcortical infarcts (VCING 1), cerebral amyloid angiopathy (VCING 2), arteriolosclerosis (VCING 3), and LATE-NC. The second included 12 neuropsychiatric symptoms drawn from NPI subdomains across the follow-up period. If these symptoms had ever been reported, they were considered to be present. Covariates were selected based on theoretical relevance and prior literature.

Odds ratios (ORs) with 95% confidence intervals (CIs) were reported to indicate the strength and direction of associations between predictors and missed diagnosis. Statistical significance was defined as a p-value less than 0.05. Model fit was assessed using R^2 and Akaike Information Criterion (AIC), and diagnostic checks for multicollinearity and model convergence were performed for all models. Convergence was achieved in all analyses.

In addition to the main models, sensitivity analyses were conducted to explore the contribution of individual neuropathological measures and neuropsychiatric symptoms to diagnostic accuracy. These analyses were exploratory and aimed to determine if any associations remained once the definition of Lewy body disease has been reduced to only definite neocortical cases.

4.3 Results

The demographic and clinical characteristics of the 467 participants included in this analysis are summarised in **Table 4.3**. The mean age at death was 84.0 years (SD = 8.12), ranging from 65.2 to 104 years. The sample comprised 42.0% females and 58.0% males. Participants had an average of 12.1 years of education (SD = 3.14), with 10.5% missing education data. Socioeconomic status, assessed using the Index of Multiple Deprivation (IMD), had a median score of 2.00 on a scale from 1 (least deprived) to 5 (most deprived). Approximately one-third of participants belonged to the least deprived quintile, and 8.6% had missing IMD data. Participants were recruited from six BDR sites, with Oxford contributing the largest proportion (33.4%) and Bristol the smallest (9.6%). Missing data for BDR site was minimal (0.4%).

Table 4.3. **Characteristics of the Study Cohort (N = 467):** Summary of demographic, clinical, and diagnostic variables for participants included in the current analysis.

		Cases (N = 467)
Age (at death)	Mean (SD)	84.0 (8.12)
	Median [Min, Max]	84.0 [65.2, 104]
Sex	Female	196 (42.0%)
	Male	271 (58.0%)
Education	Mean (SD)	12.1 (3.14)
	Median [Min, Max]	11.0 [0, 24.0]
	Missing	*49 (10.5%)*
IMD	Median [Min, Max]	2.00 [1.00, 5.00]
	Quintile 1	154 (33.0%)
	Quintile 2	120 (25.7%)
	Quintile 3	70 (15.0%)
	Quintile 4	38 (8.1%)
	Quintile 5	45 (9.6%)
	Missing	*40 (8.6%)*
BDR Site	Bristol	45 (9.6%)
	Cardiff	55 (11.8%)
	London	63 (13.5%)

Manchester	76 (16.3%)
Newcastle	70 (15.0%)
Oxford	156 (33.4%)
Missing	*2 (0.4%)*

4.3.1 Study Diagnosis and Neuropathology

The most common clinical study diagnosis was Alzheimer's disease, which was reported in 266 (32.7%) participants. In those with dementia, clinical AD was reported in 56.6% of females (N=111) and 49.4% of males (N=134). Mixed dementia was the second most frequent diagnosis, reported in 100 (12.3%) participants, with similar frequencies in females (19.4%, N=38) and males (19.2%, N=52) with dementia. Within the mixed dementia group, the majority of cases reported a suspected combination of Alzheimer's disease and vascular dementia. A study diagnosis of vascular dementia was more frequently reported in males (12.5%, N = 34) than females (5.6%, N = 11) with dementia. Less prevalent diagnoses included frontotemporal dementia (3.3%, N=27) and dementia with Lewy bodies (2.7%, N=22), each accounting for under 10% of dementia cases.

A total of 34 participants (4.2%) had a final diagnosis of mild cognitive impairment (MCI) and died before receiving an updated assessment. Additionally, 30 participants (3.7%) received a diagnosis of unspecified dementia, despite being enrolled in a dementia study. A further 283 individuals (34.8%) had no recorded clinical study diagnosis, including 15.7% (N = 73) of participants with clinical dementia (either as unspecified dementia or no diagnosis). As expected, the majority of participants without dementia had no formal study diagnosis (N=268; 77.5%), though a small number were still recorded as having AD or other dementia subtypes (**Table 4.4**).

***Table 4.4*. Clinical Study Diagnosis:** Prevalence of clinical diagnoses recorded at final assessment, stratified by sex and dementia status. Values are presented as counts and percentages within each subgroup. Clinical diagnoses include Alzheimer's disease (AD), dementia with Lewy bodies (DLB), vascular dementia (VaD), frontotemporal dementia (FTD), mixed dementia (diagnoses involving features of more than one syndrome), mild cognitive impairment (MCI), unspecified dementia, and cases with no formal clinical diagnosis.

	Dementia (N=467)		**No Dementia (N=346)**		
Clinical Groups	**Female (N=196)**	**Male (N=271)**	**Female (N=187)**	**Male (N=159)**	**Total (N=813)**
Alzheimer's disease	111 (56.6%)	134 (49.4%)	11 (5.9%)	10 (6.3%)	266 (32.7%)
Dementia with Lewy bodies	6 (3.1%)	14 (5.2%)	1 (0.5%)	1 (0.6%)	22 (2.7%)
Vascular dementia	11 (5.6%)	34 (12.5%)	4 (2.1%)	2 (1.3%)	51 (6.3%)
Frontotemporal dementia	8 (4.1%)	18 (6.6%)	0 (0%)	1 (0.6%)	27 (3.3%)
Unspecified dementia	9 (4.6%)	10 (3.7%)	4 (2.1%)	7 (4.4%)	30 (3.7%)
Mixed dementia	38 (19.4%)	52 (19.2%)	5 (2.7%)	5 (3.1%)	100 (12.3%)
Mild cognitive impairment	5 (2.6%)	2 (0.7%)	14 (7.5%)	13 (8.2%)	34 (4.2%)
No diagnosis	8 (4.1%)	7 (2.6%)	148 (79.1%)	120 (75.5%)	283 (34.8%)

In contrast to study diagnosis, the most frequent pathological group reported in dementia cases was mixed pathology, meaning that cases had fulfilled the criteria for at least two neuropathological diagnoses at autopsy. Mixed pathology accounted for 89 females (45.4%) and 116 males (42.8%) with dementia. Alzheimer's disease was the second most common neuropathology group, accounting for 20.9% of females (N = 41) and 21.4% of males (N = 58) with dementia. Approximately 15% of dementia cases (N = 70) and over 65% of cases without dementia (N = 232) did not fulfil the criteria for any neuropathological diagnosis. Cerebrovascular disease (N = 25, 3.1%) was less common than would be expected given the

prevalence of vascular dementia study diagnoses. Further frequencies of neuropathology groups in males and females with and without dementia are outlined in **Table 4.5**.

Table 4.5. Neuropathology Groups: Prevalence of primary neuropathological diagnoses stratified by sex and dementia status at final assessment. Values are presented as counts and percentages within each subgroup. Mixed pathology refers to the presence of more than one primary neuropathological diagnosis. Low pathology controls are defined as individuals without a major neurodegenerative or cerebrovascular pathology.

	Dementia (N=467)		**No Dementia (N=346)**		
Pathology Groups	**Female (N=196)**	**Male (N=271)**	**Female (N=187)**	**Male (N=159)**	**Total (N=813)**
Alzheimer's disease	41 (20.9%)	58 (21.4%)	12 (6.4%)	5 (3.1%)	116 (14.3%)
Lewy body disease	8 (4.1%)	24 (8.9%)	9 (4.8%)	5 (3.1%)	46 (5.7%)
Cerebrovascular disease	4 (2.0%)	3 (1.1%)	10 (5.3%)	8 (5.0%)	25 (3.1%)
Frontotemporal lobar degeneration	17 (8.7%)	12 (4.4%)	6 (3.2%)	9 (5.7%)	44 (5.4%)
LATE-NC	11 (5.6%)	17 (6.3%)	10 (5.3%)	17 (10.7%)	55 (6.8%)
Mixed pathology	89 (45.4%)	116 (42.8%)	13 (7.0%)	10 (6.3%)	228 (28.0%)
Low pathology controls	26 (13.3%)	41 (15.1%)	127 (67.9%)	105 (66.0%)	299 (36.8%)

Although Lewy body disease was present in 5.7% of the cohort, Lewy body dementia was only recorded in 2.7% of the cohort. Similarly, mixed pathology was reported in 28% of participants but mixed dementia was reported in only 12.3%. In contrast, dementia due to Alzheimer's disease was recorded in 32.7% of participants but at autopsy only 14.3% of participants had Alzheimer's disease as the primary pathology.

4.3.2 Cognitive trajectories of clinical and pathological diagnoses

When comparing average paths of cognitive decline of cases grouped by study diagnosis and their corresponding neuropathology groups, there are some noticeable differences in both

rate of decline and cognitive function at the final clinical assessment prior to death. The observed differences in cognitive trajectories continue to reflect the poor concordance between study diagnosis based on clinical presentation and the underlying neuropathologies reported at autopsy. These analyses are subsequently reported in greater detail in Chapter 5.

For example, a study diagnosis of Alzheimer's disease was associated with fast decline (1.96-point reduction in MMSE each year), and a large reduction in proximal MMSE score (19.9 points), compared to cognitively healthy controls. Similarly, Alzheimer's disease pathology was associated with fast decline (1.23-point reduction in MMSE each year) and a large reduction in final MMSE score (13.6). However, both rate and final cognitive score were less severe in the AD pathology group than would be expected based purely on the clinical AD group.

Furthermore, clinical Lewy body dementia was associated with the fastest rate of decline (2.66 MMSE points per year) and a significant reduction in proximal MMSE score (15.7), compared to controls. In contrast, postmortem Lewy body disease was associated with a moderate rate of decline (0.96 points per year) and a significantly smaller reduction in proximal MMSE score compared to low pathology controls.

The greatest differences in this cohort were seen when comparing clinical vascular dementia to postmortem cerebrovascular disease. While vascular dementia was associated with fast decline (1.64 points per year) and a significant reduction in final MMSE score (14.0), cerebrovascular disease was not associated with any significant change in trajectory using MMSE scores.

A study diagnosis of mixed dementia was associated with fast decline (1.49-point reduction in MMSE each year) and a large reduction in proximal MMSE score (17.4 points), compared to controls. Mixed pathology was also associated with fast decline (2.16-point reduction in MMSE each year) and a similar reduction in proximal MMSE score (19.7). The difference indicates that even cases with the most severe clinical presentation may not be diagnosed accurately during life.

Results for this analysis are reported in the Appendix.

4.3.3 Concordance between study diagnosis and neuropathology

The majority of study diagnoses provided in the Brains for Dementia Research cohort did not match the predominant neuropathology reported at autopsy. Although there are some study diagnoses (i.e. mild cognitive impairment, unspecified dementia) that do not have a corresponding neuropathology type, and vice versa (i.e. LATE), only 147 individuals (excluding controls) had a study diagnosis that fully matched the pathology observed at autopsy. Others showed partial matching between study diagnosis and neuropathology, but this did not negate the clear discrepancy.

Diagnostic accuracy can be viewed from two different perspectives. The first addresses how well neuropathology corresponds with the study diagnosis recorded during follow up. The majority of those with a study diagnosis of Alzheimer's disease did not have a primary neuropathological diagnosis of Alzheimer's disease at autopsy (67.7%). A large proportion (35%) of those with a study diagnosis of AD were partial matches indicating mixed pathology with Alzheimer's disease as a constituent part. Similarly, the majority of those with a study diagnosis of vascular dementia did not have cerebrovascular disease post-mortem (83.4%). In contrast to AD, the majority of these were not classified as cerebrovascular disease or mixed pathology with a cerebrovascular disease component. Clinicopathological concordance from a clinical perspective is summarised in **Table 4.6**.

Table 4.6. Clinicopathological concordance: Concordance between clinical study diagnosis and primary neuropathological findings, presented from a clinical perspective. A full match indicates that the clinical diagnosis was supported by corresponding neuropathological criteria. A partial match indicates partial pathological support for the clinical diagnosis (e.g., presence of one but not all expected pathologies). No match indicates absence of expected pathological findings for the given clinical diagnosis. Mixed dementia and control groups were not evaluated for partial matches due to heterogeneity and absence of a defined pathological target, respectively. Values are presented as counts and percentages within each clinical diagnosis group.

Clinical Diagnosis	Full match with neuropathology		Partial match with neuropathology		No match with neuropathology		Total number of cases
Alzheimer's disease	73	(27.4%)	110	(41.4%)	83	(31.2%)	266
Lewy body dementia	10	(45.5%)	8	(36.4%)	4	(18.2%)	22
Frontotemporal dementia	12	(44.4%)	2	(7.4%)	13	(48.1%)	27
Vascular dementia	4	(7.8%)	5	(9.8%)	42	(83.4%)	51
Mixed dementia	48	(48.0%)	--		52	(52.0%)	100
Controls	212	(74.9%)	--		71	(25.1%)	283

Approaching the same data from a neuropathology perspective (**Table 4.7**), the majority of pure AD cases had reported a study diagnosis of Alzheimer's disease either as AD or mixed dementia. In contrast, the majority of those with Lewy body disease (65.2%) or cerebrovascular disease (81.5%) had not reported a study diagnosis of Lewy body dementia or vascular dementia respectively. Similarly, those with mixed pathology at autopsy were unlikely to have a study diagnosis of mixed dementia. Conversely, those with low pathology were more likely to be grouped as controls during longitudinal follow up.

Table 4.7. **Clinicopathological concordance**: Concordance between primary neuropathological diagnoses and clinical study diagnoses, presented from a neuropathological perspective. A full match indicates that the neuropathological diagnosis was correctly identified clinically. A partial match indicates that the clinical diagnosis captured one component of the neuropathology (e.g., one pathology in a mixed case). No match indicates the absence of a corresponding clinical diagnosis. Mixed pathology and low pathology controls were not assessed for partial matches due to heterogeneity and the absence of specific expected clinical correlates. Values are presented as counts and percentages within each pathology group.

Pathology Group	**Full match with clinical diagnosis**		**Partial match with clinical diagnosis**		**No match with clinical diagnosis**		**Total number of cases**
Alzheimer's disease	73	(64.6%)	14	(12.4%)	26	(23.0%)	113
Lewy body disease	10	(21.7%)	6	(13.0%)	30	(65.2%)	46
Frontotemporal lobar degeneration	12	(50.0%)	1	(4.2%)	11	(45.8%)	24
Cerebrovascular disease	4	(14.8%)	1	(3.7%)	22	(81.5%)	27
Mixed pathology	48	(20.8%)	--		183	(79.2%)	231
Low pathology controls	212	(72.6%)	--		80	(27.4%)	292

In the dementia-only sub-cohort, the majority of study diagnoses provided in the Brains for Dementia Research cohort do not match the predominant neuropathology reported at autopsy, as illustrated in **Figure 4.1**. A total of four hundred and sixty-seven participants met the inclusion criteria.

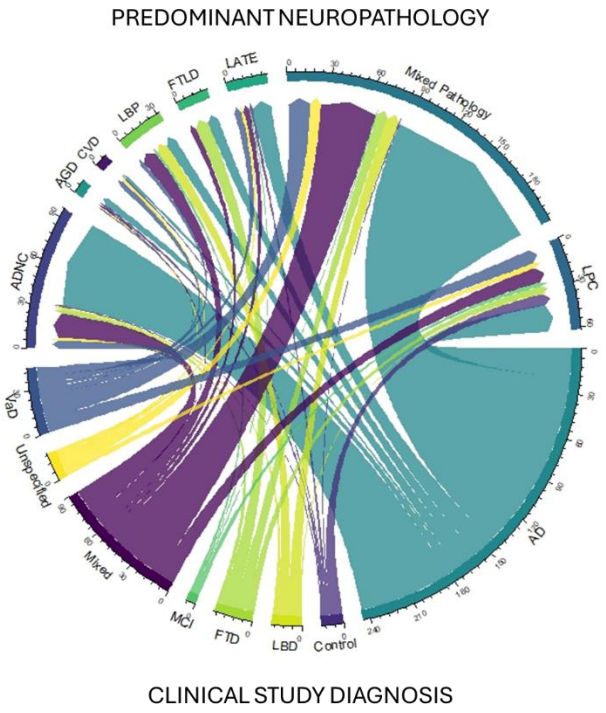

***Figure 4.1*. Comparison of Clinical Study Diagnosis and Predominant Neuropathology:** Chord diagram illustrating the distribution and correspondence between clinical study diagnoses and the predominant neuropathological findings at autopsy across all dementia cases. This figure highlights concordance and discrepancies between ante-mortem clinical assessments and post-mortem pathological confirmation.

Of the two hundred and sixty-six autopsy-confirmed Alzheimer's disease cases, two hundred and seventeen (81.6%) had a study diagnosis indicating Alzheimer's disease. One hundred and five additional people had a study diagnosis of Alzheimer's disease but did not have high Alzheimer's disease neuropathological change. While Alzheimer's disease accounted for the majority of study diagnoses, mixed pathology was present for nearly half of all cases at autopsy.

As a result, sensitivity for Alzheimer's disease was the highest (81.4%), while specificity for Alzheimer's disease was the lowest of the four study diagnoses included (49.2%). These figures indicate that while Alzheimer's disease is common there is an overreliance on Alzheimer's disease as a study diagnosis in this cohort. Conversely, sensitivity for vascular dementia was low at 50.0% and specificity was moderately high at 79.8% indicating overdiagnosis of vascular dementia in this cohort. Diagnostic accuracy is reported in **Table 4.8**.

***Table 4.8*. Diagnostic Accuracy:** Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical study diagnoses compared to neuropathological confirmation for Alzheimer's disease, Lewy body dementia, vascular dementia, and frontotemporal dementia. Note that some cases are classified in multiple diagnostic groups (e.g., AD/DLB), which may affect counts.

	N	Sensitivity	Specificity	PPV	NPV
Alzheimer's disease	266	81.4%	49.2%	67.8%	66.9%
Lewy body dementia	144	18.8%	97.5%	77.1%	72.9%
Vascular dementia	36	50.0%	79.8%	15.4%	95.6%
Frontotemporal dementia	48	33.3%	94.5%	41.0%	92.5%

Specificity for both dementia with Lewy bodies and frontotemporal dementias (as a cumulative group) was very high, at 97.6% and 94.5% respectively, indicating minimal misdiagnosis. In contrast, sensitivity for both dementia with Lewy bodies (18.8%) and frontotemporal dementia (33.3%) was significantly lower, indicating that a significant proportion of those with these pathologies did not report a corresponding study diagnosis and were missed clinically.

As the sensitivity for Lewy body disease was particularly low at 18.8%, a more in-depth analysis of these cases was undertaken examining factors influencing diagnosis accuracy.

4.3.4 Under-recognition of Lewy body disease

Of the 467 dementia cases, 144 participants had autopsy-confirmed Lewy body disease, but only 27 (18.8%) of these cases had a study diagnosis of Lewy body dementia. Participants with a missed diagnosis represented 81.3% of those with Lewy body disease. A further 8 participants reported a study diagnosis of Lewy body dementia but did not have Lewy body disease at autopsy. These misdiagnosed cases represented only 2.4% of dementia cases without limbic/neocortical Lewy body disease. Therefore, while study diagnosis of Lewy body dementia had high specificity for presence of Lewy body disease at autopsy (97.6% specificity), sensitivity was poor at 18.8%.

Of one-hundred and ninety-six females with dementia, 49 had autopsy-confirmed Lewy body disease, but only 6 of these cases had a study diagnosis of Lewy body dementia. In addition to this, two females had a study diagnosis of Lewy body dementia but did not have Lewy body disease at autopsy. In comparison, of the two hundred and seventy-one males with dementia, 95 had autopsy-confirmed Lewy body disease, but only 21 of these cases had a recorded study diagnosis of Lewy body dementia. A further 6 males had a recorded study diagnosis of Lewy body dementia with no Lewy body disease reported at autopsy. As a result, sensitivity for Lewy body disease in males (22.1%) was almost ten-percent higher than in females (12.2%). In contrast specificity was slightly higher in females (98.6%) than males (96.6%).

Sensitivity for Lewy body disease varied between BDR site, ranging between 12.5% to 28.6%. As the prevalence of Lewy body disease and clinical Lewy body dementia varied between centres, it is possible that geographical factors may influence the likelihood of an individual receiving a diagnosis of Lewy body disease during life. The highest sensitivities were seen in regions with specialist centres for Lewy body disease. However, these differences were marginal, and sample size was small.

In contrast, Lewy body disease cases with an additional pathology present were significantly less likely (11.6%) to have full or partial concordance with Lewy body disease than those with non-mixed or "pure" pathology (43.8%). Of the 112 mixed LBD cases, only 13 had received a study diagnosis of Lewy body disease. Sensitivity for Lewy body disease had an inverse relationship with level of Alzheimer's disease pathology. LBD cases with high ADNC were significantly under-recognised with 88% being missed clinically compared with 56.3% of 'pure' LBD cases (**Table 4.9**). Of the 111 clinically unrecognised Lewy body disease cases, seventy-four (67%) had high Alzheimer-type neuropathologic change and a further twenty-seven had intermediate Alzheimer-type neuropathological change. The greatest accuracy in clinical recognition was seen in LBD cases without substantial ADNC.

Table 4.9. Diagnostic Accuracy of Clinical Diagnosis for Lewy Body Disease: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical diagnosis for Lewy body disease (LBD) stratified by sex, study location, presence of co-pathology (mixed vs. non-mixed), Alzheimer's disease neuropathological change (ADNC) level, vascular pathology (VCING rating), and presence of limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC). True positive, false negative, false positive, and true negative counts are reported for each subgroup. Performance metrics indicate the diagnostic accuracy of clinical assessments compared to neuropathological findings.

Variable	Group	True positive	False negative	False positive	True negative	Sensitivity	Specificity	PPV	NPV
Overall	Dementia	27	117	8	315	18.8%	97.5%	77.1%	72.9%
Sex	Females	6	43	2	145	12.2%	98.6%	75.0%	77.1%
	Males	21	74	6	170	22.1%	96.6%	77.8%	69.7%
Location	Bristol	2	14	1	28	12.5%	96.6%	66.7%	66.7%
	Cardiff	2	11	0	42	15.4%	100%	100%	79.2%
	London	3	20	1	39	13.0%	97.5%	75.0%	66.1%
	Manchester	3	15	2	56	16.7%	96.6%	60.0%	78.9%
	Newcastle	6	15	3	46	28.6%	93.9%	66.7%	75.4%
	Oxford	11	42	1	102	20.8%	99.0%	91.7%	70.8%
Co-pathology	Mixed	13	99	2	91	11.6%	97.8%	86.7%	47.9%
	Non-mixed	14	18	6	224	43.8%	97.4%	70.0%	92.6%
ADNC Level	High ADNC	8	74	5	134	9.8%	96.4%	61.5%	64.4%

	Intermediate ADNC	8	27	2	74	22.9%	97.4%	80.0%	73.3%
	Low/No ADNC	9	10	0	61	47.4%	100%	100.0%	85.9%
VCING Rating	High	0	11	0	21	0.0%	100%	0.0%	65.6%
	Moderate	3	16	1	43	15.8%	97.7%	75.0%	72.9%
	Low	18	73	5	185	19.8%	97.4%	78.3%	71.7%
LATE-NC	Present	8	60	3	114	11.8%	97.4%	72.7%	65.5%
	Absent	19	57	5	199	25.0%	97.5%	79.2%	77.7%

Similarly, sensitivity for Lewy body disease was inversely proportional to VCING rating, ranging from 0% to 19.8%, with the highest accuracy of study diagnosis seen in those with low VCING rating. Furthermore, sensitivity for Lewy body disease in the presence of LATE-NC pathology was less than half that seen in the absence of LATE-NC pathology. Together these findings suggest that mixed pathology may influence the accuracy of study diagnosis.

Multivariable logistic regression showed that Lewy body disease with co-occurring high Alzheimer's type neuropathological change were significantly more likely to have their diagnosis of Lewy body dementia missed clinically (OR = 22.44, [4.76, 106]). In addition to this, intermediate ADNC was also associated with an increased likelihood of missed diagnosis (OR = 7.59, [1.59, 36.3]). Sensitivity analyses of specific staged changes indicated that increasing Braak NFT stage was specifically associated with missed clinical diagnosis of Lewy body dementia (OR = 2.47 [1.24, 4.92]). This association was not observed for Thal phase or CERAD score. There was also no clear association between accuracy of study diagnosis and the presence of vascular features, including infarcts, CAA and arteriolosclerosis, nor was there an association with TDP-43 (**Figure 4.2**).

In terms of neuropsychiatric symptoms, the most frequently reported clinical symptoms were hallucinations (55.6%), agitation (44.4%) and depression (44.4%). Hallucinations were more common in correctly identified DLB cases than missed DLB cases. In contrast, the most frequently reported neuropsychiatric features in missed cases were apathy (49.6%), agitation (44.4), and aberrant motor behaviour (40.2%). A second multivariate binomial regression indicated that Lewy body disease was significantly less likely to be missed clinically in those with hallucinations reported during their final assessment (OR = 0.29, 95% CI [0.10, 0.79]). No other neuropsychiatric symptoms were significantly associated with a missed study diagnosis of Lewy body dementia (**Figure 4.3**).

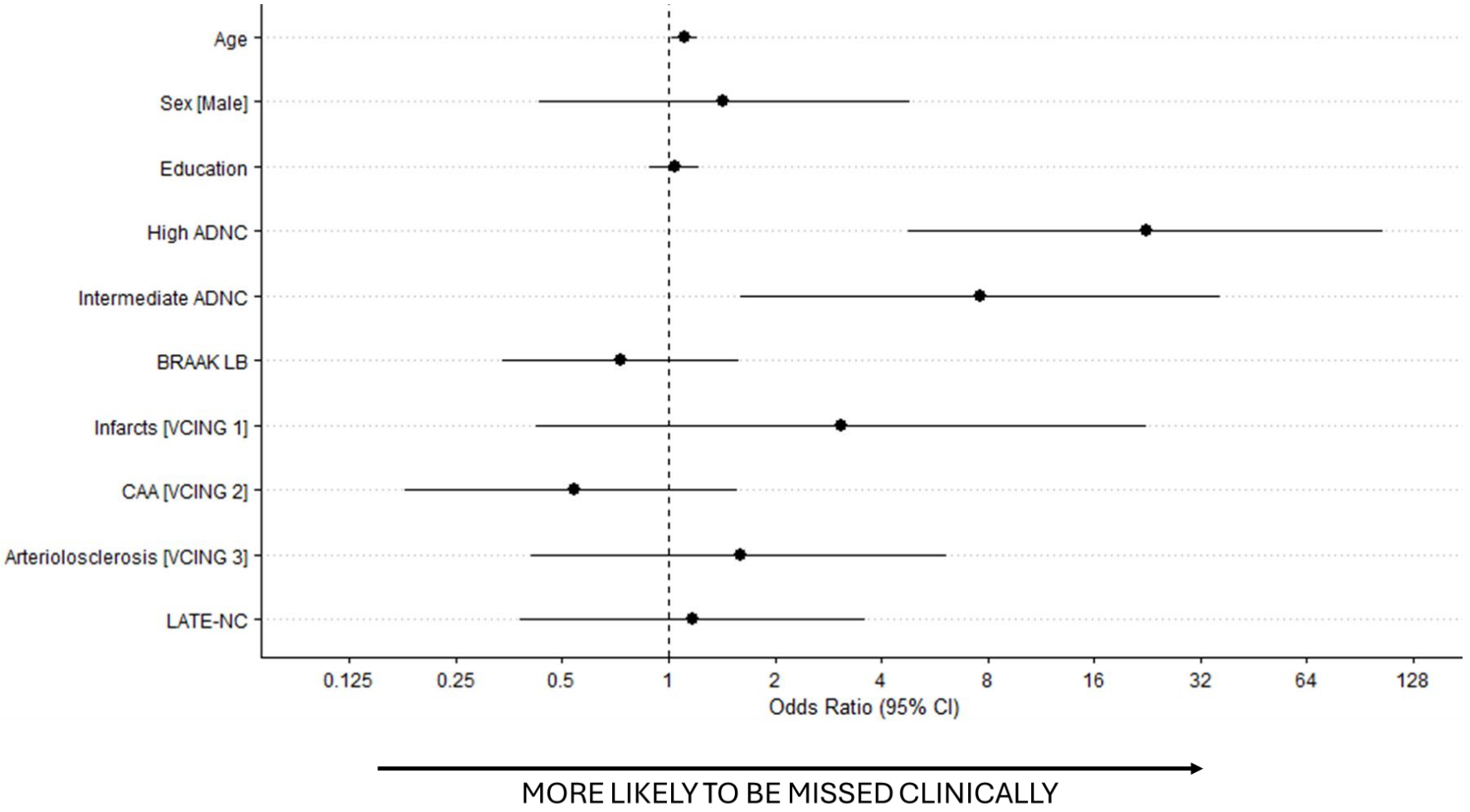

***Figure 4.2*. Neuropathological Predictors of Missed Diagnosis**: Results from a multivariable logistic regression model assessing the association between neuropathological variables and the likelihood of a missed clinical diagnosis. The model adjusts for potential confounders including age at death, sex, and education level. To address issues of small sample size and separation, Firth's penalized likelihood correction was applied. Odds ratios with 95% confidence intervals are presented for each neuropathological predictor.

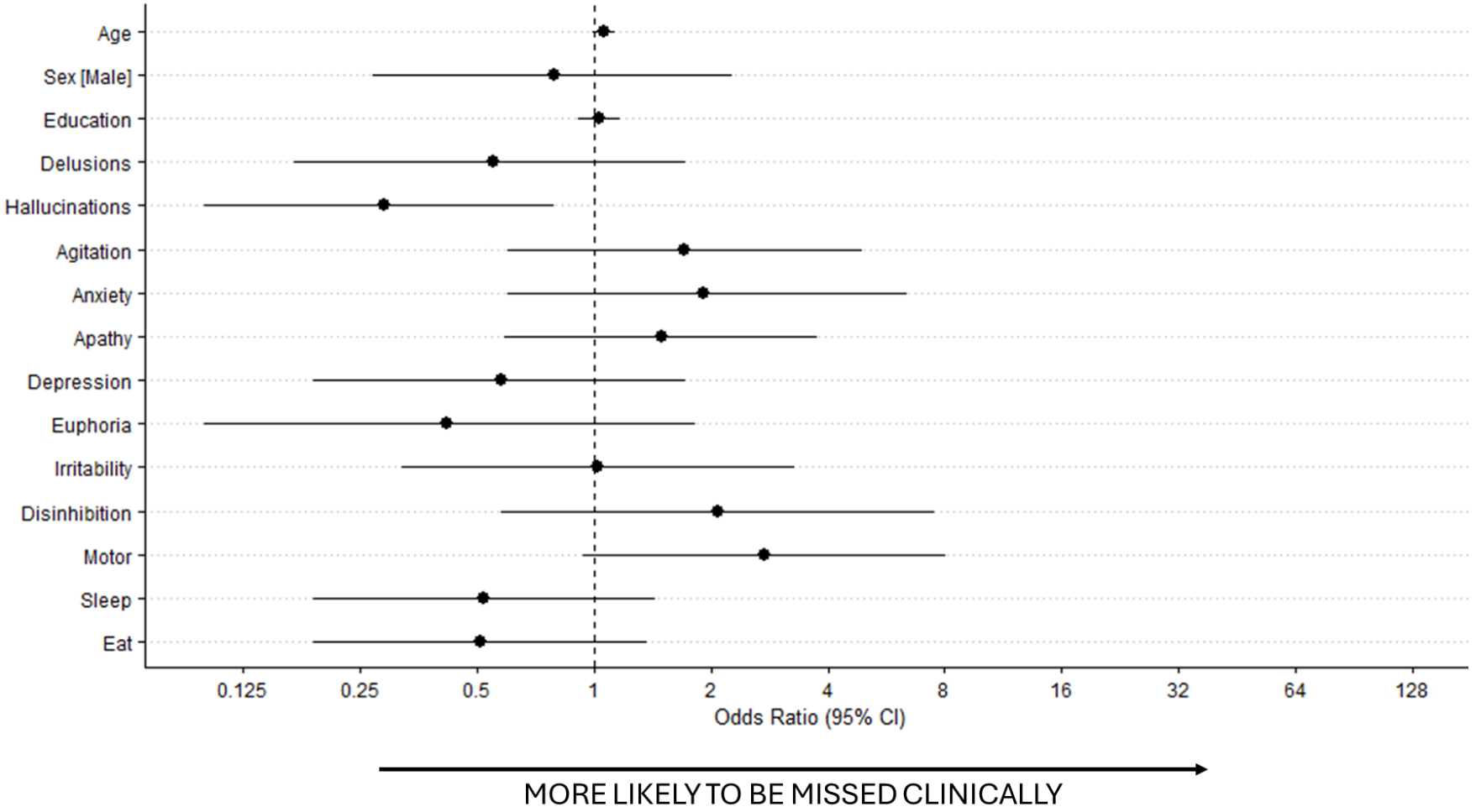

***Figure 4.3*. Neuropsychiatric Predictors of Missed diagnosis**: Multivariable logistic regression analysis evaluating neuropsychiatric symptoms as predictors of missed clinical diagnosis. The model adjusts for age at death, sex, and education level, and incorporates Firth's penalized likelihood correction to account for small sample bias and potential data separation. Odds ratios with 95% confidence intervals are shown for each neuropsychiatric predictor.

4.3.5 Sensitivity Analysis: Neocortical Lewy body disease

A sensitivity analysis was conducted after reducing the definition of Lewy body disease to only neocortical regions to determine if the low sensitivity could be due to preclinical disease states being more difficult to identify. It was theorised that the low diagnostic sensitivity observed could potentially be explained if the misdiagnosed dementia cases had died with limbic Lewy body disease prior to the development of neocortical disease. Consequently, these individuals could have been grouped as missed cases in the original models, despite having moderately widespread neuropathology, due to insufficient clinical features of Lewy body dementia to have warranted a study diagnosis.

A sensitivity analysis was therefore conducted where neocortical cases of Lewy body disease were considered sufficient for pathological confirmation, with all other conditions remaining the same. The exclusion of limbic Lewy body disease cases did not meaningfully change the results of these models. Sensitivity for neocortical Lewy body disease was slightly higher than limbic/neocortical Lewy body disease but remained relatively poor (22.4%). Similar results were seen across all variables included in the initial analysis (**Table 4.10**). Sensitivity for neocortical LBD in females remained approximately half that seen males. In addition, the association between high Alzheimer-type neuropathological change and missed Lewy body dementia remained (OR = 20.7 [3.58, 120]), as did the association between Braak NFT stage and missed LBD (OR = 2.74 [1.25, 6.02]).

The most frequently reported neuropsychiatric features at final assessment in correctly identified cases of neocortical Lewy body disease were hallucinations (59.1%), depression (45.5%), appetite and eating disorders (45.5%) and agitation (40.9%). In contrast the most frequently reported neuropsychiatric features in missed cases of neocortical Lewy body disease were apathy (51.2%), agitation (47.6%), and aberrant motor behaviour (43.9%). Hallucinations were present in 59.1% of correctly identified DLB cases, compared to 26.8% of missed DLB cases. As in the original analysis, hallucinations remained associated with a reduced likelihood of missed diagnosis (OR = 0.23 [0.06, 0.88]). In contrast, anxiety was associated with increased likelihood of missed diagnosis in neocortical Lewy body disease (OR = 6.40 [1.37, 30.0]) but was not associated with any change in odds of being missed in the original cohort.

Table 4.10. Diagnostic Accuracy of Clinical Diagnosis for *Neocortical* Lewy Body Disease: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of clinical diagnosis for *neocortical* Lewy body disease (LBD) stratified by sex, study location, presence of co-pathology (mixed vs. non-mixed), Alzheimer's disease neuropathological change (ADNC) level, vascular pathology (VCING rating), and presence of limbic-predominant age-related TDP-43 encephalopathy neuropathological change (LATE-NC). True positive, false negative, false positive, and true negative counts are reported for each subgroup. Performance metrics indicate the diagnostic accuracy of clinical assessments compared to neuropathological findings.

Variable		True positive	False negative	False positive	True negative	Sensitivity	Specificity	PPV	NPV
Overall	Dementia	22	82	13	350	21.2%	96.4%	62.9%	81.0%
Sex	Females	5	33	3	155	13.3%	98.1%	62.5%	82.4%
	Males	17	49	10	195	25.8%	95.1%	63.0%	79.9%
Location	Bristol	1	9	2	33	10.0%	94.3%	33.3%	78.6%
	Cardiff	0	4	2	49	0.0%	96.1%	0.0%	92.5%
	London	3	15	1	45	16.7%	97.8%	75.0%	75.0%
	Manchester	3	8	2	63	27.3%	96.9%	60.0%	88.7%
	Newcastle	5	11	4	50	31.3%	92.6%	55.6%	82.0%
	Oxford	10	35	2	110	22.2%	98.2%	83.3%	75.9%
Co-pathology	Mixed	7	62	7	247	10.1%	97.2%	50.0%	79.9%
	Non-mixed	15	20	6	102	42.9%	94.4%	71.4%	83.6%

ADNC Level	High ADNC	7	55	6	153	11.3%	96.2%	53.8%	73.6%
	Intermediate ADNC	8	20	2	81	28.6%	97.6%	80.0%	80.2%
	Low/No ADNC	6	5	3	67	54.5%	95.7%	66.7%	93.1%
VCING Rating	High	0	7	0	25	0.0%	100%	0%	78.1%
	Moderate	2	11	2	48	15.4%	96.0%	50.0%	81.4%
	Low	16	54	7	204	22.9%	96.7%	69.6%	79.1%
LATE-NC	Present	6	43	5	131	12.2%	96.3%	54.5%	75.3%
	Absent	16	39	8	219	29.0%	96.5%	66.7%	84.9%

4.4 Summary

In this BDR cohort, reported study diagnosis and autopsy-confirmed neuropathology were frequently mismatched. This was further complicated by the widespread presence of mixed and concomitant pathology across all dementia subtypes. There were significant discrepancies between study diagnosis and postmortem neuropathological findings in this cohort. Both Alzheimer's disease (AD) and vascular dementia (VaD) were overrepresented as study diagnoses when compared to postmortem neuropathology in this cohort. In contrast, Lewy body disease and mixed pathology were under-recognised clinically. Sex, BDR site, and concurrent pathology all influenced the likelihood of missed diagnosis in Lewy body disease. More specifically, neocortical Lewy body disease was severely under-recognised in the presence of co-occurring Alzheimer's disease pathology. This study also demonstrated clinical under-recognition of Lewy body dementia, particularly among females and in the presence of additional neuropathologies. Diagnostic accuracy varied between visit centres but remained low. Mixed and concomitant pathology in Lewy body disease was consistently associated with reduced diagnostic accuracy in the cohort.

This chapter emphasises the current discordance seen in many clinicopathological studies of dementia and highlights the need to further examine the relationship between mixed pathology and clinical presentation of dementia to improve the efficacy of clinical diagnostic criteria. The overrepresentation of Alzheimer's disease and vascular dementia as clinical diagnoses in this cohort suggest that the diagnostic criteria may favour these conditions. Clinicians may be predisposed to diagnosing these more familiar and well-established forms of dementia, particularly in cases where cognitive symptoms like memory loss are prominent. This could reflect a tendency to default to the most well-known conditions when the diagnostic picture is unclear. Alternatively, it could indicate a limitation in available diagnostic tools or methods that blur the distinctions between these types of dementia and other forms of dementia such as Lewy body dementia.

The clinical under-recognition of Lewy body disease, particularly in females and those with mixed pathologies, suggests that there may be sex-specific differences in how LBD presents or how clinicians interpret symptoms. For example, clinicians may be less likely to suspect LBD in women due to gender-based diagnostic biases or because LBD might manifest differently across sexes. Moreover, when LBD is accompanied by other neuropathologies, core features (such as visual hallucinations or motor symptoms) may be masked or

interpreted as part of another dementia, such as Alzheimer's disease. This suggests a fundamental challenge in recognising mixed and atypical dementia presentations in clinical settings, which could lead to system underdiagnosis.

The variation in diagnostic accuracy across different centres likely reflects differences in clinical expertise, diagnostic protocols, or access to specialised diagnostic tools, such as neuroimaging or biomarkers. This inconsistency suggests that some centres may have more advanced diagnostic capabilities, but even so, the overall low accuracy indicates a broader, systemic problem in diagnosing dementia across clinical settings. It points to a lack of standardised, reliable diagnostic methods that can be consistently applied across diverse clinical environments, potentially leaving room for subjective interpretation and error.

The association between mixed pathology and lower diagnostic accuracy highlights the complexity of dementia as a multifactorial and overlapping condition. When Lewy body disease coexists with other pathologies, such as Alzheimer's disease or vascular disease, the clinical symptoms may no longer fit neatly into one diagnostic category. This suggests that current diagnostic frameworks are too rigid to account for the reality of mixed or hybrid dementias, where multiple underlying diseases interact to produce complex symptom profiles. The reduced accuracy in such cases points to the need for a more nuanced approach that can better capture these overlapping pathologies, as opposed to trying to fit patients into single, mutually exclusive diagnostic categories.

Diagnostic accuracy studies are crucial for evaluating diagnostic tests, but there are several limitations that can affect their reliability. Selection bias can occur if participants are not representative of the general population, especially when drawn from specialised clinics. Small sample sizes may yield unreliable estimates of sensitivity and specificity, while the accuracy of tests is often compared to reference standards that may themselves have limitations. The performance of a diagnostic test can vary based on disease prevalence, and subjective interpretation of results can lead to inconsistencies among clinicians. Additionally, studies may not adequately reflect real-world clinical settings, lacking long-term follow-up to confirm diagnoses. overfitting of models on specific datasets can lead to poor performance on new data, and the choice of diagnostic thresholds can influence outcomes. Furthermore, advances in technology and limited reporting standards may diminish the relevance and comparability of findings. These limitations highlight the need for careful appraisal of diagnostic accuracy studies before applying their results in clinical practice.

These findings reflect deeper challenges in dementia diagnosis, revealing that the current clinical approaches may oversimplify the complexity of dementia types. The overdiagnosis of familiar conditions like Alzheimer's disease and the under-recognition of more complex or mixed pathologies (such as LBD, particularly in women) point to inherent limitations in diagnostic methods. Variability between centres further suggests that dementia diagnosis may be influenced by local factors such as expertise, resources, or clinical habits, underscoring the need for more standardised and nuanced diagnostic tools that can capture the full complexity of dementia.

Chapter 5. Trajectories of Cognitive Decline in Mixed and Concomitant Neuropathology

5.1 Background

While clinical dementias are heterogeneous, cognitive decline across multiple cognitive subdomains is a fundamental feature of all forms of dementia. Cognitive reserve is thought to be individual-specific resilience to pathology burden that accounts for the differences in susceptibility to age-related brain changes and neuropathology, with some individuals able to withstand a higher pathology burden before exhibiting a decline in cognitive function (Stern, 2012). Many factors are thought to influence cognitive reserve, such as age, education, socioeconomic status and lifestyle factors (Li et al., 2021, Evans et al., 2018). Several studies have suggested that the co-occurrence of vascular and neurodegenerative pathologies may lower cognitive thresholds and that the timing and rate of decline are influenced by the combination of pathologies present (Nelson et al., 2021).

Although numerous neuropathological studies have reported the high prevalence of mixed pathology in dementia in the ageing population, the effect of co-occurring multiple pathologies on cognitive impairment is not yet fully characterised. A common cause of cognitive impairment in the ageing population is mixed pathology; more specifically, Alzheimer's disease pathology with concomitant Lewy body disease, cerebrovascular disease, or TDP-43 inclusions (Alafuzoff and Libard, 2020, Rahimi and Kovacs, 2014, Schneider et al., 2007). However, the high prevalence of mixed pathology in dementia is often overlooked when examining relationships between neuropathological diseases and clinical symptoms such as cognitive decline. While mixed and concomitant pathology is frequently reported during neuropathological examination, it is difficult to identify during life as clinical presentation of dementia subtypes frequently overlap meaning that cases that appear one way clinically may not have the expected pathology at autopsy (Uretsky et al., 2021), with one study reporting that the majority of individuals with probable Alzheimer's disease have mixed pathology upon detailed neuropathological. Similarly, the majority of Lewy body disease cases occur in conjunction with substantial Alzheimer's disease pathology.

Previous studies of cognitive function in dementia have indicated that the presence of mixed pathology is associated with accelerated cognitive decline and complex clinical

heterogeneity and may have a synergistic effect on cognitive decline, with the combination resulting in an increased rate of decline and severity of cognitive impairment compared to a single pathology in isolation (Brenowitz et al., 2017, Kapasi, Decarli and Schneider, 2017). Most previous research has primarily focused on the transition to dementia rather than patterns of cognitive decline over time and the effect of mixed pathology is often ignored in such studies, despite mixed pathologies accounting for over 60% of all dementia cases.

Before new advancements in biomarkers and disease-modifying therapies can be applied in a meaningful way, the characterisation of the interaction between common neuropathological features of dementia and their role in cognitive decline is crucial. Few studies have fully characterised the impact of mixed pathologies on cognitive trajectory in the years preceding death with autopsy-confirmed neuropathology. Linear mixed effects modelling can be used to analyse data with hierarchical structures and repeated measures, by combining fixed effects at the population level and random effects at the subject level to account for correlations within groups.

5.1.1 Aims and Hypotheses

Using comprehensive post-mortem neuropathological assessment of donated brain tissue from longitudinally followed-up individuals in the Brains for Dementia Research cohort with and without clinical dementia, this study aimed to:

1. Characterise the relationship between neuropathological diagnostic group on cognitive profiles and trajectories in the cohort the years immediately preceding death
2. Assess the contribution of Alzheimer's disease pathology to cognitive trajectories in the presence and absence of mixed and additional subclinical pathologies.
3. Assess the contribution of Lewy body disease to trajectories of cognitive decline and specifically the influence of concomitant Alzheimer's disease pathology in Lewy body disease to cognitive trajectory.
4. Determine if there is any relationship between limbic-predominant age-related TDP-43 encephalopathy (LATE-NC) in the absence of mixed and concomitant pathology and cognitive trajectory.

Based on previous studies, it was hypothesised that cases with multiple neurodegenerative pathologies present (mixed pathology) would display different trajectories of cognitive

decline than those with only one pathology present, with mixed pathology declining at a faster rate than pure pathology and have lower levels of cognitive function in the final assessment preceding death. It was hypothesised that concomitant neurodegenerative pathologies at subclinical levels, particularly Alzheimer's disease pathology, would show faster decline in cognitive function than pure pathology, as reported in previous studies.

5.2 Methods

5.2.1 Case selection

Eight hundred and thirteen appropriate cases were included from the BDR cohort, with recruitment and diagnosis as previously outlined in Section 0 Participants and study partners completed clinical assessments every 12 months starting at study enrolment until death. Upon death, donated brain tissue underwent comprehensive neuropathological assessment.

5.2.2 Variables

Mini-Mental State Examination (MMSE) and Clinical Dementia Rating sum of boxes (CDR-SB) scores were selected as measures of global cognition for the following analyses. The MMSE is a 30-point test of function across a range of cognitive domains and the CDR-SB is an 18-point measure of function across six cognitive subdomains. In the MMSE, lower scores indicate a decline in cognitive function, while in CDR-SB, higher scores indicate decline in function. Each participant completed the MMSE and CDR at interviews with research staff every 12 months starting at study enrolment.

As outlined previously in Section 2.3, a range of neuropathology measures were used, including Thal Aβ phase (Alafuzoff et al., 2008, Thal et al., 2002), Braak NFT stage (Braak et al., 2006), CERAD score (Montine et al., 2012), ADNC level (Jack et al., 2018), Braak LB stage (Braak et al., 2003), VCING criteria and subdomains (Skrobot *et al.*, 2016), FTLD with TDP-43 or tau inclusions, TDP-43 inclusions in LATE-NC, ARTAG, hippocampal sclerosis, and PART. Neuropathology groups and classification system are as previously outlined in Chapter 2.

5.2.3 Linear Mixed Effects Modelling

Linear mixed effects modelling (LMM) assessed cognitive change in the cohort, and any effect of neuropathology group, in the years preceding death. Analyses were undertaken in R software using the packages *lme4* (Bates et al., 2015) and *lmerTest* (Kuznetsova, Brockhoff and Christensen, 2017).

Cognitive outcome, represented by either MMSE score or CDR-SB, was predicted using time to death as a continuous fixed effect, controlling for relevant covariates such as age, sex, education, and index of multiple deprivation. The models included both a random intercept and a random slope at the subject level. Akaike and Bayesian Information Criterion (AIC; BIC) were considered as complementary measures of model fit, with decrease in either representing an improvement in model fit when including a parameter. Pathology group was then incorporated into each model as a fixed effect with low pathology controls treated as the reference group for comparison.

5.2.4 Sub-Group Analyses

Following the initial analysis of cognitive trajectories across neuropathology groups, additional models were developed to explore the effects of individual and co-occurring neuropathologies. These included analyses of groups with Alzheimer's disease or Lewy body disease. Further models to investigate concomitant pathology were then developed, including Alzheimer's disease pathology in Lewy body disease, Alzheimer's disease pathology in LATE-NC, and Lewy body pathology in LATE-NC. A final analysis then examined cognitive trajectories in combinations of Alzheimer's disease, Lewy body disease, and LATE-NC. These models were constructed

5.3 Results

The sample included 538 participants, comprising 256 females and 282 males. The mean age at death was higher among females (88.0 years, SD = 7.80) compared to males (84.9 years, SD = 7.48). Years spent in full time education was similar across groups, with a mean of 12.7 years. Index of multiple deprivation (IMD) had a median of 2 across all groups. Mean follow up time was longer for females (3.20 years, SD = 3.01) than males (2.65 years, SD = 2.30), as was the number of study visits (3.15 vs 3.00 in females and males respectively). Dementia was more prevalent among males (54.6%) than females (38.7%), with an overall prevalence of 47.0% in the cohort. Sample characteristics are outlined in **Table 5.1.**

***Table 5.1*. Characteristics of the Study Cohort (N = 538)**: Summary of demographic, clinical, and diagnostic variables for participants included in the current analysis.

	Female (N = 256)	**Male (N = 282)**	**Total (N = 538)**
Age (at death)	88.0 (7.80)	84.9 (7.48)	86.4 (7.78)
	88.7 [65.5, 104]	85.1 [67.4, 104]	86.6 [65.5, 104]
Education	12.7 (3.26)	12.8 (3.30)	12.7 (3.28)
	12.0 [5.00, 25.0]	12.0 [0, 22.0]	12.0 [0, 25.0]
IMD	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]
Follow up time	3.20 (3.01)	2.65 (2.30)	2.91 (2.68)
	2.40 [0, 11.6]	2.11 [0, 12.1]	2.19 [0, 12.1]
Visits	3.15 (2.07)	3.00 (1.83)	3.07 (1.95)
	3.00 [1.00, 13.0]	3.00 [1.00, 10.0]	3.00 [1.00, 13.0]
Dementia	99 (38.7%)	154 (54.6%)	253 (47.0%)
No Dementia	157 (61.3%)	128 (45.4%)	285 (53.0%)

Briefly, in terms of predominant pathology, there were 292 low pathology controls, 113 Alzheimer's disease, 25 argyrophilic grain disease, 27 cerebrovascular disease, 46 Lewy body disease, 24 frontotemporal lobar degeneration, 55 LATE-NC, and 231 mixed pathology cases. A breakdown of the overlap between neuropathological diagnoses is outlined in **Figure 5.1** and a more detailed pathology summary for each neuropathology group is outlined in Chapter 3.

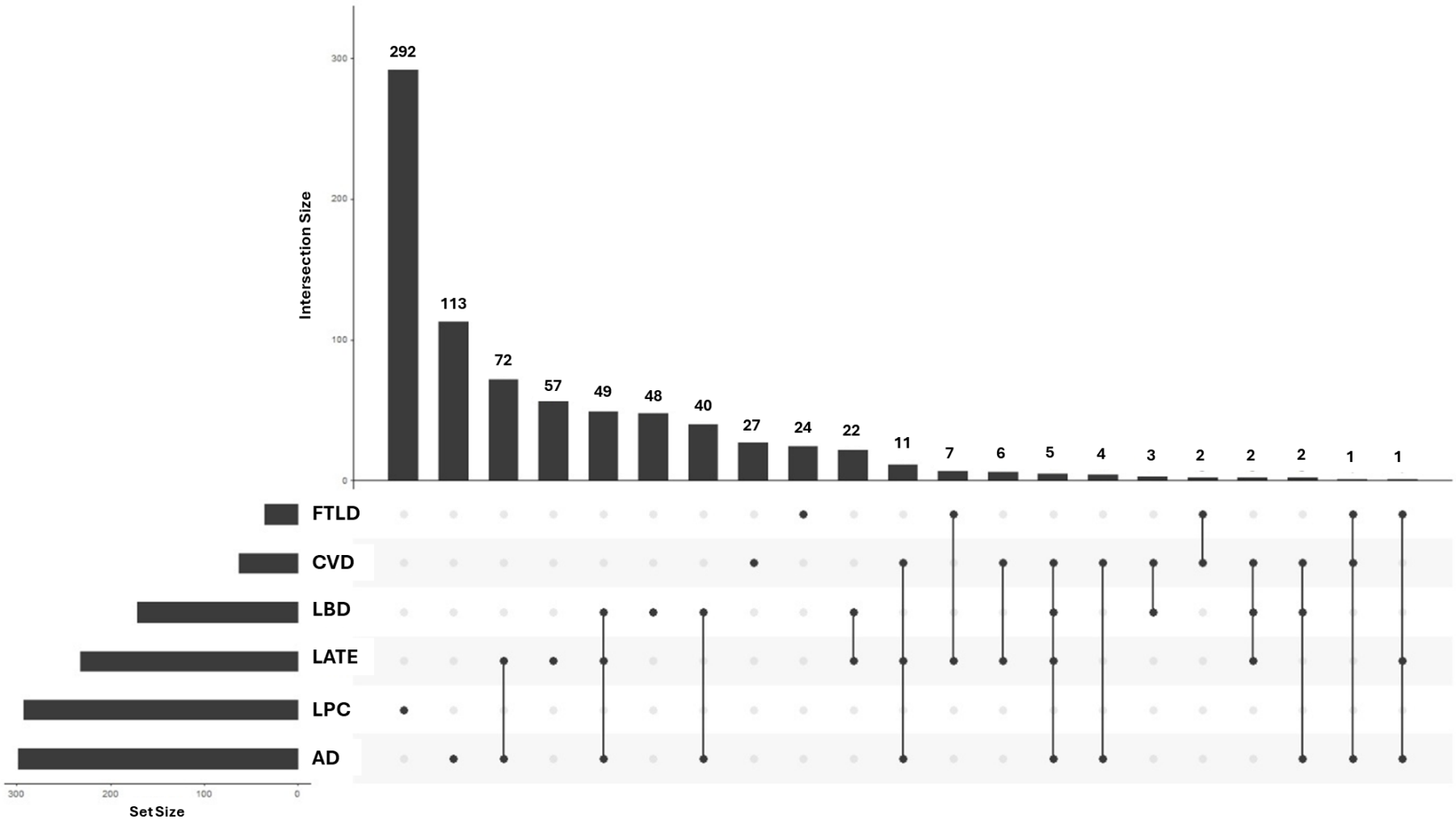

***Figure 5.1*. Frequency of, and intersections between, neuropathology groups:** Alzheimer's disease (AD), low pathology controls (LPC), limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy body disease (LBD); cerebrovascular disease (CVD), frontotemporal lobar degeneration (FTLD).

5.3.1 Neuropathology Group

As reported in Section 4.3.3, a general exploration of the relationships between each neuropathology group and rate of cognitive decline was performed to determine the direction of any further, more specific analyses. It was hypothesised that generally, mixed pathology would result in a faster decline in cognition than singular pathologies and concomitant pathology would result in faster rates of decline when compared to a more homogenous pathology phenotype. To test this assumption, a linear mixed effects model was developed using primary neuropathology group, as defined in Chapter 2, as a fixed effect predicting MMSE score in the years preceding death. The model had a log-likelihood of -4374.659, AIC of 8797.318, and BIC of 8924.17. Marginal R^2 was 0.407, while conditional R^2 was 0.918. The results reported in Table 5.2 suggest that all pathology groups were associated with a general trend towards faster decline in cognitive function when compared to low pathology controls.

Mixed pathology was associated with a significantly faster in rate of decline when compared to controls, with a 2.15-point decrease in MMSE score each year. Alzheimer's disease was associated with a significantly faster decline compared to low pathology controls, with 1.23-point annual decrease in MMSE score. Lewy body disease (0.96 [0.38, 1.55], $p < 0.001$), argyrophilic grain disease (0.78, 95% CI [0.09, 1.48], $p = 0.026$) and limbic-predominant age-related TDP-43 encephalopathy (0.76, 95% CI [0.21, 1.31], $p = 0.006$) were all associated with small but significantly faster rate of decline compared to low pathology controls. There was no significant change in rate of decline between low pathology controls and cerebrovascular disease or frontotemporal lobar degeneration. All pathologies, with the exception of cerebrovascular disease, were associated with significant predicted changes in final MMSE score, with Alzheimer's disease (13.6, 95% CI [10.8, 16.5], $p < 0.001$), frontotemporal lobar degeneration (16.1, 95% CI [9.86, 22.4], $p < 0.001$) and mixed pathology (19.7, 95% CI [17.6, 21.9], $p < 0.001$) having the highest predicted decreases in MMSE in comparison to low pathology controls. From this initial analysis, more detailed examination of the relationships between Alzheimer's disease, Lewy body disease, limbic-predominant age-related TDP-43 encephalopathy and mixed pathology and cognitive function in the years preceding death were selected. Results are reported in **Table 5.2**, with trajectories illustrated in **Figure 5.2**.

***Table 5.2*. Linear Mixed Effects Model Examining Cognitive Trajectories by Neuropathology Groups**: Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE and CDR-Sum of Boxes are reported for each neuropathological group. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

	MMSE		**CDR-SUM**	
	Intercept[1]	**Rate**[1]	**Intercept**[1]	**Rate**[1]
(Intercept)	**22.0** (15.0, 29.0), *< .001*	-	**10.0** (6.35, 13.7), *< .001*	-
TTD	**-0.42** (-0.63, -0.20), *< .001*	-	**0.31** (0.16, 0.45), *< .001*	-
Age	**-**	**0.01** (-0.06, 0.09), *0.721*	**-**	**-0.07** (-0.11, -0.03), *0.001*
Education	**-**	**0.20** (0.03, 0.37), *0.023*	**-**	**-0.14** (-0.24, -0.05), *0.002*
Alzheimer's disease	**-13.6** (-16.5, -10.8), *< .001*	**-1.23** (-1.78, -0.69), *< .001*	**8.49** (7.26, 9.72), *<.001*	**0.71** (0.38, 1.03), *< .001*
AGD	**-6.64** (-10.8, -2.46), *0.002*	**-0.78** (-1.48, -0.09), *0.026*	**2.38** (0.14, 4.62), *0.037*	**0.23** (-0.27, 0.72), *0.374*
CVD	**-0.56** (-4.60, 3.48), *0.786*	**-0.22** (-0.87, 0.43), *0.506*	**0.72** (-1.46, 2.90), *0.517*	**0.20** (-0.26, 0.66), *0.388*
Lewy body disease	**-6.98** (-10.6, -3.41), *< .001*	**-0.96** (-1.55, -0.38), *0.001*	**5.27** (3.52, 7.02), *< .001*	**0.61** (0.20, 1.01), *0.003*
FTLD	**-16.1** (-22.4, -9.86), *< .001*	**-1.13** (-2.57, 0.31), *0.125*	**9.78** (7.42, 12.1), *< .001*	**0.90** (0.22, 1.59), *0.009*
LATE-NC	**-5.06** (-8.29, -1.83), *0.002*	**-0.76** (-1.31, -0.21), *0.006*	**3.74** (2.12, 5.37), *< .001*	**0.40** (0.02, 0.77), *0.040*
Mixed pathology	**-19.7** (-21.9, -17.6), *< .001*	**-2.16** (-2.53, -1.80), *< .001*	**9.74** (8.78, 10.7), *< .001*	**0.67** (0.46, 0.88), *< .001*

[1]**Estimate** (95% CI), *p-value;* Abbreviations: TTD, time to death; AGD, argyrophilic grain disease; CVD, cerebrovascular disease; FTLD, frontotemporal lobar degeneration; LATE-NC, limbic-predominant age-related TDP-43 encephalopathy

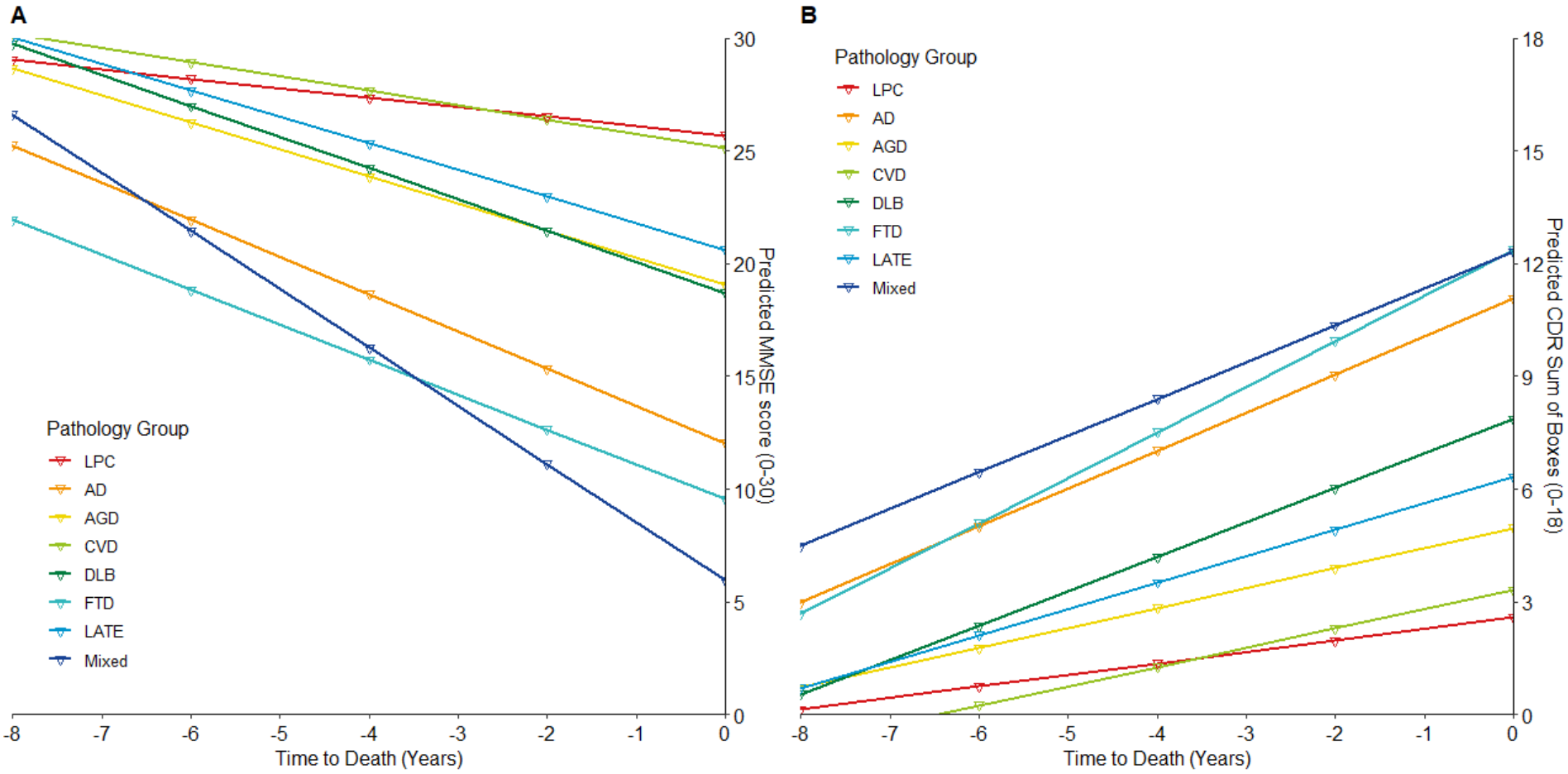

***Figure 5.2*. Neuropathology Groups**: Predicted (A) MMSE and (B) CDR Sum of Boxes for each pathology group in the final eight years preceding death, adjusting for age and education. Pathology groups include low pathology controls (LPC), Alzheimer's disease, argyrophilic grain disease (AGD), cerebrovascular disease (CVD), Lewy body disease (LBD), frontotemporal lobar degeneration (FTLD), limbic-predominant age-related TDP-43 encephalopathy (LATE-NC), and mixed pathology.

5.3.2 Cognitive Decline in Alzheimer's disease

First, the relationship between levels of overall Alzheimer's disease neuropathological change, in terms of NIA-AA score, were examined, with an additional group added for mixed pathology cases. It was hypothesised that increasing levels of Alzheimer's disease pathology would be associated with faster decline in cognition and intermediate Alzheimer's disease pathology in conjunction with other pathological entities would be associated with faster decline. To test the hypothesis that mixed and concomitant pathology would result in a faster decline in cognition than Alzheimer's disease alone, a model was developed incorporating levels of Alzheimer's disease pathology in relation to other neuropathological entities as a fixed effect predicting MMSE score (**Figure 5.3**; **Table 5.3**). The model had a log-likelihood of -3457.086, AIC of 6950.172, and BIC of 7040.902. Marginal R^2 was 0.426, while conditional R^2 was 0.920.

Intermediate Alzheimer's disease pathology, without accounting for other neurodegenerative pathologies, was associated with a 0.89-point decrease in MMSE score each year (-0.89, 95% CI [-1.30, -0.48], $p < 0.001$). However, when accounting for other neuropathological entities, intermediate Alzheimer's disease neuropathological change alone was not associated with a significant change in rate of decline (-0.35, 95% CI [-0.86, 0.15], $p = 0.169$) but was associated with a significant decrease in final MMSE score (-4.69, 95% CI [-7.69, -1.69], $p = 0.002$). Intermediate ADNC in other neurodegenerative pathologies was associated with a 1.4-point decrease in MMSE score each year (-1.40, 95% CI [-1.91, -0.89], $p < 0.001$) and a 10.71-point decrease in final MMSE (-10.71, 95% CI [-13.62, -7.81], $p < 0.001$).

Similar results were found using CDR-SB as an alternative measure of cognition, with the exception of intermediate ADNC in the absence of other neuropathological entities having a significantly different final CDR-SB score to low pathology controls. Alzheimer's disease was associated with a 1.31-point decrease in MMSE score annually (1.31, 95% CI [-1.86, -0.75], $p < 0.001$), and mixed Alzheimer's disease was associated with a 2.22-point decrease in MMSE score (-2.22, 95% CI [-2.67, -1.77], $p < 0.001$). Mixed Alzheimer's disease was associated with the greatest point change in MMSE score by final assessment (-22.36, 95% CI [-25.00, -19.72], $p < 0.001$) compared to low pathology controls. Alzheimer's disease was also

associated with a significant decline by final assessment in comparison to low pathology controls with 14.6-point decrease in MMSE score (-14.56, 95% CI [-17.50, -11.61], $p < 0.001$).

Table 5.3. Linear Mixed Effects Model Examining Cognitive Trajectories in Alzheimer's Disease Groups: Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE and CDR-Sum of Boxes are reported for participants with Alzheimer's disease pathology. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group.

	MMSE		**CDR-SUM**	
Predictors	**Intercept**[1]	**Rate**[1]	**Intercept**[1]	**Rate**[1]
(Intercept)	**22.43** (14.7, 30.2), *< .001*	-	**10.37** (6.39, 14.4), *< .001*	-
Time to death (years)	**-0.43** (-0.70, -0.16), *0.002*	-	**0.29** (0.10, 0.49), *0.003*	-
Age (years)	-	**0.03** (-0.06, 0.11), *0.525*	-	**0.05** (0.11, 0.01), *0.057*
Education (years)	-	**0.13** (-0.06, 0.33), *0.185*	-	**-0.13** (-0.24, -0.03), *0.010*
Intermediate ADNC	**-4.69** (-7.69, -1.69), *0.002*	**-0.35** (-0.86, 0.15), *0.169*	**3.24** (1.72, 4.75), *< .001*	**0.19** (-0.16, 0.55), *0.282*
Intermediate ADNC in another ND	**-10.7** (-13.6, -7.81), *< .001*	**-1.40** (-1.91, -0.89), *< .001*	**6.71** (5.30, 8.12), *< .001*	**0.72** (0.37, 1.06), *< .001*
Alzheimer's disease	**-14.6** (-17.5, -11.6), *< .001*	**-1.31** (-1.86, -0.75), *< .001*	**9.08** (7.76, 10.4), *< .001*	**0.78** (0.42, 1.13), *< .001*
Mixed AD	**-22.4** (-25.0, -19.7), *< .001*	**-2.22** (-2.67, -1.77), *< .001*	**10.6** (9.46, 11.7), *< .001*	**0.60** (0.33, 0.87), *< .001*

[1]**Estimate** (95% CI), *p-value*. Abbreviations: AD, Alzheimer's disease, ADNC, Alzheimer's disease neuropathological change, ND, neurodegenerative disease

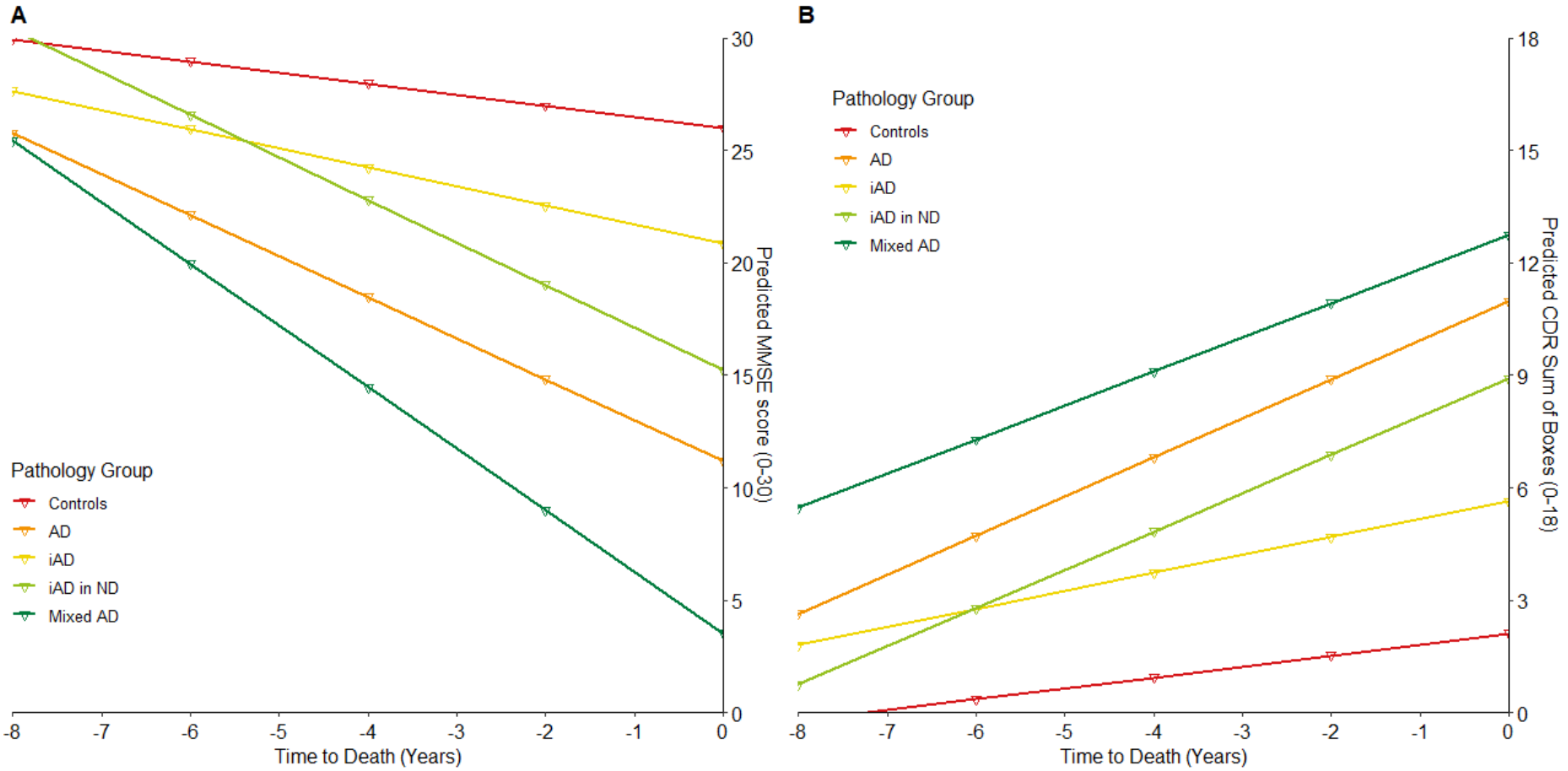

***Figure 5.3*. Alzheimer's Disease**: Predicted (A) MMSE and (B) CDR Sum of Boxes for each pathology group in the final eight years preceding death, adjusting for age and education. Pathology groups include low pathology controls, Alzheimer's disease, intermediate Alzheimer's disease, intermediate Alzheimer's disease in other neurodegenerative diseases (iAD in ND), and mixed Alzheimer's disease (i.e., multiple neuropathological diagnoses, of which one is Alzheimer's disease).

5.3.3 Cognitive Decline in Lewy body disease

The second analysis selected was the relationship between incidental, pure, and mixed Lewy body disease and cognitive decline in the years preceding death. It was hypothesised that mixed pathology in Lewy body disease would have the greatest contribution to cognitive decline when using a measure such as the MMSE. To test the hypothesis that Lewy body disease without additional pathologies would have little association with change in cognitive decline, a model was developed incorporating levels of Lewy body pathology as a fixed effect predicting MMSE score. The model had a log-likelihood of -3056.764, AIC of 6141.529, and BIC of 6210.635. Marginal R^2 was 0.367, while conditional R^2 was 0.916. CDR sum of boxes showed comparable results (**Table *5.4***).

Incidental Lewy body disease (i.e. Braak LB stages 1-3) was associated with a 5.47-point decrease in final MMSE score (-5.47, 95% CI [-8.92, -2.02], p = 0.002) when compared to low pathology controls but was not significantly associated with any change in rate of decline (-0.45, 95% CI [-1.02, 0.13], p = 0.132). Lewy body disease was associated with a 6.99-point decrease in final MMSE (-6.99, 95% CI [-10.47, -3.51], p < 0.001) and was also associated with a 0.98-point annual decrease in MMSE score (-0.98, 95% CI [-1.57, -0.38], p = 0.001) in the years preceding death, indicating a faster rate of decline than low pathology controls.

Mixed Lewy body disease was also associated with a 19.6-point decrease in final MMSE score when compared to low pathology controls and a significant 2.3-point decrease in MMSE score each year preceding death, indicating a more rapid trajectory of decline than Lewy body disease. There is little difference in trajectory between DLB and incidental Lewy body disease. Mixed DLB has a significantly faster rate of decline. An additional model of DLB grouped by Braak NFT stage indicated that increasing levels of hyperphosphorylated tau was associated with faster cognitive decline. Results are reported in **Table *5.4***, with group trajectories illustrated in **Figure 5.4**.

Table 5.4. Linear Mixed Effects Model Examining Cognitive Trajectories in Lewy Body Disease: Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE and CDR-Sum of Boxes are reported for participants with Lewy body pathology. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

	MMSE		**CDR Sum of Boxes**	
Predictors	**Intercept**[1]	**Rate**[1]	**Intercept**[1]	**Rate**[1]
(Intercept)	**27.5** (19.5, 35.4), *< .001*	-	**8.26** (3.56, 13.0), *0.001*	-
TTD	**-0.41** (-0.64, -0.18), *< .001*	-	**0.32** (0.17, 0.48), *< .001*	-
Age	-	**-0.04** (-0.12, 0.05), *0.401*	-	**-0.06** (-0.11, -0.01), *0.027*
Education	-	**0.09** (-0.11, 0.29), *0.388*	-	**-0.06** (-0.18, 0.06), *0.334*
Incidental LB	**-5.47** (-8.92, -2.02), *0.002*	**-0.45** (-1.02, 0.13), *0.132*	**3.55** (1.79, 5.32), *< .001*	**0.23** (-0.14, 0.60), *0.222*
Lewy body disease	**-6.99** (-10.5, -3.51), *< .001*	**-0.98** (-1.57, -0.38), *0.001*	**5.04** (3.20, 6.89), *< .001*	**0.59** (0.19, 1.00), *0.004*
Mixed LBD	**-19.6** (-22.1, -17.1), *< .001*	**-2.29** (-2.72, -1.85), *< .001*	**9.15** (7.92, 10.4), *< .001*	**0.71** (0.45, 0.96), *< .001*

[1]**Estimate** (95% CI), *p-value*

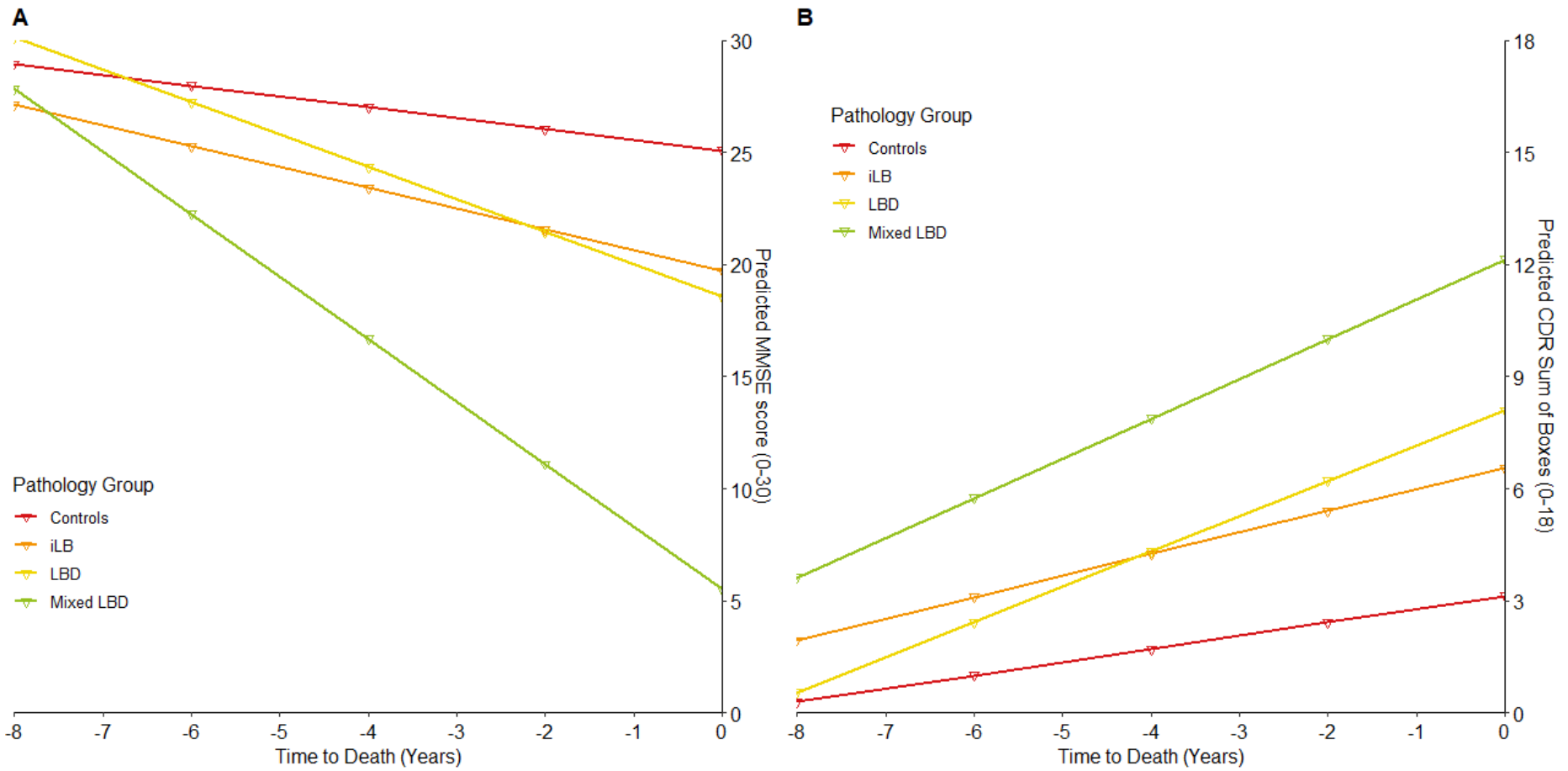

***Figure 5.4*. Lewy body disease**: Predicted (A) MMSE and (B) CDR Sum of Boxes for each pathology group in the years preceding death, adjusting for age and education. Pathology groups include low pathology controls, incidental Lewy body disease (iLB), Lewy body disease (LBD), and mixed Lewy body disease (i.e., multiple neuropathological diagnoses, of which one is Lewy body disease).

To examine whether this association between Lewy body disease and cognitive decline was influenced solely by the presence of Lewy body pathology and there were no other pathologies, such as Alzheimer's disease, contributing to the change in rate of cognitive decline, an additional model was developed incorporating different combinations of Lewy body disease and Alzheimer's disease as a fixed effect predicting MMSE score (Table 5.5; Figure 5.5). The model had a log-likelihood of -3459.712, AIC of 6954.425, and BIC of 7060.427. Marginal R^2 was 0.378, while conditional R^2 was 0.922. Incidental Lewy body disease without any substantial Alzheimer's disease pathology was not associated with any significant change in rate of decline in cognitive function (0.38, 95% CI [-0.55, 1.31], p = 0.426) or final MMSE score (1.76, 95% CI [-2.89, 6.42], p = 0.458) compared to low pathology controls.

DLB without substantial AD pathology was associated with a small but significantly faster cognitive decline (-0.85, 95% CI [-1.63, -0.08], p = 0.031) and a 4.18 decrease in final MMSE score (-4.18, 95% CI [-8.04, -0.31], p = 0.034) compared to controls. DLB with intermediate AD pathology was associated with an estimated 1.29 decrease in MMSE score each year (-1.29, 95% CI [-2.14, -0.43], p = 0.003) and a 12.5-point reduction in final MMSE score (-12.48, 95% CI [-16.85, -8.11], p < 0.001). In cases with both Alzheimer's disease and Lewy body disease, there was a significant increase in rate of decline, with an estimated 2.22-point decrease in MMSE each year preceding death (-2.22, 95% CI [-2.73, -1.71], p < 0.001). The predicted change in final MMSE scores for mixed AD/DLB (-22.09, [-24.72, -19.47], p < 0.001).

Rate of change in MMSE score was only significantly different to controls in groups containing intermediate or high levels of Alzheimer's disease pathology in the final years before death in the BDR cohort. The fastest decline in MMSE was seen in mixed AD/DLB cases, where there was a 2.22-point decrease in score each year. Lewy body disease with additional Alzheimer's type pathology had similar trajectories of decline, with a 1.29-point decrease in MMSE each year respectively. DLB and incidental LBD in the absence of AD pathology showed little to no change in rate of decline and DLB alone in the absence of AD pathology was associated with a small, significant decrease in MMSE score each year. Results are reported in **Table 5.5**, with group trajectories illustrated in **Figure 5.5**.

Table 5.5. Linear Mixed Effects Modelling of Cognitive Trajectories in Lewy Body Disease with Concomitant Alzheimer's Disease Pathology: Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE and CDR-Sum of Boxes are reported for participants with Lewy body disease with concomitant Alzheimer's disease neuropathology. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

	MMSE		**CDR Sum of Boxes**	
Predictors	**Intercept**[1]	**Rate**[1]	**Intercept**[1]	**Rate**[1]
(Intercept)	**26.6** (18.8, 34.3), *< .001*	-	**6.39** (1.89, 10.9), *0.005*	-
TTD	**-0.44** (-0.71, -0.17), *0.002*	-	**0.27** (0.08, 0.47), *0.006*	-
Age	-	**-0.02** (-0.10, 0.07), *0.686*	-	**-0.04** (-0.09, 0.01), *0.085*
Education	-	**0.09** (-0.11, 0.29), *0.372*	-	**-0.07** (-0.19, 0.05), *0.243*
Incidental LB (iLB)	**1.76** (-2.89, 6.42), *0.458*	**0.38** (-0.55, 1.31), *0.426*	**-0.81** (-3.27, 1.66), *0.521*	**-0.04** (-0.68, 0.59), *0.896*
Lewy body disease	**-4.18** (-8.04, -0.31), *0.034*	**-0.85** (-1.63, -0.08), *0.031*	**3.58** (1.31, 5.86), *0.002*	**0.67** (0.09, 1.25), *0.024*
LBD + iAD	**-12.5** (-16.9, -8.11), *< .001*	**-1.29** (-2.14, -0.43), *0.003*	**8.10** (5.89, 10.3), *< .001*	**0.73** (0.16, 1.30), *0.012*
Mixed AD/LBD	**-22.1** (-24.7, -19.5), *< .001*	**-2.22** (-2.73, -1.71), *< .001*	**10.1** (8.87, 11.4), *< .001*	**0.58** (0.28, 0.88), *< .001*

[1]**Estimate** (95% CI), *p-value;* TTD Time to death

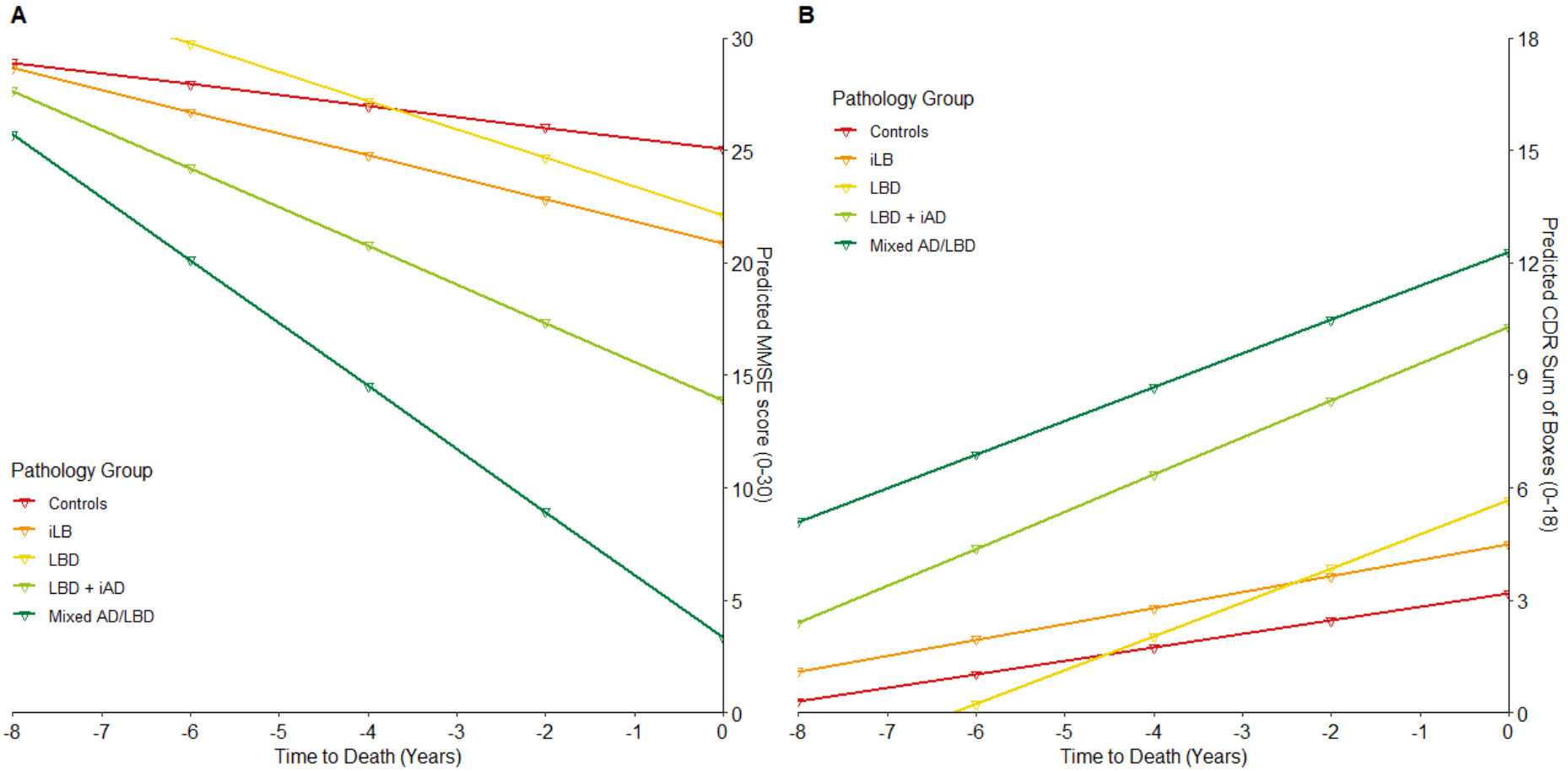

***Figure 5.5*. Alzheimer's disease pathology in Lewy body disease**: Predicted (A) MMSE and (B) CDR Sum of Boxes for each pathology group in the years preceding death, adjusting for age and education. Pathology groups include low pathology controls, incidental Lewy body disease (iLB), Lewy body disease (LBD), Lewy body disease with intermediate Alzheimer's disease pathology (LBD + iAD), and mixed Alzheimer's disease/Lewy body disease.

5.3.4 Cognitive Decline in LATE-NC

To assess if there was any significant relationship between the presence of LATE-NC and cognitive decline, a model was created incorporating LATE-NC in the presence and absence of varying levels of Alzheimer's disease pathology and Lewy body pathology. The first analysis included 193 Alzheimer's disease cases without LATE-NC, 22 LATE-NC cases with minimal ADNC, 33 LATE-NC cases with intermediate ADNC, 134 mixed Alzheimer's disease and LATE-NC cases and 292 low pathology controls. The model had a log-likelihood of -3408.658, AIC of 6853.311, and BIC of 6944.057. Marginal R^2 was 0.455, while conditional R^2 was 0.921.

Although there was a general trend towards declining cognition in the years preceding death, LATE-NC in the absence of substantial Alzheimer's disease pathology was not associated with any significant change in rate of decline (-0.21, 95% CI [-0.91, 0.48], p = 0.550) or predicted final MMSE score (-0.83, 95% CI [-5.15, 3.49], p = 0.706) when compared to low pathology controls (**Table 5.6**).

LATE-NC in the presence of intermediate Alzheimer's disease pathology was associated with a significant decrease in final MMSE score (-9.18, 95% CI [-13.39, -4.97], p < 0.001) and a significantly faster in rate of decline in the years preceding death (-1.39, [-2.19, -0.59], p = 0.001) compared to controls.

As reported in other models, Alzheimer's disease was associated with a significant decrease in final MMSE score (-15.35, 95% CI [-17.69, -13.01], p< 0.001) and a significantly faster in rate of decline (-1.75, [-2.18, -1.32], p < 0.001). The combination of Alzheimer's disease and LATE-NC appeared to have an additive effect showing a greater decrease in final MMSE score (-22.71, 95% CI [-25.44, 19.98], p < 0.001) and a significantly faster in rate of decline (-2.05, 95% CI [-2.51, -1.59], p < 0.001). Results are reported in **Table 5.6**, with group trajectories illustrated in **Figure 5.6**.

***Table 5.6*: Linear Mixed Effects Model Examining Cognitive Trajectories in LATE-NC in Alzheimer's disease:** Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE are reported for participants with LATE-NC in Alzheimer's disease. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

Predictors	**Intercept**[1]		**Rate**[1]	
(Intercept)	**22.4** (14.9, 29.9),	*< .001*	-	
TTD	**-0.43** (-0.64, -0.21),	*< .001*	-	
Age	-		**0.02** (-0.06, 0.10),	*0.647*
Education	-		**0.13** (-0.05, 0.32),	*0.165*
Alzheimer's disease	**-15.4** (-17.7, -13.0),	*< .001*	**-1.75** (-2.18, -1.32),	*< .001*
LATE-NC	**-0.83** (-5.15, 3.49),	*0.706*	**-0.21** (-0.91, 0.48),	*0.550*
LATE-NC + intermediate Alzheimer's disease	**-9.18** (-13.4, -4.97),	*< .001*	**-1.39** (-2.19, -0.59),	*0.001*
LATE-NC + Alzheimer's disease	**-22.7** (-25.4, -20.0),	*< .001*	**-2.05** (-2.51, -1.59),	*< .001*

[1]**Estimate** (95% CI), *p-value*

To examine the relationship between Lewy body pathology and LATE-NC, a second model was developed (**Table *5.7***). In this analysis, 93 Lewy body disease cases without LATE-NC, 55 LATE-NC in the absence of limbic/neocortical Lewy body disease, 78 mixed Lewy body disease and LATE-NC cases, and 292 controls. The model had a log-likelihood of -3063.447, AIC of 6162.893, and BIC of 6252.043. Marginal R^2 was 0.377, while conditional R^2 was 0.921. LATE in the absence of Lewy body pathology was associated with a small but significant change in final MMSE score (-4.89, 95% CI [-7.96, -1.82], p = 0.002) and rate of decline (-0.77, 95% CI [-1.31, -0.23], p = 0.005) compared to low pathology controls (Table 5.7). However, when accounting for intermediate Alzheimer's type pathology, as reported in the previous model, this association was not seen.

Lewy body disease in the absence of LATE-NC was associated with significant changes in both final MMSE score (-12.43, 95% CI [-15.09, -9.77], p < 0.001) and rate of decline (-1.75,

95% CI [-2.22, -1.28], p < 0.001) compared to controls (Table 5.7). The combination of Lewy body disease and LATE-NC was associated with significant changes in both final MMSE score (-19.75, 95% CI [-22.69, -16.82], p < 0.001) and rate of decline (-2.01, 95% CI [-2.51, -1.51], p < 0.001).

Table 5.7. Linear Mixed Effects Model Examining Cognitive Trajectories in LATE-NC in Lewy body disease: Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE are reported for participants with LATE-NC in Lewy body disease. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

Predictors	**Intercept**[1]	**Rate**[1]
(Intercept)	**25.9** (18.6, 33.2), *<0.001*	-
TTD	**-0.40** (-0.61, -0.18), *<0.001*	-
Age	-	**-0.02** (-0.10, 0.06)**,** *0.627*
Education	-	**0.12** (-0.06, 0.30), *0.197*
Lewy body disease	**-12.4** (-15.1, -9.77), *<0.001*	**-1.75** (-2.22, -1.28), *<0.001*
LATE-NC	**-4.89** (-7.96, -1.82), *0.002*	**-0.77** (-1.31, -0.23), *0.005*
LATE-NC + Lewy body disease	**-19.8** (-22.7, -16.8), *<0.001*	**-2.01** (-2.51, -1.51), *<0.001*

[1]**Estimate** (95% CI), *p-value*

The final analysis examined the relationship between mixed combinations of Alzheimer's disease, Lewy body disease, and LATE-NC to determine which combinations were associated with the fastest rates of decline and greatest reduction in final MMSE score. In this analysis, 80 mixed AD/LATE cases, 24 mixed DLB/LATE cases, 42 mixed AD/DLB cases, 54 mixed AD/DLB/LATE cases, and 292 low pathology controls were included. The model had a log-likelihood of –3838.358, AIC of 7728.716, and BIC of 7862.938. Marginal R^2 was 0.443, while conditional R^2 was 0.918. All mixed pathology combinations of Alzheimer's disease, Lewy body disease, and limbic-predominant age-related TDP-43 encephalopathy were associated

with significant increases in rate of cognitive decline in the years preceding death compared to low pathology controls (**Table 5.8**). Mixed Lewy body disease and LATE-NC was associated with the smallest decrease in final MMSE score (-13.85, 95% CI [-17.96, -9.75], p < 0.001) but a relatively high rate of decline with a 2.17-point decrease in MMSE score each year.

Mixed Alzheimer's disease and Lewy body disease was associated with significantly faster decline (-2.38, 95% CI [-3.54, -2.11], p < 0.001) and a 23.9 point predicted reduction in final MMSE score at final assessment (-23.88, 95% CI [-27.43, -20.33], p < 0.001). Similarly, mixed Alzheimer's disease and LATE-NC was associated with a significant decrease in final MMSE and an increased rate of cognitive decline (**Table 5.8; Figure 5.6**).

This indicates that while AD/LATE results in a lower level of cognitive function at end of life, DLB/LATE is associated with a faster rate of decline. The greatest reduction in final MMSE score was seen in participants with a combination of all three pathologies. Rate of cognitive decline in these cases was also relatively high, indicating a more rapid disease course. Similar results were seen using the CDR sum of boxes as a measure of cognition (**Figure 5.7**).

***Table 5.8*. LATE-NC in Alzheimer's disease and Lewy body disease**: Fixed effects coefficients for linear mixed effects models. Predicted intercept and rate of decline in MMSE scores of mixed LATE-NC in Alzheimer's disease and Lewy body disease, adjusting for age and education, compared to low pathology controls.

Predictors	**Intercept**[1]			**Rate**[1]		
(Intercept)	**28.4**	(20.6, 36.2),	*< .001*		-	
TTD	**-0.39**	(-0.60, -0.18),	*< .001*		-	
Age		-		**-0.04**	(-0.12, 0.05),	*0.406*
Education		-		**0.03**	(-0.17, 0.23),	*0.761*
AD + LATE-NC	**-21.3**	(-24.67, -18.0),	*< .001*	**-1.98**	(-2.59, -1.37),	*< .001*
LBD + LATE-NC	**-13.9**	(-17.96, -9.75),	*< .001*	**-2.17**	(-2.91, -1.43),	*< .001*
AD + LBD	**-19.8**	(-23.58, -16.0),	*< .001*	**-2.83**	(-3.54, -2.11),	*< .001*
AD + LBD + LATE-NC	**-23.9**	(-27.43, -20.3),	*< .001*	**-2.05**	(-2.65, -1.44),	*< .001*

[1]**Estimate** (95% CI), *p-value*

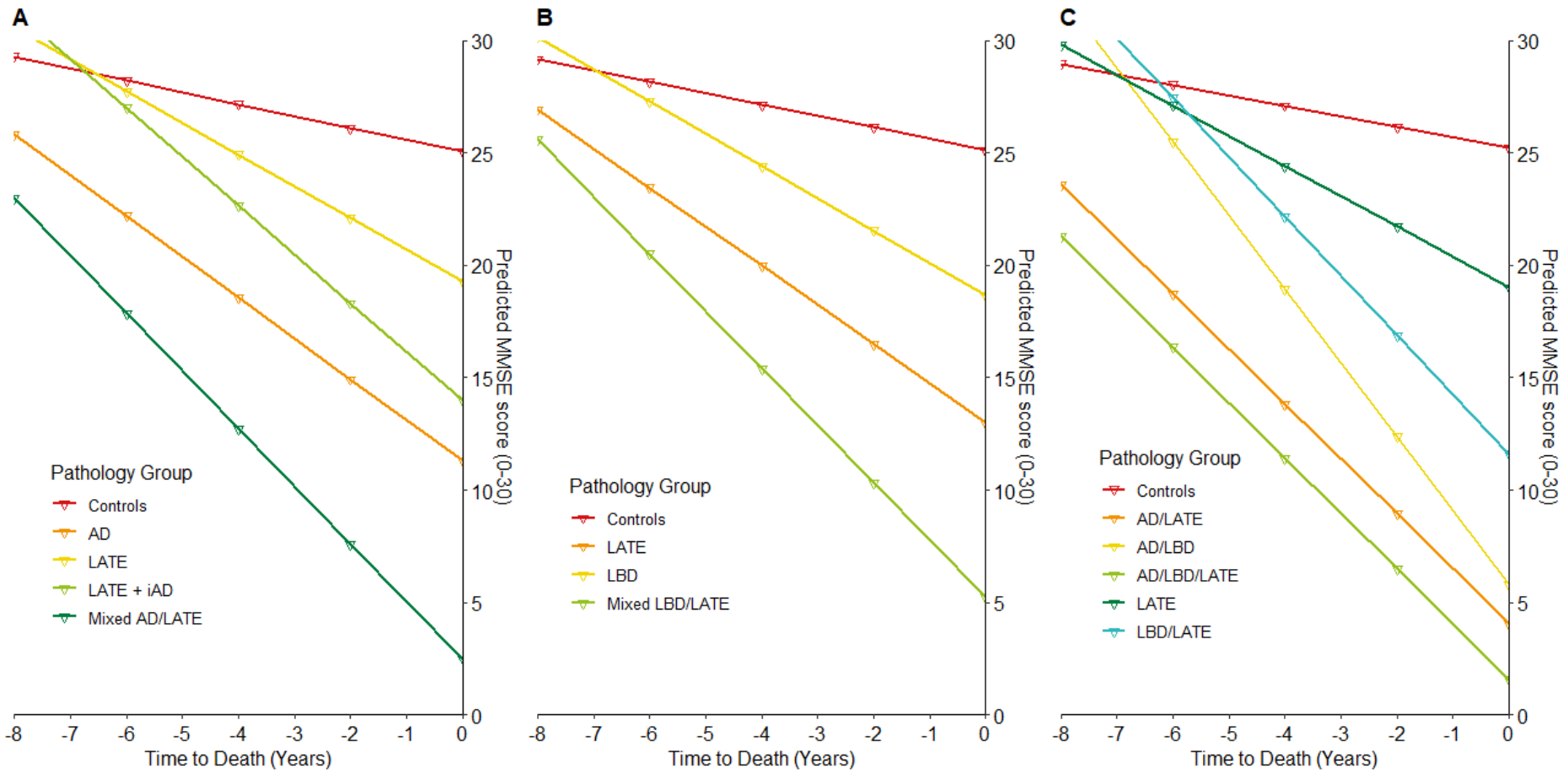

***Figure 5.6*. LATE-NC in Alzheimer's disease and Lewy body disease**: Predicted MMSE for each pathology group in the years preceding death, adjusting for age and education. Pathology groups include low pathology controls, Alzheimer's disease (AD), limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy body disease (LBD), and combinations of mixed pathology. Intersections between (A) AD and LATE; (B) LBD and LATE; and (C) AD, LBD and LATE.

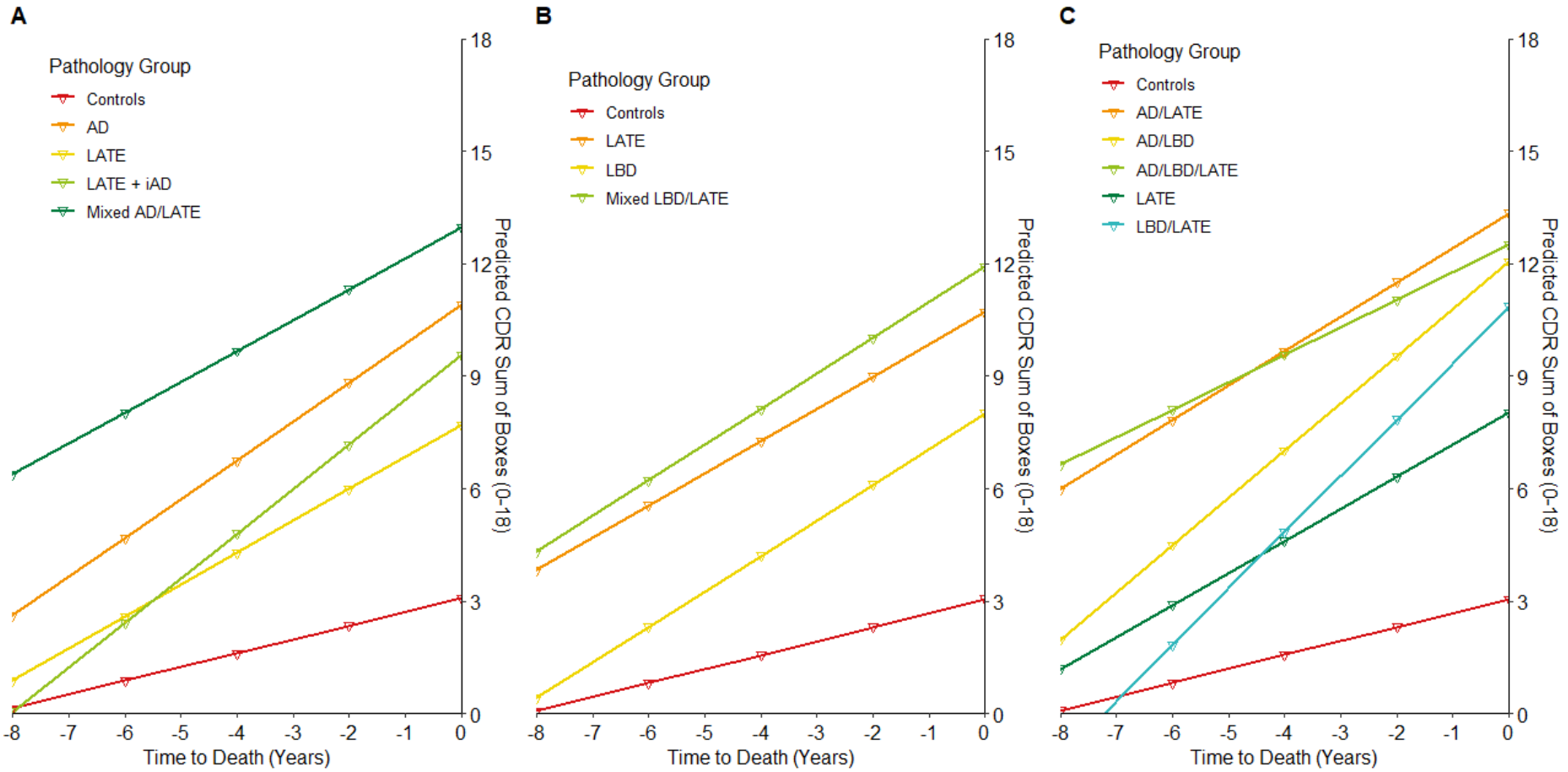

Figure 5.7 **LATE-NC in Alzheimer's disease and Lewy body disease:** Predicted CDR sum of boxes for each pathology group in the years preceding death, adjusting for age and education. Pathology groups include low pathology controls, Alzheimer's disease (AD), limbic-predominant age-related TDP-43 encephalopathy (LATE), Lewy body disease (LBD), and combinations of mixed pathology. Intersections between (A) AD and LATE; (B) LBD and LATE; and (C) AD, LBD and LATE.

5.4 Summary

The study found significantly faster decline and overall reduction in cognition in mixed neuropathology compared to low pathology controls, particularly in the presence of Alzheimer's disease pathology and LATE-NC. Almost all neuropathology groups included showed significantly faster decline and lower final cognitive function compared to low pathology controls, with the exception of cerebrovascular disease. Mixed pathology showed the fastest rate of decline within the cohort. Alzheimer's disease and frontotemporal lobar degeneration also showed fast decline and extremely low levels of proximal cognition compared to low pathology controls. Generally, there was a disparity between trajectories seen in neuropathology group and their associated study diagnoses. For example, a study diagnosis of Alzheimer's disease was associated with the most severe disease progression. Across all analyses reported here mixed pathology was associated with rapid decline and significant reduction in proximal cognition compared to low pathology controls, irrespective of the constituent components of the mixed cases. In addition to this, cognitive decline in cases with mixed pathology was faster and more severe than pathology in isolation.

Alzheimer's disease was associated with faster decline in cognition and large reductions in final cognitive state. In addition to this, increasing levels of Alzheimer's disease pathology were reflected by the increasing rates of decline and growing reductions in proximal cognition. Mixed Alzheimer's disease was associated with the fastest rate of decline and worst prognosis. Lewy body disease in the absence of concomitant Alzheimer's disease pathology was not associated with any significant change in cognitive trajectory compared to low pathology controls. Lewy body disease in the absence of intermediate Alzheimer's disease pathology was still associated with a more severe decline in cognition than low pathology controls but significantly more stable than cases with concomitant ADNC. Similarly, there was minimal change in cognitive trajectory in limbic TDP-43 pathology in the absence of Alzheimer's disease and Lewy body disease but a synergistic effect of TPD-43 pathology in Alzheimer's disease and Lewy body disease.

Linear mixed effects models are useful for predicting cognitive trajectories for specific groups but there are several associated limitations. Linear mixed effects models rely on the assumption of linearity between time and trajectory of cognitive decline. Cognitive decline may not follow a linear pattern and could be better represented by more complex, non-

linear models. As a result, the assumption of linearity could result in biased estimates of cognitive decline rates, particularly in cases where disease progression follows a more complex trajectory. A further limitation arises from the assumption that there is a single underlying trajectory for each group. This oversimplification could obscure important variations in disease progression patterns, leading to an incomplete understanding of the underlying mechanisms driving cognitive decline in different neuropathological subtypes. Linear mixed effects model are also sensitive to misspecification of random effects or correlation assumptions. These models may not adequately capture the influence of time-varying covariates or confounders on cognitive trajectories. Linear mixed effects models require large sample sizes to detect small effects reliably, which can be challenging to achieve in studies with limited availability of neuropathological data. While the BDR cohort is larger than most neuropathology series, once pathology groups and co-pathology subgroups have been assigned there is a significant reduction in sample size. As a result, much of the complexity seen in mixed and concomitant neuropathology cannot be incorporated into the analyses.

Overall, mixed pathology cases exhibited the fastest and most severe decline in cognitive function of all neuropathology groups in linear mixed effects models. More precisely, non-specific mixed pathology was associated with a faster rate of decline and greater reduction in cognition than any single pathology in isolation. Alzheimer's disease was associated with faster decline in cognition and large reductions in final cognition. Rate of cognitive decline increased with increasing levels of Alzheimer's disease neuropathological change. Concomitant Alzheimer's disease in isolation was associated with a more severe cognitive trajectory than some full neurodegenerative diseases. Lewy body disease was associated with significantly faster and more severe cognitive decline when concomitant intermediate Alzheimer's pathology was co-occurring. The cognitive trajectory of LATE-NC in isolation did not significantly differ from low pathology controls.

Chapter 6. Mixed and Concomitant Neuropathology as Predictors of Trajectory of Cognitive Decline

6.1 Background

While the linear mixed effects models utilised in the previous chapter (Chapter 5) provide valuable insights into average trajectories within pre-established neuropathology groups, the presence of distinct subgroups with shared patterns of cognitive decline may be overlooked. It is well-established that individuals within these groups often exhibit substantial variability in clinical phenotype including cognitive trajectories (Wilkosz et al., 2010). The use of latent class mixture models in this chapter offers a natural progression, allowing for the identification of latent subgroups with differing trajectory patterns and enhancing our understanding of cognitive decline in the context of neuropathology. LCMMs extend beyond average trajectories to identify latent subgroups of individuals sharing distinct patterns of decline. The method offers a unique methodological framework for identifying latent subgroups within a heterogeneous population, each characterised by distinct cognitive trajectory patterns. LCMMs are able to capture the inherent complexity and variability in cognitive trajectories, revealing the neuropathological profiles present of the underlying latent classes.

Precision medicine aims to deliver tailored interventions based on individual patient characteristics, such as neuropathology profiles and cognitive trajectory patterns. By identifying subgroups with distinct cognitive trajectories and neuropathology using latent class mixture models, factors contributing to heterogeneity in cognitive outcomes can be identified and used to inform personalised intervention strategies tailored to individual trajectory profiles. This may reveal further insights for the identification individuals at higher risk of cognitive decline. This personalised approach improves the effectiveness of intervention strategies by aligning treatments with the specific needs and trajectories of individual patients.

6.1.1 *Aims and Hypotheses*

To examine underlying cognitive trajectories further and from a different perspective, this study used longitudinal repeated cognitive assessments to:

1. Identify underlying latent classes of cognitive trajectories in full cohort.

2. Determine the value of neuropathology group as a predictor of cognitive trajectory.
3. Identify latent classes of cognitive trajectory in Alzheimer's disease and the value of mixed and concomitant pathology as a predictor of latent class.
4. Identify latent classes of cognitive trajectory in Lewy body disease and the value of mixed and concomitant pathology as a predictor of latent class.
5. Identify latent classes of cognitive trajectory in LATE-NC and the value of mixed and concomitant pathology as a predictor of latent class.

Based on previous studies, it was hypothesised that low pathology controls, single pathology dementia and mixed pathology dementia would have different cognitive trajectories, with low pathology controls showing little to no decline in the years preceding death. It was also hypothesised that mixed pathology would be a more accurate predictor of faster cognitive decline and greater reduction in proximal cognition than single pathology cases.

6.2 Methods

6.2.1 Case selection

Five hundred and thirty-eight participants with at least two antemortem MMSE assessments were selected from the Brains for Dementia Research neuropathology cohort. Recruitment and diagnostic criteria are outlined in Chapter 2. Participants and study partners completed clinical assessments every 12 months starting at study enrolment until death. At death, donated brain tissue underwent comprehensive neuropathological assessment.

6.2.2 Variables

The Mini-Mental State Examination (MMSE) was selected as the primary measure of cognition for the analyses. The MMSE is a 30-point scale assessing multiple cognitive domains, with lower scores indicating greater cognitive impairment. A minimum of two MMSE scores was required for inclusion in the analyses. Covariates included age, sex, years spent in full-time education, and index of multiple deprivation (IMD) as a measure of socioeconomic status.

A range of neuropathology measures were used to characterise latent classes, including Thal Aβ phase (Alafuzoff et al., 2008, Thal et al., 2002), Braak NFT stage (Braak et al., 2006), CERAD score (Montine et al., 2012), ADNC level (Jack et al., 2018), Braak LB stage (Braak et al., 2003), VCING criteria and subdomains (Skrobot *et al.*, 2016), FTLD with TDP-43 or tau

inclusions, TDP-43 inclusions in LATE-NC, ARTAG, hippocampal sclerosis, and PART. Neuropathology groups and classification system are as previously outlined in Chapter 2.

6.2.3 Latent Class Mixed Modelling

Latent class mixed modelling (LCMM) was employed to identify distinct unobserved subgroups within heterogenous populations based on observed variables using the *lcmm* package in R (Proust-Lima, Philipps and Liquet, 2017). LCMM is a probabilistic modelling approach that allows classification of individuals into latent classes based on patterns of longitudinal cognitive scores, capturing unobserved heterogeneity in cognitive decline and overall reduction in cognitive function. The categorisation of cases into classes based on cognitive profiles provides a clearer representation of the variability in disease progression.

The approach assumes that the population comprises multiple latent subgroups, each characterised by similar rates of decline and reductions in cognition. Maximum likelihood estimation was used to fit models ranging from one to six latent classes. Model selection was guided primarily by the Bayesian Information Criterion (BIC), with preference given to models with the lowest BIC, reasonable class sizes, and clinically interpretable trajectories.

All models included fixed effects for age, sex, years in full-time education, and index of multiple deprivation as covariates to adjust for demographic and socioeconomic factors influencing cognitive trajectories. These covariates were included as predictors of the intercept and slope but were not class-specific, allowing for adjustment without imposing differential effects across latent classes.

Model parameters were estimated via iterative optimisation algorithms, with convergence assessed through log-likelihood stabilisation and posterior classification probabilities. Cases were assigned to latent classes based on their highest probability of class membership. Missing MMSE or covariate data were handled using listwise deletion, resulting in slightly reduced sample sizes for specific analyses.

The model assumes that longitudinal heterogeneity in MMSE decline can be explained by a finite number of underlying latent classes, with class-specific intercepts and slopes capturing variation in cognitive decline. Within each class, change over time is assumed to follow a linear trajectory. Alternative functional forms were not explored, and model selection was based solely on the number of classes using fit indices and interpretability criteria.

6.2.4 Statistical Analyses

Fixed effects estimates for class-specific intercepts and slopes were reported with standard errors and p-values derived from Wald tests. To examine the association between neuropathological diagnoses and latent cognitive trajectories, multinomial logistic regression models were fitted, treating either the stable cognitive trajectory or low pathology control groups as reference categories. Odds ratios with confidence intervals (CI) and p-values were reported to quantify the likelihood of membership in declining trajectory classes relative to stable classes across neuropathology groups.

6.3 Results

Latent class analyses of cognitive trajectories were conducted across five separate cohorts derived from the overall neuropathology sample. These included: all individuals with neuropathological data available (N = 538); a subset with intermediate to high Alzheimer's disease pathology (N = 262); cases with limbic or neocortical Lewy body disease (N = 101); cases with LATE-NC present (N = 131); and cases with mixed pathology involving more than one neuropathological diagnosis (N = 121). Each of these subgroups was analysed independently to evaluate heterogeneity in patterns of cognitive decline in the years preceding death. **Table 6.1** provides an overview of the basic demographic and clinical characteristics for each of the five analytic cohorts used in the latent class mixture models. These variables are included to facilitate comparison between groups and to contextualise the subsequent trajectory analyses.

***Table 6.1*. Characteristics of the Study Cohorts:** Summary of demographic and clinical variables for participants included in the current analyses.

	All Cases (N = 538)	**AD (N = 262)**	**LBD (N = 101)**	**LATE-NC (N = 131)**	**Mixed (N = 121)**
Age (at death)	86.4 (7.78)	86.5 (7.39)	85.0 (7.40)	86.0 (7.68)	87.3 (7.29)
	86.6 [65.5, 104]	86.2 [67.8, 104]	84.6 [67.8, 98.8]	85.5 [67.8, 104]	86.2 [67.8, 104]
Female (%)	256 (47.6%)	115 (43.9%)	40 (39.6%)	55 (41.9)	49 (40.5%)
Male (%)	282 (52.4%)	147 (56.1%)	61 (60.4%)	76 (58.1)	72 (59.5%)
Years in education	12.7 (3.28)	12.5 (3.38)	12.3 (3.58)	12.5 (3.46)	12.2 (3.52)
IMD	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]

6.3.1 All Cases

The first analysis aimed to identify latent classes of trajectories within the full neuropathology cohort (N = 538). Six models were evaluated to assess model fit using the Bayesian Information Criterion (BIC). The initial single-class model yielded a BIC of 9113.120. Introduction of a two-class model substantially improved model fit (BIC = 8362.133), with each class accounting for approximately half the cohort. A three-class model further improved fit (BIC = 8351.483), as did a four-class model (BIC = 8342.039). Models with five or six classes did not offer additional improvements and introduced classes that were too small and indistinct to be interpreted meaningfully. Model fit is reported in **Table 6.2**

***Table 6.2*. Model Fit Statistics for Full Cohort Latent Class Models:** Model fit indices for latent class models ranging from one to six classes are presented, including number of classes (N), log-likelihood (loglik), number of parameters (npm), Bayesian Information Criterion (BIC), and the percentage distribution of cases across each latent class. Model selection was guided by BIC and class interpretability.

Model	**N**	**loglik**	**npm**	**BIC**	**% class 1**	**% class 2**	**% class 3**	**% class 4**	**% class 5**	**% class 6**
Model A	1	-4534.175	10	9113.120	100					
Model B	2	-4145.220	14	8362.133	56.3	43.7				
Model C	3	-4124.849	18	8351.483	5.56	55.7	38.7			
Model D	**4**	**-4122.166**	**22**	**8342.039**	**52.3**	**14.8**	**8.2**	**23.7**		
Model E	5	-4105.624	26	8340.548	18.7	52.0	7.59	20.7	0.93	
Model F	6	-4094.940	30	8349.854	5.93	18.9	7.41	52.2	12.6	2.96

The four-class model was therefore selected for further analysis due to its identification of four clear groups with distinct and interpretable trajectories, while maintaining an improved fit over the standard mixed model. This model comprised one large group that accounted for approximately half the cohort (N = 282), two medium sized groups that together accounted for 40% of cases (N = 128; N = 87), and one small group accounting for the remaining 8% of the cohort (N = 41).

The first class identified (N = 282, 52%) represented a large group of stable or slowly declining individuals that were characterised by a higher level of cognitive function in the decade preceding death (B = 31.9, SE = 1.20) and minimal decline in cognition over this period (B = -0.06, SE = 0.04). The second class identified (N = 87, 16%) represented a group

of fast declining individuals (B = -2.16, B = 0.24) with an intermediate level of cognitive function immediately preceding death (B = 17.4, SE = 1.47).

The third class (N = 41, 8%) represented a small group with a moderate rate of decline in cognitive function (B = -1.01, SE = 0.14) and a moderately reduced final level of cognitive function (B = 26.6, SE = 1.43). The final class (N = 128, 24%) showed a rapid rate of cognitive decline in the years preceding death (B = -3.52, SE = 0.34) and a low final level of cognitive function by end of life (B = 3.00, SE = 2.05). Results are reported in **Table *6.3*** and **Figure *6.1***. Plots with individual trajectories are provided in **Appendix I.**

Table 6.3. **Latent Class Model of the Neuropathology Cohort:** Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death from the latent class model. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific.

Class Effects	**Intercept**[1]	**Slope**[1]
Class 1 [N = 282]	**31.9** (1.20), *< .001*	**-0.06** (0.04), *.178*
Class 2 [N = 87]	**3.00** (2.05), *.144*	**-3.52** (0.34), *< .001*
Class 3 [N = 41]	**26.6** (1.43), *< .001*	**-1.01** (0.14), *< .001*
Class 4 [N = 128]	**17.4** (1.47), *< .001*	**-2.16** (0.24), *< .001*
Covariates		
Age	**-0.06** (0.01), *< .001*	-
Sex (Male)	**-0.04** (0.18), *.843*	-
Years in education	**0.08** (0.03), *.003*	-
Deprivation	**-0.05** (0.07), *.479*	-

[1]**Estimate** (SE), *p-value*

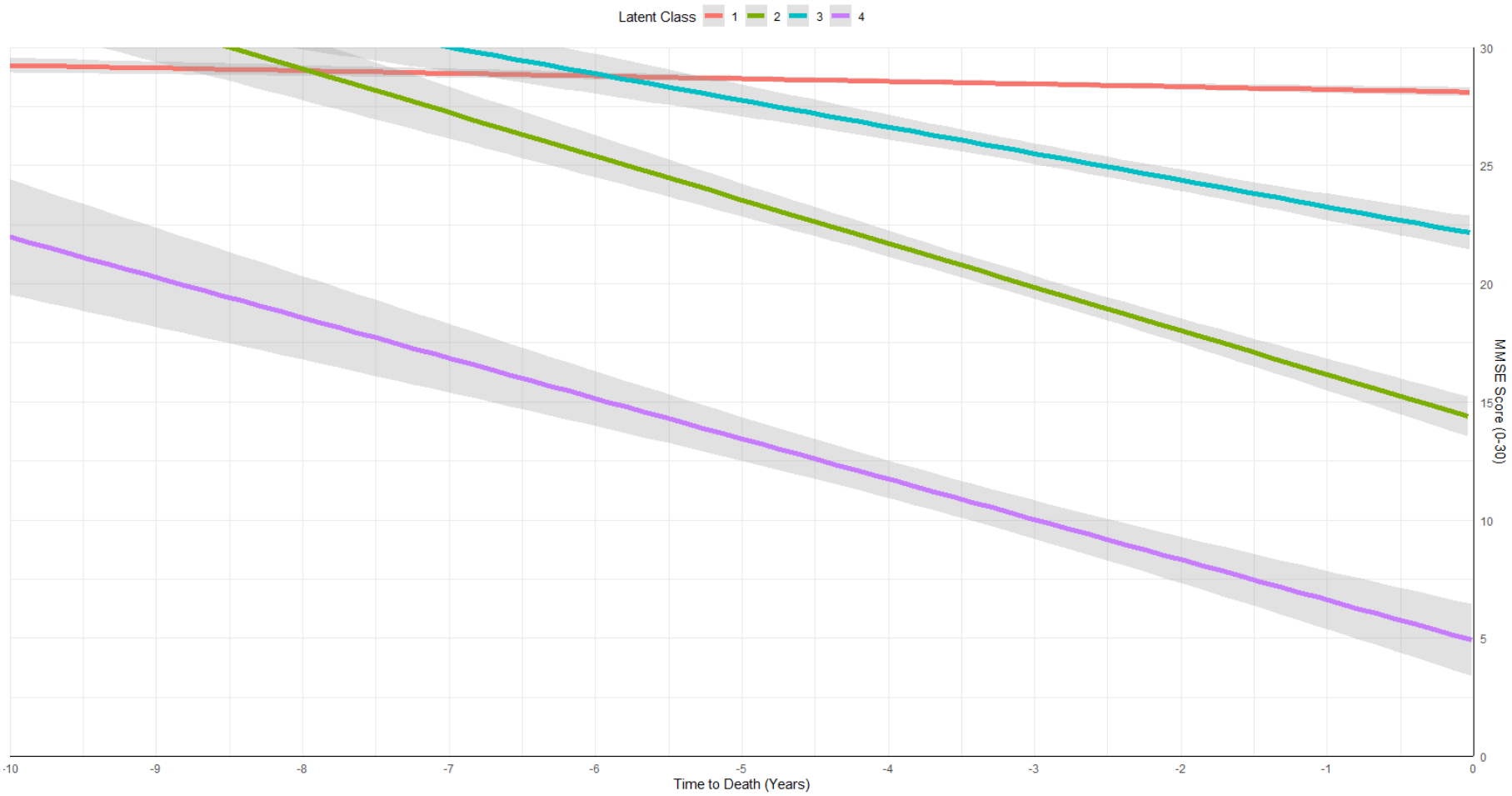

Figure 6.1. Cognitive Trajectories in the Neuropathology Cohort: Four distinct classes of cognitive decline identified through latent class mixture modelling in the full cohort (N = 538). Model adjusts for age at death, sex, years in education, and deprivation index. Class 1 represents a stable or minimal trajectory of decline with preserved cognitive function. Class 2 reflects a pattern of rapid decline from an intermediate baseline. Class 3 is characterised by moderate decline, and Class 4 by fast and severe cognitive deterioration over time.

Class membership varied substantially across diagnostic groups and is reported in **Table *6.4***. In Alzheimer's disease, 41% progressed with a fast trajectory of cognitive decline, 28% had an intermediate trajectory, 22% had a stable trajectory and 9% had a moderate trajectory. In Lewy body disease, 39% progressed with a stable trajectory, 21% had a moderate trajectory, 25% had an intermediate trajectory and 14% had a fast trajectory. In LATE-NC, 53% had a stable trajectory, 24% had an intermediate trajectory, 16% had a moderate trajectory and 8% had a rapid trajectory. In mixed pathology, 59% had a fast trajectory, 27% had an intermediate trajectory, 8% had a stable trajectory and 6% had a moderate trajectory. In low pathology controls, 83% had a stable trajectory and the remaining 17% were split approximately evenly between the other three trajectories of decline.

Multinomial logistic regression further quantified these associations and are also reported in **Table *6.4***. Compared to low pathology controls, individuals with Alzheimer's disease (OR = 19.1, 95% CI [7.51, 48.5], $p < .001$), frontotemporal dementia (OR = 29.6, 95% CI [4.24, 206], $p = .001$), LATE-NC (OR = 4.96, 95% CI [1.86, 13.3], $p = .001$), Lewy body disease (OR = 8.97, 95% CI [2.93, 27.5], $p < .001$), and mixed pathology (OR = 42.1, 95% CI [17.2, 103], $p < .001$) were all significantly more likely to be in the intermediate decline class than in the non-declining group (Class 1). Alzheimer's disease, LBD and mixed pathology were also overrepresented in both the moderately declining and rapidly declining group. LATE-NC was overrepresented in the moderately declining group whereas argyrophilic grain disease and frontotemporal dementia were overrepresented in the rapidly declining group.

Table 6.4. Class Allocation for Neuropathology Groups: Distribution of latent cognitive trajectory classes by pathology group, and results from multinomial logistic regression examining neuropathology group as a predictor of trajectory class. Low pathology controls and non-decliners serve as the respective reference groups in the logistic model. Values indicate case count and percentage within each subgroup. Logistic regression results are presented as odds ratio (95% CI), p-value

Class Counts (%)	**AD (N = 58)**	**AGD (N = 20)**	**CVD (N = 23)**	**FTD (N = 12)**	**LATE (N = 38)**	**LBD (N = 28)**	**Mixed (N = 121)**	**LPC (N = 238)**
Class 1	13 (22.4%)	11 (55.0%)	18 (78.3%)	2 (16.7%)	20 (52.6%)	11 (39.3%)	10 (8.3%)	197 (82.8%)
Class 2	16 (27.6%)	2 (10.0%)	2 (8.7%)	3 (25.0%)	9 (23.7%)	7 (25.0%)	33 (27.3%)	15 (6.3%)
Class 3	5 (8.6%)	2 (10.0%)	2 (8.7%)	0 (0.0%)	6 (15.8%)	6 (21.4%)	7 (5.8%)	13 (5.5%)
Class 4	24 (41.4%)	5 (25.0%)	1 (4.3%)	7 (58.3%)	3 (7.9%)	4 (14.3%)	71 (58.7%)	13 (5.5%)
Logistic Model								
Class 2 vs Class 1	**19.1** (7.51, 48.5), *<.001*	**2.17** (0.42, 11.1), *0.352*	**1.44** (0.30, 6.93), *0.648*	**29.6** (4.24, 206), *0.001*	**4.96** (1.86, 13.3), *0.001*	**8.97** (2.93, 27.5), *<.001*	**42.1** (17.2, 103), *<.001*	-
Class 3 vs Class 1	**7.49** (2.22, 25.3), *0.001*	**2.21** (0.41, 11.8), *0.352*	**1.61** (0.33, 7.96), *0.558*	**0.00** (0.00, 0.00), *<.001*	**3.37** (1.11, 10.3), *0.033*	**9.96** (3.00, 33.0), *<.001*	**9.88** (3.16, 30.9), *<.001*	-
Class 4 vs Class 1	**28.2** (11.4, 69.7), *<.001*	**7.99** (2.32, 27.5), *0.001*	**0.91** (0.11, 7.52), *0.929*	**45.3** (8.06, 255), *<.001*	**2.69** (0.68, 10.7), *0.158*	**4.36** (1.17, 16.2), *0.028*	**114** (46.6, 280), *<.001*	-

[1]**Estimate** (SE), *p-value*

6.3.2 Alzheimer's disease

To further evaluate the relationship between Alzheimer's disease pathology and trajectories of cognitive decline, a sub-cohort of cases with intermediate to high Alzheimer's disease was selected (N = 262). Six latent class models were evaluated: the initial single-class model yielded a BIC of 4732.882. A two-class model improved fit (BIC = 4586.679), with each class comprising roughly half the cohort. The three-class model further improved fit (BIC = 4576.049), while the four-class did not (BIC = 4586.776). Fit did not improve with a five- or the six-class model. As a result of its distinct classes of cognitive trajectory and improved fit, the three-class model was selected for subsequent analyses. Model fit is reported in **Table 6.5**.

***Table 6.5*. Model Fit Statistics for Alzheimer's Disease Latent Class Models**: Model fit indices for latent class models ranging from one to six classes are presented, including number of classes (N), log-likelihood (loglik), number of parameters (npm), Bayesian Information Criterion (BIC), and the percentage distribution of cases across each latent class. Model selection was guided by BIC and class interpretability.

Model	N	loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5	% class 6
AD_1	1	-2338.599	10	4732.882	100					
AD_2	2	-2254.361	14	4586.679	34.7	65.3				
AD_3	**3**	**-2237.909**	**18**	**4576.049**	**10.7**	**34.4**	**55.0**			
AD_4	4	-2232.135	22	4586.776	27.1	34.0	10.7	28.2		
AD_5	5	-2228.590	26	4601.956	6.11	10.7	26.3	32.1	24.8	
AD_6	6	-2225.055	30	4617.160	8.40	8.78	16.8	30.9	12.2	22.9

Table *6.6* summarises the fixed effects estimates for final MMSE score and rate of decline over the 10 years preceding death. All models were adjusted for age, sex, education, and deprivation index. The first class (N = 28, 11%) represented a group of moderately declining individuals (B = -1.06, SE = 0.23) with low baseline MMSE and a plateau of no cognitive function for a long period prior to death (B = -1.41, SE = 2.87). The second class identified (N = 90, 34%) was relatively stable with slow gradual decline in cognitive function in the years preceding death (B = -0.24, SE = 0.08). The third class identified (N = 144, 55%) represented a group of rapidly declining individuals with relatively high baseline cognitive function but low cognitive function by time of death (B = -2.94, SE = 0.20). None of the covariates were significant predictors of cognitive trajectory in this model.

Table 6.6. **Latent Class Model of the Alzheimer's Disease Sub-Cohort**: Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific.

Class Effects	**Intercept**[1]	**Slope**[1]	**Intercept vs class 3**
Class 1 [N=28] (moderate)	**-1.41** (2.87), *.623*	**-1.06** (0.23), *< .001*	**1.78** (0.25), *<.001*
Class 2 [N = 90] (slow/stable)	**27.4** (2.64), *< .001*	**-0.24** (0.08), *.004*	**-0.62** (0.16), *<.001*
Class 3 [N = 144] (fast)	**7.14** (2.76), *.010*	**-2.94** (0.20), *< .001*	-
Covariates			
Age	**-0.02** (0.03), *.470*	-	-
Sex (Male)	**-0.46** (0.39), *.245*	-	-
Years in education	**0.10** (0.06), *.091*	-	-
Deprivation	**0.01** (0.19), *.957*	-	-

[1]**Estimate** (SE), *p-value*

Analysis of class membership by AD pathology subgroup revealed notable differences in cognitive trajectories (**Table 6.7**). Plots with individual trajectories are provided in **Appendix II.** Among those with intermediate AD pathology alone, 72% were assigned to the slow/stable trajectory class, 25% to the moderate decline class, and only 4% to the fast decline class. In contrast, among those with intermediate AD pathology plus other substantial neuropathologies, 43% followed a stable trajectory, 55% had a moderate trajectory, and less than 2% experienced rapid decline. In cases with AD pathology alone, 28% were slow/stable, 57% moderate, and 15% rapidly declining. In the mixed AD pathology group, 11% were in the slow/stable class, 71% in the moderate class, and 18% in the fast-declining class.

Multinomial logistic regression (**Table 6.7**) showed that, compared to the intermediate AD pathology group, those with Alzheimer's disease alone were significantly more likely to follow a fast-declining trajectory (OR = 9.45, 95% CI [1.80, 49.5], p = .008). This effect was

even stronger in individuals with mixed AD pathology (OR = 30.5, 95% CI [5.90, 157], p < .001). Additionally, all pathology subgroups, including intermediate AD with other pathologies (OR = 3.61, 95% CI [1.56, 8.38], p = .003), Alzheimer's disease (OR = 5.82, 95% CI [2.41, 14.0], p < .001), and mixed AD (OR = 18.6, 95% CI [7.32, 47.2], p < .001), were significantly more likely to fall within the fast or moderate decline classes relative to the slow/stable reference group. These findings support the presence of distinct cognitive trajectories associated with different AD pathology profiles and underscore the exacerbating effect of co-pathologies on cognitive decline in the context of Alzheimer's disease.

Table 6.7 Class Allocation for Alzheimer's Disease Pathology Subgroups: Distribution of latent cognitive trajectory classes by Alzheimer's disease pathology subgroup, and results from multinomial logistic regression examining neuropathology group as a predictor of trajectory class. Class 1 represents minimal decline, Class 2 moderate decline, and Class 3 faster decline. Intermediate Alzheimer's disease (iAD) and the moderate trajectory class (Class 2) serve as the respective reference groups in the logistic model. Values indicate case count and percentage within each subgroup. Logistic regression results are presented as odds ratio (95% CI), p-value

Class Counts (%)	**iAD (N=53)**	**iAD in ND (N=58)**	**AD (N=60)**	**Mixed AD (N=91)**
Class 1	2 (3.8%)	1 (1.7%)	9 (15.0%)	16 (17.6%)
Class 2	38 (71.7%)	25 (43.1%)	17 (28.3%)	10 (11.0%)
Class 3	13 (24.5%)	32 (55.2%)	34 (56.7%)	65 (71.4%)
Logistic Model				
Class 1 vs Class 2	-	**0.83** (0.07, 9.86), *0.881*	**9.45** (1.80, 49.5), *0.008*	**30.5** (5.90, 157), *<.001*
Class 3 vs Class 2	-	**3.61** (1.56, 8.38), *0.003*	**5.82** (2.41, 14.0), *<.001*	**18.6** (7.32, 47.2), *<.001*

[1]**Estimate** (SE), *p-value*; Intermediate Alzheimer's disease and Class 2 are the respective reference groups.

Results are reported in **Table *6.6*** and **Figure 6.2Figure *6.1***. Plots with individual trajectories are provided in **Appendix II.**

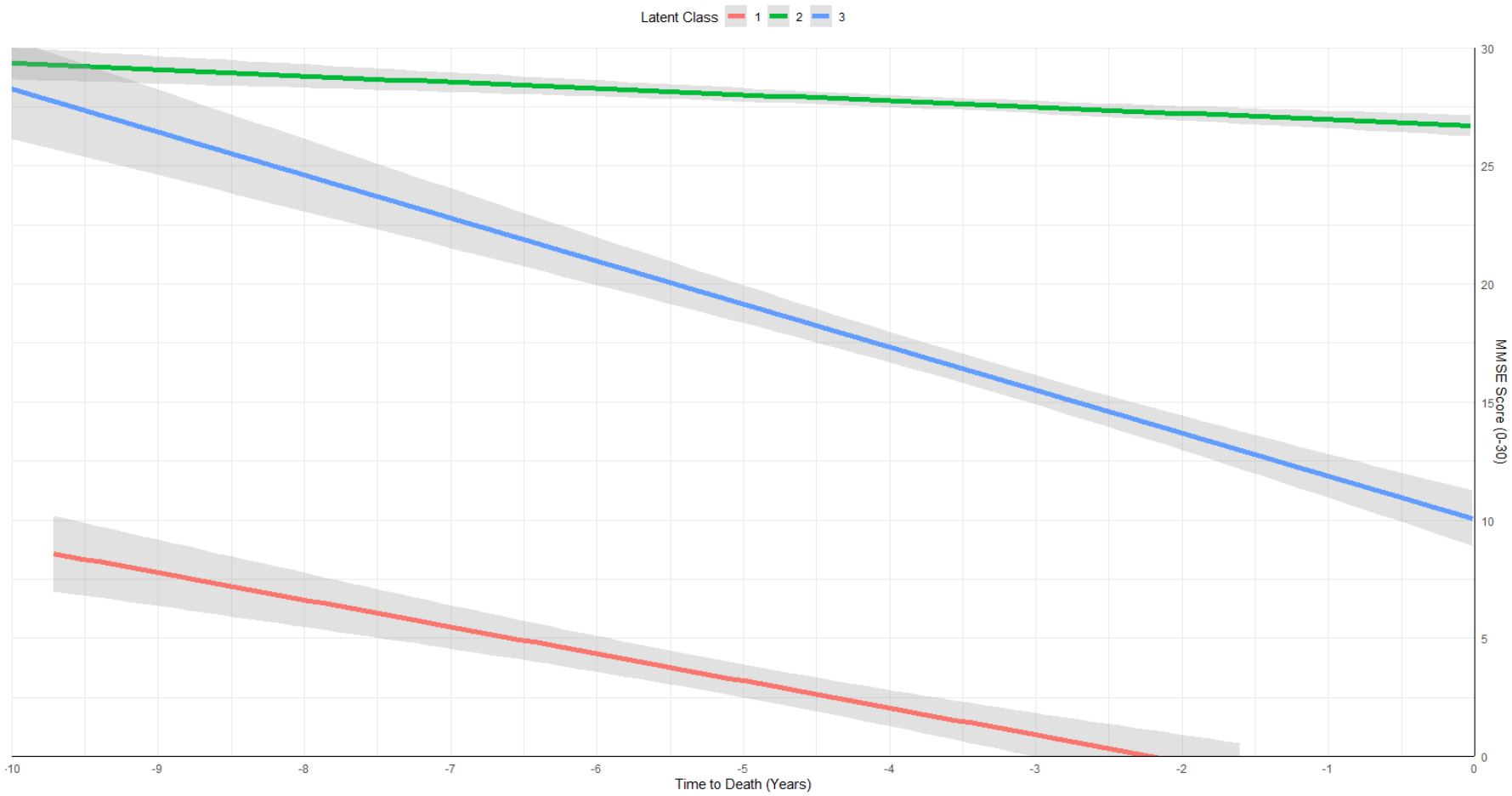

***Figure 6.2*. Cognitive Trajectories in Alzheimer's Sub-Cohort:** Three classes of cognitive trajectory identified by latent class mixture modelling of cases in the Alzheimer's disease sub-cohort, adjusting for age, sex, education and deprivation.

6.3.3 Lewy body disease

A sub-cohort of 101 cases with incidental (Braak LB stages 1-3) and limbic/neocortical (Braak LB stages 4-6) Lewy body disease was selected for analysis of distinct cognitive trajectories. Five latent class mixed models were evaluated. The initial single-class model yielded a BIC of 2007.139. The two-class model showed improved fit with a BIC of 1978.495, while the three-class model (BIC = 1991.096) and higher-class models did not improve fit based on the BIC. Consequently, the two-class model was selected. Model fit is reported in Table 6.8.

***Table 6.8*. Model Fit Statistics for Lewy Body Disease Latent Class Models:** Model fit indices for latent class models ranging from one to six classes are presented, including number of classes (N), log-likelihood (loglik), number of parameters (npm), Bayesian Information Criterion (BIC), and the percentage distribution of cases across each latent class. Model selection was guided by BIC and class interpretability.

	G	loglik	npm	BIC	%class1	%class2	%class3	%class4
Model A	1	-1323.63	10	2007.139	100			
Model B	**2**	**-1265.71**	**14**	**1978.495**	**24.8**	**75.2**		
Model C	3	-1258.68	18	1991.096	33.3	30.4	36.3	
Model D	4	-1247.6	22	1993.830	7.41	17.0	33.3	42.2

Table *6.9* presents the fixed effects estimated for final MMSE score and rate of decline over the 10 years prior to death, adjusting for age, sex, education, and deprivation index. Class 1 (N = 25, 24.8%) exhibited relatively stable cognition with a higher final MMSE (intercept = 31.2, SE = 4.47, $p < .001$) and a gradual decline (slope = -0.28, SE = 0.16, $p = .082$). Class 2 (N = 76, 75.2%) was characterised by significantly lower final cognition (intercept = 9.75, SE = 4.61, $p = .034$) and rapid decline (slope = -3.09, SE = 0.30, $p < .001$). Among covariates, none showed significant associations with intercept or slope. Alzheimer's disease (AD) as a co-occurring pathology was observed in 84% of Class 2 cases compared to 36% of Class 1 cases. Mixed AD/LBD cases were significantly more likely to belong to the fast-declining Class 2, with an odds ratio (OR) of 29.5 (95% CI [6.75, 129], $p < .001$). Similarly, intermediate AD pathology was present in 10.5% of Class 2 and 16% of Class 1 cases. Lewy body disease cases with intermediate AD pathology had an OR of 6.54 (95% CI [1.16, 36.9], $p = 0.034$) for membership in Class 2 in comparison to Class 1. Class trajectories are shown in **Figure *6.3***.

Table 6.9. Latent Class Model of the Lewy Body Disease Sub-Cohort: Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific.

Class Effects	**Intercept**	**Slope**	**Intercept vs class 2**
Class 1 (slow)	**31.2** (4.47), *< .001*	**-0.28** (0.16), *.082*	**-1.09** (0.27), *< .001*
Class 2 (fast)	**9.75** (4.61), *.034*	**-3.09** (0.30), *< .001*	-
Covariates			
Age	**-0.07** (0.05), *.207*	-	-
Sex (Male)	**-1.08** (0.88), *.222*	-	-
Years in education	**0.15** (0.14), *.268*	-	-
Deprivation	**-0.43** (0.31), *.163*	-	-

[1]**Estimate** (SE), *p-value*

Table *6.10* shows class distributions within Lewy body disease subgroups and results of multinomial logistic regression with neuropathology group predicting trajectory class. Class 1 represents slower decline and serves as the reference, along with limbic/neocortical Lewy body disease. Odds ratios indicate increased likelihood of fast decline in Lewy body disease cases with intermediate AD and mixed pathology.

Table 6.10. Class Allocation for Lewy Body Disease Sub-Groups: Distribution of latent classes by neuropathology, and results from multinomial logistic regression examining neuropathology as a predictor of latent class. Lewy body disease and the class 1 serve as the respective reference groups in the logistic model. Values indicate count (%) within each subgroup. Logistic regression results are presented as odds ratio (95% CI), p-value.

Class Counts (%)	**LBD (N = 16)**	**LBD + iAD (N = 12)**	**Mixed LBD (N = 73)**
Class 1 [N = 25]	12 (75.0%)	4 (33.3%)	9 (12.3%)
Class 2 [N = 76]	4 (25.0%)	8 (66.7%)	64 (87.7%)
Logistic Model			
Class 2 vs Class 1		**6.54** (1.16, 36.9), *0.034*	**29.5** (6.75, 129), *< .001*

[1]**Estimate** (SE), *p-value*

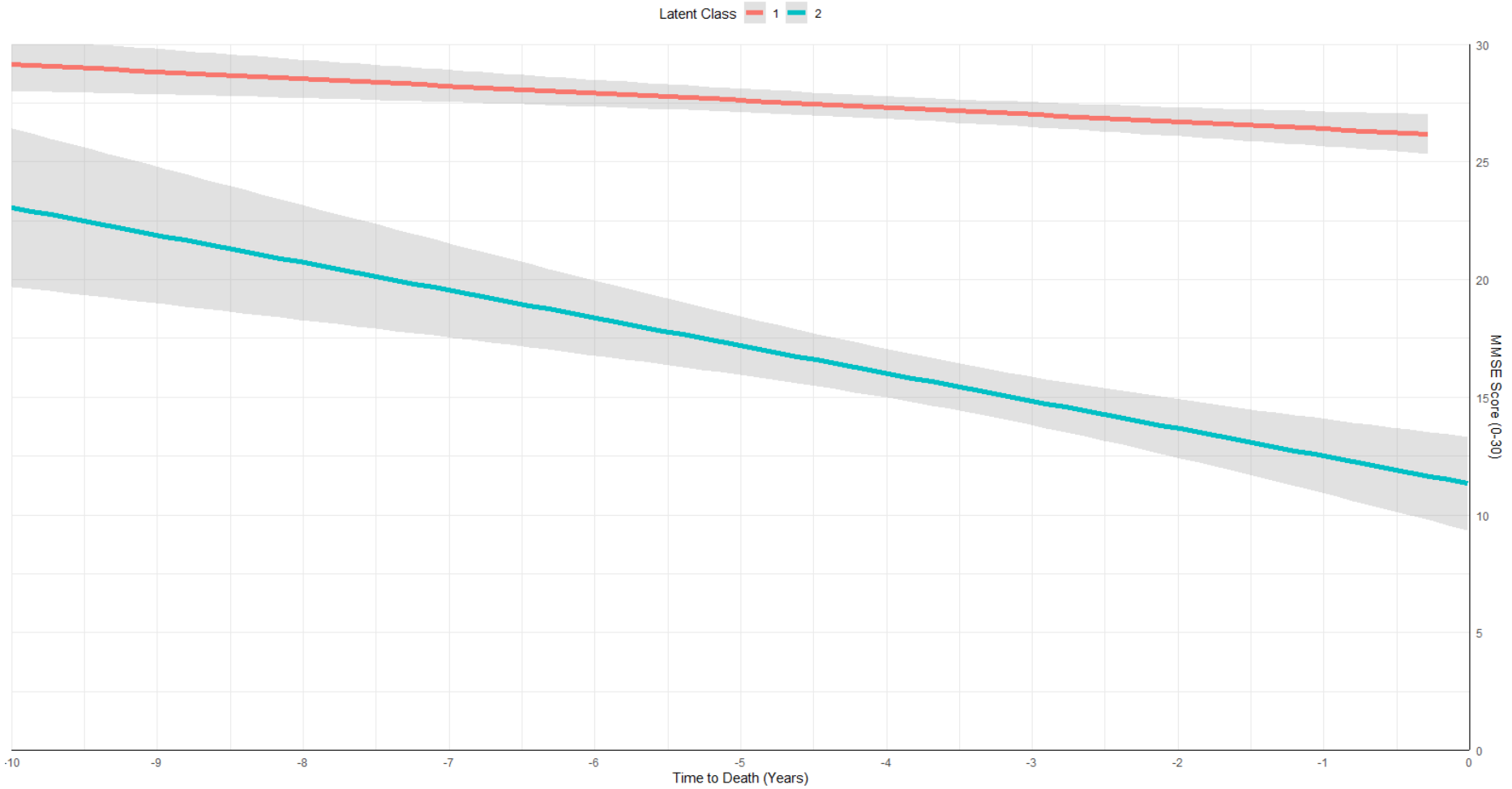

Figure 6.3. Cognitive Trajectories in Lewy Body Disease Sub-Cohort: Two classes of cognitive trajectory identified by latent class mixture modelling of cases in the limbic/neocortical Lewy body disease sub-cohort, adjusting for age, sex, education and deprivation.

6.3.4 LATE-NC

A sub-cohort of 131 cases with confirmed LATE-NC pathology and sufficient longitudinal cognitive data were selected for further analysis to identify distinct classes of cognitive trajectories within this group. Models with one, two, and three latent classes were fitted to the data, adjusting for age, sex, education, and deprivation index. Model fit was evaluated using the Bayesian Information Criterion (BIC), with lower values indicating better fit. The single-class model yielded a BIC of 2436.186. The two-class model provided improved fit with a BIC of 2404.439, while the three-class model (BIC = 2408.614) did not further improve fit, supporting the selection of the two-class model. Model fit statistics are reported in **Table 6.11**.

***Table 6.11*. Model Fit Statistics for LATE-NC Models**: Model fit indices for latent class models ranging from one to six classes are presented, including number of classes (G), log-likelihood (loglik), number of parameters (npm), Bayesian Information Criterion (BIC), and the percentage distribution of cases across each latent class. Model selection was guided by BIC and class interpretability.

	G	loglik	npm	BIC	%class1	%class2	%class3	%class4
Model A	1	-1193.72	10	2436.186	100			
Model B	**2**	**-1168.09**	**14**	**2404.439**	**29.8**	**70.2**		
Model C	3	-1156.14	18	2408.614	27.5	12.2	60.3	
Model D	4	-1148.18	22	2411.609	9.92	26.0	26.7	37.4

Table *6.12.* Latent Class Model of the LATE-NC Sub-Cohort: Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific. summarises the fixed effects estimates for final MMSE score and rate of cognitive decline for each class over the 10 years preceding death. Covariates were modelled as fixed effects common to all classes. Analysis of class membership by AD pathology subgroup revealed notable differences in cognitive trajectories (**Figure 6.4**). Plots with individual trajectories are provided in **Appendix III.** Class 1 (N = 39, 30%) exhibited a moderate and statistically significant reduction in final MMSE score (B = 15.4, SE = 7.57, p = 0.042) and a slow but statistically significant rate of decline (B = -0.65, SE = 0.19, p < 0.001). Class 2 (N = 92, 70%) was characterised by a lower, non-significant reduction in final MMSE score (B = -4.94, SE =

7.45, p = 0.508) and a fast and statistically significant decline in cognition (B = -2.82, SE = 0.27, p < 0.001). Among covariates, years of education was positively associated with final MMSE score (B = 0.25, SE =0.12, p =0.033). Age, sex, and deprivation index were not significantly related to intercept or slope.

Table 6.12. Latent Class Model of the LATE-NC Sub-Cohort: Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific.

Class Effects	**Intercept**	**Slope**	**Intercept vs class 2**
Class 1 (slow)	**15.4** (7.57), .042	**-0.65** (0.19), *< .001*	**-0.99** (0.23), *<.001*
Class 2 (fast)	**-4.94** (7.45), .508	**-2.82** (0.27), *< .001*	
Covariates			
Age	**0.07** (0.07), *.330*	-	-
Sex (Male)	**0.30** (0.72), *.671*	-	-
Years in education	**0.25** (0.12), *.033*	-	-
Deprivation	**-0.12** (0.32), *.697*	-	-

[1]**Estimate** (SE), *p-value*

Table *6.13* outlines the distribution of cognitive trajectory classes within LATE-NC subgroups defined by co-occurring neuropathologies. Isolated LATE-NC cases predominantly exhibited the slow trajectory (Class 1: 88.9%), whereas mixed pathology groups, including LATE-NC combined with intermediate Alzheimer's disease (iAD), Alzheimer's disease (AD), Lewy body disease, and other mixed combinations, showed a higher proportion of fast decliners (Class 2). Specifically, 86% of AD/LATE, 78% of LBD/LATE, and 93% of AD/LBD/LATE cases followed the fast decline trajectory.

Table 6.13. Class Allocation for LATE-NC Subgroups: Distribution of latent cognitive trajectory classes by LATE-NC subgroup, and results from multinomial logistic regression examining neuropathology group as a predictor of trajectory class. Class 1 represents slower decline; Class 2 represents faster decline. Isolated LATE-NC and the slow trajectory class

serve as the respective reference groups in the logistic model. Values indicate case count and percentage within each subgroup. Logistic regression results are presented as odds ratio (95% CI), p-value.

Class Counts (%)	**LATE (N=18)**	**LATE + iAD (N=20)**	**AD/LATE (N=36)**	**LBD/LATE (N=18)**	**AD/LBD/LATE (N=30)**	**Mixed LATE (N=9)**
Class 1	16 (88.9%)	10 (50.0%)	5 (13.9%)	4 (22.2%)	2 (6.7%)	2 (22.2%)
Class 2	2 (11.1%)	10 (50.0%)	31 (86.1%)	14 (77.8%)	28 (93.3%)	7 (77.8%)
Logistic Model						
Class 2 vs Class 1	-	**7.39** (1.25, 43.6), *0.027*	**54.6** (8.66, 344), *<.001*	**32.1** (4.64, 222), *0.001*	**140** (15.6, 1270), *<.001*	**27.8** (2.98, 259), *0.004*

[1]**Estimate** (SE), *p-value*

Multinomial logistic regression, using isolated LATE-NC and slow trajectory as reference categories, demonstrated significantly increased offs of fast cognitive decline in all mixed pathology groups: LATE with intermediate AD pathology (OR = 7.39, 95% CI [1.25, 43.6], p = .027), mixed AD/LATE (OR = 54.6, 95% CI [8.66, 344], p < .001), mixed LBD/LATE (OR = 32.1, 95% CI [4.64, 222], p = .001), mixed AD/LBD/LATE (OR = 140, 95% CI [15.6, 1270], p < .001), and other mixed LATE combinations (OR = 27.8, 95% CI [2.98, 259], p = .004).

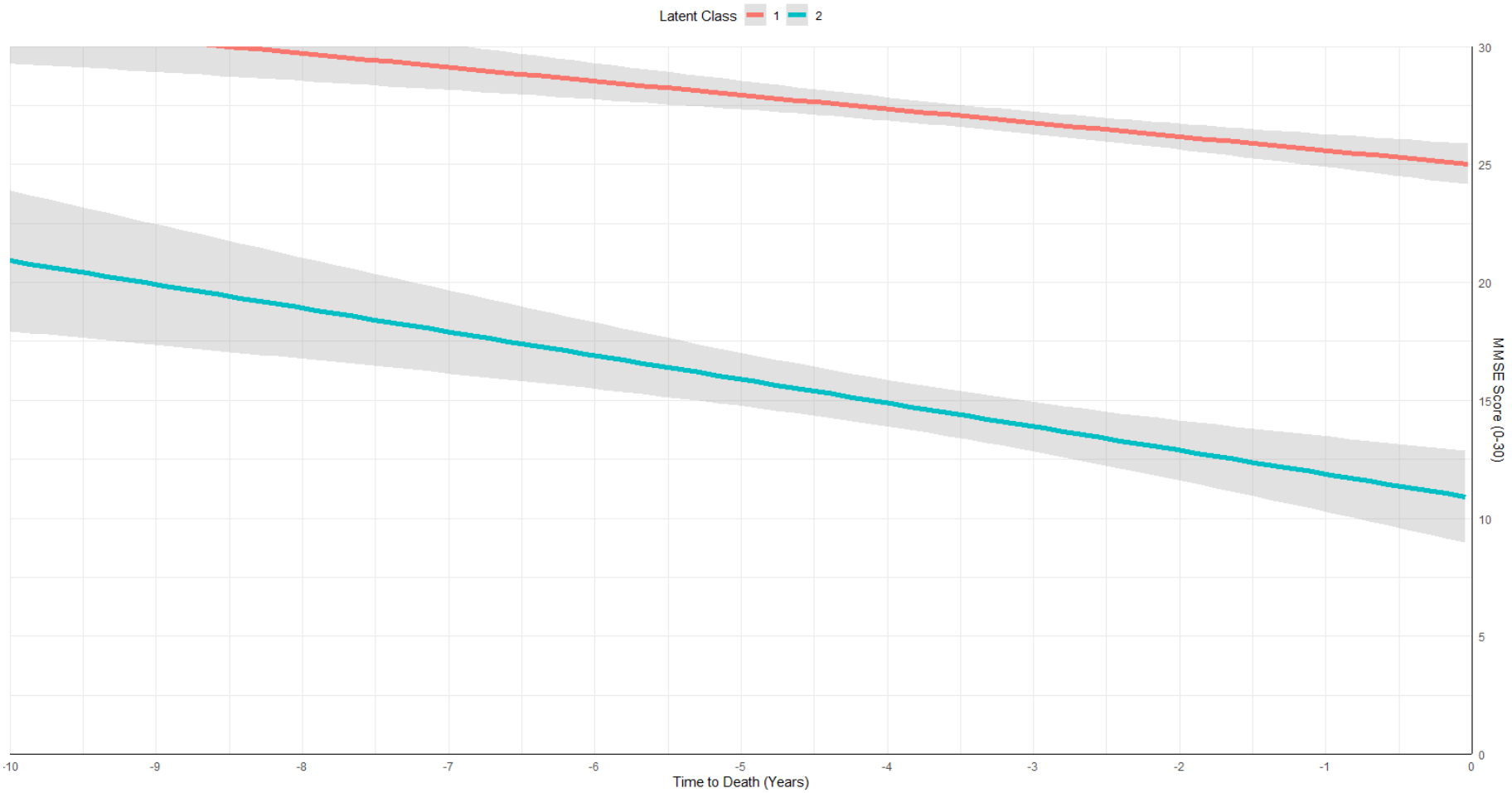

***Figure 6.4*. Cognitive Trajectories in the LATE-NC Sub-Cohort**: Two distinct classes of cognitive decline identified through latent class mixture modelling in individuals with LATE-NC pathology. Models adjust for age at death, sex, years in education, and deprivation index. Class 1 represents a slower trajectory of decline; Class 2 reflects a faster, more severe decline in MMSE scores over time.

6.3.5 Mixed Pathology

A sub-cohort of 121 cases exhibiting mixed neuropathology and sufficient longitudinal cognitive data was selected for further analysis of cognitive trajectories. Three latent class mixed models were fit to this sub-cohort to identify distinct trajectories of cognitive decline: a one-class model, a two-class model and a three-class model. Model fit was evaluated using the Bayesian Information Criterion (BIC), with lower values indicating better fit. The one class model yielded a BIC of 2319.489. The two-class model showed improved fit with a BIC of 2302.618. The three-class model did not further improve fit, yielding a higher BIC of 2315.178. Consequently, the two-class model was selected for interpretation. Model fit statistics are reported in **Table 6.14**.

***Table 6.14*. Model Fit Statistics for Mixed Pathology Models:** Model fit indices for latent class models ranging from one to six classes are presented, including number of classes (N), log-likelihood (loglik), number of parameters (npm), Bayesian Information Criterion (BIC), and the percentage distribution of cases across each latent class. Model selection was guided by BIC and class interpretability.

	G	loglik	npm	BIC	%class1	%class2	%class3	%class4
Model A	1	-1103.9	10	2319.489	100			
Model B	**2**	**-1086.37**	**14**	**2302.618**	**13.3**	**86.7**		
Model C	3	-1081.87	18	2315.178	13.3	50.0	36.7	
Model D	4	-1076.73	22	2328.778	13.3	34.2	31.7	20.8

Table *6.15* details the fixed effects estimates for each latent class, representing final MMSE score and annual rate of cognitive decline over the 10-year period, adjusted for age, sex, years of education and deprivation index. Analysis of class membership by AD pathology subgroup revealed notable differences in cognitive trajectories. Plots with individual trajectories are provided in **Appendix IV.** Class 1 (N =16, 13% of the cohort) was characterised by a non-significant intercept estimate (B = -0.59, SE = 8.73, p = 0.946) and a moderate but statistically significant rate of decline (B = -0.95, SE =0.33, p = 0.004). This class is labelled moderate due to the relatively less steep slope of decline. Class 2 (N = 105, 87%) had a higher, non-significant intercept estimate (B = 8.89, SE = 8.30, p = 0.285) and a significantly steeper rate of decline (B = -2.79, SE = 1.10, p = 0.019), thus denoted severe. Among covariates, maleness was significantly associated with lower final MMSE scores. Age,

education, and deprivation were not significantly associated with intercept or slope estimates.

Table 6.15. Latent Class Model of the Mixed Pathology Sub-Cohort: Fixed effects estimates for final MMSE (intercept) and rate of decline (slope) in the 10 years preceding death. The model adjusts for age, sex, years of education, and deprivation index. P-values indicate significance of parameter estimates. Covariates were included in the model but are not class specific.

Class Effects	**Intercept**[1]	**Slope**[1]	**Intercept vs class 2**
Class 1 (moderate)	**-0.59** (8.73), .946	**-0.95** (0.33), *.004*	**-1.91** (0.31), *<.001*
Class 2 (severe)	**8.89** (8.30), .285	**-2.79** (0.24), *< .001*	
Covariates			
Age	**0.02** (0.08), *.840*	-	-
Sex (Male)	**-2.57** (1.10), *.019*	-	-
Years in education	**-0.16** (0.16), *.330*	-	-
Deprivation	**0.19** (0.36), *.604*	-	-

[1]**Estimate** (SE), *p-value*

Table *6.16* presents the distribution of these latent classes within each neuropathological component of the mixed pathology subgroup. Notably, all 16 individuals in Class 1 exhibited both Alzheimer's disease and LATE-NC pathology. Of these, 7 also had limbic or neocortical Lewy body disease. The majority of cases in each neuropathology group fell within Class 2, indicating faster cognitive decline.

Table 6.16. Class Allocation for Mixed Pathology: Distribution of latent cognitive trajectory classes by neuropathology component within the mixed pathology subgroup. Class 1 represents slower cognitive decline; Class 2 represents faster cognitive decline. Values indicate case count and percentage within each neuropathology group.

Class Counts (%)	**AD (N = 93)**	**LBD (N = 73)**	**CVD (N = 15)**	**LATE-NC (N = 91)**
Class 1 [N = 16]	16 (17.2%)	7 (9.6%)	0 (0%)	16 (17.6%)
Class 2 [N = 105]	77 (82.8%)	66 (90.4%)	15 (100%)	75 (82.4%)

6.4 Summary

A latent class analysis of the full neuropathology cohort revealed four classes of cognitive trajectories. This included a large group of slow (or stable) decliners which accounted for approximately half the cohort. The main neuropathology groups with stable cognitive trajectories were low pathology controls, cerebrovascular disease, argyrophilic grain disease, LATE-NC and Lewy body disease. The three remaining groups of cognitive trajectories were relatively small. Fast decliners typically had Alzheimer's disease, frontotemporal lobar degeneration, LATE-NC, Lewy body disease or mixed pathology as an assigned neuropathology group. A group of Lewy body disease and LATE-NC showed a moderate trajectory of decline. A quarter of the cohort showed a rapid and extreme trajectory of cognitive decline. These cases were primarily mixed pathology, Alzheimer's disease or frontotemporal lobar degeneration.

A latent class analysis of cases with at least intermediate Alzheimer's disease pathology revealed three classes of cognitive trajectory. This included a large group of fast decliners which accounted for over half the group. The main neuropathology groups in this class were mixed AD, AD and intermediate AD in other neurodegenerative diseases. A smaller group of moderate decliners with severe impairment was also identified. Cases in this class were thirty times more likely to have mixed AD pathology than intermediate AD.

Latent class analyses of cases with Lewy body disease and LATE-NC revealed two classes of cognitive trajectory each. In both cases, mixed pathology was thirty times more likely to have a more severe trajectory of cognitive decline than pure pathology. Latent class analysis of only mixed pathology cases also revealed two trajectories of cognitive decline. Only cases with AD/LATE or AD/LBD/LATE combinations of mixed pathology were assigned to the small group (13%) representing a more severe trajectory of cognitive decline.

Although latent class models provided a more detailed categorisation of cognitive trajectories without the influence of subjective neuropathology groups, the method is primarily a descriptive and exploratory technique. As a result, there are limitations when it comes to making causal inferences. The first major limitation is that latent class models assume that each individual belongs to a single latent class which may oversimplify the complexity of cognitive decline and lead to misclassification of cases. Latent class models may not fully capture the temporal dynamics of cognitive decline as they assume that class

membership remains static over time. This assumption may not align with the progressive nature of dementia where individuals may transition between cognitive states as the disease evolves.

In addition, latent class models rely on subjective decision regarding the number and composition of latent classes which can introduce uncertainty and variability in estimated trajectories. Overfitting or underfitting leads to an inaccurate number of classes. Determining the optimal number of classes involves a balance between model fit indices, theoretical considerations, and interpretability. Missing data and incomplete follow-up can also lead to biased estimated trajectories and inaccuracies in the classification of individuals into latent classes. Latent class modelling is also sensitive to measurement errors. If the variable used is imprecise or subject to measurement error, both class assignment and the estimation of trajectory may be affected. The interpretation of results from latent class models requires careful consideration of potential biases and limitations inherent in the model assumptions and estimation procedures.

Overall, mixed pathology cases were significantly more likely to be assigned to the fastest declining group in latent class mixture models of cognitive trajectory. In all latent class models reported in this study, mixed pathology was disproportionately represented among the fast decliners. The presence of Alzheimer's pathology is a strong predictor of cognitive decline and may act synergistically with other common age-related neuropathologies, accelerating cognitive decline.

The consistent association of mixed pathology with a rapidly declining cognitive trajectory suggests that the presence of multiple neuropathologies is a strong predictor of rapid deterioration in cognition. This suggests that mixed pathology may represents a more severe form of cognitive impairment and the interaction between multiple pathological processes has a synergistic effect on cognition, resulting in faster cognitive decline and more severe reduction in cognitive functions by the end of life.

Chapter 7. Transitions Between Cognitive States in Dementia with Mixed and Concomitant Neuropathology

7.1 Background

Understanding the transitions between cognitive states in dementia, particularly in the context of mixed and concomitant pathology, is useful for identifying factors influencing disease progression. While each neuropathological subtype exhibits distinct pathological features, the exact consequences of multiple co-existing neuropathologies on specific aspects of clinical dementia remain unclear.

The presence of mixed pathology poses significant challenges for clinical diagnosis and management, as it often results in heterogeneous clinical presentations and variable rates of cognitive decline. Recent evidence suggests that the combination of different neuropathologies may exert synergistic effects on cognitive function, accelerating the trajectory of decline and exacerbating clinical symptoms (Kapasi, Decarli and Schneider, 2017, Brenowitz et al., 2017). Concomitant neuropathology further complicates the clinical picture making accurate prognosis and treatment decisions challenging (Bayram, Coughlin and Litvan, 2022).

Previous research has highlighted the association between mixed and concomitant pathology and more rapid cognitive decline in dementia, emphasising the need for a comprehensive understanding of the transitions between cognitive states in this context. While linear mixed effects models and latent class models are useful in identifying longitudinal cognitive trajectories that are theoretical and unseen without the use of statistical methods, these changes are not as readily perceptible in clinical settings as pre-existing clinical measures such as a discrete Clinical Dementia Rating (CDR) score.

Multistate modelling offers a framework to model the dynamic transitions between cognitive states in dementia and characterising the heterogenous nature of dementia progression by representing individuals as transitioning between distinct cognitive states over time. By incorporating information on neuropathological burden and composition, multistate modelling can identify key predictors of transitions between cognitive states and provide supportive evidence for more accurate prognostic decisions and personalised treatment strategies.

7.1.1 Aims and Hypotheses

To examine the contribution of mixed and concomitant post-mortem neuropathology to transitions between cognitive states of dementia, this study aimed to utilise multistate modelling to:

1. Characterise the relationship between post-mortem neuropathology and transitions to mild cognitive impairment (MCI) and dementia in the cohort.
2. Assess the relationship between levels of pathology and transitions to MCI and dementia.
3. Assess the association between co-occurring neuropathologies in Alzheimer's disease, Lewy body disease, cerebrovascular disease and LATE-NC and transitions to MCI and dementia.
4. Assess the contribution of concomitant pathology in Alzheimer's disease, Lewy body disease, cerebrovascular disease and LATE-NC to MCI and dementia.

Based on previous studies and results included in this thesis, it was hypothesised that a greater burden of pathology would be associated with a greater risk of severe dementia. It was thought that cases with multiple neurodegenerative diseases would have a greater risk of transition to dementia. It was also hypothesised that concomitant pathology would be associated with a higher risk of transition to MCI/dementia than pure pathology alone but a lower risk than mixed pathology.

7.2 Methods

7.2.1 Case Selection

This analysis included post-mortem brains donated to the Brains for Dementia Research project between 2008 and 2020. Selected cases included all participants who had reached age 65 at baseline and completed at least one Clinical Dementia Rating assessment prior to death. At the time of data locking, 617 deceased participants met these criteria and had undergone comprehensive neuropathological assessment making them suitable for inclusion in the analysis. Participants with incomplete CDR assessments or missing key covariate data were excluded from model estimation. The AD model included 412 participants (including 139 controls); the LBD model included 366 (188 controls); the CVD

model included 278 (208 controls); and the LATE-NC model included 408 participants (208 controls).

7.2.2 Variables

Cognitive state at each assessment was classified using the Clinical Dementia Rating global score (CDR-GS). A score of 0 indicated normal cognition, 0.5 indicated mild cognitive impairment (MCI), 1 indicated mild dementia, 2 indicated moderate dementia and 3 indicated severe dementia. Scores from 1 to 3 were combined to represent a single dementia state. Demographic variables included age, sex, years in full-time education, and Index of Multiple Deprivation (IMD), reflecting individual and socioeconomic factors known to influence cognitive trajectories in later life. These variables were selected based on established evidence of their influence on cognition, with age and education representing biological and cognitive reserve factors respectively.

Neuropathological diagnoses were established according to standard criteria outlined previously in Chapter 2. Alzheimer's disease pathology was defined using Thal Aβ phase, Braak NFT stage, CERAD score, and NIA-AA ADNC rating. Lewy body disease was classified using Braak LB stages. Cerebrovascular disease was graded as low, moderate, or high based on the extent of macro- and micro-vascular lesions as outlined in the VCING guidelines. LATE-NC, ARTAG, PART, and FTLD were defined as binary presence/absence variables. For each major pathology, mixed cases were defined as cases that met diagnostic criteria for more than one major neuropathological disease and concomitant pathology referred to the presence of additional findings that did not reach diagnostic thresholds. Details of neuropathological definitions and groupings are described further in Section 2.3.

For each of the four key neuropathologies (Alzheimer’s disease, Lewy body disease, LATE-NC, and cerebrovascular disease), three categorical variables were created to investigate level of neuropathological burden, number of coexisting pathologies, and the presence of concomitant pathology. Level of neuropathological burden was categorised based on NIA-AA level of Alzheimer’s disease neuropathological change, Braak Lewy body staging, VCING rating, and the presence of LATE-NC. Number of coexisting pathologies was quantified as the number of neuropathological diagnostic criteria met (with a maximum of 4). Concomitant pathology was defined as the presence of subthreshold neuropathology as previously outlined in Section 2.3.

7.2.3 Multistate Modelling

To examine transitions between states of cognition and death, a multistate hidden Markov model was applied using the *msm* package for R (Jackson, 2007). This modelling approach was selected due to its capacity to account for transitions between multiple disease states over time, while incorporating the exact timing of assessments and allowing for the possibility of non-linear, non-monotonic progression. Multistate models are particularly well suited for representing complex disease process where individuals may experience both progression and, occasionally, reversion between clinical states prior to death. Consequently, multistate modelling can be utilised to examine transitions if cognitive decline is considered a disease with multiple distinct states.

This modelling framework allowed for the examination of transition probabilities between transient disease states and an absorbing death state, based on the timing and sequence of observed cognitive assessments (Jackson, 2011).

Multistate models assume that transition probabilities depend only on the current state (Markov assumption) and that transitions occur in continuous time. These assumptions may not fully capture the complexity of cognitive decline, particularly if unobserved heterogeneity or misclassification is present. Additionally, models may be sensitive to irregular assessment intervals and right-censoring, which were accounted for using interval-censored estimation.

Two model structures were explored in this analysis, with both employing a continuous bidirectional illness-death structure in which individuals could progress or regress between three or five transient 'disease' states (cognitive impairment) prior to death (absorbing state).

7.2.4 Model Structure

Initially, a six-state model was specified to capture more nuanced degrees of dementia severity. In this model the transient states included normal cognition, mild cognitive impairment, and three states of dementia severity (mild, moderate, and severe), in addition to the absorbing state of death. Participants were assigned to these states based on reported CDR scores, as illustrated in **Figure 7.1**.

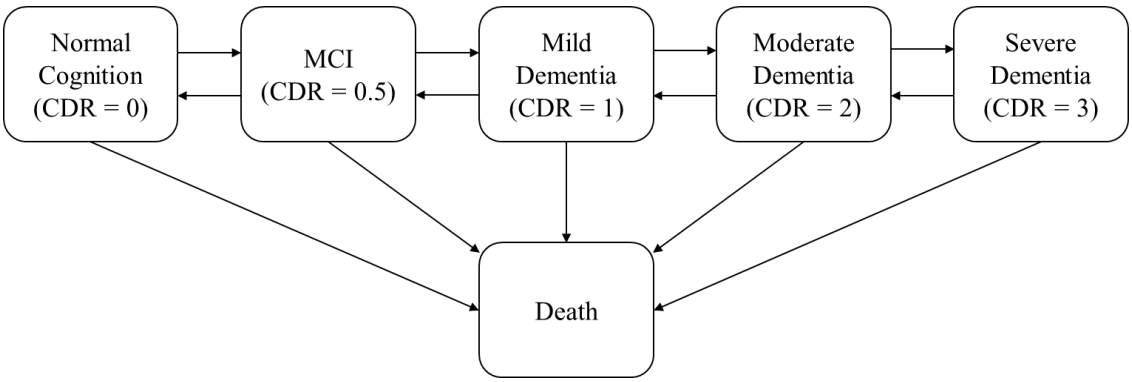

Figure 7.1. **Six-State Conceptual Diagram**: Bidirectional illness-death model illustrating transitions between five transient cognitive 'disease' states (normal cognition, mild cognitive impairment, and mild, moderate, and severe dementia), and one absorbing state (death). The model allows for both progression and potential reversion between cognitive states prior to death.

To address sample size limitations and facilitate interpretation, a simplified four-state model was also specified. This model retained normal cognition, mild cognitive impairment, and dementia as transient disease states, with all levels of dementia collapsed into a single category. Death remained the absorbing state. Appropriate state allocation of participants was again based on Clinical Dementia Rating (CDR) global scores, as outlined in **Figure 7.2**

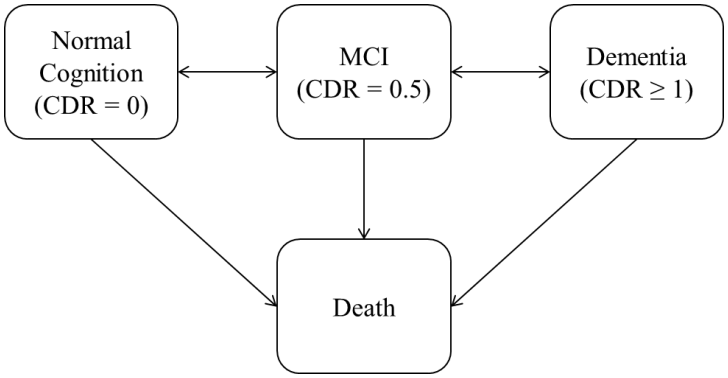

Figure 7.2. **Four-State Conceptual Diagram**: Bidirectional illness-death model illustrating transitions between three transient cognitive 'disease' states (normal cognition, mild cognitive impairment, and dementia), and one absorbing state (death). Individuals may progress or regress between cognitive states before ultimately transitioning to death.

In both models, transitions were assumed to occur in continuous time and were estimated from the observed interval between assessments. The model accommodates variable follow-up durations, in addition to right-censoring for participants who died without

transitioning through all intermediate states. The exact timing of transitions was treated as interval-censored, reflecting the fact that cognitive state was only observed at discrete clinical visits.

7.2.5 Estimation and Model Fitting

Maximum likelihood estimation was used to estimate transition intensities, and all models were run using the Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimisation algorithm as implemented in *msm*. Convergence was assessed through inspection of log-likelihood values, gradient norms, and stability of parameter estimates. Model fit was evaluated using Akaike Information Criterion (AIC), with lower values indicating better fit, and log-likelihood, with proximity to zero indicating better fit. Alternative model specifications were explored but did not improve model fit.

Transition probabilities were derived from estimated intensity matrices. Transition intensities were exponentiated to yield hazard ratios for interpretability, representing the relative risk of transitioning between cognitive states in comparison to the reference group. Ninety-five percent confidence intervals were derived from the standard errors of the estimated parameters. In cases where small sample sizes led to model convergence issues, results were interpreted with caution. Model instability was identified through non-converging log-likelihoods or excessively wide confidence intervals, and such issues were noted in results as appropriate.

7.2.6 Statistical Analysis

Adjusted models were also constructed to examine the influence of covariates including age, sex, years of education, and deprivation index. These were incorporated as proportional effects on transition intensities, allowing for assessment of how individual characteristics modified the likelihood of transitioning between cognitive states. Demographic and neuropathology variables included as covariates are described in more depth in Section 2.3 and remain the same as in all previous chapters.

To examine the effect of specific neuropathologies on transitions between cognitive states, three separate models were constructed for each major neuropathology group: Alzheimer's disease, Lewy body disease, cerebrovascular disease, and LATE-NC. Each model incorporated a different categorical variable capturing either the presence and severity of

pathology, the presence of co-occurring neuropathologies, or the presence of concomitant low-level pathology. All models were adjusted for age and years of education and used a low pathology-specific reference group consisting of participants with low overall neuropathology burden and absent of the neuropathology being examined. All analyses were conducted using R version 4.3.2, with the *msm* package.

7.3 Results

At study entry, 227 participants were classified as cognitively normal, 88 had mild cognitive impairment, 95 had mild dementia, 76 had moderate dementia, and 113 had severe dementia. By final assessment prior to death, 247 participants had severe dementia,62 had moderate dementia, 45 had mild dementia, 81 had mild cognitive impairment and 164 remained cognitively normal.

As with the six-state model, 227 participants were classified as cognitively normal controls and 88 had mild cognitive impairment, and 284 had dementia at study entry. By the final assessment prior to death, 354 participants had progressed to dementia, 81 had mild cognitive impairment and 164 remained cognitively normal. Transitions between cognitive states for the four-state model over the follow up period are summarised in **Table 7.1**.

***Table 7.1*. State Transitions in the Unadjusted Four-State Model:** Observed transitions between cognitive states across the follow-up period. Values indicate the number of individual transitions from each cognitive state (rows) to subsequent states (columns), including transitions to death. Transitions reflect observed movement between states based on longitudinal assessments, unadjusted for covariates. Multiple transitions per individual are possible across different time points.

	To Normal Cognition	To MCI	To Dementia	To Death
From Normal cognition	380	76	17	164
From MCI	29	147	65	81
From Dementia	1	11	758	354

These figures reflect observed transitions based on repeated Clinical Dementia Rating assessments. Individuals could experience multiple transitions between states over time. All participants ultimately transitioned to death. Further information is included in the Appendix.

7.3.1 Demographics

Participants were followed up for 4.51 years ± 2.23 (0.97, 11.4), with a median of 3 visits per participant (range: 1 – 10). **Table 7.2** summarises demographic and clinical characteristics of participants grouped by final cognitive classification: normal cognition (N = 164), mild cognitive impairment (MCI; N = 81), and dementia (N = 354).

Participants with MCI were the oldest at death (mean = 89.0 years, SD = 7.40), followed by those with normal cognition (85.9, SD = 7.51), and those with dementia (85.5, SD = 8.00). The median age ranged from 86.4 in the cognitively unimpaired to 90.9 years in MCI and 85.9 years in dementia. Sex distribution also varied across groups, with females representing 56.1% (N = 92) of the cognitively normal group, 54.3% (N = 44) of the MCI group, but only 42.9% (N = 152) of those with dementia. Years spent in full time education was slightly higher in the cognitively unimpaired group (mean = 13.3, SD =3.01) compared to MCI (13.2, SD = 3.53), and notably lower in dementia (12.0, SD = 3.17). Index of Multiple Deprivation (IMD) was similar across groups, with a consistent median value of 2 (range: 1 – 5).

***Table 7.2*. Overview of Demographics by Cognitive Classification at Death:** Demographic and clinical characteristics of participants grouped by final cognitive status at death: normal cognition (N = 164), mild cognitive impairment (MCI; N = 81), and dementia (N = 354). Values are reported as mean (standard deviation) for continuous variables, or median [range] for categorical variables.

	Normal Cognition (N = 164)	**Mild Cognitive Impairment (N = 81)**	**Dementia (N = 354)**
Age (years)	85.9 (7.51)	89.0 (7.40)	85.5 (8.00)
	86.4 [68.7, 103]	90.9 [70.2, 104]	85.9 [67.4, 104]
Sex (Female)	92 (56.1%)	44 (54.3%)	152 (42.9%)
Education (years)	13.3 (3.01)	13.2 (3.53)	12.0 (3.17)
IMD (1-5)	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]
Time from baseline to death (years)	5.26 (2.06)	5.12 (2.36)	4.03 (2.15)
	5.15 [0.994, 10.3]	5.51 [0.197, 11.4]	3.75 [0.222, 10.1]
Number of visits	3.00 [1.00, 10.0]	4.00 [1.00, 8.00]	4.00 [1.00, 10.0]

Time from baseline to death showed a decreasing trend with decline in cognition: mean durations were 5.26 years (SD = 2.06) for normal cognition, 5.12 years (SD = 2.36) for MCI, and 4.03 years (SD = 2.15) for dementia (**Table 7.2**). Median durations were 5.15 years [0.99-10.3], 5.51 years [0.20-11.4], and 3.75 years [0.22-10.1] respectively. The number of follow-up visits was broadly similar across groups with a median of 3 [1-10] for normal cognition, and 4 for MCI [1-8] and dementia [1-10].

Neuropathological characteristic as postmortem neuropathological assessment also differed substantially by final cognitive state and are outlined in

Table 7.3. Alzheimer's disease related neuropathological changes increased across the cognitive continuum. Median Thal Aβ phase increased from 2 [0-5] in normal cognition, to 3 [0-5] in MCI, and 5 [0-5] in dementia. Similarly. Braak neurofibrillary tangle (NFT) stage rose from 2 [0-5] to 3. [1-6] and 5 [0-6] respectively. Median CERAD scores also showed consistent increase across cognitive states: 0 [0–3] in normal cognition, 1.00 [0–3] in MCI, and 3.00 [0–3] in dementia. Lewy body pathology (Braak LB stage) remained low across all groups.

Table 7.3. **Overview of Neuropathology by Final Cognitive State**: Summary of neuropathological findings across participants stratified by cognitive status at the final clinical assessment prior to death. Semi-quantitative staging scores for Alzheimer's disease–related pathology (Thal Aβ phase, Braak neurofibrillary tangle [NFT] stage, and CERAD score) and Lewy body pathology (Braak LB stage) are presented as medians [range]. Binary variables reflect the presence of specific pathologies and are reported as counts (%).

	Normal Cognition (N = 164)	**Mild Cognitive Impairment (N = 81)**	**Dementia (N = 354)**
Thal AB phase	2.00 [0, 5.00]	3.00 [0, 5.00]	5.00 [0, 5.00]
Braak NFT stage	2.00 [0, 5.00]	3.00 [1.00, 6.00]	5.00 [0, 6.00]
CERAD score	0 [0, 3.00]	1.00 [0, 3.00]	3.00 [0, 3.00]
Braak LB stage	0 [0, 6.00]	0 [0, 6.00]	0 [0, 6.00]
Infarcts (VCING 1)	18 (11.0%)	12 (14.8%)	39 (11.0%)
CAA (VCING 2)	34 (20.7%)	30 (37.0%)	146 (41.2%)
Arteriolosclerosis (VCING 3)	31 (18.9%)	16 (19.8%)	96 (27.1%)
LATE-NC	14 (8.5%)	15 (18.5%)	157 (44.4%)
FTLD	6 (3.7%)	5 (6.2%)	31 (8.8%)
ARTAG	6 (3.7%)	7 (8.6%)	22 (6.2%)
Hippocampal sclerosis	1 (0.6%)	3 (3.7%)	41 (11.6%)
PART	61 (37.2%)	19 (23.5%)	31 (8.8%)

Vascular and non-AD pathologies also varied by cognitive status. The frequency of large subcortical infarcts was 11% in both normal cognition (N = 12) and dementia (N = 39), but slightly higher at 4.8% in MCI. Cerebral amyloid angiopathy (CAA) was observed in 20.7% of those with normal cognition, increasing to 37.0% in MCI and 41.2% in dementia. Arteriolosclerosis prevalence rose from 18.9% in normal cognition, to 19.8% in MCI, and 27.1% in dementia. LATE-NC was present in only 8.5% of cognitively normal individuals, 18.5% of those with MCI, and in 44.4% of dementia cases. Hippocampal sclerosis was rare in individuals without dementia (0.6% in normal cognition and 3.7% in MCI) but more frequent

in dementia (11.6%). Conversely, primary age-related tauopathy (PART) decreased in prevalence with greater impairment in cognition, present in 37.2% of cognitively normal individuals, 23.5% of those with MCI, and only 8.8% of those with dementia. Frontotemporal lobar degeneration (FTLD) and ARTAG showed no consistent pattern, occurring at low frequencies across all groups.

7.3.2 Demographics

At baseline, the mean age of the cohort was 81.4 years (SD = 7.89, [65, 102]). rising to 86.1 years (SD = 7.86, [67, 104]) by final assessment. In both the four-state model and six-state models increasing age was significantly associated with a greater risk of progression from normal cognition to mild cognitive impairment. As reported in **Table 7.4**, the hazard ratio for this transition in the four-state model was 1.08 (95% CI [1.05, 1.12]), indicating an 8% increase in risk per year of age. This association was replicated in the six-state model, with the same HR for the transition from normal cognition to MCI (**Table 7.5**). In contrast, age was not significantly associated with risk of subsequent transitions, including progression from MCI to dementia or from one dementia stage to another.

***Table 7.4*. Effect of Demographic Covariates on Cognitive Transitions in the Four-State Model**: Hazard ratios (HRs) and 95% confidence intervals (CIs) for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia, based on a four-state multistate model. Models are adjusted for age, sex (reference: female), years in full-time education, and Index of Multiple Deprivation. A hazard ratio >1 indicates increased risk of transition per unit increase in the covariate.

	Normal Cognition to Mild Cognitive Impairment	**MCI to All Dementia**
Baseline	0.13 (0.10, 0.17)	0.28 (0.21, 0.36)
Age (years)	**1.08 (1.05, 1.12)**	0.99 (0.96, 1.03)
Sex (male)	0.85 (0.54, 1.33)	1.09 (0.65, 1.83)
Education (years)	0.98 (0.92,1.05)	**0.89 (0.81, 0.97)**
IMD	0.86 (0.71, 1.05)	0.95 (0.76, 1.20)

Of the 599 cases included from the original neuropathology cohort, 288 (48.1%) were female. In both models, sex was not significantly associated with transition risk to any state.

In the four-state model (**Table 7.4**), male sex was associated with a slightly lower risk of transition to MCI (HR = 0.85, 95% CI: 0.54–1.33) and a higher, but non-significant, risk of progression from MCI to dementia (HR = 1.09, 95% CI: 0.65–1.83). The six-state model yielded similar findings across transitions (**Table 7.5**), including from MCI to mild dementia (HR = 1.14, 95% CI: 0.65–2.00) and from moderate to severe dementia (HR = 0.71, 95% CI: 0.47–1.08).

***Table 7.5*. Effect of Demographic Covariates on Transitions Between Cognitive States in the Six-State Model**: Hazard ratios (HRs) and 95% confidence intervals (CIs) derived from a six-state multistate model. Model adjusted for age, sex (reference: female), years in full-time education, and Index of Multiple Deprivation. A hazard ratio >1 indicates increased risk of transition per unit increase in the covariate.

	Normal Cognition to MCI	**MCI to Mild Dementia**	**Mild to Moderate Dementia**	**Moderate to Severe Dementia**
Baseline	0.14 (0.11, 0.18)	0.22 (0.17, 0.30)	0.72 (0.59, 0.89)	0.92 (0.75, 1.12)
Age	**1.08 (1.05, 1.12)**	1.00 (0.96, 1.03)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)
Sex (male)	0.86 (0.55, 1.36)	1.14 (0.65, 2.00)	0.81 (0.50, 1.29)	0.71 (0.47, 1.08)
Education	0.99 (0.92, 1.05)	**0.89 (0.81, 0.97)**	0.99 (0.93,1.05)	**1.09 (1.03, 1.16)**
IMD	0.87 (0.71, 1.06)	0.88 (0.68, 1.12)	1.03 (0.88, 1.20)	1.09 (0.94, 1.27)

Mean time spent in full time education was 12.5 years (SD = 3.23, [0, 25]). Educational attainment had a protective effect in both models. In the four-state model, each additional year of education was associated with a significantly reduced risk of transition from MCI to dementia (HR = 0.89, 95% CI: 0.81–0.97; **Table 7.4**). This finding was reflected in the six-state model, where education was also protective for the initial transition from MCI to mild dementia (HR = 0.89, 95% CI: 0.81–0.97; **Table 7.5**). Interestingly, education was associated with a 9% increase in risk of progression from moderate to severe dementia in the six-state model (HR = 1.09, 95% CI: 1.03–1.16), a potentially counterintuitive finding that may reflect underlying differences in the progression of clinically manifest dementia among individuals with higher cognitive reserve.

The median index of multiple deprivation quintile of the cohort was 2, indicating lower than average deprivation. Socioeconomic status, indexed using the Index of Multiple Deprivation (IMD), was not significantly associated with any transition between cognitive states. Across both models, hazard ratios were close to 1 and confidence intervals crossed zero (**Table 7.4** and **Table 7.5**), suggesting no consistent relationship between deprivation and cognitive decline within this cohort. The final multistate model (four-states) showed good fit, with a log-likelihood of -1801.41 and an Akaike Information Criterion (AIC) of 3672.823. For all subsequent analyses, only age and education were included as covariates to enable model convergence.

7.3.3 Transitions in Individual Neuropathologies

Several individual neuropathological markers were significantly associated with risk of transitions between cognitive states (**Table 7.6**; **Table 7.7**). In both the four-state and six-state models, Alzheimer's disease related neuropathological changes demonstrated the strongest associations with progression risk.

Thal Aβ phase was significantly associated with approximately a 25% increase in risk of transition from MCI to dementia per additional phase in both models (HR = 1.24, 95% CI [1.07, 1.45] in the four-state; HR = 1.25, 95% CI [1.07, 1.47] in the six-state model). No significant change in risk was found for any earlier or later transitions (**Table 7.6**; **Table 7.7**).

Braak NFT stage showed a consistent, dose-dependent effect across models. Each unit increase in NFT stage was associated with a 32% increase in risk of transition from normal cognition to MCI (HR = 1.32, 95% CI [1.11, 1.57]) and a 33% increase in risk of transition to dementia (1.33 [1.14, 1.55]) in the four-state model (**Table 7.6**). In the six-state model, NFT stage was similarly associated with a 31% increase in risk of transition from normal cognition to MCI (HR = 1.31, 95% CI [1.10, 1.57]) and a 37% increase in risk of transition from MCI and mild dementia (HR = 1.37, 95% CI [1.16, 1.61]), but not further transitions (**Table 7.7**).

CERAD score, reflecting neuritic plaque burden, was associated with a 30% increase in risk of transition to MCI (HR = 1.30, 95% CI [1.05, 1.61]) and a 47% increase in risk of transition to dementia (HR = 1.47, 95% CI [1.21, 1.78]) per point increase in score in the four-state model (**Table 7.6**). These associations were reflected in the six-state model across three transitions (**Table 7.7**): normal cognition to MCI (HR = 1.29, 95% CI [1.04, 1.59]), MCI to mild dementia

(HR = 1.48, 95% CI [1.20, 1.83]), and mild dementia to moderate dementia (HR = 1.24, 95% CI [1.04, 1.48]).

When CERAD score was treated categorically, frequent plaques were associated with markedly higher risks. In the four-state model, there was a 30% increase in risk of transition to MCI (1.30 [1.05, 1.61]) and a 47% increase in risk of transition to dementia (1.47 [1.21, 1.78]). In the six-state model, there was a 236% increase in risk of transition from normal cognition to MCI (2.36 [1.24, 4.48]), a 157% increase in risk of transition from MCI to mild dementia (2.57 [1.40, 4.69]) and an 87% increase in risk of transition from mild to moderate dementia (1.87 [1.09, 3.22]).

Alzheimer's disease neuropathological change (ADNC) rating showed significant effects when stratified. In the four-state model, intermediate ADNC was associated with a 132% increase in risk of transition to MCI and high ADNC was associated with a 329% increase in risk of transition to dementia. In the six-state model, this increase in risk was only associated with the initial transition to dementia (5.04, [1.38, 18.5]). Low ADNC was not associated with any significant change in risk of transition between cognitive states in either model.

Braak Lewy body (LB) stage was significantly associated with a 12% increase in risk of transition from MCI to dementia (1.12 [1.01, 1.23]) per Braak stage in the four-state model (**Table 7.6**). Each unit increase was associated with a 14% increase in risk of transition from MCI to mild dementia (1.14 [1.02, 1.27]) in the six-state model (**Table 7.7**). No significant associations were observed in later transitions. When analysed categorically, only Braak LB stage 6 showed a significant increase in risk of transition from MCI to dementia (2.39 [1.14, 5.02]) compared to Braak LB stage 0, highlighting the role of extensive Lewy body pathology in accelerating cognitive decline.

Among vascular pathologies, only large subcortical infarcts were significantly associated with increased risk of progression from MCI to dementia (HR = 1.93, 95% CI [1.10, 3.39]) in the four-state model (**Table 7.6**). This indicates that the presence of large subcortical infarcts increases the risk of transition to dementia by 93%. No significant associations were seen in the six-state model for large subcortical infarcts, or any other vascular markers were not independently associated with transition risk (**Table 7.7**).

None of the additional pathologies included (LATE-NC, frontotemporal lobar degeneration, aging-related tau astrogliopathy, hippocampal sclerosis, or primary age-related tauopathy) showed significant associations with cognitive transitions in either model (**Table 7.6**; **Table 7.7**), with the exception of a reduced risk in the final transition (moderate to severe dementia) associated with ARTAG (HR = 0.52, 95% CI [0.29, 0.95]).

Overall, the most robust and consistent predictors of clinical progression were markers of Alzheimer's disease pathology, particularly Braak NFT stage and CERAD score. These associations were most prominent during earlier clinical transitions (e.g. normal cognition to MCI, and MCI to mild dementia). As the changes in risk were primarily associated with the initial transition to dementia, only the output of simplified four-state model (normal cognition, mild cognitive impairment, dementia, and death) are reported for subsequent analyses. Results for the four-state and six-state models are reported in **Table 7.6** and **Table 7.7** respectively.

***Table 7.6*. Association Between Neuropathological Variables and Clinical Transitions:** Hazard ratios (95% confidence interval) derived from four-state multistate models examining the effect of individual neuropathologies on the risk of clinical transition from normal cognition to mild cognitive impairment (MCI), and from MCI to all-cause dementia. Models are adjusted for age and years of education. HR > 1 indicates increased risk of transition per unit increase or presence of pathology.

Covariate	Normal to MCI	MCI to All Dementia
Thal Aβ phase	1.13 (0.98, 1.30)	**1.24 (1.07, 1.45)**
Braak NFT stage	**1.32 (1.11, 1.57)**	**1.33 (1.14, 1.55)**
CERAD score	**1.30 (1.05, 1.61)**	**1.47 (1.21, 1.78)**
Braak LB stage	1.10 (0.97, 1.26)	**1.12 (1.01, 1.23)**
Large subcortical infarcts	1.22 (0.65, 2.32)	**1.93 (1.10, 3.39)**
Cerebral amyloid angiopathy (CAA)	1.04 (0.63, 1.71)	0.94 (0.57, 1.55)
Arteriolosclerosis	1.02 (0.59, 1.76)	1.55 (0.90, 2.68)
LATE-NC	1.36 (0.76, 2.41)	1.32 (0.80, 2.18)
Frontotemporal lobar degeneration (FTLD)	1.43 (0.55, 3.73)	1.65 (0.70, 4.02)
Aging-related tau astrogliopathy (ARTAG)	1.35 (0.58, 3.14)	0.56 (0.17, 1.85)
Hippocampal sclerosis (HpSc)	2.05 (0.56, 7.59)	1.44 (0.46, 4.49)
Primary age-related tauopathy (PART)	0.73 (0.42, 1.24)	0.59 (0.30, 1.17)

***Table 7.7*. Association Between Neuropathological Variables and Clinical Transitions**: Six-state multistate model results examining the impact of individual neuropathologies on transitions between cognitive states. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented for transitions from normal cognition to MCI, MCI to mild dementia, mild to moderate dementia, and moderate to severe dementia. All models are adjusted for age and years in full-time education. HR > 1 indicates increased risk of transition per unit increase in pathology stage or presence of pathology.

	Normal to MCI	MCI to Mild Dementia	Mild to Moderate Dementia	Moderate to Severe Dementia
Thal Aβ phase	1.13 (0.97, 1.30)	**1.25 (1.07, 1.47)**	1.11 (0.96, 1.29)	0.99 (0.86, 1.13)
Braak NFT stage	**1.31 (1.10, 1.57)**	**1.37 (1.16, 1.61)**	1.11 (0.98, 1.25)	0.96 (0.84, 1.09)
CERAD score	**1.29 (1.04, 1.59)**	**1.48 (1.20, 1.83)**	**1.24 (1.04, 1.48)**	1.04 (0.87, 1.23)
Braak LB stage	1.10 (0.96, 1.25)	**1.14 (1.02, 1.27)**	1.03 (0.95, 1.12)	0.99 (0.92, 1.07)
Infarcts	1.22 (0.64, 2.32)	1.93 (0.96, 3.87)	0.77 (0.40, 1.48)	0.90 (0.48, 1.68)
Cerebral amyloid angiopathy (CAA)	1.05 (0.64, 1.73)	0.87 (0.50, 1.51)	1.33 (0.84, 2.12)	1.27 (0.83, 1.95)
Arteriolosclerosis	1.02 (0.59, 1.77)	1.68 (0.93, 3.01)	0.81 (0.49, 1.34)	0.93 (0.59, 1.47)
LATE-NC	1.35 (0.76, 2.41)	1.33 (0.78, 2.27)	1.37 (0.91, 2.07)	0.73 (0.51, 1.06)
Frontotemporal lobar degeneration (FTLD)	1.36 (0.51, 3.63)	1.89 (0.76, 4.71)	2.18 (0.78, 6.09)	2.01 (0.96, 4.20)
Aging-related tau astrogliopathy (ARTAG)	1.39 (0.60, 3.21)	0.47 (0.14, 1.54)	2.00 (0.73, 5.44)	**0.52 (0.29, 0.95)**
Hippocampal sclerosis (HpSc)	2.22 (0.61, 8.06)	1.26 (0.32, 4.91)	0.91 (0.45, 1.84)	0.79 (0.46, 1.35)
Primary age-related tauopathy (PART)	0.73 (0.43, 1.26)	0.59 (0.29, 1.20)	0.66 (0.38, 1.16)	1.17 (0.55, 2.50)

[1]**Hazard Ratio** (95% CI)

7.3.4 Transitions in Neurodegenerative Diseases

A multistate model was used to assess the effect of primary neuropathology on transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia (**Table 7.8**; **Figure 7.3**). Neuropathologies included Alzheimer's disease (AD), argyrophilic grain disease (AGD), cerebrovascular disease (CVD), frontotemporal lobar degeneration (FTLD), limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC), Lewy body disease (LBD), and mixed pathology (two or more coexisting major pathologies). The model was adjusted for age and years in full-time education, and comparisons were made against a reference group of low pathology controls (N = 206, 34.4%).

In this model (logLik = -1121.382, AIC = 1943.28), mixed pathology (N = 186, 31.1%) showed a 136% increase in risk of transition to mild cognitive impairment (HR = 2.36, 95% CI [1.21, 4.63]) and a 278% increase in risk of transition to dementia (HR = 3.78, 95% CI [1.99, 7.16]). Alzheimer's disease (N = 75, 12.5%) was associated with a 168% increase in risk of transition to mild cognitive impairment (Hazard Ratio = 2.68, 95% CI [1.09, 6.59]) and a 234% increase in risk of transition to dementia (HR = 3.34, 95% CI [1.41, 7.91]).

Cerebrovascular disease (N = 21, 3.5%) was associated with a 150% increase in risk of transition to mild cognitive impairment (2.50 [1.16, 5.35]) and a 239% increase in risk of transition to dementia (3.39 [1.45, 7.92]). Lewy body disease (N = 37, 6.2%) was associated with a 184% increase in risk of transition to mild cognitive impairment [2.84 (1.24, 6.45]) but was not associated with any significant increase in risk of transition to dementia.

Argyrophilic grain disease (N = 19, 3.2%), frontotemporal lobar degeneration (N = 13, 2.2%), and LATE-NC (N = 42, 7.0%) were not associated with any statistically significant changes in risk of transition in this model. For FTLD, the very wide confidence interval for the transition to MCI (HR = 2.76, 95% CI [0.00, 1540]) suggests non-convergence of the model for this category, likely due to small sample size and the higher probability that individuals with FTLD entered the study after developing dementia. While this model estimates the effect of dominant pathology at autopsy on clinical progression, it does not account for combinations of mixed pathology or concomitant pathology. Results are summarised in **Table 7.8** and illustrated in **Figure 7.3**.

***Table 7.8* Association Between Primary Neuropathology and Risk of Transition to MCI and Dementia:** Hazard ratios (95% confidence interval) from a four-state model evaluating the risk of clinical transition from normal cognition to mild cognitive impairment (MCI), and from MCI to all-cause dementia. Primary neuropathology was included as a categorical variable, with a low pathology control group serving as the reference category. The model was adjusted for age and years in full-time education. An HR > 1 indicates increased risk of transition compared to low pathology controls.

	Normal to MCI	**MCI to All Dementia**
Baseline Transition Intensity	0.18 (0.13, 0.25)	0.31 (0.24, 0.40)
Age	**1.07 (1.03, 1.11)**	1.00 (0.97, 1.03)
Education	0.97 (0.91, 1.04)	**0.88 (0.81, 0.96)**
Alzheimer's disease	**2.68 (1.09, 6.59)**	**3.34 (1.41, 7.91)**
Argyrophilic grain disease	1.45 (0.43, 4.92)	2.67 (0.85, 8.42)
Cerebrovascular disease	**2.50 (1.16, 5.35)**	**3.39 (1.45, 7.92)**
Frontotemporal lobar degeneration	2.76 (0.00, 1540)	2.67 (0.47, 15.1)
LATE-NC	1.65 (0.71, 3.83)	0.68 (0.21, 2.22)
Lewy body disease	**2.84 (1.24, 6.45)**	1.70 (0.61, 4.78)
Mixed pathology	**2.36 (1.21, 4.63)**	**3.78 (1.99, 7.16)**

[1]**Hazard Ratio** (95% Confidence Interval).

N.B. The model for frontotemporal lobar degeneration did not fully converge due to limited data and estimates should be interpreted with caution.

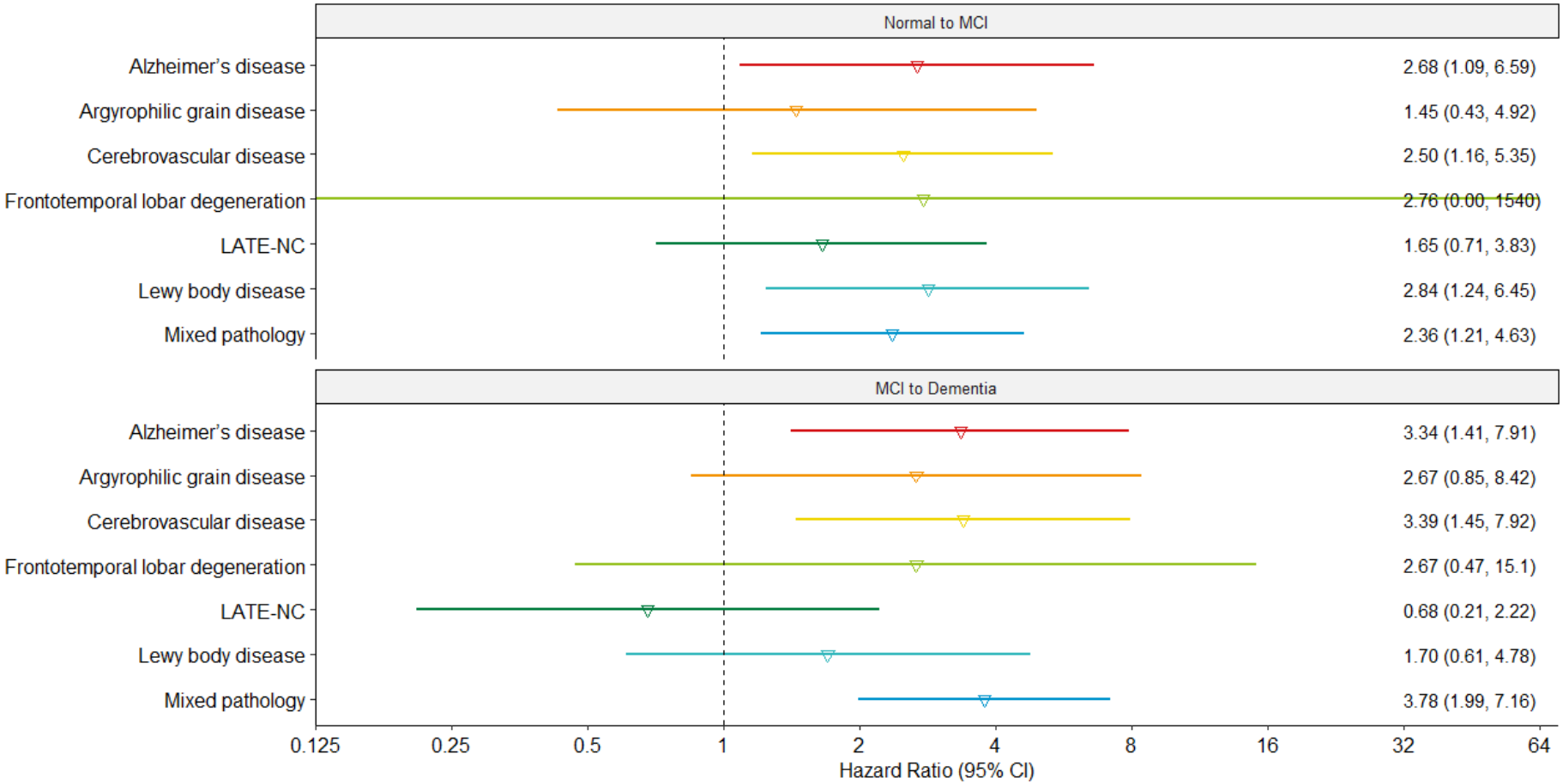

Figure 7.3 **Risk of Cognitive Transition by Primary Neuropathology**: Hazard ratios with 95% confidence intervals for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia, derived from a multistate model including neuropathological diagnosis as a categorical variable. The model is adjusted for age and years of education. The reference group is individuals with low neuropathological burden. Note: The estimate for frontotemporal lobar degeneration (FTLD) did not converge due to small sample size and instability in the model.

7.3.5 Transitions in Alzheimer's disease

To evaluate the influence of Alzheimer's disease (AD) pathology on cognitive decline, three separate models were constructed, each incorporating a different categorical variable describing severity, mixed pathologies and presence of additional low-level pathology. All models were adjusted for age and years of education. A common reference group of individuals with low level pathology (N = 139) was used in all three models.

In the first model, AD pathology was grouped by severity (logLik = -934.2631; AIC = 1985.378). Individuals with intermediate Alzheimer's disease pathology alone (i.e. no additional neuropathological diagnoses; N = 46) was associated with a 214% increase in risk of transition to mild cognitive impairment (3.14, [1.52, 6.48]), whereas high Alzheimer's disease (N = 75) was associated with a 284% increase in risk of transition to dementia (3.84, [1.57, 9.40]). Mixed Alzheimer's disease (i.e. Alzheimer's disease and at least one additional neuropathological diagnosis) was associated with significant increases in risk of transition to both MCI (2.73, [1.14, 6.54]) and dementia (3.04, [1.39, 6.62]).

The second model examined co-occurring major neuropathologies. In this analysis (logLik = -829.3686; AIC = 1742.737), all AD subgroups were significantly associated with increased risk of transition to dementia: Alzheimer's disease alone (4.32 [1.91, 9.77]), AD with one additional neuropathological diagnosis (3.22 [1.58, 6.60]), and AD with multiple additional neuropathologies (4.08 [1.43, 11.6]). No subgroup showed a statistically significant increase in risk of transition to MCI. The third model split AD cases based on the presence of concomitant low-level pathology. In this model (logLik = -894.6544; AIC = 1823.375), individuals with pure Alzheimer's disease remained associated with a significant increase in transition to dementia (3.53 [1.45, 8.62]) but Alzheimer's disease with concomitant low-level pathology was associated with increases in risk of transition to both MCI (8.85 [1.94, 40.4]) and dementia (6.23 [1.64, 23.6]). Mixed Alzheimer's disease remained associated with increased risk of transition to dementia (3.16 [1.63, 6.13]).

Across all three models, the presence of AD pathology was consistently associated with increased risk of progression to dementia, especially when co-pathologies were also present. The impact on earlier transition to MCI was more variable and appeared more pronounced when low-level concomitant pathology was included. Results from these three models are shown in **Table 7.9** and illustrated in **Figure 7.4**.

***Table 7.9*. Risk of Cognitive Transition in Alzheimer's Disease and Co-Pathologies:** Hazard ratios with 95% confidence intervals for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia. Estimates are derived from three multistate models evaluating the effect of Alzheimer's disease (AD) pathology with varying levels of severity, co-occurring neuropathologies, and concomitant neuropathologies. Analyses are adjusted for age and years in full-time education. The reference group is low pathology controls.

	Normal to MCI	**MCI to Dementia**
Intermediate Alzheimer's disease pathology (N = 46)	**3.14 (1.52, 6.48)**	1.48 (0.54, 4.07)
Alzheimer's disease (N = 75)	2.21 (0.78, 6.29)	**3.84 (1.57, 9.40)**
Mixed Alzheimer's disease (N = 152)	**2.73 (1.14, 6.54)**	**3.04 (1.39, 6.62)**
Multiple pathology		
Alzheimer's disease (N = 75)	1.77 (0.66, 4.77)	**4.32 (1.91, 9.77)**
Alzheimer's disease + one co-occurring neuropathology (N = 96)	1.68 (0.62, 4.55)	**3.22 (1.58, 6.60)**
Alzheimer's disease + more than one co-occurring neuropathology (N = 56)	3.39 (0.85, 13.5)	**4.08 (1.43, 11.6)**
Concomitant pathology		
Pure Alzheimer's disease (N = 47)	1.14 (0.33, 3.93)	**3.53 (1.45, 8.62)**
Alzheimer's disease with additional low-level pathology (N = 28)	**8.85 (1.94, 40.4)**	**6.23 (1.64, 23.6)**
Mixed Alzheimer's disease (N = 152)	2.13 (0.93, 4.88)	**3.16 (1.63, 6.13)**

[1]**Hazard Ratio** (95% CI)

N.B.: "Pure AD" refers to AD pathology in the absence of other major co-pathologies; "low-level pathology" refers to subthreshold findings not meeting criteria for any major diagnostic group.

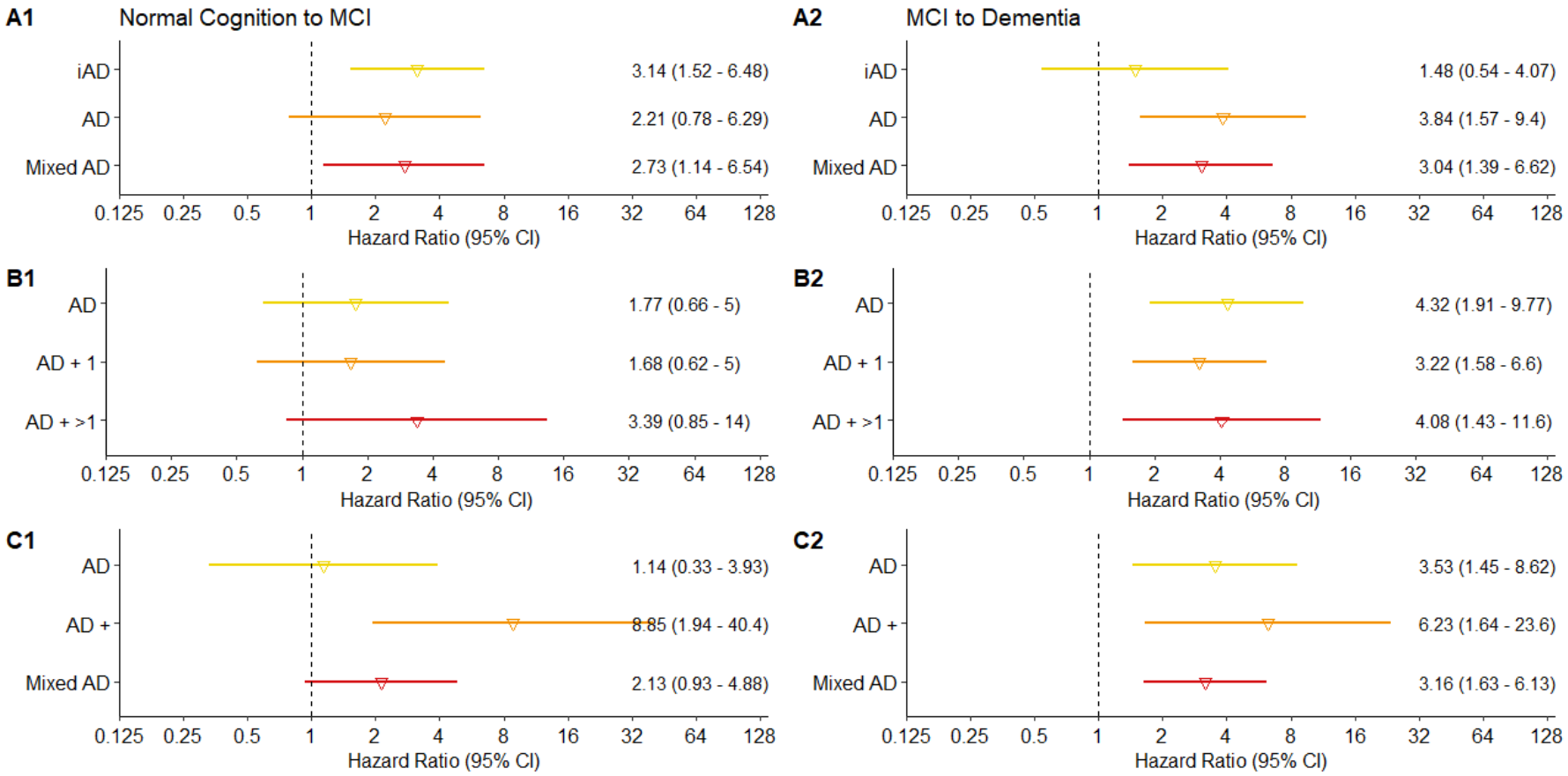

***Figure 7.4*. Transitions in Alzheimer's disease:** Hazard ratios (95% CI) for transitions from normal cognition to mild cognitive impairment (MCI), and MCI to dementia in: (A1-2) Intermediate AD (iAD), Alzheimer's disease (AD), and mixed Alzheimer's disease (Mixed AD); (B1-2) Alzheimer's disease (AD), Alzheimer's disease with one additional pathology (AD + 1), Alzheimer's disease with more than one additional pathology (AD + >1); (C1-2) Alzheimer's disease (AD), Alzheimer's disease with concomitant low-level pathology (AD +), mixed Alzheimer's disease (Mixed AD). All models are adjusted for age and years of education, with low pathology controls serving as the reference group. "Pure AD" refers to Alzheimer's disease in the absence of other major co-pathologies.

7.3.6 Transitions in Lewy body disease

To evaluate the impact of Lewy body disease on cognitive decline, three separate models were constructed, each incorporating a different categorical variable describing the presence/severity, co-occurrence with other neuropathologies, or concomitant pathology. All models were adjusted for age and years of education. A common reference group of individuals with low overall neuropathological burden (N = 188) was used in all three models.

In the severity model (logLik = -1298.32; AIC = 2439.82), neither incidental Lewy body disease (N = 38) nor Lewy body disease (N = 37) was associated with any significant change in risk of transition to mild cognitive impairment or dementia, compared to low pathology controls. In contrast, mixed Lewy body disease (N = 103) was associated with a 183% increase in risk of transition to MCI (2.83 [1.17, 6.86]) and a 334% increase in risk of transition to dementia (4.34 [2.15, 8.78]) compared to low pathology controls.

In the multiple pathology model (logLik = -1111.035; AIC = 2306.07), pure LBD (i.e. LBD without co-occurring pathologies) was not significantly associated with any change in risk compared to low pathology controls in this model. However, Lewy body disease in the presence of one co-occurring pathology was associated with a significant increase in risk of progression to dementia (4.01 [1.95, 8.26]). The risk remained elevated in the presence of more than one co-occurring pathology (4.93 [1.59, 15.3]). These results suggest that the presence and number of co-pathologies play a key role in accelerating clinical progression in individuals with LBD.

In the concomitant pathology model (logLik = -1285.01; AIC = 2298.34), all cases of LBD were accompanied by some degree of additional low-level pathology. As a result, further analysis of LBD without any concomitant pathology was not possible in this cohort and findings from this model were consistent with those reported in the first model.

These results collectively highlight that Lewy body pathology alone may not significantly increase the risk of cognitive decline, but the co-occurrence of other pathologies, particularly in mixed pathology cases, is associated with significant increases in risk of transition to both MCI and dementia. Results from these models are reported in **Table 7.10** and **Figure 7.5**

***Table 7.10*. Risk of Cognitive Transition in Lewy Body Disease and Co-Pathologies:** Hazard ratios with 95% confidence intervals for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia. Estimates are derived from three multistate models evaluating the effect of Lewy body pathology with varying levels of severity, co-occurring neuropathologies, and concomitant neuropathologies. Analyses are adjusted for age and years in full-time education. The reference group is low pathology controls.

	Normal to MCI[1]	**MCI to Dementia[1]**
Incidental Lewy body disease (N = 38)	0.86 (0.38, 1.98)	1.97 (0.81, 4.80)
Limbic/neocortical Lewy body disease (N = 37)	1.79 (0.71, 4.47)	1.85 (0.66, 5.15)
Mixed Lewy body disease (N = 103)	**2.83** (1.17, 6.86)	**4.34** (2.15, 8.78)
Multiple pathology		
Lewy body disease (N = 37)	2.13 (0.85, 5.32)	1.83 (0.67, 4.98)
Lewy body disease + one co-occurring neuropathology (N = 53)	2.84 (0.85, 9.50)	**4.01** (1.95, 8.26)
LBD + more than one co-occurring neuropathology (N = 50)	2.56 (0.46, 14.3)	**4.93** (1.59, 15.3)
Concomitant pathology		
Lewy body disease + additional low-level pathology (N = 37)	1.99 (0.80, 4.94)	1.84 (0.66, 5.18)
Mixed Lewy body disease (N = 103)	**3.09 (1.28, 7.46)**	**3.73 (1.93, 7.19)**

[1]**Hazard Ratio** (95% CI)

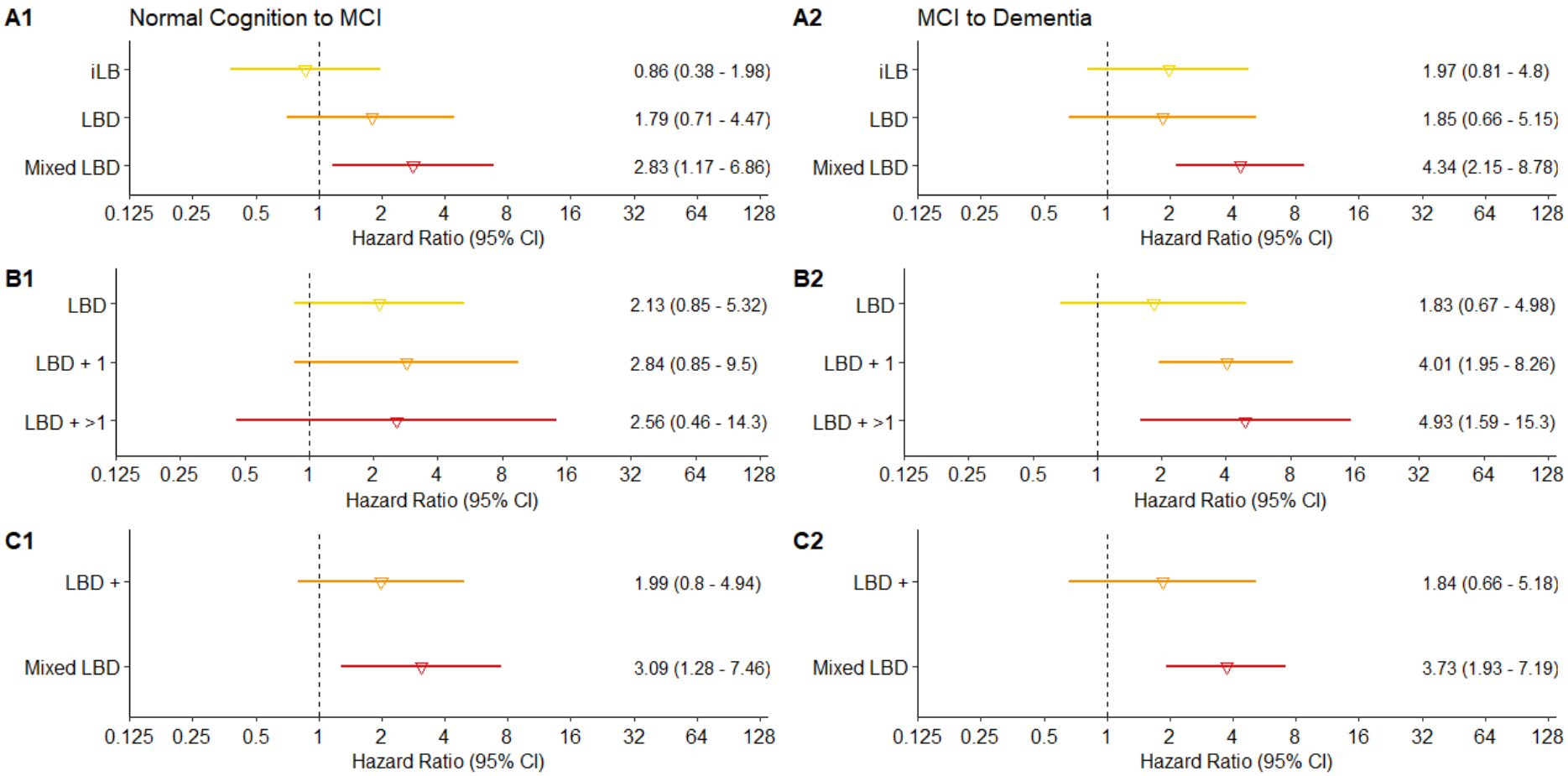

***Figure 7.5*. Transitions in Lewy body disease**: Hazard ratios (95% CI) for transitions from normal cognition to mild cognitive impairment (MCI), and MCI to dementia in (A1-2) Intermediate LBD (iLB), Lewy body disease (LBD), and mixed Lewy body disease (Mixed LBD); (B1-2) Lewy body disease (LBD), Lewy body disease with one additional pathology (LBD + 1), Lewy body disease with more than one additional pathology (LBD + >1); (C1-2) Lewy body disease with concomitant low-level pathology (LBD +), mixed Lewy body disease (Mixed LBD). All models are adjusted for age and years of education, with low pathology controls serving as the reference group.

7.3.7 Transitions in LATE-NC

To assess the effect of limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) on cognitive decline, three separate multistate models were constructed. Each model incorporated a categorical variable capturing a distinct aspect of LATE-NC: presence/severity, co-occurrence with other major pathologies, and the presence of additional low-level pathology. All models were adjusted for age and years of education. A common reference group (N = 208) of individuals with low overall neuropathological burden was used in all three models.

In the severity model (logLik = -1438.28; AIC = 2749.38), LATE-NC alone was not significantly associated with risk of transition from normal cognition to MCI or from MCI to dementia (**Table 7.11**). However, mixed LATE-NC (i.e. LATE-NC in combination with other major pathologies) was associated with a 116% increased risk of transition to MCI (HR = 2.16, 95% CI [1.03, 4.49]) and a 238% increased risk of transition to dementia (3.28, [1.73, 6.22]), compared to low pathology controls.

In the multiple pathology model (logLik = -1256.98; AIC = 2597.96), LATE-NC in the absence of co-occurring pathologies was not associated with any significant change in risk of transition between cognitive states compared to low pathology controls, although there did appear to be a non-significant trend towards an increase in risk. An increased risk in transition from MCI to dementia associated with mixed LATE-NC was observed more clearly when LATE-NC occurred alongside one (2.63, [1.28, 5.39]) or more (4.43, [1.62, 12.1]) co-occurring neuropathologies.

In the concomitant pathology model (logLik = -1468.28; AIC = 2734.24), all individuals with LATE-NC also had at least some degree of additional low-level pathology, preventing further stratification. Consequently, results from this model reflect those already reported in the multiple pathology analysis. Within this context, mixed LATE-NC remained significantly associated with increased risk of both transitions—normal cognition to MCI (HR = 2.15, 95% CI [1.08, 4.29]) and MCI to dementia (HR = 2.92, 95% CI [1.53, 5.55]). Results are outlined in **Table 7.11** and illustrated in **Figure 7.6**.

***Table 7.11*. Risk of Cognitive Transition in LATE-NC and Co-Pathologies:** Hazard ratios with 95% confidence intervals for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia. Estimates are derived from three multistate models evaluating the effect of LATE pathology with varying levels of severity, co-occurring neuropathologies, and concomitant neuropathologies. Analyses are adjusted for age and years in full-time education. The reference group is low pathology controls.

	Normal to MCI	**MCI to Dementia**
LATE-NC (N = 57)	1.29 (0.54, 3.08)	0.97 (0.35, 2.73)
Mixed LATE-NC (N = 143)	**2.16 (1.03, 4.49)**	**3.28 (1.73, 6.22)**
Multiple pathology		
LATE-NC (N = 57)	1.26 (0.54, 2.95)	1.37 (0.56, 3.35)
LATE-NC + one co-occurring neuropathology (N = 84)	1.74 (0.76, 3.99)	**2.63 (1.28, 5.39)**
LATE-NC + more than one co-occurring neuropathology (N = 59)	2.46 (0.60, 10.1)	**4.43 (1.62, 12.1)**
Concomitant pathology		
LATE-NC + additional low-level pathologies (N = 57)	1.23 (0.52, 2.88)	1.56 (0.66, 3.70)
Mixed LATE-NC (N = 143)	**2.15 (1.08, 4.29)**	**2.92 (1.53, 5.55)**

[1]**Hazard Ratio** (95% CI)

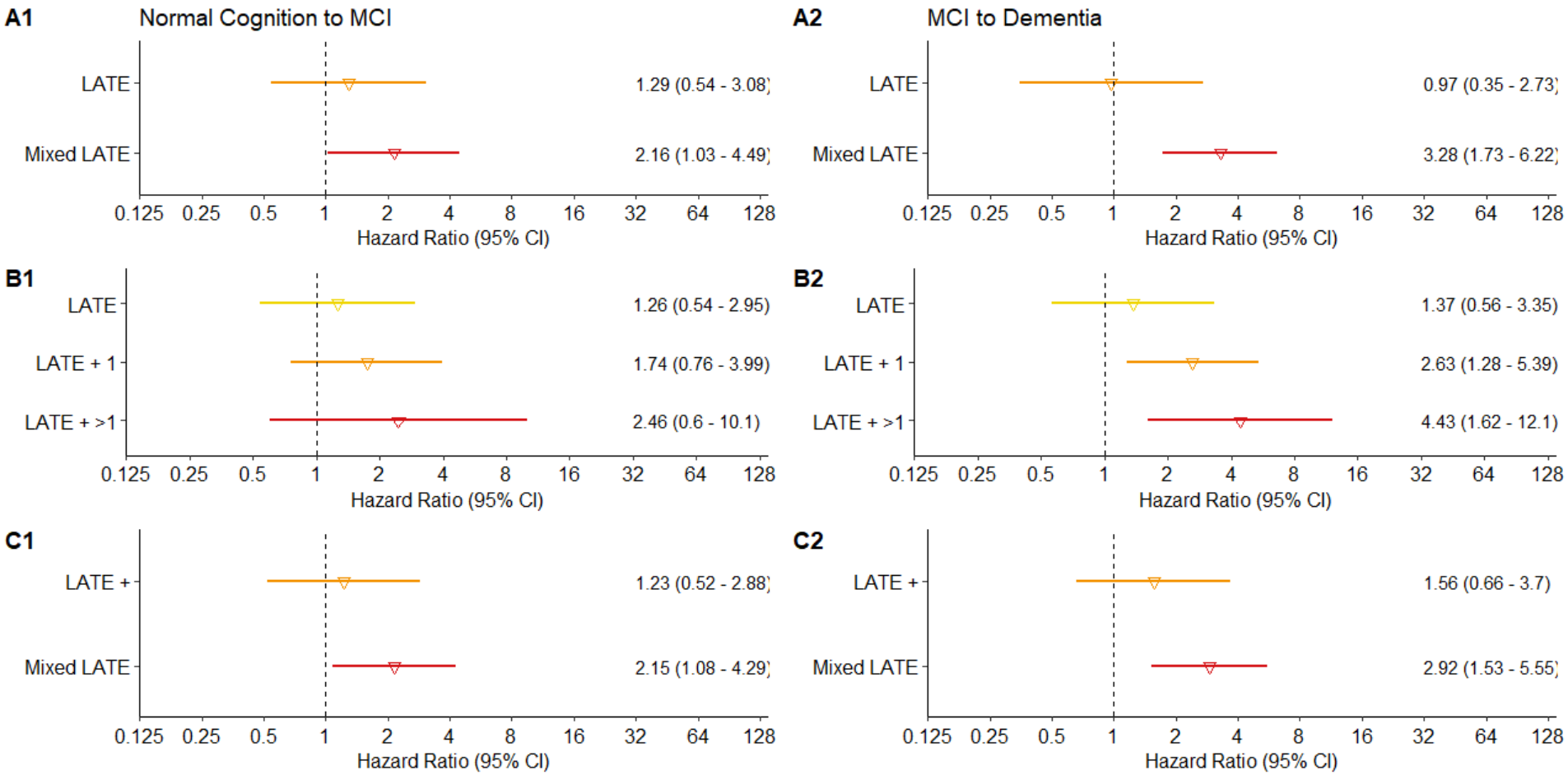

***Figure 7.6*. Transitions in LATE-NC**: Hazard ratios (95% CI) for transitions from normal cognition to mild cognitive impairment (MCI), and MCI to dementia in (A1-2) Limbic-predominant age-related TDP-43 encephalopathy (LATE), and mixed LATE; (B1-2) LATE, LATE with one additional pathology (LATE + 1), LATE with more than one additional pathology (LATE + >1); (C1-2) LATE with concomitant low-level pathology (LATE +), mixed LATE. All models are adjusted for age and years of education, with low pathology controls serving as the reference group.

7.3.8 Transitions in cerebrovascular disease

To assess the impact of cerebrovascular disease (CVD) on cognitive decline, three separate models were constructed, each incorporating a different categorical variable reflecting the severity, co-occurrence with other pathologies, and the presence of additional low-level cerebrovascular pathology. All models were adjusted for age and years of education, using a common reference group (N = 208) of individuals with low overall neuropathological burden.

In the severity model (logLik = -1029.37; AIC = 2003.84), high cerebrovascular pathology (VCING high) was associated with a significant 252% increase in risk of transition from MCI to dementia (3.52 [1.33, 9.29]) compared to low pathology controls. Moderate cerebrovascular disease was not associated with any significant change in risk of transition to any state. Mixed cerebrovascular disease was associated with a 377% increase in risk of transition to dementia (4.77 [1.10, 20.7]).

In the multiple pathology model (logLik = -860.869; AIC = 1805.738), cerebrovascular disease without any other major co-pathologies was associated with a significant 200% increase in risk of progression from MCI to dementia (3.00 [1.01, 8.97]). However, the presence of one or more co-occurring neuropathologies did not confer a statistically significant increase in risk for either transition, though wide confidence intervals reflect limited statistical power for this model.

In the concomitant pathology model (logLik = -1023.37; AIC = 2006.38), all individuals with CVD also had some level of additional low-level pathology, precluding further stratification. As a result, estimates in this model are equivalent to those reported in the first model. Within this model, CVD with low-level concomitant pathology was significantly associated with 216% increase in risk of transition to dementia (3.16 [1.22, 8.15]), while mixed CVD remained associated with an 338% increase in risk of transition to dementia (4.38 [1.02, 18.7]). Results from these models are presented in **Table 7.12** and illustrated in **Figure 7.7**.

***Table 7.12*. Risk of Cognitive Transition in Cerebrovascular Disease and Co-Pathologies:** Hazard ratios with 95% confidence intervals for transitions from normal cognition to mild cognitive impairment (MCI), and from MCI to dementia. Estimates are derived from three multistate models evaluating the effect of cerebrovascular pathology with varying levels of severity, co-occurring neuropathologies, and concomitant neuropathologies. Analyses are adjusted for age and years in full-time education. The reference group is low pathology controls.

	Normal to MCI	**MCI to All Dementia**
Moderate CVD (N = 25)	1.77 (0.71, 4.41)	1.94 (0.59, 6.36)
High CVD (N = 21)	1.96 (0.88, 4.33)	**3.52 (1.33, 9.29)**
Mixed CVD (N = 24)	1.45 (0.24, 8.73)	**4.77 (1.10, 20.7)**
Multiple pathology		
Cerebrovascular disease (N = 21)	1.90 (0.86, 4.18)	**3.00 (1.01, 8.97)**
Cerebrovascular disease + one co-occurring neuropathology (N = 8)	1.31 (0.26, 6.72)	2.32 (0.27, 19.8)
Cerebrovascular disease + more than one co-occurring neuropathology (N = 15)	1.24 (0.13, 11.8)	9.35 (0.79, 111)
Concomitant pathology		
CVD + additional low-level pathology (N = 21)	1.84 (0.84, 4.03)	**3.16 (1.22, 8.15)**
Mixed CVD (N = 24)	1.35 (0.25, 7.28)	**4.38 (1.02, 18.7)**

[1]**Hazard Ratio** (95% CI)

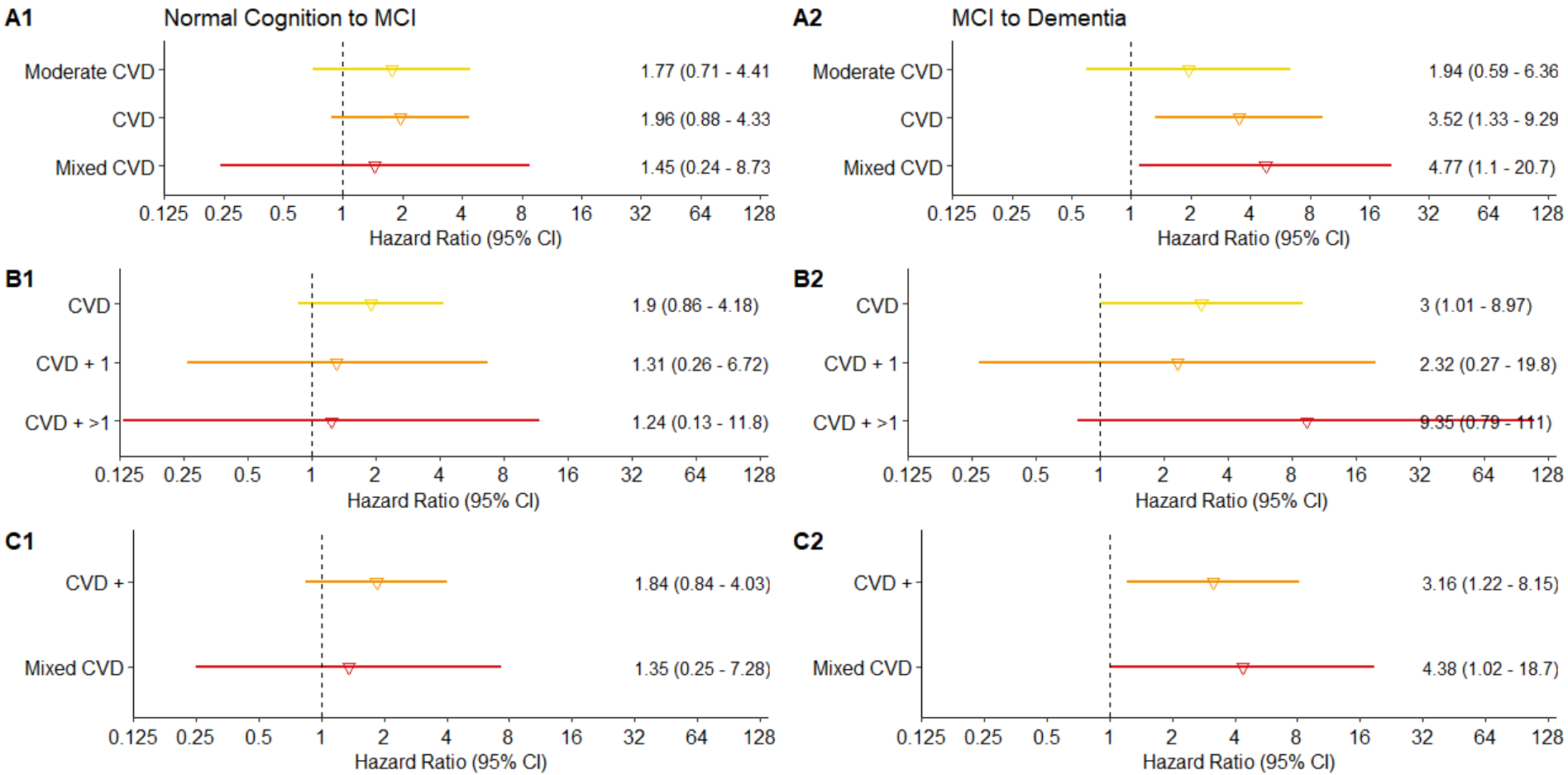

Figure 7.7. **Transitions in cerebrovascular disease**: Hazard ratios (95% CI) for transitions from normal cognition to mild cognitive impairment (MCI), and MCI to dementia in (A1-2) Moderate CVD, cerebrovascular disease (CVD), and mixed cerebrovascular disease (Mixed CVD); (B1-2) Cerebrovascular disease (CVD), cerebrovascular disease with one additional pathology (CVD + 1), cerebrovascular disease with more than one additional pathology (CVD + >1); (C1-2) Cerebrovascular disease with concomitant low-level pathology (CVD +), mixed cerebrovascular disease (Mixed CVD). All models are adjusted for age and years of education, with low pathology controls serving as the reference group.

7.4 Summary

In terms of demographic variables, age and education were associated with change in risk of transition between cognitive states. Increasing age was associated with an increased risk of MCI. Higher education showed a protective effect against transition to dementia but an increased risk of transition from moderate to severe dementia. Increasing stages of amyloid-B, neurofibrillary tangle, neuritic plaques and Lewy body pathology were associated with faster progression from mild cognitive impairment to dementia. The presence of large subcortical infarcts was also associated with faster progression. Increased levels of neurofibrillary tangle pathology was associated with faster progression from normal cognition to mild cognitive impairment. In addition, increased severity of neuritic plaque pathology was associated with increased risk of transition from normal cognition to mild cognitive impairment and transition from mild dementia to moderate dementia. In contrast, ARTAG was associated with a reduced risk of transition from moderate to severe dementia.

In terms of neuropathology groups, Alzheimer's disease, Lewy body disease, cerebrovascular disease and mixed pathology were all associated with increased risk of transition to MCI and transition to dementia compared to low pathology controls. Alzheimer's disease with any number of co-occurring pathologies was associated with increased risk of transition to dementia, suggesting that the presence of additional pathology is not as influential in transitions through clinical states of dementia in Alzheimer's disease. In addition, intermediate Alzheimer's disease pathology was associated with an increase in risk of transition to MCI which could potentially be a group of participants with early stages of Alzheimer's disease who died before pathology progressed far enough to result in clinical dementia. Cerebrovascular disease was associated with increased risk of transition to dementia. The presence of additional low-level or co-occurring pathologies did not appear to have any clear effect on risk of transition.

Both Lewy body disease and LATE-NC were only associated with an increased risk of transition to dementia in the presence of additional co-occurring neuropathologies. There were no cases of pure Lewy body disease or LATE-NC in the cohort and those with additional low-level pathology did not show any significant change in risk of transition. In contrast to Alzheimer's disease, mixed pathology was associated with an increase in risk of transition to both MCI and dementia, suggesting that Lewy body pathology and LATE-NC may have a

synergistic effect on clinical progression and the co-occurrence of such pathologies may result in a worse prognosis.

Although multistate models provide clinically tangible results, there are several limitations to the use of multistate models for a complex condition such as dementia. The Markov assumption in multistate models assumes that transitions between cognitive states depend solely on the state an individual is currently in. By assuming this is the case, multistate models may oversimplify the temporal dynamics of cognitive decline. Multistate models are also limited by the assumption that there is a single underlying transition process for each group which may not fully account for the heterogeneity in transitions between cognitive states within and between pathology groups. This limitation could lead to the misclassification of individuals into cognitive subgroups and obscure important variations in disease progression patterns. Multistate models require large numbers of observed transitions to estimate transition probabilities reliably, which can be challenging to achieve in clinicopathological studies with limited sample sizes or incomplete follow-up data. While the BDR cohort is large for a neuropathological cohort with longitudinal data, it is not on the same magnitude as cohort studies primarily collecting clinical data over a set time period. As a result, some groups used in this analysis were quite small. Furthermore, some cases in the cohort had limited transitions due to short follow up times.

The results indicate that mixed pathology significantly influences progression to clinical dementia. The consistent association between mixed pathology and increased risk of transition to dementia, compared to low pathology controls and isolated pathology types, suggests that the combination of multiple neuropathological processes exacerbates cognitive decline and highlights the complexity of dementia. Moreover, the compounded effect of multiple pathologies necessitates a more comprehensive understanding of the aetiology and progression of dementia.

Chapter 8. Discussion

The overarching aim of the study was to investigate the extent of the impact and contribution of mixed and concomitant neuropathology to the clinical presentation of dementia, using longitudinal clinical and post-mortem neuropathological data available in the Brains for Dementia Research programme. It was hypothesised that identifying such relationships could provide insights into the complexities and interactions between common neuropathologies of age-related dementia.

8.1 Key Results

In summary, mixed pathology was the most common pathology profile. Concomitant pathology was common and observed in all pathology groups. Clinical study diagnoses often misaligned with postmortem neuropathology. There was an overreliance on Alzheimer's disease and vascular dementia clinically, whereas Lewy body disease and mixed dementia were under recognised. In Lewy body disease, concordance rates varied by sex, geographic location, and the presence of additional pathologies.

Mixed pathology was consistently associated with greater impairment and faster decline in cognition, regardless of constituent pathologies. Mixed pathology was associated with the greatest risk of transition from mild cognitive impairment to dementia. Concomitant Alzheimer's disease pathology was responsible for cognitive decline seen in both LATE-NC and Lewy body disease. LATE-NC was not independently associated with cognitive decline but had a synergistic effect on cognition in other neurodegenerative diseases.

8.1.1 Prevalence of Mixed and Concomitant Neuropathology in the Brains for Dementia Research Cohort

As reported in 0, there was a frequent overlap between age-associated neuropathologies and an absence of clear delineation between neuropathological profiles in the Brains for Dementia Research programme. Mixed pathology was the most common neuropathology profile in this study. Disregarding the extensive presence of concomitant low-level pathology throughout this BDR cohort, mixed pathology (i.e., two or more co-occurring pathology types) was the most frequent pathology type recorded at postmortem, representing over 28% of all cases. Over 40% of dementia cases had sufficient pathology for two or more neuropathological diagnoses at postmortem. Almost all dementia cases had intermediate to high levels of Alzheimer's disease pathology. The presence and co-existence of these

neuropathologies was not exclusive to dementia, with approximately 6% of cognitively healthy controls reported to have multiple neuropathological diagnoses. Concomitant pathology (i.e. multiple pathologies below the neuropathological diagnostic threshold) was also widespread within the cohort and was not exclusive to dementia. Prevalence of concomitant low-level pathology varied between pure (i.e., non-mixed) cases (27-71%) and mixed cases (37-53%) of Alzheimer's disease, Lewy body disease, cerebrovascular disease, and LATE-NC.

8.1.2 Discordance between clinical diagnosis and post-mortem neuropathology.

As reported in Chapter 4, there were significant discrepancies between study diagnosis and postmortem neuropathological findings in this cohort. Both Alzheimer's disease and vascular dementia were overrepresented as clinical study diagnoses when compared to postmortem neuropathological diagnosis in this cohort. This study also demonstrated a clinical under-recognition of Lewy body dementia, particularly among females and in the presence of additional neuropathologies. Diagnostic accuracy varied between visit centres but remained low. Mixed pathology in Lewy body disease was consistently associated with reduced diagnostic accuracy in the cohort.

8.1.3 Trajectories of Cognitive Decline in Mixed and Concomitant Neuropathology

As reported in Chapter 5, almost all neuropathology groups showed faster decline and lower final cognitive function than low pathology controls. Cerebrovascular disease was not associated with a significant change in cognitive trajectory. Mixed pathology cases exhibited the fastest and most severe decline in cognitive function of all neuropathology groups in linear mixed effects models. More precisely, non-specific mixed pathology was associated with a faster rate of decline and greater reduction in cognition than any single pathology in isolation. Alzheimer's disease was associated with faster decline in cognition and large reductions in final cognition. Rate of cognitive decline increased with increasing levels of Alzheimer's disease neuropathological change. Concomitant Alzheimer's disease in isolation was associated with a more severe cognitive trajectory than some full neurodegenerative diseases. Lewy body disease was only associated with a fast and severe decline in cognition when concomitant intermediate Alzheimer's pathology was also present. The cognitive trajectory of cases of LATE-NC in isolation did not significantly differ from low pathology controls and LATE-NC was not associated with any significant change in cognitive trajectory

once additional neuropathologies or concomitant Alzheimer's pathology had been accounted for.

8.1.4 Mixed and Concomitant Neuropathology as Predictors of Trajectory of Cognitive Decline

As reported in 0, mixed pathology cases were significantly more likely to be assigned to the fastest declining group in latent class mixture models of cognitive trajectory and mixed pathology was disproportionately represented among the fast decliners across all models. The consistent association of mixed pathology with a rapidly declining cognitive trajectory suggests that the presence of multiple neuropathologies is a strong predictor of rapid deterioration in cognition. Cases with concomitant Alzheimer's disease neuropathological change were significantly more likely to belong to the fast decliner group. Cases with LATE-NC as a component of the mixed pathology were significantly more likely to be fast decliners (0). Specifically, every case in the fastest declining group had LATE-NC as a component of the mixed pathology.

8.1.5 Transitions Between Cognitive States in Dementia with Mixed and Concomitant Neuropathology

As reported in Chapter 7, mixed pathology was consistently associated with increased risk of transition to dementia compared to low pathology controls and isolated neuropathology types. Although individual pathologies were associated with an increased risk of transition to dementia compared to low pathology controls, the risk of transition to dementia was significantly higher in mixed pathology cases compared to those same pathologies in isolation. Concomitant Alzheimer's pathology was also associated with an increased risk of transitioning between cognitive states (Chapter 7). LATE-NC was not independently associated with an increased risk of transition between cognitive states but was in the presence of additional neuropathologies (Chapter 7). These findings remained consistent with those seen in previous analyses for this particular cohort but again contradict results reported in different cohorts. Although LATE-NC alone did not appear to significantly drive cognitive transitions in the multistate models reported here, the co-occurrence of LATE-NC did increase the risk of transition to further cognitive states in other neurodegenerative diseases (Chapter 7).

8.2 Cross-Chapter Discussion

Mixed and concomitant pathology at all levels of abundance are common in the ageing brain (Irwin et al., 2017, Robinson et al., 2018b). While this is not a novel finding, this study provides additional data for the mounting evidence that pure pathology is not the norm (Robinson *et al.*, 2023). It is extremely uncommon to have only one pathology type. Even Alzheimer's disease neuropathological changes consist of multiple different pathologies, some of which exist at the interface between proteopathy and vascular (i.e. cerebral amyloid angiopathy). Further to this, most dementia cases have additional pathologies at postmortem which are thought to have a synergistic or additive effect on cognitive decline.

Although it is difficult to determine the exact contribution of each disease process to cognitive impairment as the study was observational rather than experimental, the accumulation of additional proteinopathies and cerebrovascular changes is typically associated with more severe decline in cognitive function. Despite the lack of clear delineation between pathologies frequently associated with dementia, these conditions are still clinically treated as distinct disorders, with clinical trials and research often focusing on a single pathology type in isolation.

8.2.1 Mixed and concomitant pathology is common.

As reported in 0, mixed pathology was the most common neuropathological profile in individuals with dementia. The high prevalence of mixed pathology reported in this cohort reflects results reported in other clinicopathological studies of dementia by Rahimi , and Kovacs (2014), Schneider et al. (2007), Alafuzoff , and Libard (2020), and Robinson et al. (2023). A review by Rahimi , and Kovacs (2014) compared the prevalence of mixed pathologies across community-based studies in Europe, the US, and Japan. Prevalence of mixed pathology varied between 10% and 74%, depending on the definition used, and was typically higher in cognitively impaired populations (Rahimi and Kovacs, 2014). Schneider et al. (2007) reported that the presence of mixed pathologies increased the likelihood of dementia by three times compared to isolated pathologies. Similarly, Alafuzoff , and Libard (2020) found mixed pathology was present in 66% of subjects with cognitive impairment in a study of 80-89 year olds and Robinson et al. (2023) reported that the majority of cases of neurodegenerative disease will exhibit multiple pathologies. It has been estimated that at least 50% of over 65s, regardless of cognitive status, have multiple pathologies at postmortem (Godrich et al., 2022, Robinson et al., 2023).

Concomitant or additional low-level pathology in neurodegenerative disease was also widespread throughout the Brains for Dementia Research cohort, with varying prevalence depending on primary neuropathological diagnosis (0). Similar results have been reported in previous studies, including Robinson et al. (2023), Robinson et al. (2018b) and (McAleese et al., 2021). Robinson et al. (2023) reported that additional pathologies were the norm rather than an exception, particularly in age-related neurodegenerative disease (Robinson et al., 2023). Robinson et al. (2018b) reported an almost universal presence of tau pathology in one cohort and little difference in the prevalences of concomitant pathology between neurodegenerative diseases and low pathology controls (Robinson et al., 2018b). In a study using an earlier iteration of the Brains for Dementia Research cohort, McAleese et al. (2021) reported additional pathologies in 69.9% of cases and that the presence of additional pathologies increased the risk of transition from mild cognitive impairment to dementia.

The results reported in 0 align with a growing body of evidence suggesting that mixed pathologies are not only common but are the norm rather than the exception in age-related dementia (Jellinger and Attems, 2015). Mixed pathologies are present in a significant proportion of dementia cases and most have some level of additional pathology that might not be sufficient to meet an arbitrary threshold of relevance. The presence of concomitant low-level pathology in ostensibly pure cases fits into this broader context of overlapping pathologies. Most cases have some additional pathology, even if it does not meet an arbitrary threshold of being relevant. However, figures for concomitant pathology can vary between studies due to the subjective categories and cut offs definitions. These findings extend existing knowledge by showing that the presence of multiple pathologies is not limited to mixed dementia but also occurs in cases classified as having a single predominant pathology. This complexity may be contributing to the variability seen in clinical presentation and disease progression, and variable response to treatment observed across the dementia spectrum.

An additional finding reported in 0 was that mixed and concomitant pathology was not always associated with clinical dementia. Numerous previous studies, including Ganz et al. (2018), Nichols et al. (2023), and (Bennett et al., 2012c) have reported the presence of neuropathology in cognitively healthy controls, particularly in older populations. Ganz et al. (2018) assessed the prevalence of age-related neuropathologies in self-reported cognitively healthy centenarians. The study found that although cognitive performance was sensitive to

the increase of neuropathological hallmarks of dementia, some individuals were able to maintain high cognitive functioning in the presence of considerable amounts of multiple pathologies. Similarly, Nichols *et al.* (2023) reported that in a large neuropathology cohort there was a strong, but not deterministic, association between the co-occurrence of pathology and cognitive state. In the Religious Orders Study and the Memory and Ageing Project, neuropathology was frequently reported in the brains of older people without dementia or mild cognitive impairment (Bennett et al., 2006, Bennett et al., 2012c). More specifically, Alzheimer's disease pathology and large infarcts were common in those without cognitive impairment and were associated with subtle changes in episodic and working memory (Bennett et al., 2012c).

Resilience to the accumulation of neuropathology has previously been reported by (Latimer et al., 2017), (Perls, 2021), (Andersen, 2020), (Robinson et al., 2018a), and (Walker and Richardson, 2023). The consistency of these findings with previous literature further highlights the complexity and non-linear relationship between postmortem neuropathology and cognition. The lack of exclusivity of mixed and concomitant pathology to dementia suggests that the presence of neuropathological changes does not necessarily correlate directly with the severity of clinical symptoms. This aligns with previously proposed concepts in the field, including cognitive reserve, neural plasticity and resilience to the accumulation of neuropathology which provide potential explanations for this phenomenon and subject-specific susceptibility to cognitive decline (Gómez-Isla and Frosch, 2022). These findings highlighting the complexity and multimorbidity of the brain pathologies that underlie dementia and suggest that prevention efforts and treatments should be a multipronged approach.

Together these findings suggest that neurodegenerative diseases may not be as pathologically distinct as originally theorised (Boyle et al., 2018). The frequent overlap of neuropathologies in dementia suggests that the pathogenesis of dementia is more complex and that there are more pervasive and subtle interactions in neurodegenerative disease than previously recognised. These relationships between pathologies are complex, with multiple mechanisms potentially contributing to the clinical manifestations of dementia.

The consistently high prevalence of mixed pathology challenges the traditional model for dementia that attributes constellations of clinical symptoms to single isolated pathologies (Sin Chin, 2023). This supports the broader hypothesis that dementia is often the result of

complex interactions between neurodegenerative and vascular conditions. Classical models frame dementia as a shared condition that can arise from a range of different but discrete neuropathologies, such as Alzheimer's disease, Lewy body disease or cerebrovascular disease. However, a single isolated pathology resulting in clinical dementia is often not the reality. A possible explanation for the frequent overlap could be that there may be interrelated mechanisms driving these processes or a shared underlying molecular cause, such as proteostasis impairment or deficient autophagy, that could be responsible for the initiation of numerous pathological pathways (Spires-Jones, Attems and Thal, 2017). This prevalence underscores the importance of considering a comprehensive approach to diagnosing and understanding dementia. Clinicians and researchers must account for the possibility of multiple overlapping pathologies when evaluating patients and developing therapeutic strategies.

Existing theoretical models may need to be revised to fully incorporate the coexistence of multiple pathologies, considering the complex interactions between them and the possibility of shared pathogenic pathways. Furthermore, the persistent overlap between all pathologies emphasises the need for integrated disease models that combine various aspects of neurodegeneration, vascular disease, and other contributing factors, providing a more comprehensive understanding of dementia and its progression. Future studies should ensure that mixed dementia is defined as combinations of Alzheimer's disease, Lewy body disease, cerebrovascular disease, and LATE-NC (Robinson *et al.*, 2023), rather than the historical definition which is largely limited to the combination of Alzheimer's disease and vascular dementia (Fierini, 2020).

8.2.2 The impact of mixed pathology on diagnostic accuracy.

As reported in Chapter 4, clinical study diagnosis often did not reflect postmortem neuropathology in this cohort. Clinical diagnoses of Alzheimer's disease and vascular dementia were overrepresented, while Lewy body dementia and mixed dementia were underrepresented (Chapter 4). Previous studies by Selvackadunco et al. (2019), Andersson et al. (2020), and Grandal Leiros et al. (2018) have shown similar patterns of discordance between clinical diagnosis and postmortem neuropathology in dementia cohort. However, there are distinct differences in subgroup variability across these studies. A study of the Brains for Dementia Research cohort by Selvackadunco et al. (2019) reported that, in more than a third of cases, there was a mismatch between clinical diagnosis and neuropathology.

Similarly, Andersson et al. (2020) reported full diagnostic concordance in 61% of cases in a small hospital-based study, with significant variability between diagnoses. The lowest concordance in this study was reported in vascular dementia, where only 31% of cases were correctly identified (Andersson et al., 2020). Grandal Leiros et al. (2018) report in a small cohort that almost a third of participants were not correctly diagnosed during life, with significant under-recognition of vascular dementia. A study by Beach et al. (2012) showed similar findings in terms of Alzheimer's disease, reporting a high sensitivity of 70.9-87.3% and relatively low specificity of 44.3-70.8% in a large clinicopathological cohort.

Both over-recognition and under-recognition reported here and in previous studies could be a consequence of shared and overlapping clinical symptoms between multiple dementia subtypes. Clinical diagnosis of dementia is already complex and is always probable or possible, rather than definitive, cause of dementia which can only be confirmed with postmortem neuropathology. The overrepresentation of these two diagnoses suggests that in some cases, potentially where the full diagnostic pathway had not been completed, Alzheimer's disease and vascular dementia may have been used as a default or catch-all diagnosis for patients presenting with general cognitive decline in the absence of additional symptoms that are typically associated with Lewy body and frontotemporal dementias. Well-established diagnostic criteria, higher prevalence rates, and greater familiarity of both healthcare providers and the general population with AD and VaD, compared to less common dementias, may also be contributing to the discordance.

A further finding reported in Chapter 4 was the clinical under-recognition of Lewy body disease. Successful identification of Lewy body disease in clinical settings was lower in females and varied by location. The clinical prevalence of Lewy body dementia and postmortem incidence of Lewy body disease are frequently inconsistent and individuals are consistently more likely to receive a clinical diagnosis of Lewy body disease in regions with specialist centres (Lebouvier et al., 2013). Previous studies have shown similar disparities between the prevalence of Lewy body dementias in clinical settings and the incidence of Lewy body disease in postmortem studies (Rizzo et al., 2018, Skogseth et al., 2017). A meta-analysis of 22 studies by Rizzo et al. (2018) reported a sensitivity of 60% and a specificity of 93.8% for Lewy body dementia, indicating that many cases with Lewy body disease are missed clinically rather than misdiagnosed. The study concluded that while the criteria for Lewy body disease has improved over time, a significant proportion of cases are still missed.

Similarly, Skogseth et al. (2017) reported a sensitivity of 73% and a specificity of 93% for the diagnosis of probable Lewy body dementia. Reported values for sensitivity and specificity are likely to be higher than in real-life settings or population-based studies due to inclusion criteria selecting specifically for Lewy body dementia, often referred from specialist centres (Rizzo et al., 2018, Skogseth et al., 2017). Potential explanations for the under-recognition of Lewy body disease could be overlapping, variable and fluctuating symptoms. It is also possible that some participants were reluctant to disclose or intentionally omitted the presence of hallucinations with carers or clinicians, out of social stigma or fears of unwanted consequences, such as escalated clinical intervention or involuntary admittance to assisted living. As a result, core features of Lewy body disease may not have been reported and clinical diagnoses are based on misleading or inaccurate information.

In the BDR cohort, females were less likely to receive a clinical diagnosis of Lewy body dementia (Chapter 4). These findings reflect results reported in previous studies. A study by Bayram et al. (2021) showed increased likelihood of delayed or missed diagnosis in females. More frequently missed Lewy body disease in females may reflect gender differences in symptom interpretation, actual differences in the manifestation of symptoms, or the way in which these are reported by patients and perceived by healthcare providers. Bayram et al. (2021) reported significant differences in the clinical presentation of LBD between sexes. The frequency of coexisting pathologies, such as Alzheimer's disease pathology, in females may also be contributing to the under recognition of LBD in females (Bayram, Coughlin and Litvan, 2022). A review by (Chiu et al., 2023) concluded that sex differences in clinical presentation and co-occurring pathology may be influencing diagnostic accuracy for Lewy body disease in females. Ensuring that clinicians are aware of the diverse presentations of LBD, regardless of gender, is crucial for improving diagnostic accuracy.

Sensitivity for Lewy body disease was also consistently lower in cases with additional neuropathological diagnoses (Chapter 4). Previous studies by Merdes et al. (2003), Bayram, Coughlin , and Litvan (2022), Chatterjee et al. (2021), Lemstra et al. (2017), and Malek-Ahmadi et al. (2019) have also indicated that mixed and concomitant pathology is associated with differences in clinical presentation. Merdes et al. (2003) reported that the level of concomitant Alzheimer's disease pathology had an influence on clinical characteristics, and consequently diagnostic accuracy, in Lewy body disease. Cases of Lewy body disease with lower abundance of neurofibrillary tangles were more likely to report visual hallucinations

than those with a higher abundance of neurofibrillary tangles and more likely to be accurately diagnosed (75% vs 39%) (Merdes et al., 2003). Bayram, Coughlin , and Litvan (2022) reported worse cognitive decline and a lower likelihood of typical Lewy body disease clinical phenotype when concomitant Alzheimer's disease was also present. Lemstra et al. (2017) reported that Lewy body dementia cases with an Alzheimer's disease biomarker profile were more likely to have a more severe clinical manifestation and at greater risk of institutionalisation and mortality. Chatterjee et al. (2021) reported that individuals with both Alzheimer's disease and Lewy body disease were more likely to have memory symptoms that those with Lewy body disease only. Similarly, Malek-Ahmadi et al. (2019) reported that while cognitive trajectory did not differ between groups, participants with clinically undetected Lewy body disease had lower prevalences of parkinsonism and visual hallucinations compared to clinically diagnosed cases.

The impact of mixed pathology on clinicopathological concordance highlights the diagnostic difficulties in cases where multiple neuropathological processes coexist. Clinicians rely on clinical symptoms and cognitive assessments to diagnose neurodegenerative diseases, but the presence of mixed pathologies can obscure the clinical presentation, resulting in misdiagnosis or an incomplete understanding of the patient's condition. The low clinicopathological concordance in mixed pathology cases reported across multiple studies suggests that the interactions between different neuropathological processes can lead to atypical or overlapping clinical presentations. The identification of common pathways and underlying pathophysiological basis of mixed pathology could provide insights into how and why these interactions occur and affect disease progression. Understanding the specific mechanisms through which different pathologies co-develop, interact, and ultimately influence clinical symptoms is essential for developing more accurate diagnostic criteria and targeted therapies.

Together, these findings suggest that it is the presence of mixed or concomitant pathology that mediates the relationship between clinical presentation and missed diagnosis in Lewy body disease. The discrepancies observed in this study suggest that clinical diagnosis based purely on symptomatology and non-invasive tests will not always reflect the complete underlying neuropathological profile, further highlighting the challenges clinicians face in distinguishing between dementia subtypes based purely on clinical presentation. These findings underscore the persistent issue of diagnostic misalignment in clinicopathological

studies and have significant implications for the success of clinical trials, treatment efficacy, and symptom management. The implementation of effective biomarkers may aid in understanding the clinical complexity, heterogeneity, and similarities of dementia subtypes.

In some cases, diagnostic criteria have been updated to acknowledge the presence of mixed pathology but, given the low clinicopathological concordance reported here, this may not be reflected clinically yet. This underscores the need for further research into the diagnostic criteria and the development and implementation of biomarkers that can accurately reflect the presence of multiple neuropathologies, particularly in Lewy body disease. Future studies should focus on developing and validating biomarkers that can detect and differentiate between various pathologies in vivo, potentially through cerebrospinal fluid analysis, blood tests, or advanced imaging techniques. Further improvements to diagnostic criteria could have significant implications on dementia research, quality of life, disease management, and clinical trial efficacy.

8.2.3 Mixed pathology and decline in cognitive function

As reported in Chapter 5 and Chapter 6, almost all neuropathologies, with the exception of cerebrovascular disease, were significantly associated with faster decline and greater cognitive impairment than low pathology controls, with rates varying between neuropathology groups (Chapter 5). A similar study by Boyle et al. (2017) using the same methods reported comparable results, showing varied effects of age-related neuropathologies on the trajectory of late life cognitive decline, with the exception of microinfarcts and arteriolosclerosis. Across all analyses in this study, mixed pathology was consistently associated with a faster decline in cognition, more severe impairments in cognitive function, and worse clinical prognosis (Chapter 5; Chapter 6). Mixed pathology cases were, on average, associated with the fastest decline in cognitive function (Chapter 5), significantly more likely to be assigned as “fast decliners” (Chapter 6), and consistently associated with an increased risk of transition from mild cognitive impairment to dementia (Chapter 7). In Alzheimer’s disease, Lewy body disease, and LATE-NC, mixed pathology was associated with faster decline than each pathology in isolation (Chapter 5). Furthermore, mixed pathology was also consistently associated with increased risk of transition between cognitive state (Chapter 7).

Many other studies have reported that mixed pathology at postmortem is associated with more severe clinical symptoms, including greater decline in cognition, during life, than single

pathology cases (Chatterjee et al., 2021, Schneider et al., 2007, Boyle et al., 2018). Schneider et al. (2007) observed that mixed Alzheimer's disease and cerebrovascular pathology was associated with more rapid cognitive decline than Alzheimer's disease alone and Boyle et al. (2018) reported that mixed pathologies, particularly the combination of Alzheimer's disease with Lewy bodies, were associated with steeper declines in cognitive function than any single pathology. A review by Kapasi, Decarli , and Schneider (2017) found that the presence of both concomitant low-level pathology and additional neurodegenerative diseases in Alzheimer's disease consistently lowered the threshold for clinical diagnosis of dementia. Additional studies by Brenowitz et al. (2017), (Gu et al., 2022), and Robinson et al. (2021) provide further supporting evidence for these findings and suggest potential mechanisms of interaction. Brenowitz et al. (2017) reported that in their study the differences in rates of progression between isolated pathologies and mixed pathologies were less than would be expected if each pathology contributed independently to progression. This supports results reported in Chapter 5, where additional neuropathological diagnoses had a synergistic, rather than additive, effect on rates of cognitive decline. (Gu et al., 2022) reported that mixed AD/DLB cases were associated with double the rate of cognitive decline compared to pure AD. Robinson et al. (2021) reported abundant and significant interactions between Alzheimer's disease, Lewy body pathology, and TDP-43 that influence clinical progression, with the distribution of Lewy boy pathology being significantly different in the presence of Alzheimer's disease.

As reported in Chapter 5, Chapter 6, and Chapter 7, concomitant Alzheimer's disease appeared to be driving cognitive decline in both LATE-NC and Lewy body disease. Neither LATE-NC nor Lewy body disease was associated with any significant change in cognitive trajectory compared to low pathology controls in the absence of additional pathologies or concomitant intermediate level Alzheimer's disease neuropathological change. Furthermore, concomitant Alzheimer's disease in Lewy body disease was associated with clinical under-recognition. These findings were consistent across all three longitudinal analyses and suggest that concomitant Alzheimer's disease in both Lewy body disease and LATE-NC may be responsible for the decline in cognition observed. Intermediate ADNC was also associated with being a fast decliner (0) and increased risk of transition to dementia (Chapter 7) compared to low pathology controls.

Previous studies consistently report that concomitant Alzheimer's disease pathology is a prevalent additional pathology across all forms of dementia (McAleese *et al.*, 2021) and is highly correlated with cognitive decline (Montine et al., 2022). These findings extend evidence from previous observational studies suggesting that Alzheimer's pathology specifically accelerates cognitive decline in cases with LATE-NC and LBD (Thomas et al., 2020). Understanding the impact of concomitant Alzheimer's pathology on cognitive state transitions has important implications for predicting disease progression. Patients with Alzheimer's pathology might be more prone to rapid transitions between cognitive states, which can help in identifying those at higher risk for accelerated decline. This knowledge is critical for clinicians in adapting monitoring and intervention strategies to better manage the progression of cognitive impairment.

The finding that concomitant AD pathology alone can lead to more severe cognitive decline than some full neurodegenerative diseases highlights the need for early and accurate diagnosis of AD. As mentioned in 8.2.2, the presence of concomitant Alzheimer's disease in other neurodegenerative diseases may significantly alter clinical manifestations. These findings suggests that moderate levels of Alzheimer's disease pathology not only exacerbate the impact of other neuropathological changes but may also independently lead to clinically significant reductions in cognitive function. These findings underscore the importance of developing targeted treatments that specifically address the underlying mechanisms of AD pathology. Potential mechanisms that could be responsible for the consistent association of increasing levels of concomitant Alzheimer's disease pathology with greater impairments in cognitive function include greater neuronal burden, impairment of compensatory mechanisms, and increased inflammation.

Together these findings show a consistent relationship between mixed pathology and more severe deficits in cognitive function, accelerated decline in cognition, and worse clinical prognosis, supporting the growing body of evidence suggesting that the additive and synergistic effect of mixed pathology is a critical factor in the pathogenesis of dementia. These findings strongly suggest that the co-occurrence of multiple pathologies significantly exacerbates clinical progression to dementia. While Alzheimer's disease alone is a strong predictor of dementia, its effects are amplified when combined with other pathologies such as TDP-43 proteinopathy or Lewy bodies. The disproportionate representation of mixed pathology cases highlights the importance of considering mixed pathology as a common

pathology underlying clinical dementia and the application of biomarkers for multiple neuropathologies in clinical settings.

The findings reported here provide further longitudinal evidence demonstrating that mixed pathology significantly exacerbates the trajectory of cognitive decline in large neuropathology cohort, resulting in a more severe trajectory than all other pathology groups. The identification of concomitant Alzheimer's disease pathology as a key factor in fast cognitive decline has important implications for risk stratification (Rabinovici et al., 2017):. Individuals with concomitant Alzheimer's pathology may require closer monitoring and more aggressive therapeutic interventions to manage cognitive symptoms. By understanding the factors that contribute to rapid decline, clinicians can better identify high-risk individuals and adjust treatment plans.

In addition to the co-existence of multiple pathologies in the ageing brain, there is growing evidence of functional links and interactions between these co-pathologies (Tomé and Thal, 2021). Complex protein interactions within shared pathways have been associated with both ageing and Alzheimer's disease (Robinson et al., 2021). These interactions can result in the pathologic phosphorylation, misfolding, and aggregation of various proteins inclusive of TDP-43 and tau. The presence of multiple pathologies may also exacerbate neuroinflammatory processes, leading to accelerated neurodegeneration. In the context of mixed pathologies, the inflammatory response might be more intense or prolonged, thereby accelerating cognitive decline. Chronic inflammation has been implicated in the progression of various neurodegenerative diseases, and the presence of multiple pathologies could amplify this response, accelerating neuronal damage and cognitive impairment.

There are several potential mechanisms that could be responsible for the significant impact of moderate levels of Alzheimer's disease pathology reported here. First, Alzheimer's disease pathology is already a combination of different pathology types (neuritic plaques, neurofibrillary tangles) arising from multiple aggregated misfolded proteins (amyloid B and tau). Most other pathology types included here are the result of only one type of protein inclusion (e.g. a-synuclein in Lewy body disease, TDP-43 in LATE-NC). The addition of moderate level Alzheimer's disease is at least two extra pathology types, tripling the number of misfolded and aggregating proteins present.

Several studies have reported interactions between neurodegenerative pathologies. For example, Aβ produced in neurons drains along perivascular drainage channels and accumulates as CAA, intrinsically linking Alzheimer's disease pathology and vascular pathology. Transgenic mouse models with overexpression of neuronal APP develop CAA in addition to amyloid plaques (Calhoun et al., 1999). Furthermore, Aβ deposition results in capillary CAA which interferes with blood flow and is associated with allocortical microinfarcts in the CA1 region of the hippocampus (Hecht et al., 2018, Thal et al., 2009). Cross-seeding between Aβ and α-synuclein have been previously described by Ono et al. (2012).

Haggerty et al. (2011) have reported on the synergistic effects of α-synuclein and tau, indicating an interaction between Alzheimer's disease and Lewy body disease. TDP-43 cytoplasmic inclusions in Alzheimer's disease can resemble the shape of neurofibrillary tangles and may co-localise with phosphorylated tau (Higashi et al., 2007). Findings from previous human neuropathological studies (Josephs et al., 2019b, Latimer et al., 2019) have also suggested a potential synergistic relationship between tau and TDP-43. However, McAleese et al. (2020) report that the presence of LATE-NC with Alzheimer's disease does not increase amyloid or tau burden and Niblock *et al.* (2016) report that TDP-43 does not regulate the expression or splicing of tau in Alzheimer's disease. This suggests that TDP-43 may contribute to Alzheimer's disease through alternative independent mechanisms.

A review by (Spires-Jones, Attems and Thal, 2017) highlights additional pathogenic links between the aggregation of Aβ, tau, α-synuclein and TDP-43. Lau, Ramer , and Tremblay (2023) hypothesise that increasing glial senescence may sustain and drive accumulation and spread of Alzheimer's disease pathologies, glial ageing, and further senescence. As a result, the presence of concomitant Alzheimer's disease could exacerbate cognitive decline and neuronal loss in other neurodegenerative diseases.

8.2.4 LATE-NC not independently associated with cognitive decline

LATE-NC is frequently observed alongside other neuropathologies in dementia (McAleese et al., 2017) and has recently been proposed as an independent pathological condition (Nelson, 2021, Nelson et al., 2022b). However, the exact clinical presentation of this pathological entity has been debated (Josephs et al., 2019a). Typically, neurodegenerative diseases are defined by a distinct clinical condition with associated neuropathological changes. LATE-NC has been defined by the reverse. In this cohort, the majority of cases with LATE-NC were

found to have additional or mixed pathologies (0). Truly isolated LATE-NC was not common and not exclusive to dementia cases. The prevalence of LATE-NC reported in this study aligns with prevalence figures reported in previous clinicopathological studies of dementia (Nichols et al., 2023, Nelson, 2021, Brayne et al., 2009, Robinson et al., 2023).

As reported consistently throughout Chapter 5, Chapter 6, and Chapter 7, LATE-NC was not independently associated with cognitive decline in the absence of additional pathologies or concomitant Alzheimer's disease pathology in any analysis in this study. The cognitive trajectory of LATE-NC alone did not differ significantly from that of low pathology controls (Chapter 5) but was associated with faster decline in cognition, greater overall reduction in cognitive function, and increased risk of transition to clinical dementia in the presence of additional pathologies or concomitant Alzheimer's disease pathology (Chapter 7). Cases with LATE-NC as a component of mixed pathology were more likely to be present in the fastest declining group (0) and the presence of LATE-NC in Lewy body disease was also associated with low sensitivity for clinical diagnosis (Chapter 4).

Results relating to cognitive decline contradict the findings of previously published research. Studies by Harrison et al. (2021) and Nelson (2021) have suggested that LATE-NC alone is sufficient to cause clinically relevant cognitive impairment and should be considered a distinct neuropathological entity with its own clinical presentation. Harrison et al. (2021) reported that LATE-NC was a distinct cause of dementia from Alzheimer's disease and was strongly associated with hippocampal sclerosis and arteriolosclerosis. However, this study had a relatively small sample size (N=98) and did not appear to examine cognitive trajectories over time. Nelson (2021) reported cognitive impairment in LATE-NC cases with little to no Alzheimer's disease pathology but also did not examine cognitive trajectories over time. Bayesian hierarchical modelling of a significantly larger study using ADCC data by Thomas et al. (2020) strongly indicated that LATE-NC was independently associated with cognitive decline. While it is possible that some studies may not account for concomitant Alzheimer's disease pathology, many others do (Thomas et al., 2020). As the presence of Alzheimer's disease in this specific study was defined as intermediate or high ADNC, it is unlikely that concomitant pathology was responsible for the association.

The finding that LATE-NC, when combined with other neuropathologies, contributed to a more rapid cognitive decline suggesting that the presence of LATE-NC can exacerbate the cognitive decline associated with other pathologies. Previous studies have identified a

similar relationship between co-existing LATE-NC pathology and cognition in other neurodegenerative diseases (James et al., 2016). In a study by McAleese et al. (2020), mixed AD/LATE-NC cases were associated with more severe reduction in final MMSE compared to Alzheimer's disease in isolation. This finding provides further supporting evidence for the synergistic effect of LATE-NC and further insights into the interaction between different neuropathologies and their collective impact on cognitive decline.

While previous studies assessing the clinical phenotype of LATE-NC cases that have consistently reported cognitive decline independent to other pathologies, the findings reported here suggest that the presence of additional neuropathologies might be necessary to drive cognitive decline in LATE-NC, providing evidence to suggest that LATE-NC may not be a distinct neuropathological entity. The presence of additional neuropathologies may be necessary to result in clinically measurable cognitive decline in LATE-NC and further studies are needed to fully characterise this relationship. In the absence of additional neuropathologies, LATE-NC may not be the primary driver of cognitive decline. It is possible that previous studies may not have accounted for intermediate level Alzheimer's disease pathology when assessing its contribution to cognitive decline. The common co-occurrence with other neurodegenerative diseases suggests that LATE-NC may act synergistically with other pathologies rather than being a sole contributor to cognitive decline. Cytoplasmic TDP-43 inclusions may be an indicator of cellular dysfunction and have been linked to oxidative stress, kinase dysfunction, and autophagy impairment (McAleese et al., 2017).

An alternative explanation for these observations could be that the difference between a neuropathological diagnosis of LATE-NC Stage 3 and FTLD-TDP are almost identical, differentiated only by an arbitrary count of TDP-43 inclusions in the middle frontal gyrus (Robinson et al., 2020). It is possible that some cases defined as LATE-NC could also be defined as FTLD-TDP. TDP-43 pathology in LATE-NC is restricted to a relatively small topographical region. The staging criteria for LATE-NC is not as restrictive or well-defined as those of other neurodegenerative pathologies.

Another potential explanation for differences in clinical phenotype could be variability within pathologies. A study by (Katsumata et al., 2020) reports distinct clinicopathologic clusters of individuals with TDP-43 proteinopathy, supporting the theory that different 43 proteinopathy may result in different clinical presentations. Similarly, Tomé et al. (2020)

reported that TDP-43 aggregates occurring in Alzheimer's disease varied in composition, suggesting that different molecular patterns may influence clinical manifestations.

The observation that LATE-NC increases the risk of cognitive transitions in the presence of additional pathologies, but not independently, suggests a synergistic interaction at the neuropathological level. Josephs et al. (2016) outlines a distinct progression pattern of TDP-43 in Alzheimer's disease. This suggests that the coexistence of the two pathologies may be intrinsically linked or interactions between the two pathologies may exacerbate cognitive decline. This could be a possible explanation for the lack of significant associations between LATE-NC and cognitive decline in the absence of additional neurodegenerative diseases.

Together these findings suggest that further research into LATE-NC is necessary. Although LATE-NC alone may not be sufficient to result in clinically detectable cognitive decline, the presence of LATE-NC does appear to at least have a synergistic effect on cognitive decline in other neurodegenerative diseases, resulting in worse clinical prognosis, faster decline and greater cognitive impairment. The inconsistent and unclear relationship between LATE-NC and cognitive impairment highlights the need for comprehensive neuropathological assessment and the importance of considering the full neuropathological profile in all aspects of dementia research and care.

This suggests that the clinical impact of LATE-NC is highly dependent on the co-occurrence of additional neuropathologies and provides further insights into the clinical presentation of a relatively newly defined neuropathological entity. The findings indicate that LATE-NC does not independently increase the risk of transition between cognitive states. However, the presence of LATE-NC alongside other pathologies increases the risk of transition, suggesting that the clinical significance of LATE-NC is context-dependent. This aligns with previous analyses of the same cohort but contrasts with findings from other studies. The results imply that LATE-NC may not be a standalone driver of cognitive decline but rather interacts with other neurodegenerative conditions to influence cognitive trajectory. This finding enriches the understanding of LATE-NC as a relatively newly defined neuropathological entity, emphasising the importance of considering the presence of comorbidities in clinical settings.

In research settings, the influence of LATE-NC on cognitive decline and clinical manifestations of dementia should be examined. In clinical settings, LATE-NC should be considered as a component of mixed pathology in cases where patients experience rapid decline in cognitive

function. Further studies are needed to fully characterise the clinical phenotype of this relatively new and unusually defined neuropathological entity. Understanding the molecular and cellular mechanisms underlying interactions between TDP-43 pathology and other neurodegenerative disease could provide critical insights into the pathophysiology of mixed dementias and highlight potential targets for therapeutic intervention.

8.3 Strengths and Implications

The key strengths of the study are demonstrated through the broad scope of neuropathology and longitudinal statistical methods applied to a relatively large clinicopathological cohort. This section covers the wider implications of the findings, considering their contributions to existing theories and potential practical applications. These insights may inform future research and impact developments within the dementia field.

8.3.1 Strengths

This study used a robust methodological framework utilising advanced statistical methods, including linear mixed effects models, latent class mixture models, and multistate models, to investigate the impact of mixed and concomitant pathology on dementia within a large neuropathology cohort.

The application of longitudinal statistical methods to a large neuropathology cohort containing both dementia cases and cognitively healthy controls with associated clinical data is relatively uncommon. The methodology of the study significantly enhanced the depth and reliability of the findings, advancing understanding of the complex interplay between neuropathological factors and cognitive outcomes over time. This is reflected by the consistency of the results.

A further strength of the study methodology was the use of advanced statistical techniques, including as linear mixed effects models, latent class mixture models, and multistate models. These methods were particularly suited for analysing longitudinal data, enabling exploration of how different pathologies, and combinations of these pathologies, interacted with cognitive function over time. By utilising these sophisticated analytical tools, subtle changes in cognitive function associated with varying degrees and combinations of neuropathological burden were captured, after accounting for individual specific variability.

The size and diversity of the Brains for Dementia Research neuropathology cohort was crucial for enhancing the generalisability and robustness of the findings. Although the BDR programme is not as large as some other cohort studies of dementia, such as the NACC, the neuropathology cohort remains larger than the majority of autopsy series. Furthermore, the inclusion of both individuals with dementia and cognitively healthy controls – a principal strength of BDR – allowed for comparison and contrast of pathological profiles between these groups, offering insights into specific pathological mechanisms that differentiate normal ageing from pathological cognitive decline (Francis, Costello and Hayes, 2018).. This comparative approach strengthened the internal validity of the findings and supported broader implications for clinical diagnosis and treatment strategies.

Many studies implement strict exclusion criteria in order to remove cases with multiple pathology from cohorts under the assumption that these cases are nonconforming and only obscure results. Others do not clarify how mixed pathology has been accounted for when interpreting findings. While these studies are useful for showing the impact of one pathological process, the results give an artificially narrow view of the disease and are likely only applicable to a small subset of cases. As a consequence, results from many studies using only cases with “pure” pathology show a narrow picture of classical cases that are unlikely to be represent the experience of a significant proportion of dementia cases. Brains for Dementia Research benefits from a wide scope.

Longitudinal clinical assessments conducted as part of the study provided a comprehensive evaluation of cognitive trajectories over time. This longitudinal perspective was essential for capturing the dynamic nature of dementia progression, including variability in disease onset, progression rates, and response to interventions. By examining cognitive decline longitudinally, the study identified pathologies predictive of more severe disease progression, and potential windows for therapeutic intervention and personalised treatment approaches tailored to individual patient neuropathological profiles.

The integration of neuropathological assessments with clinical data represented another key strength of the study. This multidimensional approach enabled researchers to correlate specific neuropathological findings with clinical manifestations of cognitive decline. Such correlations were essential for unravelling the underlying mechanisms of dementia and identifying biomarkers that may serve as early indicators or targets for therapeutic intervention. Standardised protocols for data collection, data quality and validation

procedures throughout the study ensured the reliability and validity of the findings and minimised biases and confounding factors. Maintaining high data integrity enhanced the credibility of the conclusions and strengthened the foundation for future research in dementia and related neurodegenerative disorders.

8.3.2 Implications

The results reported in this study raise important questions about the mechanisms underlying these interactions, posing further questions for future research into how coexisting pathologies may influence neuroinflammation, synaptic integrity and neurodegeneration. The consistency of the results suggests a need for further research in order to develop more comprehensive models that account for interactions between multiple different neuropathologies. Theoretical frameworks should be expanded to consider the cumulative effects of multiple neuropathologies rather than treating age-related neurodegenerative dementias as isolated conditions.

The prevalence of mixed pathology, accompanied by its consistent association with worse clinical outcomes, may necessitate a re-evaluation and modification of current diagnostic criteria for age-related dementias. Theoretical frameworks may need to incorporate mixed pathology as a standard consideration to better predict cognitive trajectories and provide the most suitable treatment strategies. This may also influence priorities in biomarker utilisation and development. As mixed pathology is a prevalent neuropathological profile, the identification of biomarkers that reflect the presence of multiple pathologies could enhance diagnostic accuracy and prognostic predictions. This could lead to exploring multi-targeted interventions aimed at slowing decline by addressing multiple underlying pathologies simultaneously.

The primary practical implication of this study is the importance of prioritising mixed pathology in both clinical and research settings. This study has demonstrated a high prevalence of mixed and concomitant pathology in the ageing brain, with mixed pathology representing the most common neuropathological profile in dementia. The co-existence of neuropathologies is not exclusive to dementia. These findings underscore the need for clinicians to consider mixed pathology as a cause of dementia and routinely assess for multiple neurodegenerative diseases. This could involve the utilisation of advanced biomarker and imaging techniques. The early identification of mixed pathology, particularly

specific components, would allow clinicians to administer personalised treatments based on patient-specific clinical presentation and symptoms when they become available.

This study has also demonstrated disparities between clinical and neuropathological diagnoses, suggesting that many patients never receive an accurate clinical diagnosis during life and are likely not receiving accurate information on clinical prognosis, expected trajectory of disease, or optimal treatment. For example, Lewy body disease is associated with neuroleptic sensitivity. This also raises questions about results originating from solely clinical based studies of dementia that do not include neuropathological confirmation of disease, which remains the gold standard of diagnosis in the field.

Early and accurate clinical diagnosis of dementia subtypes is essential for effective treatment and management, prognosis and trajectory estimation and improving quality of life for patients and carers. Implications of worse clinical prognosis in mixed pathology may extend to societal and economical models of healthcare. The increased burden on healthcare systems due to faster cognitive decline among patients with mixed pathology may necessitate new approaches in resource allocation, healthcare planning and policy development.

Furthermore, the uncertainties in clinical diagnosis, particularly given the abundance of mixed pathology, have implications for clinical trials. Clinical trials and other clinic-based studies rely on probable or possible diagnoses. As seen in this study, these diagnoses are often inaccurate or incomplete, regularly overlooking the common co-occurrence of additional neuropathologies. The inclusion of potential mixed pathology cases in clinical trials may be contributing to unexpected outcomes. The impact of concomitant pathologies on clinical presentation, including cognitive decline, may be contributing the limited success in clinical trials of therapies targeting single proteins (e.g. anti-AB or anti-tau) (King, Bodi and Troakes, 2020).

Similarly, the validation of proposed biomarkers as a diagnostic tool has relied on clinical diagnoses rather than postmortem neuropathological confirmation. It may not be possible to determine the true accuracy of potential biomarkers until these cohorts have reached postmortem. Future studies should collect longitudinal biomarker data for participants who are willing to enrol in brain donation programmes. Although it may take several decades to

come to fruition, it would provide high-quality data on the longitudinal accuracy of potential biomarkers.

8.4 Limitations

While there are many strengths to the dataset and methods used, there are also several limitations. The limitations of this study arise from three main areas: cohort composition, clinical data, and neuropathology measures. The main limitations of the study are outlined below.

8.4.1 Cohort Composition

Brain banking studies are never an exact replica of the general population in terms of cohort composition but are an essential data source in providing valuable insights into the neuropathology of dementia and normal ageing (Francis, Costello and Hayes, 2018). However, studies of this nature face a range of limitations, including selection bias, demographic homogeneity, and limited sample sizes. These factors mainly influence the composition of the cohort and can impact the generalisability and robustness of research (Shepherd, Alvendia and Halliday, 2019). The main limitations of the Brains for Dementia Research cohort are frequently reported across all brain banking studies and are outlined in this section and Francis et al. (2019).

A key limitation of BDR is selection bias (Gauthreaux *et al.*, 2024). Recruitment for the BDR programme involved a self-referral selection process which is not unusual in brain banking enrolment. As a result, the cohort is not representative of the general population in the United Kingdom (Francis, Costello and Hayes, 2018). Participants who volunteer for brain donation are more likely to have a higher level of education, better health awareness, and a greater interest in medical research, which can skew results and complicate data analysis. As a consequence, the results of brain banking studies can often be limited by a healthy volunteer effect. Typically, individuals who enrol in research studies are healthier, more educated and less socially or economically deprived than the general population. As this cohort includes cognitively healthy controls as a significant control group, the differences reported between cases and controls may appear to be more evident than in population-based studies where there is a greater spectrum of cognitive function. Additionally, the demographic homogeneity of BDR is also a major limitation. As with the majority of brain banking studies, the BDR cohort is skewed towards a white, middle-class, well-educated population, with notably poor representation of minority groups. Brain banking studies often

lack diversity in terms of age, ethnicity, and socioeconomic status. This limits the applicability of findings across different demographic groups.

A limitation that is more specific to Brains for Dementia Research is the decision to exclude participants who experienced major cerebrovascular events such as strokes or large haemorrhages. Although this was intended to reduce complexity, excluding the most severe cerebrovascular disease (CVD) cases reduces the ability to represent the full range of dementia patients typically seen in clinical practice.

Cerebrovascular disease appears to be less common in this cohort than in other similar studies. This is likely a vast underestimate due to the strict exclusion criteria implemented in BDR that remove all participants who have had a stroke or haemorrhage and therefore any figures reported regarding the prevalence of CVD should not be taken as an indicator of negligible impact of CVD on clinical dementia.

This exclusion may bias the sample towards milder forms of dementia, potentially skewing results and hindering a comprehensive understanding of dementia's diverse causes and impacts. Vascular pathology has been consistently associated with cognitive decline in dementia. However, due to the exclusion of severe CVD cases in this study, results appear to suggest that cerebrovascular pathology is not a major contributing factor to cognitive decline. This is unlikely to be true. This issue could be avoided in future studies by allowing the inclusion of participants who have had major vascular events. Moreover, omitting severe CVD cases might underestimate the overall burden of cerebrovascular pathology in dementia and limit insights into how vascular factors interact with other neurodegenerative processes. Such exclusions limit the applicability to real-world patient populations. Clinically, findings may not fully translate to patient care settings where both vascular and neurodegenerative pathologies often coexist.

8.4.2 Clinical Data

Further limitations arise from the clinical data collected during longitudinal follow up. In the BDR cohort, participants do not have a formal clinical diagnosis as part of the study protocol, but self-report clinical diagnosis at registration (Francis, Costello and Hayes, 2018). To enhance the quality of the data, confirmation of participant diagnostic status during life through primary health care settings could be implemented to the study protocol. The absence of formal clinical diagnoses poses several limitations. Firstly, it makes accurate

classification of dementia types (such as Alzheimer's disease, vascular dementia) challenging, potentially leading to misclassification of cases reported in this study. As a result, it becomes more difficult to establish clear correlations between clinical symptoms and neuropathological findings. Formal clinical diagnoses provide a framework for understanding how specific pathological changes relate to the clinical presentation of dementia. Moreover, the lack of clinical diagnoses may limit the generalisability of study findings to broader dementia populations where clinical diagnoses guide treatment and management decisions. Additionally, formal clinical diagnoses serve as a critical benchmark for validating neuropathological findings. Without them, the accuracy of observed pathology in relation to clinical syndromes may be harder to ascertain.

A further limitation of the study is the limited clinical measures available. While the MMSE is widely used to assess cognitive function, it has several limitations. Scores are not domain specific and do not cover critical areas like executive function and visuospatial ability. The test can exhibit ceiling effects, where high-functioning individuals score too high, and floor effects, where severely impaired individuals score too low, masking the true extent of cognitive deficits. Cultural and educational biases may lead to inaccurate assessments in diverse populations, as some items assume a certain level of literacy and numeracy. The MMSE often lacks sensitivity to early or mild cognitive impairment, potentially missing early stages of decline. Non-cognitive factors like anxiety, depression, and fatigue can influence results, confounding the assessment. Variability in administration and scoring among practitioners can lead to inconsistencies, affecting reliability. Additionally, the MMSE may lack temporal stability, making it difficult to track changes in cognitive function over time.

8.4.3 Neuropathology Data

Similarly, limitations also arise from the neuropathological data. Semi-quantitative neuropathology measures rely on visual assessment by pathologist, which introduces a significant degree of subjectivity and interrater variability. Different pathologists may interpret and rate the same pathology differently, leading to inconsistencies and variability in and reducing the reliability of the data. As a result, results can vary significantly between laboratories, limiting the comparability and reproducibility of the data.

The use of semi-quantitative neuropathology data presents several limitation that can impact the accuracy and reliability of research findings (Attems, Neltner and Nelson, 2014). The limited precision of semi-quantitative scales can obscure subtle but important

differences in pathology. The lack of granularity makes it difficult to detect small but clinically relevant changes, potentially missing nuances in disease progression. The reduced sensitivity of semi-quantitative measures further complicates their use. The lack of precision in semi-quantitative scales may not capture low levels of pathology or slight variations between individuals, which may lead to an underestimation of disease burden or progression.

Semi-quantitative measures are rarely sensitive enough to distinguish between the variability in abundance, topography and morphology of pathology in different cases of the same neuropathology stage. Many semi-quantitative measures are also subject to a ceiling effect where a disproportionate group of cases are present in the highest category. This can reduce the value of the data and restrict the strength of the associations drawn from analyses. Further to this, several neuropathology types were categorised as either “Present” or “Absent or Not Reported”. The grouping of Absent and Not Reported cases together may have resulted in the incorrect categorisation of cases. Some pathologies, such as TDP-43 in LATE-NC, aggregate with a unilateral distribution. This means that examining one hemisphere of the brain may not provide an accurate picture of the presence or absence of these pathologies resulting in false negatives.

Another limitation arising from neuropathology studies of this nature is confirmation bias. With immunohistochemistry, it is only possible to find preselected pathologies that have been specifically stained for. The focus on pre-established biomarkers in the field, such as tau and Aβ, may result in emerging biomarkers, that could potentially have a greater association with cognitive decline being overlooked. For example, TDP-43 in LATE-NC and transmembrane protein 106B are recently discovered aggregates in the ageing brain that had previously gone unnoticed as they were not stained for (Feng, Lacrampe and Hu, 2021, Nicholson and Rademakers, 2016).

There are several limitations that arise from the specific staging systems used in BDR neuropathological assessments. For example, the TDP-43 staging systems rely on arbitrary cut-offs, vague classifications and the assumption that the pathology is associated with its own clinical condition (Nelson et al., 2022b). Furthermore, the Vascular Cognitive Impairment Neuropathology Guidelines (VCING) rating used to assess cerebrovascular disease pathology (Skrobot *et al.*, 2016) has several limitations that impact its utility and accuracy. Due to the limited sensitivity and scope of the VCING rating, it is not possible to

capture subtle or early changes in cerebrovascular pathology. The categorical nature of VCING might miss slight but significant variations, resulting in an underestimation of the extent of the disease.

By classifying pathology severity into broad categories, finer details and variations in the extent and impact of cerebrovascular lesions are obscured, potentially overlooking important nuances. While it focuses on cerebrovascular pathology, it may not comprehensively assess other related pathologies that contribute to cognitive impairment, such as neurodegenerative changes. This narrow focus can result in an incomplete understanding of the overall disease process, failing to capture the full spectrum of factors influencing cognitive decline. Moreover, the correlation between the VCING rating and clinical outcomes is not always strong. This discrepancy makes it challenging to directly link cerebrovascular pathology ratings with specific clinical symptoms or disease progression. The inability to consistently correlate pathology with clinical manifestations limits the practical applicability of the rating in predicting patient outcomes.

A further limitation of this particular cohort is the level of missing neuropathology data from specific sites, particularly at the beginning of the study. While neuropathological assessments across the cohort are generally thorough and complete, there are some instances in which cases have limited neuropathological staging data and appear to have restricted data available or alternative staging systems used. This is likely due to limited time and funding. However, the issue appears to only be present in data collected from brain donations made at one visit centre which underwent neuropathological at another brain bank, suggesting unequal resource allocation for external brain donations and unequal or non-random missingness of data which can affect data analysis downstream.

8.5 Future Research Directions

The findings of this study open up several avenues for further exploration. While the current research provides valuable insights into the relationship between mixed pathology and cognitive decline, further investigation is necessary to address the limitations of this study and verify results in different cohorts. Future studies in this research area could address the limitations outlined previously by diversifying study populations, expanding statistical methodologies, and exploring new variables, all of which would improve the applicability and impact of findings.

Future studies would benefit from an increase in demographic heterogeneity. The cohort composition of the majority of longitudinal studies of dementia with brain donation is narrowly conscribed, skewed towards a white, well-educated, middle-class subsection of society. For example, participants from areas of greater deprivation are significantly less likely to sign up for studies that include brain donation (Gao et al., 2015). The current reliance on homogenous populations may limit the applicability of results across different populations. This introduces a number of issues when analysing the data and limits the conclusions that can be drawn from it. Expanding the study population to include more diverse demographic, geographic, and socioeconomic groups is essential for enhancing the generalisability of findings. Ensuring the inclusion of individuals from diverse backgrounds could potentially improve the applicability of results to a variety of demographic groups, including those of different ethnicities, cultures, and socioeconomic backgrounds.

An additional potential area for further research would be extend the observation period of longitudinal data collection. A longer follow-up would allow for a more comprehensive understanding of long-term trends, patterns, and outcomes. A limitation of this particular cohort was the fact a significant proportion of the cohort began the follow-up period with pre-established dementia, impacting the ability of statistical models to fully examine temporal relationships between cognition and neuropathology. Extended follow-up periods could allow models to capture a fuller picture of cognitive decline spanning from normal cognition to end of life.

This study has further emphasised the importance of continuing to fund longitudinal studies of dementia where brain donation is a key component. Future studies should aim to collect longitudinal clinical and biomarker data for participants willing to enrol in brain donation programmes. This would optimise the value of biomarker data and provide useful insights

into the relationships between clinical presentation, biomarker data, and postmortem neuropathology. Although it may take several decades to come to fruition, it would provide high-quality data on the longitudinal accuracy of potential biomarkers and clinical diagnoses. The addition of quantitative methods to determine pathological burden would provide more valuable data for downstream analysis. In addition, the implementation of neuroimaging, slide scanners, and digital pathological image analysis in the Brains for Dementia Research could enrich the quality of the data available, expand the range of methods used by researchers for disease staging, and enable the implementation of machine learning techniques.

The decision to not include formal clinical diagnoses in a clinicopathological study of dementia is a significant limiting factor. In the absence of formal clinical diagnoses, it is impossible to accurately determine diagnostic accuracy. Future studies should prioritise including a formal diagnostic procedure in study protocols for those donating brain tissue so that postmortem neuropathological confirmation of clinical diagnoses can be verified. Although it is likely that the study diagnoses available in this data reflect the experience of the average patient, it seems counterintuitive to not confirm these diagnoses for the integrity of the data. While there are a number of clinical measures available, none of the cognitive measures provided domain specific scores. The addition of a cognitive measure such as the Addenbrookes Cognitive Examination (ACE) would add significantly more value to the data collected and provide greater detail about domain specific decline in cognition in relation to neuropathology profiles.

The findings from this study leave unresolved questions and highlight the need for further studies of the underlying pathological processes in dementia, particularly the complex interactions between different pathology types and how these interactions may influence clinical presentation. Future studies using this cohort could also investigate other areas of clinical presentation. For example, the relationship between neuropsychiatric symptoms of dementia and combinations of mixed pathology.

8.6 Conclusions

In conclusion, this study emphasises the significance of mixed pathology as a contributing factor to cognitive decline in dementia. Despite its clinical relevance, mixed pathology remains clinically underrepresented as a diagnosis. These findings underscore the significance of research in mixed and concomitant pathology, as they not only advance theoretical understanding but also provide practical insights that can inform real-world applications and policy decisions that would benefit both individuals living with dementia and carers.

The research contributes to the field by addressing existing gaps in the literature and offering a nuanced perspective on the contribution of mixed and concomitant neuropathology to dementia. The study provides further supporting evidence that the traditional single pathology models of dementia do not reflect the experience of the majority of patients living with dementia. By integrating advanced longitudinal statistical methods with postmortem neuropathology data, the study enhances the credibility of the results and establishes a foundation for further research.

Future research should focus on mixed pathology as a common neuropathology type in dementia, as these avenues hold the potential to build upon the insights gained from this study. Pursuing such directions will facilitate a deeper understanding and promote the development of more effective solutions in dementia research.

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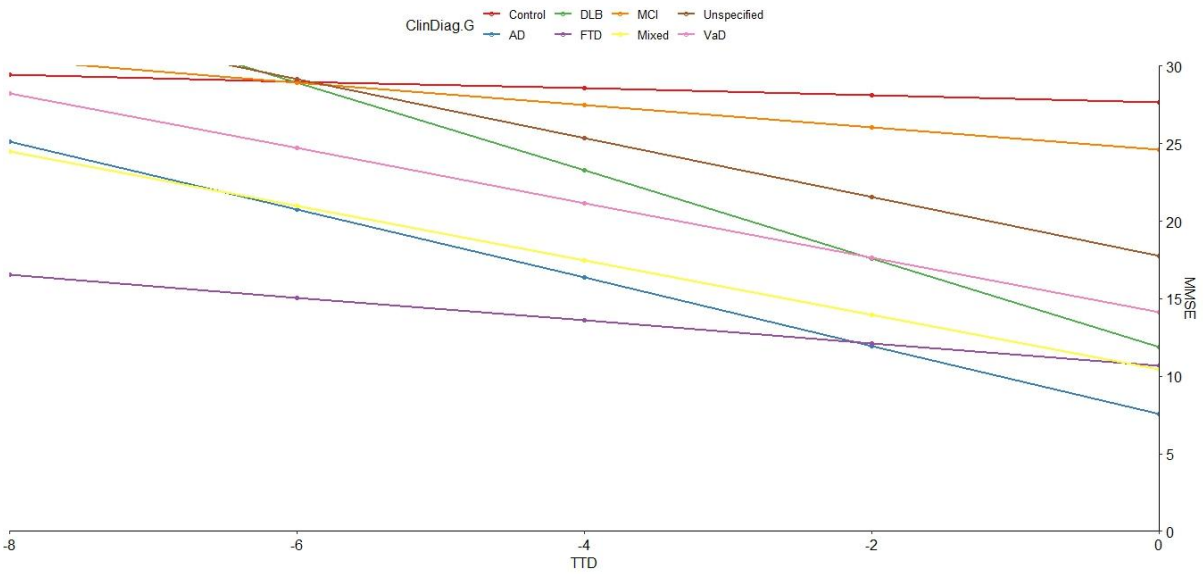
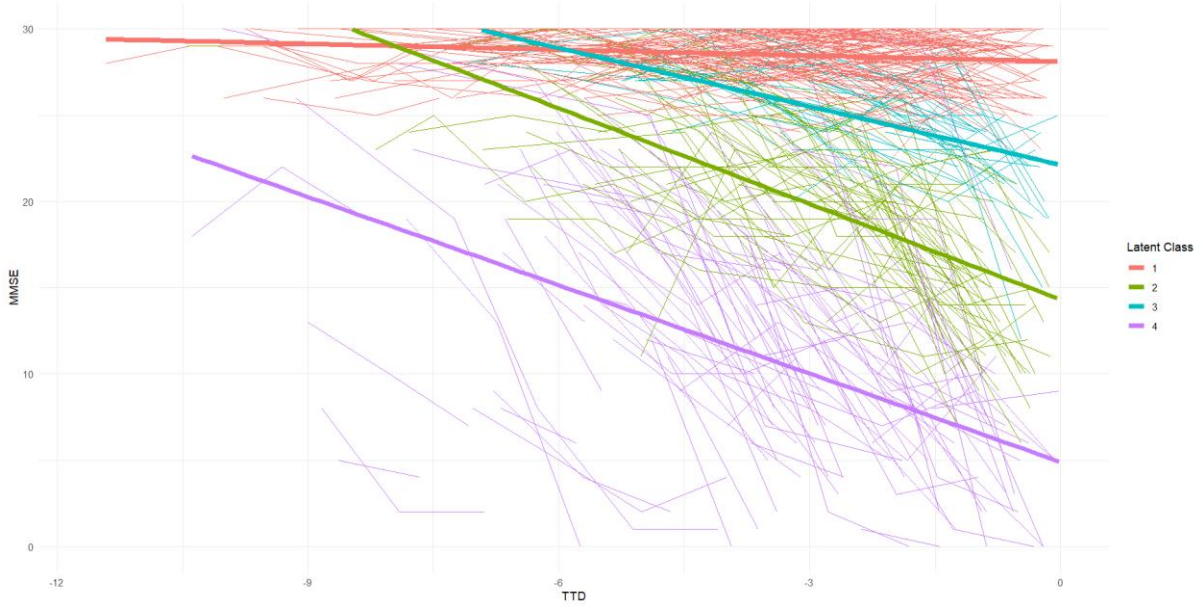
Appendix

Appendix I. **Linear Mixed Effects Model Examining Cognitive Trajectories by Clinical Diagnosis:** Fixed effect estimates for final cognitive scores (intercepts) and rates of decline (slopes) in MMSE and CDR-Sum of Boxes are reported for each neuropathological group. Models include random intercepts and slopes to account for individual variability over time, and are adjusted for age, education, and time to death (TTD). Low pathology controls serve as the reference group. Estimates are presented with 95% confidence intervals and corresponding p-values.

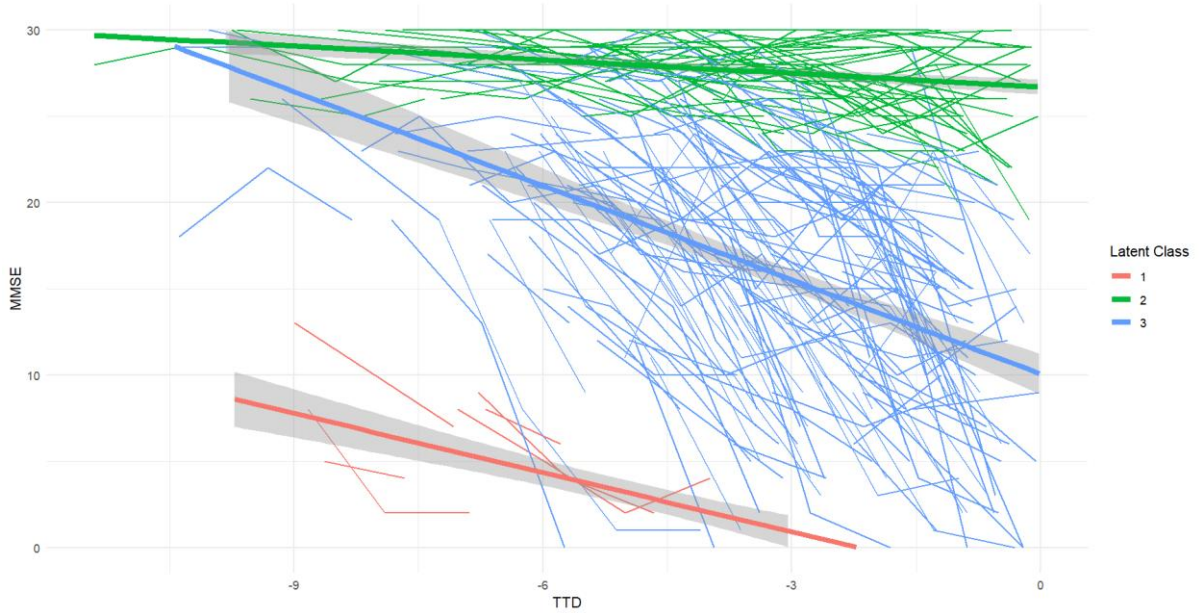
	MMSE	
	Intercept[1]	**Rate**[1]
(Intercept)	**30.1** (23.4, 36.9), *< .001*	-
TTD	**-0.22** (-0.41, -0.03), *0.021*	-
Age	-	**-0.04** (-0.11, 0.03), *0.263*
Education	-	**0.07** (-0.09, 0.23), *0.383*
Alzheimer's disease	**-20.1** (-22.0, -18.24), *< .001*	**-1.97** (-2.31, -1.63), *< .001*
Lewy body dementia	**-15.8** (-20.4, -11.1), *< .001*	**-2.62** (-3.47, -1.76), *< .001*
Frontotemporal dementia	**-17.0** (-22.6, -11.4), *< .001*	**-0.51** (-1.73, 0.71), *0.410*
Vascular dementia	**-13.6** (-16.7, -10.5), *< .001*	**-1.54** (-2.11, -0.98), *< .001*
Unspecified dementia	**-9.94** (-13.7, -6.19), *< .001*	**-1.68** (-2.37, -1.00), <. 001
Mild cognitive impairment	**-3.07** (-6.32, 0.17), *0.063*	**-0.50** (-1.00, -0.00), *0.048*
Mixed dementia	**-17.2** (-20.0, -14.5), *< .001*	**-1.53** (-2.03, -1.04), *< .001*



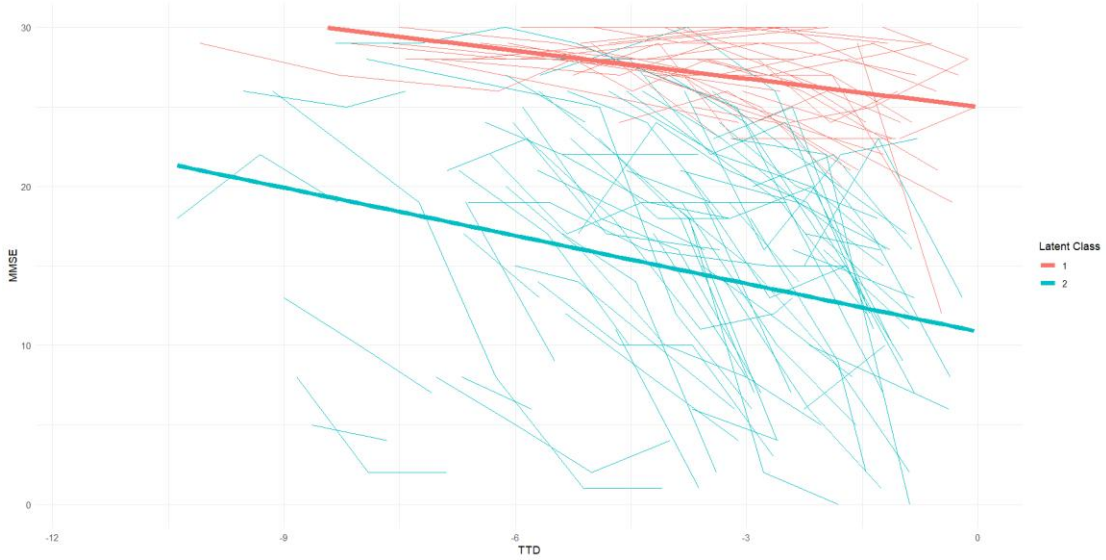
***Appendix II*. Clinical Diagnosis:** Predicted MMSE for each clinical group in the final eight years preceding death, adjusting for age and education. Clinical diagnoses include cognitively healthy controls, Alzheimer's disease (AD), Lewy body dementia (DLB), mild cognitive impairment (MCI), unspecified dementia, frontotemporal dementia (FTD), mixed dementia (Mixed), and vascular dementia (VaD).



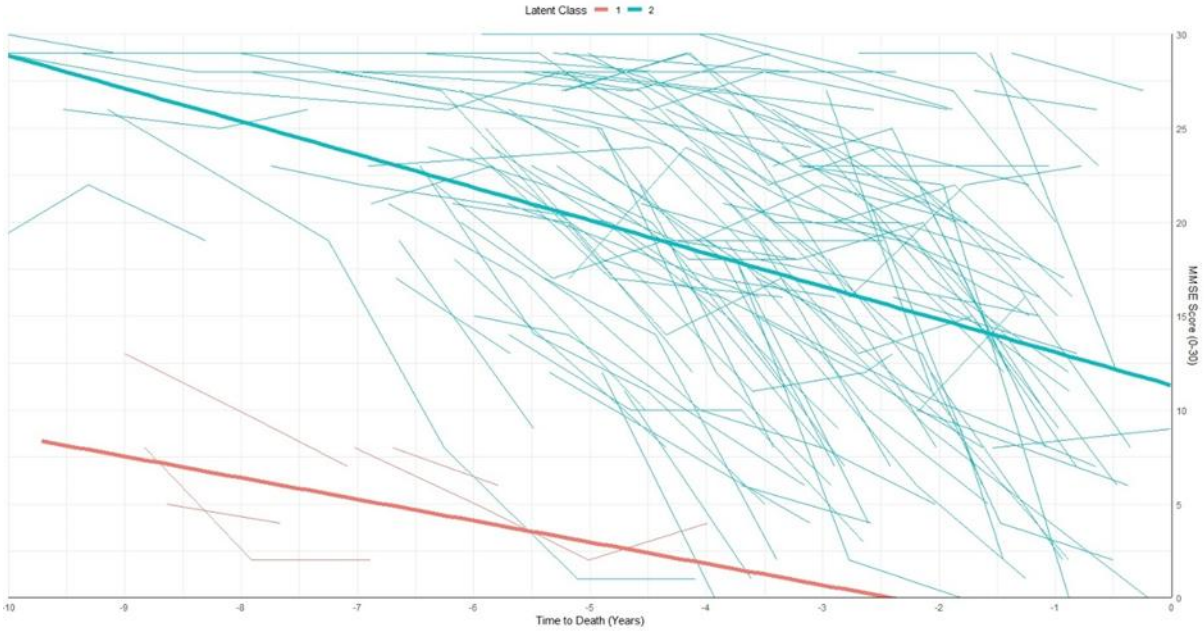
***Appendix III*. Individuals Longitudinal Trajectories of All Cases (N = 538):** Longitudinal cognitive data of all cases included in the model with four latent classes. Individual participant cognitive scores are displayed over time to illustrate within-class variability and overall trends.



Appendix IV. **Individuals Longitudinal Trajectories of Alzheimer's disease (N = 262):** Longitudinal cognitive data of all cases included in the Alzheimer's disease model with three latent classes. Individual participant cognitive scores are displayed over time to illustrate within-class variability and overall trends**.**



Appendix V. **Individuals Longitudinal Trajectories of LATE-NC (N = 131):** Longitudinal cognitive data of all cases included in the LATE-NC model with three latent classes. Individual participant cognitive scores are displayed over time to illustrate within-class variability and overall trends.

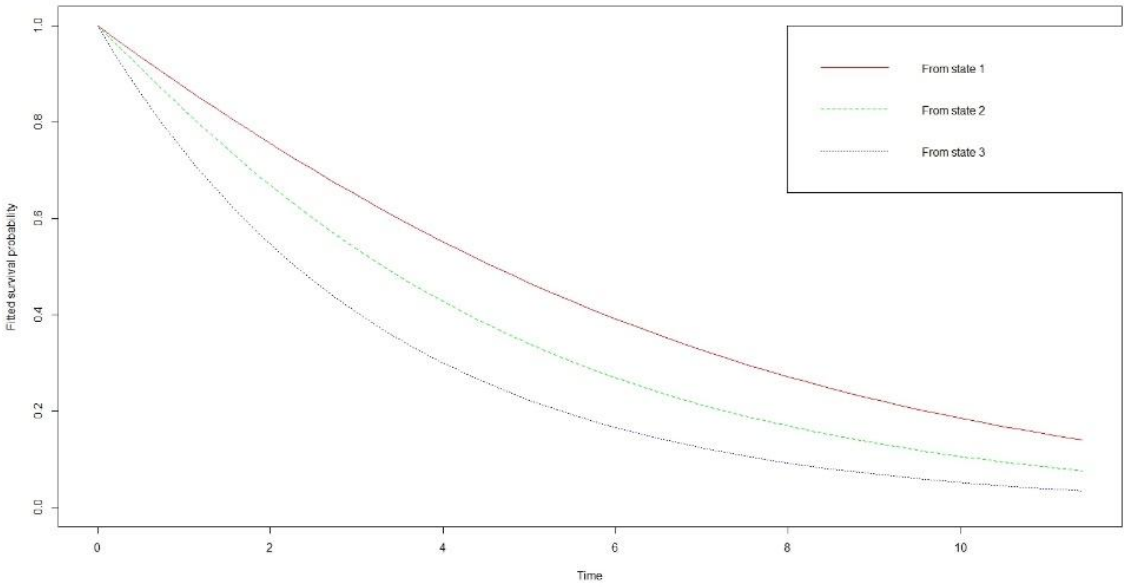


***Appendix VI*. Individuals Longitudinal Trajectories of Mixed Pathology (N = 121):**
Longitudinal cognitive data of all cases included in the mixed pathology model with three latent classes. Individual participant cognitive scores are displayed over time to illustrate within-class variability and overall trends**.**

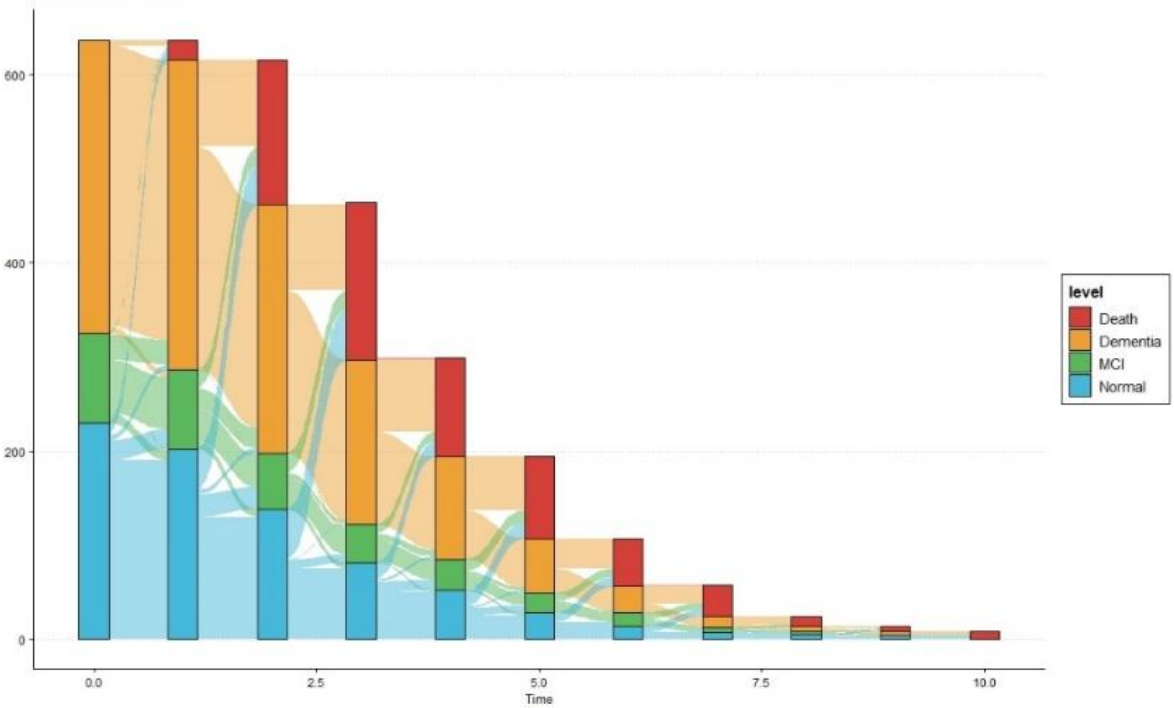
***Appendix VII*. Demographic and Neuropathological Characteristics of Alzheimer's Disease Cases, Stratified by Assigned Latent Class**. Demographic variables, including age at death, sex, years in full time education, and index of multiple deprivation for each latent class and overall. Neuropathological diagnoses are detailed by pathology group prevalence and common pathology combinations across classes. Additional neuropathology variables are also reported. Mean (SD) or median [range] for continuous variables, and count (%) for categorical variables.

	Class 1 (N=28)	**Class 2 (N=90)**	**Class 3 (N=144)**	**Overall (N=262)**
Age (at death)	84.9 (9.08)	87.3 (6.89)	86.3 (7.31)	86.5 (7.39)
	84.1 [67.8, 99.5]	87.3 [71.1, 99.0]	85.9 [68.8, 104]	86.2 [67.8, 104]
Female	14 (50.0%)	45 (50.0%)	56 (38.9%)	115 (43.9%)
Male	14 (50.0%)	45 (50.0%)	88 (61.1%)	147 (56.1%)
Education	12.6 (3.22)	13.1 (3.32)	12.1 (3.41)	12.5 (3.38)
Index of Multiple Deprivation	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]	2.00 [1.00, 5.00]
Pathology Group				
AD	9 (32.1%)	17 (18.9%)	32 (22.2%)	58 (22.1%)
AGD	1 (3.6%)	3 (3.3%)	0 (0%)	4 (1.5%)
CVD	0 (0%)	5 (5.6%)	1 (0.7%)	6 (2.3%)
FTD	0 (0%)	1 (1.1%)	0 (0%)	1 (0.4%)
DLB	0 (0%)	5 (5.6%)	7 (4.9%)	12 (4.6%)
LATE	0 (0%)	8 (8.9%)	12 (8.3%)	20 (7.6%)
Low pathology controls	2 (7.1%)	38 (42.2%)	13 (9.0%)	53 (20.2%)
Mixed	16 (57.1%)	13 (14.4%)	79 (54.9%)	108 (41.2%)
Pathology Combination				
AD/DLB/LATE	8 (28.6%)	2 (2.2%)	18 (12.5%)	28 (10.7%)
AD/LATE	8 (28.6%)	3 (3.3%)	22 (15.3%)	33 (12.6%)
AD/DLB	0 (0%)	2 (2.2%)	20 (13.9%)	22 (8.4%)

AD/DLB/CVD	0 (0%)	1 (1.1%)	0 (0%)	1 (0.4%)
AD/DLB/CVD/LATE	0 (0%)	1 (1.1%)	1 (0.7%)	2 (0.8%)
AD/FTD/LATE	0 (0%)	1 (1.1%)	0 (0%)	1 (0.4%)
CVD/LATE	0 (0%)	1 (1.1%)	2 (1.4%)	3 (1.1%)
DLB/LATE	0 (0%)	2 (2.2%)	7 (4.9%)	9 (3.4%)
AD/CVD/FTD	0 (0%)	0 (0%)	1 (0.7%)	1 (0.4%)
AD/CVD/LATE	0 (0%)	0 (0%)	5 (3.5%)	5 (1.9%)
DLB/CVD	0 (0%)	0 (0%)	1 (0.7%)	1 (0.4%)
DLB/CVD/LATE	0 (0%)	0 (0%)	1 (0.7%)	1 (0.4%)
FTD/LATE	0 (0%)	0 (0%)	1 (0.7%)	1 (0.4%)
Other Pathology Variables				
iAD	4 (14.3%)	64 (71.1%)	48 (33.3%)	116 (44.3%)
AD	24 (86.7%)	26 (28.9%)	98 (66.7%)	146 (55.7%)
Thal AB	5.00 [3.00, 5.00]	4.00 [1.00, 5.00]	5.00 [2.00, 5.00]	5.00 [1.00, 5.00]
Braak NFT	6.00 [4.00, 6.00]	4.00 [3.00, 6.00]	5.00 [3.00, 6.00]	5.00 [3.00, 6.00]
CERAD	3.00 [2.00, 3.00]	2.00 [0, 3.00]	3.00 [0, 3.00]	3.00 [0, 3.00]
iLBD	2 (7.1%)	3 (3.3%)	7 (4.9%)	12 (4.6%)
LBD	8 (28.6%)	13 (14.4%)	49 (34.0%)	70 (26.7%)
Braak LB	0 [0, 6.00]	0 [0, 6.00]	0 [0, 6.00]	0 [0, 6.00]
Infarcts	1 (3.6%)	13 (14.4%)	11 (7.6%)	25 (9.5%)
CAA	13 (46.4%)	33 (36.7%)	53 (36.8%)	99 (37.8%)
Arteriolosclerosis	7 (25.0%)	17 (18.9%)	33 (22.9%)	57 (21.8%)
LATE	16 (57.1%)	18 (20.0%)	66 (45.8%)	100 (38.2%)



***Appendix VIII*. Four-State Model Survival Plot**: Survival probabilities for each cognitive state (State 1, Normal Cognition; State 2, Mild Cognitive Impairment; State 3, Dementia) over time.



***Appendix IX*. Movement Between Cognitive States Over Follow-Up in the Four-State Model.** Transitions across the transient and absorbing states tracked from baseline assessment to death. Participants entering the death state are excluded from subsequent time point.

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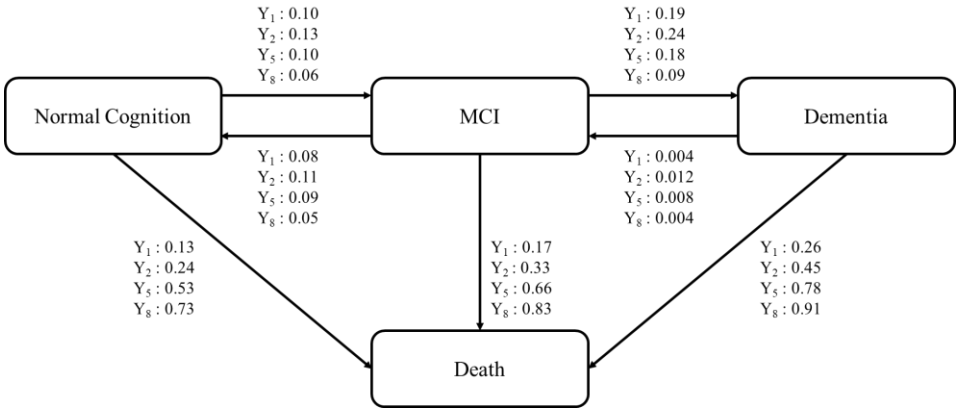
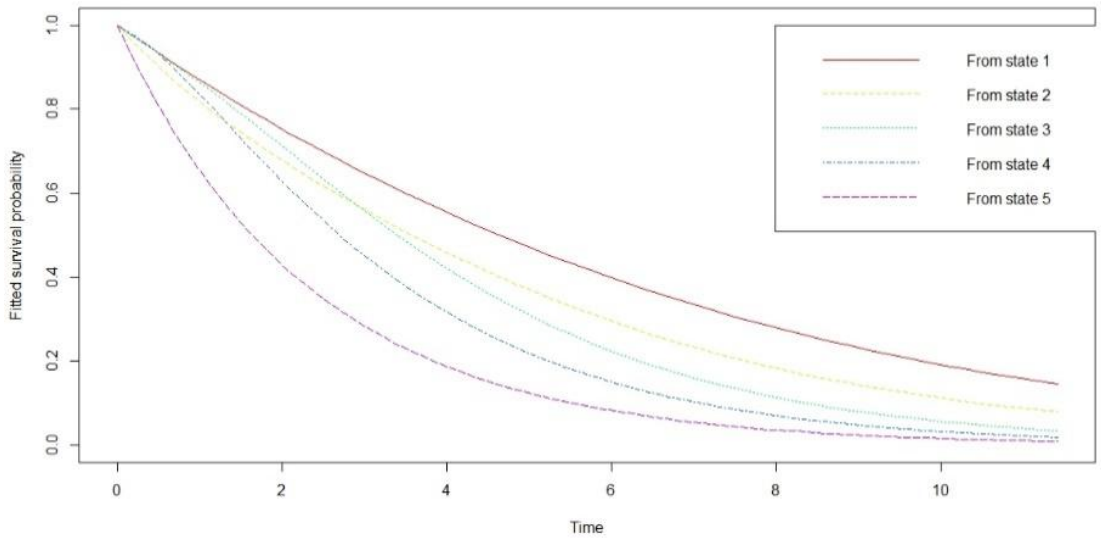
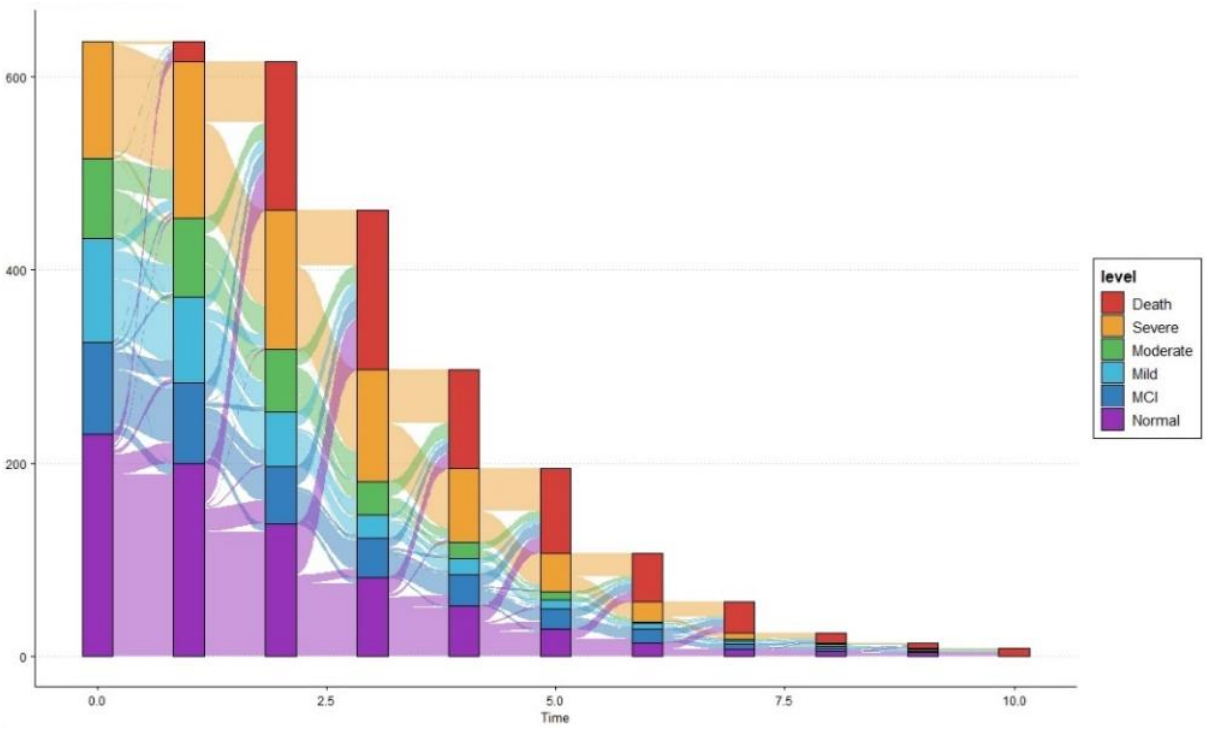


Appendix X. **Four-State Model without Covariates:** Probabilities of transitions between cognitive states (Normal Cognition, Mild Cognitive Impairment, Dementia) at 1, 2, 5, and 8 years, derived from a four-state model without adjustment for covariates to characterise the natural progression of cognitive decline over time.



Appendix XI**. Six-State Model Survival Plot**: Survival probabilities for each cognitive state (State 1, Normal Cognition; State 2, Mild Cognitive Impairment; State 3, Mild Dementia; State 4, Moderate Dementia; State 5, Severe Dementia) over time.



***Appendix XII*. Movement Between Cognitive States Over Follow-Up in the Six-State Model.** Transitions across the transient and absorbing states tracked from baseline assessment to death. Participants entering the death state are excluded from subsequent time point.

Alternative Analysis: Pathology Count

Of the 617 participants included, 237 had no neuropathological diagnosis at postmortem. One hundred and ninety-seven had only one neuropathological diagnosis. One hundred and twenty-four had two co-occurring neuropathological diagnoses and fifty-five had four co-occurring neuropathological diagnoses. In the four-state model, each additional neuropathological diagnosis reported at autopsy was associated with a 48% increase in risk of transition from MCI to dementia (HR = 1.48, 95% CI [1.19, 1.85]) indicating that cerebral multimorbidity is associated with worse prognosis, in comparison to the absence of any neuropathological diagnosis. Neuropathology count was non-significantly associated with a 27% increase in risk of transition to MCI per each additional neuropathological diagnosis (HR = 1.27%, 95% CI [0.99, 1.63]) compared to those without any neuropathological diagnosis. In the six-state model, each additional pathology was associated with a 54% increase in risk of transition to mild dementia (HR = 1.54, [1.19, 1.85]), but no further transitions were associated with any significant change in risk of transition. The probability of transition from MCI to dementia after five years was 67% with one neuropathological diagnosis. With two and three neuropathological diagnoses, this probability increased to an 85% and 93% probability of transition to dementia respectively.

***Appendix XIII*. Alternative Analysis: Neuropathological Diagnosis Count**. Hazard ratios [95% confidence interval] for transitions between cognitive states, adjusting for age and neuropathological diagnosis count [0-4], in the four- and six-state models.

	Baseline Transition Probability (1 Year)	**Covariates**	
		Age	**Pathology count**
to MCI	**0.17**	**1.07**	**1.27**
	[0.13, 0.22]	[1.04, 1.11]	[0.99, 1.63]
to Dementia	**0.34**	**1.00**	**1.48**
	[0.27, 0.43]	[0.97, 1.03]	[1.19, 1.85]
		Age	**Pathology count**
to MCI	**0.16**	**1.07**	**1.25**
	[0.13, 0.21]	[1.04, 1.11]	[0.97, 1.61]
to Mild Dementia	**0.31**	**0.99**	**1.54**
	[0.25, 0.40]	[0.96, 1.02]	[1.22, 1.95]
to Moderate Dementia	**0.67**	**1.02**	**1.15**
	[0.55, 0.83]	[1.00, 1.04]	[0.95, 1.39]
to Severe Dementia	**0.84**	**1.00**	**0.94**
	[0.68, 1.03]	[0.98, 1.02]	[0.78, 1.12]

Alternative Analysis: Mixed Pathology Combinations

In the six-state model, compared to low pathology controls (N = 208), mixed AD/LBD (AD+LBD+; N = 85) was associated with a 270% increase in risk of transition from normal cognition to MCI (HR = 3.70, 95% CI [1.08, 12.6]) and a 208% increase in risk of transition from MCI to mild dementia (HR = 4.08, 95% CI [1.89, 8.82]). In the four-state model, mixed AD/LBD was only associated with increased risk of transition from MCI to dementia (HR = 3.67, 95% CI [1.72, 7.84]).

In the six-state model, Alzheimer's disease in the absence of Lewy body disease (AD+LBD-; N = 152) was associated with an increased risk of transition from MCI to dementia (HR = 2.38, 95% CI [1.15, 4.93]), whereas Lewy body disease in the absence of Alzheimer's disease (AD-LBD+; N = 59) was associated with an increased risk of transition from normal cognition to MCI (HR = 2.17, 95% CI [1.02, 4.60]). In the four-state model, these associations remained with an additional increase in risk of transition from MCI to dementia (HR = 2.27, 95% CI [1.06, 4.88]) for Lewy body disease (AD-LBD+).

In the six-state mode, compared to low pathology controls (N = 208), there was no association between mixed AD/CVD (AD+CVD+; N = 15) or CVD (AD-CVD+; N = 29) and any change in risk of transition between cognitive states in either model. Alzheimer's disease in the absence of cerebrovascular disease (AD+CVD-; N = 222) was associated with an increased risk of transition to both MCI (HR = 2.07, 95% CI [1.03, 4.15]) and dementia (HR = 2.77, 95% CI [1.43, 5.36]). Comparable results were seen in the four-state model.

Mixed AD/LATE (AD+LATE+; N = 117) was associated with an increased risk of transition to MCI (HR = 2.14, 95% CI [0.91, 5.05]) and mild dementia (HR = 3.12, 95% CI [1.41, 6.92]) in the six state model. In the four-state model, AD/LATE was associated with an increased risk of transition to dementia only (HR = 2.62, 95% CI [1.28, 5.39]). Alzheimer's disease in the absence of LATE (AD+LATE-; N = 120) was associated with an increased risk of transition to dementia, whereas LATE in the absence of Alzheimer's disease (AD-LATE+; N = 83) was not. Comparable results were seen in the four-state model.

Output for other mixed combinations are reported in Appendix XIV-XVI.

***Appendix XIV*. Alternative Analysis: Mixed Pathology Combinations in Alzheimer's Disease**. Hazard ratios [95% confidence interval] for transitions between cognitive states in individuals with Alzheimer's disease, stratified by the presence or absence of co-occurring Lewy body disease, cerebrovascular disease, and LATE-NC in the six- and four-state models.

	Normal Cognition to MCI	**MCI to Mild Dementia**	**Mild to Moderate**	**Moderate to Severe**
AD+LBD+	**3.70**	**4.08**	**1.43**	**1.39**
	[1.08, 12.6]	[1.89, 8.82]	[0.79, 2.60]	[0.65, 2.95]
AD+LBD-	**1.86**	**2.38**	**1.27**	**1.33**
	[0.88, 3.92]	[1.15, 4.93]	[0.70, 2.31]	[0.64, 2.78]
AD-LBD+	**2.17**	**2.13**	**1.04**	**0.96**
	[1.02, 4.60]	[0.95, 4.77]	[0.52, 2.08]	[0.41, 2.23]
AD+CVD+	**2.37**	**10.8**	**0.38**	**1.06**
	[0.20, 27.6]	[0.77, 153]	[0.50, 2.87]	[0.32, 3.51]
AD+CVD-	**2.07**	**2.77**	**1.44**	**1.27**
	[1.03, 4.15]	[1.43, 5.36]	[0.83, 2.48]	[0.64, 2.53]
AD-CVD+	**1.70**	**2.14**	**1.03**	**1.80**
	[0.80, 3.64]	[0.59, 7.81]	[0.29, 3.64]	[0.49, 6.64]
AD+TDP+	**2.14**	**3.12**	**1.70**	**1.04**
	[0.91, 5.05]	[1.41, 6.92]	[0.93, 3.11]	[0.51, 2.12]
AD+TDP-	**1.95**	**3.17**	**1.20**	**1.87**
	[0.79, 4.81]	[1.49, 6.75]	[0.65, 2.21]	[0.91, 3.84]
AD-TDP+	**1.38**	**1.59**	**1.51**	**1.30**
	[0.67, 2.81]	[0.75, 3.34]	[0.76, 3.01]	[0.60, 2.78]

	Normal Cognition to MCI	**MCI to Dementia (All)**
AD+LBD+	**3.41**	**3.67**
	[0.98, 11.9]	[1.72, 7.84]
AD+LBD-	**1.86**	**2.61**
	[0.88, 3.91]	[1.32, 5.16]
AD-LBD+	**2.16**	**2.27**
	[1.02, 4.59]	[1.06, 4.88]
AD+CVD+	**1.70**	**5.54**
	[0.20, 14.1]	[0.63, 48.7]
AD+CVD-	**2.09**	**2.84**
	[1.04, 4.18]	[1.52, 5.30]
AD-CVD+	**1.73**	**2.36**
	[0.81, 3.66]	[0.91, 6.15]
AD+LATE+	**2.23**	**2.62**
	[0.94, 5.25]	[1.28, 5.39]
AD+LATE-	**1.92**	**3.31**
	[0.78, 4.74]	[1.65, 6.65]
AD-LATE+	**1.36**	**1.74**
	[0.67, 2.78]	[0.98, 3.59]

***Appendix XV*. Alternative Analysis: Mixed Pathology Combinations in Lewy Body Disease**. Hazard ratios [95% confidence interval] for transitions between cognitive states in individuals with Lewy body disease, stratified by the presence or absence of co-occurring Alzheimer's disease, cerebrovascular disease, and LATE-NC in the six- and four-state models.

6 STATE	**Normal Cognition to MCI**	**MCI to Mild Dementia**	**Mild to Moderate**	**Moderate to Severe**
AD+LBD+	**3.70**	**4.08**	**1.43**	**1.39**
	[1.08, 12.6]	[1.89, 8.82]	[0.79, 2.60]	[0.65, 2.95]
AD+LBD-	**1.86**	**2.38**	**1.27**	**1.33**
	[0.88, 3.92]	[1.15, 4.93]	[0.70, 2.31]	[0.64, 2.78]
AD-LBD+	**2.17**	**2.13**	**1.04**	**0.96**
	[1.02, 4.60]	[0.95, 4.77]	[0.52, 2.08]	[0.41, 2.23]
LBD+CVD+	**0.03**	**16.0**	**0.48**	**0.84**
	[0.00, NA]	[0.79, 321]	[0.08, 3.03]	[0.19, 3.63]
LBD+CVD-	**2.39**	**2.64**	**1.28**	**1.37**
	[1.22, 4.67]	[1.34, 5.22]	[0.73, 2.25]	[0.67, 2.82]
LBD-CVD+	**1.77**	**2.07**	**0.83**	1.97
	[0.86, 3.67]	[0.61, 7.02]	[0.25, 2.74]	[0.68, 2.74]
LBD+LATE+	**3.13**	**3.47**	**1.58**	**1.17**
	[1.07, 9.16]	[1.50, 8.04]	[0.85, 2.94]	[0.55, 2.48]
LBD+ LATE-	**1.89**	**2.74**	**1.04**	**1.76**
	[0.84, 4.22]	[1.23, 6.12]	[0.54, 2.01]	[0.79, 3.89]
LBD- LATE+	**1.33**	**1.46**	**1.50**	**1.33**
	[0.68, 2.59]	[0.70, 3.07]	[0.80, 2.83]	[0.64, 2.76]

4 STATE	**Normal Cognition to MCI**	**MCI to Dementia**
AD+LBD+	**3.41**	**3.67**
	[0.98, 11.9]	[1.72, 7.84]
AD+LBD-	**1.86**	**2.61**
	[0.88, 3.91]	[1.32, 5.16]
AD-LBD+	**2.16**	**2.27**
	[1.02, 4.59]	[1.06, 4.88]
LBD+CVD+	**0.07**	**25.0**
	[0.00, 17600]	[0.01, 6830]
LBD+CVD-	**2.49**	**2.77**
	[1.27, 4.88]	[1.44, 5.31]
LBD-CVD+	**1.78**	**2.10**
	[0.86, 3.68]	[0.79, 5.61]
LBD+LATE+	**3.63**	**3.12**
	[1.32, 9.98]	[1.48, 6.55]
LBD+ LATE-	**1.98**	**2.74**
	[0.88, 4.43]	[1.31, 5.74]
LBD- LATE+	**1.34**	**1.63**
	[0.69, 2.61]	[0.80, 3.32]

Appendix XVI. **Alternative Analysis: Mixed Pathology Combinations in LATE-NC**. Hazard ratios [95% confidence interval] for transitions between cognitive states in individuals with LATE-NC, stratified by the presence or absence of co-occurring Alzheimer's disease (AD), Lewy body disease (LBD), and cerebrovascular disease (CVD) in the six- and four-state models.

	Normal Cognition to MCI	**MCI to Mild Dementia**	**Mild to Moderate**	**Moderate to Severe**
AD+LATE+	**2.14**	**3.12**	**1.70**	**1.04**
	[0.91, 5.05]	[1.41, 6.92]	[0.93, 3.11]	[0.51, 2.12]
AD+LATE-	**1.95**	**3.17**	**1.20**	**1.87**
	[0.79, 4.81]	[1.49, 6.75]	[0.65, 2.21]	[0.91, 3.84]
AD-LATE+	**1.38**	**1.59**	**1.51**	**1.30**
	[0.67, 2.81]	[0.75, 3.34]	[0.76, 3.01]	[0.60, 2.78]
LBD+LATE+	**3.13**	**3.47**	**1.58**	**1.17**
	[1.07, 9.16]	[1.50, 8.04]	[0.85, 2.94]	[0.55, 2.48]
LBD+LATE-	**1.89**	**2.74**	**1.04**	**1.76**
	[0.84, 4.22]	[1.23, 6.12]	[0.54, 2.01]	[0.79, 3.89]
LBD-LATE+	**1.33**	**1.46**	**1.50**	**1.33**
	[0.68, 2.59]	[0.70, 3.07]	[0.80, 2.83]	[0.64, 2.76]
CVD+LATE+	**1.01**	**4.00**	**0.82**	**1.08**
	[0.21, 4.89]	[0.44, 36.4]	[0.20, 3.34]	[0.37, 3.14]
CVD+LATE-	**1.85**	**2.70**	**1.18**	**2.08**
	[0.85, 4.02]	[0.98, 7.47]	[0.34, 4.01]	[0.43, 10.1]
CVD-LATE+	**1.67**	**1.83**	**1.59**	**1.23**
	[0.90, 3.11]	[0.94, 3.54]	[0.91, 2.79]	[0.59, 2.56]

	Normal Cognition to MCI	**MCI to Dementia**
AD+LATE+	**2.23**	**2.62**
	[0.94, 5.25]	[1.28, 5.39]
AD+LATE-	**1.92**	**3.31**
	[0.78, 4.74]	[1.65, 6.65]
AD-LATE+	**1.36**	**1.74**
	[0.67, 2.78]	[0.98, 3.59]
LBD+LATE+	**3.63**	**3.12**
	[1.32, 9.98]	[1.48, 6.55]
LBD+LATE-	**1.98**	**2.74**
	[0.88, 4.43]	[1.31, 5.74]
LBD-LATE+	**1.34**	**1.63**
	[0.69, 2.61]	[0.80, 3.32]
CVD+LATE+	**1.24**	**2.59**
	[0.25, 6.19]	[0.49, 13.7]
CVD+LATE-	**1.87**	**2.88**
	[0.87, 4.01]	[1.25, 6.63]
CVD-LATE+	**1.68**	**1.97**
	[0.90, 3.12]	[1.04, 3.71]