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PRACTICAL APPROACH

Differentiating Prodromal Dementia with Lewy Bodies from Prodromal Alzheimer's Disease: A Pragmatic Review for Clinicians

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ABSTRACT

This pragmatic review synthesises the current understanding of prodromal dementia with Lewy bodies (pDLB) and prodromal Alzheimer's disease (pAD), including clinical presentations, neuropsychological profiles, neuropsychiatric symptoms, biomarkers, and indications for disease management. The core clinical features of dementia with Lewy bodies (DLB)—parkinsonism, complex visual hallucinations, cognitive fluctuations, and REM sleep behaviour disorder are common prodromal symptoms. Supportive clinical features of pDLB include severe neuroleptic sensitivity, as well as autonomic and

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neuropsychiatric symptoms. The neuropsychological profile in mild cognitive impairment attributable to Lewy body pathology (MCI-LB) tends to include impairment in visuospatial skills and executive functioning, distinguishing it from MCI due to AD, which typically presents with impairment in memory. pDLB may present with cognitive impairment, psychiatric symptoms, and/or recurrent episodes of delirium, indicating that it is not necessarily synonymous with MCI-LB. Imaging, fluid and other biomarkers may play a crucial role in differentiating pDLB from pAD. The current MCI-LB criteria recognise low dopamine transporter uptake using positron emission tomography or single photon emission computed tomography (SPECT), loss of REM atonia on polysomnography, and sympathetic cardiac denervation using *meta*-iodobenzylguanidine SPECT as indicative biomarkers with slowing of dominant frequency on EEG among others as supportive biomarkers. This review also highlights the emergence of fluid and skin-based biomarkers. There is little research evidence for the treatment of pDLB, but pharmacological and non-pharmacological treatments for DLB may be discussed with patients. Non-pharmacological interventions such as diet, exercise, and cognitive stimulation may provide benefit, while evaluation and management of contributing factors like medications and sleep disturbances are vital. There is a need to expand research across diverse patient populations to address existing disparities in clinical trial participation. In conclusion, an early and accurate diagnosis of pDLB or pAD presents an opportunity for tailored interventions, improved healthcare outcomes, and enhanced quality of life for patients and care partners.

Keywords: Biomarkers; Clinical diagnosis; Early-stage dementia; Mild cognitive impairment; Neuropsychological profile; Psychiatric symptoms; Treatment planning

Key Summary Points

Core features of dementia with Lewy bodies (DLB) (parkinsonism, visual hallucinations, cognitive fluctuations, and REM sleep behaviour disorder) are common in the prodromal, or predementia, phase.

Prodromal DLB (pDLB) can present with cognitive impairment, psychiatric symptoms, and/or recurrent episodes of delirium. Therefore, pDLB is an umbrella term which includes, but is not limited to, presentations with mild cognitive impairment.

The neuropsychological profile in pDLB tends to demonstrate greater weaknesses in visuospatial skills and executive functioning, while prodromal Alzheimer's disease (pAD) typically reflects weaknesses in language and memory.

Imaging and fluid biomarkers may be helpful in differentiating between pDLB and pAD; however, co-pathology is common and patients with positive biomarkers for Alzheimer's pathology may also have underlying Lewy body pathology.

INTRODUCTION

The conceptual framework of the prodromal, or predementia, stages of neurodegenerative disease has evolved over the last two decades.

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Individuals with neurodegenerative disease can experience cognitive, motor, psychiatric, sleep, and/or autonomic symptoms prior to meeting established criteria for dementia. Early identification of the underlying aetiology associated with the clinical syndrome is vital to inform prognosis, which impacts care planning and treatment. As disease-modifying therapies evolve, recognising early clinical symptoms of neurodegenerative disease will be of increasing importance for clinical trials as well as clinical management.

In this review, we compare the clinical features, neuropsychological profiles, biomarkers, and management among people with prodromal dementia with Lewy bodies (pDLB) and prodromal Alzheimer's disease (pAD). This article is based on previously conducted studies and contains no new studies with human participants or animals performed by any of the authors.

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is conceptualised as an early, or predementia, stage of neurodegenerative disease including dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). The definition of MCI due to AD (MCI-AD, also known as pAD) according to the National Institute on Aging-Alzheimer's Association (NIA-AA) is provided in Fig. 1. In 2020, an estimated 12.23 million people in the USA were living with MCI, and this number is expected to increase to 21.55 million by 2060 [1]. pAD accounts for approximately half of these MCI cases [2]. Aetiological diagnosis at the MCI stage can be challenging, as different pathologies have overlapping clinical phenotypes, and the complete clinical syndrome may not be exhibited. Nevertheless, there are clinical and biological features that can help characterise the underlying aetiology in prodromal disease.

CLINICAL PRESENTATION OF PRODROMAL DLB

After AD, DLB is the second most common neurodegenerative dementia [3]. Like Parkinson's disease (PD), the prevalence of DLB is expected rise in the coming years [4]. People with DLB often experience diagnostic delays and are misdiagnosed with other neurodegenerative or psychiatric conditions, contributing to increased burden on patients and care partners, difficulty planning for the future, and unsuitable treatment strategies [5, 6]. Early and accurate identification of DLB is therefore critical.

Recognising that pDLB could represent an important point at which disease-modifying interventions could be introduced, the international DLB community recently reached a consensus on research criteria of pDLB. The group agreed that MCI often characterised the predementia phase of DLB. However, unlike the prodromal phase of AD (pAD), that there other non-MCI presentations of prodromal DLB and pDLB is not necessarily synonymous with MCI in Lewy body disease (MCI-LB). The criteria therefore describe three phenotypic states which could be considered as prodromal phases of DLB: (1) cognitive symptom-onset; (2) psychiatric-onset; and (3) delirium-onset pDLB [7]. Therefore, prodromal DLB is a term which is not necessarily synonymous with MCI.

Cognitive-Onset

MCI-LB is the most common prodromal presentation of DLB. In alignment with DLB criteria, pDLB research criteria classify cases as "probable" or "possible" MCI-LB based on core clinical features and diagnostic biomarkers. Patients must meet the essential criteria for MCI (as defined by lack of functional impairment according to NIA-AA for MCI-AD; Fig. 1) [7, 8]. Thereafter, individuals are classified as having probable MCI-LB if exhibiting at least two of four core clinical features: REM sleep behaviour

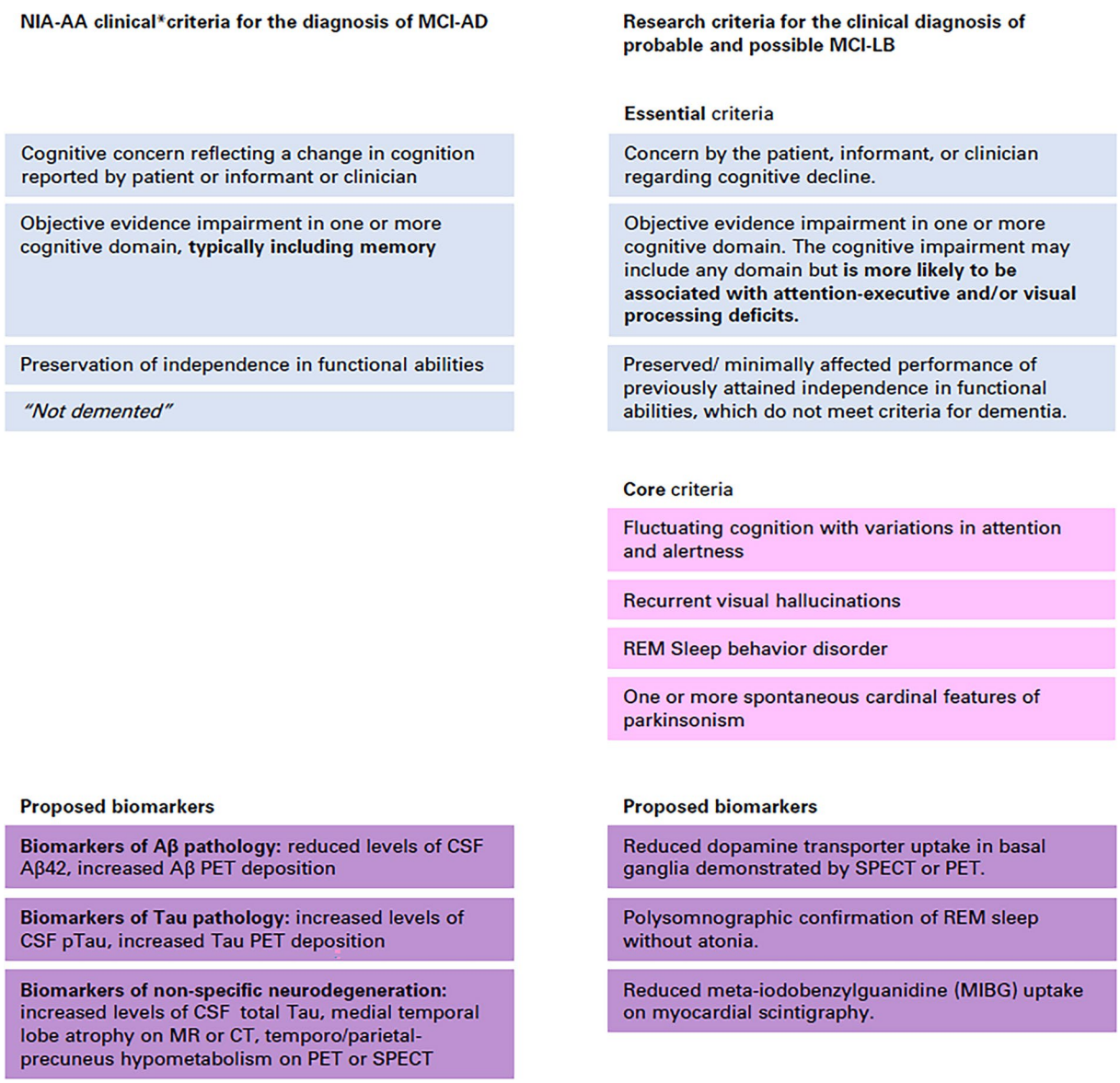

Fig. 1 A comparison of diagnostic criteria for and mild cognitive impairment with Lewy bodies (MCI-LB) and mild cognitive impairment due to Alzheimer's disease (MCI-AD). The three essential criteria for MCI-LB [7] are broadly analogous to the NIA-AA definition of MCI-AD [44]. *Aβ* amyloid beta peptide, *CSF* cerebrospinal fluid, *CT* computed tomography, *MR* magnetic resonance imaging, *PET* positron emission tomography, *SPECT* single photon emission computed tomography

disorder (RBD), parkinsonism, cognitive fluctuations, and visual hallucinations. Alternatively, one core feature and one proposed biomarker (discussed later in this manuscript) also support a probable MCI-LB diagnosis. Individuals exhibiting one core feature without proposed biomarkers qualify for a diagnosis of possible MCI-LB (Fig. 2) [7]. Among cases in which a single core clinical feature is present, abnormal biomarkers can increase diagnositic certainty. Approximately 40% of patients with DLB have two or more core clinical features and abnormal scores on brief cognitive screening measures at least 3–4 years prior to dementia diagnosis [9].

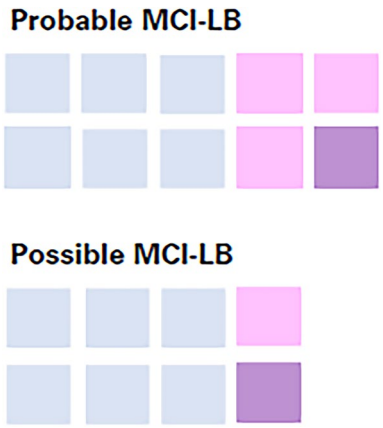

Fig. 2 Probable and possible mild cognitive impairment with Lewy bodies (MCI-LB). In addition to the presence of all three essential criteria (blue), two core features (pink), or one core feature and one positive proposed biomarker (purple), are required for a diagnosis of MCI-LB. The presence of either a positive biomarker or core feature in addition to all three essential criteria is suggestive of possible MCI-LB [7]

People with MCI who progress to DLB demonstrate a higher frequency of parkinsonism, fluctuating cognition, and RBD compared to those who progress to AD [10, 11].

Psychiatric-Onset

There are several case reports of an initial primary psychiatric presentation of DLB, including depression, psychosis, anxiety, and catatonia [12–15]. While cognitive symptoms may also be present, there may be a lag between the onset of psychiatric symptoms and cognitive decline in DLB [16]. According to pDLB criteria, the presence of visual hallucinations, subtle parkinsonism, or RBD in individuals with late-onset psychiatric presentations should alert clinicians towards the possibility of pDLB. The potential of several neurotropic agents to cause parkinsonism should be considered in any assessment, and the risk of neuroleptic sensitivity integrated into decisions around treatment strategies for pDLB. This area has received less attention than MCI, but new data are emerging [12, 17].

Delirium-Onset

Delirium is the least commonly reported of pDLB presentations [18] and can be challenging to identify, as hallucinations and cognitive fluctuations are features of all-cause delirium. Patients with DLB are at greater risk of hospitalisation with delirium than those with AD [19] and DLB may present with an episode of delirium prior to dementia diagnosis [20]. Delirium incidence in patients with DLB (17.2/100 person years) was higher than those with AD (3.2/100 person years) in the year prior to dementia diagnosis [21]. Clinicians should consider MCI-LB in the differential diagnosis in people presenting with recurrent, unexplained, or prolonged delirium [7]. Iatrogenic causes should be among those considered in assessment of patients with possible delirium-onset DLB.

Core and Supportive Features in pDLB

The prevalence and relevance of core and supportive DLB features during the pDLB phase is not well understood; however, RBD is perhaps best established as a prodromal feature of DLB [7, 22] and can precede other clinical symptoms by several years [23]. Idiopathic RBD (iRBD) can be a feature of both prodromal PD and pDLB. The clinical symptoms in these two disorders can overlap significantly, and there is, at present, insufficient evidence to determine whether they evolve differently. In individuals with isolated RBD, the temporal evolution of motor, cognitive and non-motor symptoms appear to differ between those who convert to DLB and those who convert to PD [24]. People with iRBD are more likely to phenoconvert to DLB if they also demonstrate reduced attention/executive performances and visuospatial abilities [25]. However these relationships have been derived at the group level, and cannot yet be applied in clinical practice for individual prediction.

Up to 60% of patients with DLB demonstrate motor symptoms (e.g. postural instability, tremor, bradykinesia) in the 5 years prior to

a dementia diagnosis. This prevalence increases to 82% in the year prior to DLB diagnosis [9]. Parkinsonian symptoms have been reported in 50–70% of individuals with MCI-LB [26, 27]. Subtle parkinsonism is more common in individuals with pDLB than those with pAD [10, 28, 29]. A thorough neurological exam focusing on extrapyramidal signs is necessary at each visit. In a cohort from the UK, 41% of probable MCI-LB cases developed dementia over a mean 2.2 years follow-up and increased LB diagnostic features were associated with an increased risk of conversion to dementia [30].

Fluctuations in alertness, attention, and arousal [31] are challenging to detect in pDLB but can occur in up to 42% of cases [9, 22, 26]. Fluctuations are observed more frequently in pDLB than in pAD [28, 29]. Fluctuations can be exacerbated by poor sleep or less stimulating environments, or medications with anticholinergic properties, while periods of lucidity may coincide with novel or stimulating environments [32]. Use of standardised instruments should be encouraged to detect fluctuations, as these symptoms may be more subtle in pDLB [33–35].

Visual hallucinations typically occur after the onset of cognitive symptoms [22] and are thought to be present in only 20–25% of individuals with pDLB [9]. When the definition of visual hallucinations was expanded to include misidentifications, passage illusions (e.g. shadows moving in peripheral vision), and extracampine hallucinations (e.g. sense of presence), approximately 65% of patients with pDLB endorsed these symptoms [26]. Therefore, tools that detect subtle forms of hallucinations may provide additional insight related to the possibility of pDLB [36, 37] (Fig. 3).

Several supportive DLB symptoms can emerge pDLB, but these are often not specific and are commonly seen in other neurodegenerative disorders, particularly synucleinopathies (e.g. PD and multiple system atrophy (MSA)). Olfactory dysfunction (e.g. anosmia, olfactory hallucinations) can be a prodromal symptom in synucleinopathies, including DLB [16, 23]. Although anosmia can occur in AD, it is more commonly reported in DLB and is more predictive of Lewy body (LB) pathology [38, 39]. Autonomic symptoms are reported more frequently in MCI-LB compared to other MCI syndromes. The most common autonomic symptoms in pDLB include dry mouth (43.8%), constipation (34.7%), sexual dysfunction (32.8%), and rhinorrhoea (27.9%) [26]. Among individuals with iRBD who phenoconvert to DLB, changes in colour vision presented as an early symptom [23].

Neuropsychiatric symptoms other than visual hallucinations are prevalent in pDLB [7]. The most common neuropsychiatric symptoms at the time of DLB diagnosis are apathy and depression [9, 27], which are reported more frequently in pDLB than in pAD [29, 36, 40, 41]. Anxiety is often more severe in pDLB than pAD and may result in the need for psychiatric hospitalisation [42, 43]. Hallucinations in non-visual modalities (e.g. auditory, olfactory) may also be present in pDLB [7]. Given the high frequency of neuropsychiatric symptoms early in the disease, clinicians assessing patients with late-onset psychiatric disease may consider obtaining biomarkers to further differentiate pDLB from primary psychiatric presentations.

CLINICAL PRESENTATION OF MCI-AD

MCI-AD criteria are met with high likelihood if individuals have additional positive biomarkers for amyloid beta (Aβ) and neuronal injury (described further in Biomarkers). The presence of two copies of the high-risk apolipoprotein E 4 (APOE4) allele or an autosomal dominant mutation associated with AD (*APP*, *PS1*, *PS2*) indicates that cognitive impairment is likely a prodrome of AD in these individuals [44].

NEUROPSYCHOLOGICAL PROFILES

The cognitive profile of DLB is typically marked by greater deficits in attention, executive functioning, and visuospatial abilities relative to AD, which is typically characterised by impairment in memory [44, 45]. Similar patterns have been observed in MCI-LB and MCI-AD, respectively [29, 44, 46, 47].

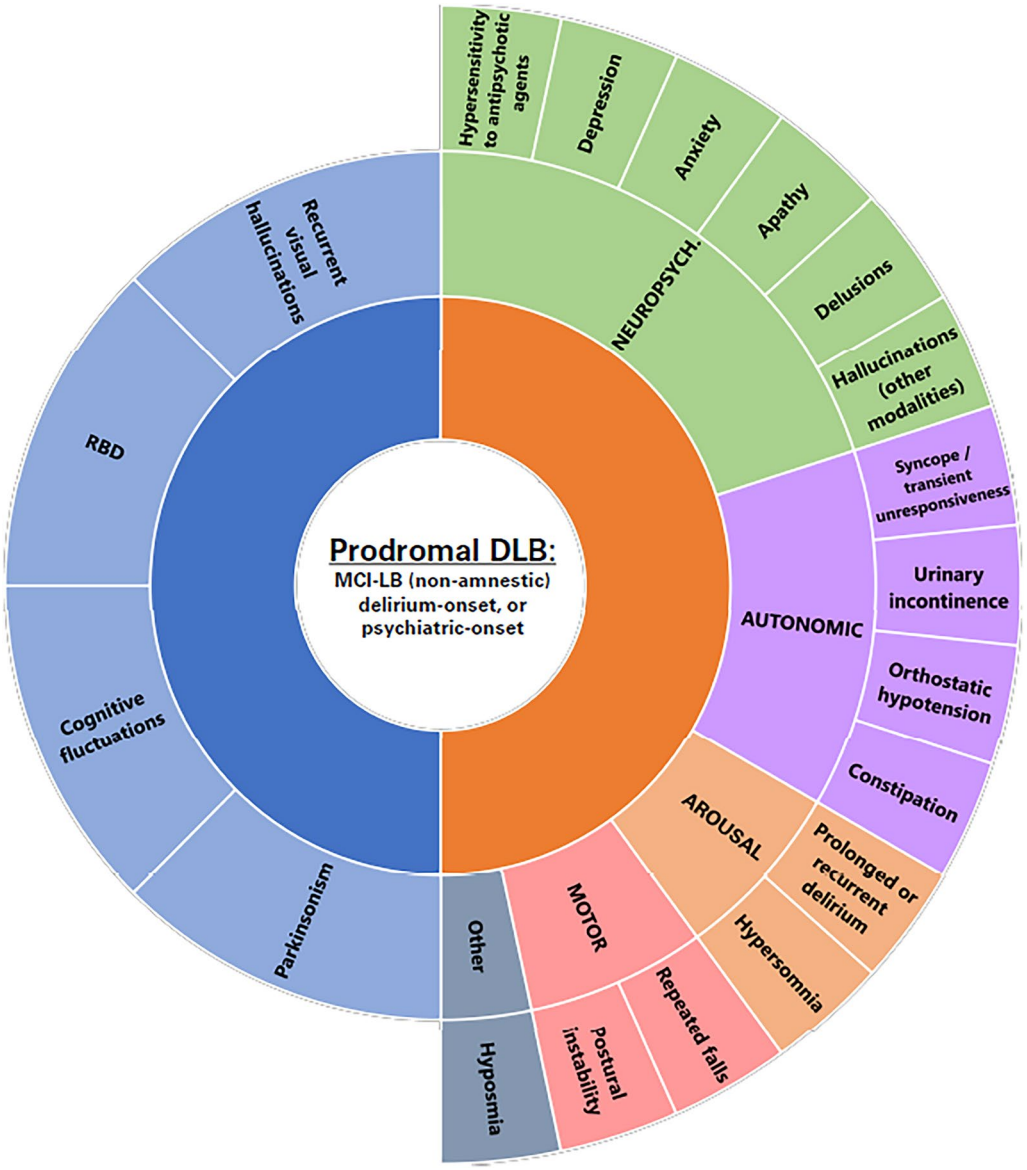

Fig. 3 Prodromal features of dementia with Lewy bodies. *DLB* dementia with Lewy bodies, *MCI-LB* mild cognitive impairment with Lewy bodies, *RBD* REM sleep behaviour disorder. Notably, prodromal DLB (pDLB) can present with cognitive impairment, psychiatric symptoms, and/or recurrent episodes of delirium. Therefore, pDLB is an umbrella term which includes, but is not limited to, presentations with mild cognitive impairment

Amnestic MCI is characterised by a predominant impairment in memory, while non-amnestic MCI is characterised by impairment in non-memory domains, including visuospatial abilities and executive functions. Non-amnestic MCI is associated with a tenfold risk of conversion to DLB, while amnestic MCI profiles are more likely to progress to AD [44, 48].

Patients with MCI-LB often perform below expectation on complex constructive tasks, including copying a figure and drawing a clock [47]. Visuospatial problems may manifest as pareidolic misperceptions [37, 40, 49]. Some individuals with MCI-LB may also demonstrate reduced verbal fluency [40], inattentive errors on timed tasks [29], slowed processing speed [46],

and executive dysfunction [27, 46, 50]. Individuals with MCI-LB may demonstrate memory impairment relative to cognitively healthy older adults [29, 50]; however, memory impairments in MCI-LB are typically less severe compared to MCI-AD, often with preserved recognition of previously learned material [27, 47]. It is important to recognise that the aforementioned profiles are based on group means and cognitive performances, even on screening measures, are influenced by age, education, language, and cultural factors, and should be interpreted accordingly. Furthermore, intraindividual variability in cognitive performances is also observed among healthy adults [44, 51].

Some studies report faster rates of cognitive decline in MCI-LB relative to MCI-AD [30, 52]. However, there are also studies showing a broadly similar mean trajectory on brief cognitive screening measures in MCI-LB and MCI-AD [47]. In one study, the mean time to develop DLB from the MCI baseline evaluation was 2.6 ± 2 years [48]. Comprehensive neuropsychological evaluations can be helpful in distinguishing MCI-LB from MCI-AD [40, 48] but the additional presence of DLB core clinical features likely increases diagnostic accuracy in clinical practice [40].

NEUROPATHOLOGY

Postmortem neuropathological confirmation remains the gold standard for diagnosis in DLB and AD [31, 53]. Neuropathological diagnosis of DLB is based on the accumulation of misfolded alpha-synuclein (α-syn) in LB and neurites in the central nervous system [31]. The majority of clinically diagnosed DLB cases also have loss of the pigmented dopaminergic neurons within the substantia nigra pars compacta; however, this is not an essential criterion for a pathological diagnosis. Different histopathological staging systems have been proposed for LB pathology reflecting that pathological changes can occur in topographically restricted regions at early stages, with more diffuse changes seen in advanced disease [31, 54–56].

AD pathology is characterised by extracellular amyloid beta peptide (Aβ) plaques, and intracellular neurofibrillary tau tangles. Importantly, in both DLB and pDLB it is not only possible to possess AD co-pathology but that "pure" disease is very uncommon [7, 31]. At least half of individuals with DLB have AD-related pathological changes at autopsy, and almost two-thirds of individuals with AD demonstrate α-syn pathology [57, 58]. Diagnostic criteria for each acknowledge and integrate the high likelihood of co-pathology, and there is little evidence differentiating pDLB from pDLB/AD in the clinical setting. Although a handful of research centres may leverage multimodal biomarker panels in the characterisation of pDLB [59], the suboptimal utility of these tools in pDLB, discussed elsewhere in this paper, requires that interpretation of results should occur in the clinical context of the patient, since pure cases seem to be the exception, not the rule.

The degree of AD pathology affects the expression of DLB-related symptoms [60]; the likelihood of a typical DLB phenotype is higher in those with more severe LB pathology, whereas the likelihood of a DLB phenotype decreases as the severity of AD pathology increases [31, 61, 62]. Diagnostic classification schemes therefore require assessment of both pathologies [31]. The prevalence of co-pathology has important clinical implications for the correct interpretation of biomarkers used to distinguish pDLB from pAD.

BIOMARKERS

Biomarkers are increasingly incorporated into diagnostic criteria, and clinical practice, to improve diagnostic accuracy in AD and DLB. Arguably, in vivo biomarkers are essential in early stages (e.g. MCI) where clinical features may be more subtle or absent. Biomarkers serve several purposes, as they can (1) provide evidence of neuronal injury (e.g. atrophy on structural magnetic resonance imaging, MRI); (2) detect the presence of abnormal proteins (e.g. α-syn, Aβ, or tau); or (3) confirm the presence of clinical disease features (e.g. polysomnogram) [44, 63]. In this section, we will discuss

Table 1 Suggested biomarkers for clinical practice in mild cognitive impairment with Lewy bodies (MCI-LB) and mild cognitive impairment due to Alzheimer's disease (MCI-AD)

Type of biomarker	MCI-LB	MCI-AD
Diagnostic	Dopamine transporter imaging: reduced update in the basal ganglia	Amyloid and tau PET: increased burden
	PSG confirmation of RBD	Cerebrospinal fluid: low levels of amyloid-β42 or abnormal amyloid-β42/40 plus high levels of phosphorylated tau181
	MIBG: reduced uptake	
Supportive	qEEG: showing slowing and dominant frequency variability	Biomarkers for neurodegeneration:
		FDG-PET: abnormal temporoparietal uptake
	MRI: relative preservation of the medial temporal lobe, and insular thinning	MRI: atrophy (in particular in the medial temporal lobe)
	FDG-PET: low occipital uptake	Cerebrospinal fluid: high levels of total tau

DaTSCAN dopamine transporter single photon emission computerized tomography, *FDG-PET* fluorodeoxyglucose positron emission tomography, *MCI* mild cognitive impairment, *MIBG* iodine-123 *meta*-iodobenzylguanidine myocardial scintigraphy, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PSG* polysomnography, *qEEG* quantitative electroencephalogram

the diagnostic criteria and the current literature regarding clinical and research biomarkers for pDLB and pAD, with an emphasis on established biomarkers (Table 1).

The 2011 National Institute on Aging (NIA)/Alzheimer's Association (AA) recommendations for use of biomarkers in the clinical diagnostic criteria for MCI-AD are outlined in Table 1 [44]. More recently, the amyloid/tau/neurodegeneration (ATN) framework has been utilised in research settings to identify neuropathological changes in prodromal and overt AD [64, 65]. The limitations of AD biomarker use in clinical practice have been reviewed elsewhere [64] and include the risk of false negative results and the challenge of incidental findings with evidence that cognitively unimpaired individuals can have neurodegenerative pathological changes. The increasing adoption of the ATN framework has concentrated efforts especially on the identification of in vivo signatures of Aβ and tau pathology, and whilst this may have important future therapeutic implications, it may not have discriminatory value in situations where co-pathology may be common, as in DLB. Recent successful trials with α-syn biomarkers have motived a unified "neuronal α-synuclein disease" (NSD) biological framework for DLB and PD that parallels the ATN framework of AD [66] and is briefly discussed below.

The 2020 consensus criteria for MCI-LB were established as research criteria. Proposed biomarkers closely mirror the indicative biomarkers established in diagnostic criteria for DLB which were chosen especially owing to their increased specificity for LB pathology, and ability in some cases to differentiate them from AD. These proposed and potential pDLB biomarkers are outlined in Table 1 [7]. Although some biomarkers are under investigation and are not accessible in a clinical setting, biomarker results from research efforts are at times made available to clinicians and shared with the study participant.

New prospective trials of positron emission tomography (PET) and cerebrospinal fluid α-syn biomarkers in prodromal and early PD show excellent test performance and have motivated a new "NSD" biological framework for DLB and PD akin to the ATN framework of AD [66]. Similar to the MCI-LB 2020 report and ATN frameworks, the early goal of the NSD framework is to speed up therapeutic development in a research setting, but future studies will almost certainly evaluate the clinical performance of combined NSD and ATN frameworks for accurate diagnosis of DLB and AD. However, relying on only one disease biomarker (pAD or pDLB) may be insufficient, and clinicians should consider the likelihood of different co-pathologies contributing to the clinical profile. This can be detected by

combined use of multiple biomarkers for different pathologies and suggest a diagnosis of mixed MCI.

Structural Neuroimaging

Although visual assessment of medial temporal lobe (MTL) volume is considered the most accessible and feasible biomarker for discriminating between pDLB and pAD [67], and hippocampal atrophy is a well-established early marker of AD [68–70], a recent Cochrane review found that both hippocampal (sensitivity 73%, specificity 71%) and MTL volume (sensitivity 64%, specificity 65%) demonstrated insufficient accuracy in detecting early AD, and that structural imaging should not be used as a means of differentiating AD from other dementias.

The preservation of MRI hippocampal volumes in patients with MCI has been suggested to have utility in differentiating in pDLB from pAD (sensitivity 85%, specificity 61%) with a higher risk of phenoconversion to DLB than AD [7, 71]. However, a recent systematic review concluded that MTL atrophy may not effectively discriminate pDLB and pAD [72], which may be due to significant AD co-pathology in DLB.

Nuclear Medicine Imaging

PET and single photon emission computed tomography (SPECT) are functional imaging techniques which use radioactive tracers to assess brain perfusion/metabolism, synaptic integrity (such as availability of dopaminergic or sympathetic nerve terminals), or presence of pathological proteins, such as Aβ plaques. Their availability and diagnostic utility have encouraged incorporation of molecular imaging biomarkers into diagnostic criteria.

Glucose Metabolism Imaging

18-Fluorodeoxyglucose (FDG)-PET is more commonly used than Aβ-PET and tau-PET for the distinction between DLB and AD. FDG is a proxy for brain metabolism and of neurodegeneration, and is included in diagnostic criteria for both DLB and AD [31, 65]. Temporoparietal hypometabolism classically characterises AD [73], although atypical patterns have been recognised [74]. The typical FDG-PET signature of DLB of occipital hypometabolism with relative sparing of the mid and posterior cingulate cortex (known as the 'cingulate island sign') [31, 75] has been shown to be more specific (90%) in distinguishing pDLB from pAD, albeit with low sensitivity (59%) [76]. Hypometabolism in the primary visual cortex may be observed in pDLB [76–80] and can also extend to parietal and temporal cortex [76, 78, 79]. More extensive hypometabolism could indicate higher likelihood of phenoconversion to DLB [81].

Dopamine Transporter Imaging

[^{123}I]-2-β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)nortropane (FP-CIT) is one of several radiotracers capable of quantifying presynaptic dopamine functioning. FP-CIT is an indicative biomarker for DLB with a moderate to high utility in differentiating DLB from AD (86%; sensitivity 80%, specificity 92%) [82–84]. Although FP-CIT is proposed as a biomarker for MCI-LB [7], comparatively few studies have investigated its accuracy in prodromal cohorts. In patients with probable pDLB and pAD, FP-CIT demonstrated an accuracy of 76% (sensitivity 66%, specificity 88%) [85, 86].

Although abnormal FP-CIT findings are more likely in patients with MCI-LB and clinical parkinsonism compared to those without [86, 87], abnormal FP-CIT findings have been observed in half of individuals with probable pDLB who do not have parkinsonism suggesting that dopaminergic deficits can precede clinical parkinsonism in pDLB [78]. Abnormal FP-CIT findings are commonly reported in patients with iRBD and predict phenoconversion to a synucleinopathy [88]. One limitation of dopamine transporter imaging is that it may not distinguish between forms of atypical parkinsonism, as findings can be abnormal in MSA and progressive supranuclear palsy [89].

Amyloid and Tau PET

Functional imaging methods using Aβ and tau tracers have been incorporated into clinical and research criteria to diagnose established and pAD and select patients for novel therapies [73]. As a result of significant co-pathology, neither Aβ-PET nor tau-PET can accurately distinguish DLB from AD and these methods have been investigated little in pDLB [90–97]. Both Aβ and tau-PET positivity may help predict more rapid cognitive decline in DLB [95, 98, 99], but widespread adoption of these tracers has been limited in clinical settings because of technical and resource-related factors discussed elsewhere [94]. Currently, there are no reliable tracers for α-syn pathology, although efforts are currently underway.

[^{123}I]-meta-iodobenzylguanidine Cardiac Scintigraphy

[^{123}I]-*meta*-iodobenzylguanidine (MIBG) cardiac scintigraphy is an indicative biomarker in DLB [31] and a proposed biomarker in MCI-LB [7]. Reduced uptake of the noradrenaline analogue MIBG reflects denervation secondary to cardiac α-syn pathology and has good sensitivity (77%) with excellent specificity (94%) in differentiating DLB from AD [100]. A study using a combination of MIBG and FP-CIT in MCI-AD and MCI-LB (including five pathologically confirmed cases) found that MIBG had a sensitivity of 59% and specificity 88% for differentiating probable MCI-LB from MCI-AD [101]. As LB pathology is hypothesised to adopt a caudo-rostral pattern of propagation [102, 103], abnormalities in cardiac MIBG scintigraphy may occur earlier in the course of MCI-LB than abnormalities in FP-CIT [85, 104].

Other Molecular Tracers

Other PET tracers are largely beyond the scope of this review but, briefly, tracers for the cholinergic system have been used both in AD and DLB because of the well-known strong cholinergic deficit in both disorders [105]. Recently, some studies have explored PET tracers for neuroinflammation and synaptic density in DLB [106, 107] and AD [108, 109]. The findings are still preliminary, and studies are research-oriented, so the clinical implications of these recent approaches remain unknown.

Polysomnography

Loss of REM atonia with witnessed dream enactment behaviours captured by overnight video-polysomnography (PSG) is the gold standard for RBD diagnosis [110] and a proposed biomarker in research criteria for pDLB [7]. Different cut-offs for accepted quantities of REM sleep without atonia have been proposed depending on the protocol used [111], and manual detection and quantification can be time-consuming and requires specialised expertise. Several screening instruments have been developed for RBD, which are easily administered in clinical settings where PSG assessment is not available. A detailed review on the performance of RBD screening scales is presented elsewhere [112].

Electroencephalography

EEG is a widely available, non-invasive neurophysiological tool that may identify early-stage abnormalities in DLB and AD. The characteristic EEG pattern in the DLB and PD dementia continuum includes stable or intermixed slowing of posterior dominant frequency, reduced or absent reactivity to eye opening, and widespread increase in slow-wave frequency power [31, 113–117]. Using quantitative EEG methods, Bonanni et al. [118] identified typical DLB changes in patients with MCI-LB with a shift of the occipital dominant frequency towards fast-theta or "pre-alpha" band (below 8 Hz) and associated dominant frequency variability greater than 1.5 Hz. When followed longitudinally, 83% of individuals with MCI-LB with this specific EEG pattern at baseline converted to DLB after 3 years. Longitudinal EEG changes (follow-up for at least 2 years) were predictive of more rapid progression to DLB, including higher EEG severity score (visual EEG assessment by clinical neurophysiologist) and reduced power in the alpha-2 frequency band [119].

The common EEG findings seen in AD are less specific and overlap somewhat with DLB, manifesting mainly as diffuse slowing, evidenced by reduced alpha (and beta) power accompanied by increasing delta and theta power [120, 121]. EEG studies specifically in MCI-AD population are more limited, but the overall pattern remains similar with remarkable alpha power reduction and mild slowing of the posterior dominant rhythm within the alpha range [122–124]. Patients with AD appear to have decreased slow-wave sleep and REM sleep, associated with increased Aβ burden, and may be an emerging area of interest in MCI-AD [125].

Several studies reported early posterior EEG slowing (e.g. slower dominant frequency shifting towards pre-alpha and lower bands) as a specific feature of MCI-LB compared to healthy controls and MCI-AD [126, 127], although significant overlap has been recognised [128]. EEG abnormalities are more prominent in MCI-LB than MCI-AD [129], as individuals with MCI-LB exhibit pronounced slow-wave activity, which could also be evidenced as frontal intermittent rhythmic delta activity (FIRDA), compared to MCI-AD [130].

EEG changes have been also suggested to be sensitive to dysfunction in the cholinergic system and therefore may be predictive of response to cholinergic medications in both AD and DLB [115, 128, 131]. While promising, quantitative EEG methods have yet to be cross-validated in other cohorts. Therefore, EEG remains a 'potential' rather than 'proposed' biomarker for pDLB [7].

Cerebrospinal Fluid

CSF biomarkers for AD, measuring $A\beta_{42}$, $A\beta_{40}$, t-tau, and phosphorylated tau ($p\text{-}tau_{181}$) are in widespread clinical use and are included in the diagnostic criteria for AD [44]. Specifically, the presence of low CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio is consistent with AD pathology and has been shown to be useful in identifying MCI-AD [44, 53, 65]. Although increased Aβ and tau burden in the brain are more common with older age, their presence at early stages or in younger individuals may be more useful as a strong predictor of AD [44, 132–136]. Care must be taken when translating normative CSF biomarker values across different ethnic and racial backgrounds, with studies reporting lower AD biomarkers in patients with AD who identify as Black compared to patients identifying as White and non-Hispanic [137].

In DLB, t-tau and $p\text{-}tau_{181}$ levels are typically within normal limits compared to elevated levels in pAD [132, 133, 138]. Although normal CSF profile in terms of $A\beta_{42}$, $A\beta_{40}$, t-tau, and p-tau has good negative predictive value for pAD, an abnormal profile does not necessarily exclude pDLB. AD CSF markers alongside DLB can be a negative prognostic marker for rapid progression of cognitive decline [139].

Other CSF biomarkers remain restricted to research use. Many recent studies have shown great promise in the use of protein misfolding amplification assays including real-time quaking-induced conversion (RT-QuIC, and protein misfolding cyclic amplification (PMCA), for differentiation of DLB and other synucleinopathies from AD and controls [140, 141].

Blood, Skin, and Saliva Biomarkers

Plasma

Although not yet in common clinical use, significant progress has been made in blood-based biomarkers in AD including both Aβ and phosphorylated-tau neuropathology detection. Plasma biomarkers can predict conversion to AD from normal cognition or MCI, and promising data has emerged from combining plasma and other accessible biomarkers for better prediction about risk of developing future AD [142, 143]. Palmqvist and colleagues [142] found that combining plasma p-tau, brief cognitive testing, and *APOE* genotyping improved the predictive accuracy of phenoconversion to MCI-AD or AD among individuals with subjective cognitive decline.

Plasma neurofilament light (NfL) polypeptide is a more established marker of neuronal injury; though NfL level changes are associated with cognitive decline [144, 145], they consistently predict diagnostic conversion to

a specific pathologic syndrome [144]. Widely variable results across studies may stem from different types of plasma markers measured and methodologies used to extract the levels [143]. It remains to be seen how combination(s) of other non-Aβ/non-tau plasma biomarkers may improve diagnostic and prognostic values [146]. Plasma and serum α-syn levels are still under investigation as potential biomarkers in synucleinopathies. Preliminary data suggest decreased plasma and serum α-syn levels in individuals with DLB [147] but has yet to be tested in pDLB.

Skin Biomarkers

There is growing interest in the potential diagnostic role of skin biopsies to detect prodromal stages of synucleinopathies, particularly in people with iRBD [148, 149], but it remains to be seen how well this assay can distinguish between DLB, PD, and MSA. Newer techniques of protein amplification, including RT-QuIC, are promising [150, 151] but not widely used in clinical settings at this time. Early data does not show a utility for this assay in distinguishing between DLB and other synucleinopathies [151]. Skin biopsies have not been well studied in AD or pAD. Prior investigations included changes in non-fibrillar Aβ, and skin fibroblasts [152–154], but the clinical utility, especially in pAD, remains unclear.

Saliva

Saliva is an easily accessible peripheral source for biomarkers. Current barriers for implementation in clinical practice include non-specific and non-standardised methodology (e.g. saliva collection; methods to stimulate salivary flow), low protein concentration in saliva, high intra- and inter-individual variability or fluctuations in salivary biomarker protein concentrations [146]. Salivary α-syn has been investigated in PD [155], but there are no published studies investigating salivary biomarkers in pDLB or DLB. Early trials also show that biopsy of the submandibular gland is promising [156] but requires further investigation.

AD-specific salivary biomarkers that have been studied include Aβ1–40, Aβ1–42, p-tau, t-tau, and lactoferrin [146]. Less is known about diagnostic use of these salivary markers in pAD, but most studies have found increased $A\beta_{1-42}$ levels in patients at risk for AD; salivary p-tau and t-tau levels have been more variable [157–160]. More research is needed to address how salivary markers may distinguish AD from other neurodegenerative diseases.

EARLY INTERVENTION AND DISEASE MANAGEMENT

In clinical practice, it is common to base some of the recommendations provided to those with pDLB on evidence collected in pAD. Clinicians should evaluate and address potential contributing factors, such as polypharmacy, sleep, or mood disturbances and comorbid medical conditions, and metabolic deficiencies (e.g. vitamin B_{12}). Anticholinergic and sedative medication affect cognitive performance and increase the risk of progression to dementia and opportunities to reduce such agents should be sought [8, 161, 162].

Non-pharmacological strategies to improve brain health or cognitive reserve should be explored (e.g. adherence to a Mediterranean diet or adoption of aerobic exercise), both associated with lower risk of conversion to dementia [8, 163]. Cognitive stimulation, particularly through social activities, is associated with improvements in progression and improve cognition [164, 165].

There are few studies specifically investigating non-pharmacological strategies to decrease DLB risk [166] or psychotherapeutic interventions in pDLB [167, 168]. Pharmacological approaches to pDLB closely resemble DLB. Where appropriate, clinicians should consider pharmacological approaches for non-motor features, including mood, anxiety, irritative bladder symptoms, and constipation. As in DLB, antipsychotics should be prescribed with caution in pDLB because of the risk of neuroleptic sensitivity [169, 170]. Levodopa-carbidopa should be considered for parkinsonism in MCI-LB, while balancing risk of worsening of neuropsychiatric symptoms [171]. Melatonin and clonazepam may mitigate the risk of injury in RBD [172] but consideration of associated side effects is critical [173]. Other

sleep disturbances, including sleep apnoea, should also be evaluated and rectified [174, 175]. Antihypertensive agents can interfere with cognition and energy, as well as contribute to falls through exacerbation of orthostatic hypotension [176]. Evaluation and management of metabolic and dietary abnormalities is recommended in pAD [8] but, in the absence of identified deficiencies, dietary supplements are not recommended [177].

Acetylcholinesterase inhibitors (AChEI) are the mainstay of symptomatic therapy in both AD [178] and DLB [179]. Although some mild benefits of donepezil in pAD have been observed [180], prescription does not affect phenoconversion and is therefore not recommended in pAD [8, 181, 182]. Large trials of AChEI have not been conducted in pDLB but may improve visual hallucinations and cognitive fluctuations [183]. Although there is little evidence to support the use of memantine in pAD or pDLB, some improvement in neuropsychiatric features may be observed [183].

There are no disease-modifying therapies for pDLB. Anti-amyloid monoclonal antibodies (such as aducanumab and lecanemab) have received accelerated approval for the treatment of early AD by the US Food and Drug Administration (FDA) but have not been studied in DLB. The high prevalence of AD co-pathology in this group [184] suggests that a role for anti-amyloid antibodies should be explored in the coming years.

CALL FOR DIVERSITY

There is a critical need to expand DLB and AD research across diverse populations, including different ethnic, racial, sex, gender, and sexual minority, socioeconomic, and neurodivergent groups, as well as people in different geographic locations [185]. Currently available data in dementia, driving the clinical diagnostic criteria, mostly stem from individuals identifying as White from North America or Europe, often with high levels of education [186].

Individuals from minoritised racial and ethnic groups can be at a higher risk for AD and related dementias [187]. Social determinants of health, discrimination, lifelong stress, access to care, and intersectionality of the factors contributing to disparities need to be addressed. Such factors also contribute to the exclusion of ethnic and racially diverse groups from clinical trials, which poses another important issue in research [188]. An estimated 95% of the participants in AD clinical trials conducted before December 2019 identified as White [189], substantially limiting the applicability of findings. Efforts to increase diversity, sample size, and data harmonisation from different AD [190] and DLB consortia are growing [191] and culturally competent teams are working towards overcoming barriers to reach and recruit participants from diverse backgrounds.

Sex (i.e. biological and physiological differences between female and male individuals) and gender (i.e. socially constructed roles and behaviours) have become increasingly important factors in neurodegeneration [192]. Several studies in DLB and AD support sex differences for protective and risk factors [193–195]. Although it has long been thought that men are at higher risk of developing DLB, emerging data suggests that prevalence may be similar in men and women [3, 196]. In contrast, the prevalence of AD is higher in women [197]. Sex and gender differences in AD and DLB are not limited to prevalence [184, 198, 199]. Women with LB pathology are at greater risk of underdiagnosis or misdiagnosis [184, 190]. Sex differences for prodromal biomarkers need to be further investigated to guide and improve the accuracy of pDLB diagnostic criteria.

CONCLUSION

Diagnosis of prodromal neurodegenerative diseases is key to our understanding of the evolution of disease and developing disease-modifying treatments. Early and accurate diagnosis can help guide appropriate management and improve healthcare outcomes for patients through identifying appropriate social supports for patients and their care partners and referring patients to recommended therapies such as

physical, occupational, and/or speech therapy. The diagnosis of pDLB or pAD should be considered an opportunity to encourage lifestyle changes to promote brain health including exercise, sleep, and a healthy diet.

In clinical practice, differential diagnosis is commonly based on the phenotype, including clinical examinations and neuropsychological evaluations. However, for individuals with clinical exam findings and neuropsychological testing results that do not provide a clear distinction between pAD and pDLB, both established and proposed biomarkers may provide increased diagnostic certainty of pathophysiological processes associated with the clinical syndrome and therefore guide treatment.

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REFERENCES

1. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). Alzheimers Dement. 2021;17(12):1966–75.
2. Gillis C, et al. Estimating prevalence of early Alzheimer's disease in the United States, accounting for racial and ethnic diversity. Alzheimers Dement. 2023;19(5):1841–8.
3. Kane JPM, et al. Clinical prevalence of Lewy body dementia. Alzheimers Res Ther. 2018;10(1):19.
4. GBD 2016 Neurology Collaborators. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(11):939–53.
5. Galvin JE, et al. Lewy body dementia: the caregiver experience of clinical care. Parkinsonism Relat Disord. 2010;16(6):388–92.
6. Nelson PT, et al. Low sensitivity in clinical diagnoses of dementia with Lewy bodies. J Neurol. 2010;257(3):359–66.
7. McKeith IG, et al. Research criteria for the diagnosis of prodromal dementia with Lewy bodies. Neurology. 2020;94(17):743–55.
8. Petersen RC, et al. Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(3):126–35.
9. Wyman-Chick KA, et al. Prodromal dementia with Lewy bodies: evolution of symptoms and predictors of dementia onset. J Geriatr Psychiatry Neurol. 2021:8919887211023586.
10. Sadiq D, et al. Prodromal dementia with Lewy bodies and prodromal Alzheimer's disease: a comparison of the cognitive and clinical profiles. J Alzheimers Dis. 2017;58(2):463–70.
11. Cagnin A, et al. Clinical and cognitive phenotype of mild cognitive impairment evolving to dementia with Lewy bodies. Dement Geriatr Cogn Dis Extra. 2015;5(3):442–9.
12. Mellergaard C, et al. Characterising the prodromal phase in dementia with Lewy bodies. Parkinsonism Relat Disord. 2023;107:105279.
13. Valença AM, et al. Case report: depression× dementia with Lewy bodies in the elderly: the importance of differential diagnosis. Front Psych. 2022;13:1059150.
14. Kanemoto H, et al. Characteristics of very late-onset schizophrenia-like psychosis as prodromal dementia with Lewy bodies: a cross-sectional study. Alzheimers Res Ther. 2022;14(1):137.
15. Utsumi K, et al. Characteristics of initial symptoms and symptoms at diagnosis in probable dementia with Lewy body disease: incidence of symptoms and gender differences. Psychogeriatrics. 2020;20(5):737–45.
16. Fujishiro H, et al. Prodromal dementia with Lewy bodies. Geriatr Gerontol Int. 2015;15(7):817–26.
17. Urso D, et al. Neuroimaging biomarkers in a patient with probable psychiatric-onset prodromal dementia with Lewy bodies. Neurology. 2022;99(15):654–7.
18. Hansen N, et al. Delirium-onset of prodromal dementia with Lewy bodies—putative brainstem-related pathomechanism and clinical relevance. Front Aging Neurosci. 2022;14: 829098.
19. Vardy E, et al. History of a suspected delirium is more common in dementia with Lewy bodies than Alzheimer's disease: a retrospective study. Int J Geriatr Psychiatry. 2014;29(2):178–81.
20. Jicha GA, et al. Prodromal clinical manifestations of neuropathologically confirmed Lewy body disease. Neurobiol Aging. 2010;31(10):1805–13.
21. FitzGerald JM, et al. The incidence of recorded delirium episodes before and after dementia diagnosis: differences between dementia with Lewy bodies and Alzheimer's disease. J Am Med Dir Assoc. 2019;20(5):604–9.
22. Choudhury P, et al. The temporal onset of the core features in dementia with Lewy bodies. Alzheimers Dement. 2022;18(4):591–601.

23. Fereshtehnejad SM, et al. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. Brain. 2019;142(7):2051–67.
24. de Natale ER, Wilson H, Politis M. Predictors of RBD progression and conversion to synucleinopathies. Curr Neurol Neurosci Rep. 2022;22(2):93–104.
25. Marchand DG, et al. Detecting the cognitive prodrome of dementia with Lewy bodies: a prospective study of REM sleep behavior disorder. Sleep. 2017;40(1):zsw014.
26. Blanc F, et al. Prodromal characteristics of dementia with Lewy bodies: baseline results of the MEMENTO memory clinics nationwide cohort. Alzheimers Res Ther. 2022;14(1):96.
27. van de Beek M, et al. Prodromal dementia with Lewy bodies: clinical characterization and predictors of progression. Mov Disord. 2020;35(5):859–67.
28. Cagnin A, et al. Clinical and cognitive phenotype of mild cognitive impairment evolving to dementia with Lewy bodies. Dementia Geriatr Cogn Disord Extra. 2015;5(3):442–9.
29. Donaghy PC, et al. Mild cognitive impairment with Lewy bodies: neuropsychiatric supportive symptoms and cognitive profile. Psychol Med. 2022;52(6):1147–55.
30. Hamilton CA, et al. Progression to dementia in mild cognitive impairment with Lewy bodies or Alzheimer disease. Neurology. 2021;96(22):e2685–93.
31. McKeith IG, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB Consortium. Neurology. 2017;89(1):88–100.
32. Matar E, et al. Cognitive fluctuations in Lewy body dementia: towards a pathophysiological framework. Brain. 2020;143(1):31–46.
33. Thaipisuttikul P, et al. Development and validation of a screening instrument for cognitive fluctuation in patients with neurocognitive disorder with Lewy bodies (NCDLB): the Mayo Fluctuations Scale-Thai version. Gen Psychiatr. 2018;31(1):e000001.
34. Lee DR, et al. The dementia cognitive fluctuation scale, a new psychometric test for clinicians to identify cognitive fluctuations in people with dementia. Am J Geriatr Psychiatry. 2014;22(9):926–35.
35. Walker MP, et al. Quantification and characterization of fluctuating cognition in dementia with Lewy bodies and Alzheimer's disease. Dement Geriatr Cogn Disord. 2000;11(6):327–35.
36. Galvin JE, et al. Characterization of dementia with Lewy bodies (DLB) and mild cognitive impairment using the Lewy body dementia module (LBD-MOD). Alzheimers Dement. 2021;17(10):1675–86.
37. Hamilton CA, et al. Utility of the pareidolia test in mild cognitive impairment with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry. 2021;36(9):1407–14.
38. Savica R, et al. Lewy body pathology in Alzheimer's disease: a clinicopathological prospective study. Acta Neurol Scand. 2019;139(1):76–81.
39. Thomas AJ, et al. Olfactory impairment in mild cognitive impairment with Lewy bodies and Alzheimer's disease. Int Psychogeriatr. 2022;34(6):585–92.
40. Donaghy PC, et al. Neuropsychiatric symptoms and cognitive profile in mild cognitive impairment with Lewy bodies. Psychol Med. 2018;48(14):2384–90.
41. Liu C, et al. Neuropsychiatric profiles in mild cognitive impairment with Lewy bodies. Aging Ment Health. 2021;25(11):2011–7.
42. Segers K, et al. Anxiety symptoms are quantitatively and qualitatively different in dementia with Lewy bodies than in Alzheimer's disease in the years preceding clinical diagnosis. Psychogeriatrics. 2020;20(3):242–6.
43. Jaramillo-Jimenez A, et al. Prodromal dementia with Lewy bodies and recurrent panic attacks as the first symptom: a case report. Front Neurol. 2022;13:839539.
44. Albert MS, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270–9.
45. Ferman TJ, et al. Neuropsychological differentiation of dementia with Lewy bodies from normal aging and Alzheimer's disease. Clin Neuropsychol. 2006;20(4):623–36.
46. Ciafone J, et al. The neuropsychological profile of mild cognitive impairment in Lewy body dementias. J Int Neuropsychol Soc. 2020;26(2):210–25.
47. Hamilton CA, et al. Cognitive decline in mild cognitive impairment with Lewy bodies or Alzheimer disease: a prospective cohort study. Am J Geriatr Psychiatry. 2021;29(3):272–84.
48. Ferman TJ, et al. Nonamnestic mild cognitive impairment progresses to dementia with Lewy bodies. Neurology. 2013;81(23):2032–8.
49. Donaghy PC, et al. Symptoms associated with Lewy body disease in mild cognitive impairment. Int J Geriatr Psychiatry. 2017;32(11):1163–71.
50. Kemp J, et al. Cognitive profile in prodromal dementia with Lewy bodies. Alzheimers Res Ther. 2017;9(1):19.
51. Costa AS, et al. Going beyond the mean: intraindividual variability of cognitive performance in prodromal and early neurodegenerative disorders. Clin Neuropsychol. 2019;33(2):369–89.
52. Hamilton CA, et al. Prospective predictors of decline v. stability in mild cognitive impairment with Lewy bodies or Alzheimer's disease. Psychol Med. 2020;51(15):2590–8.
53. McKhann GM, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–9.
54. Braak H, et al. Staging of the intracerebral inclusion body pathology associated with idiopathic Parkinson's disease (preclinical and clinical stages). J Neurol. 2002;249(Suppl 3):iii1–5.

55. Beach TG, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta Neuropathol. 2009;117(6):613–34.
56. Attems J, et al. Neuropathological consensus criteria for the evaluation of Lewy pathology in post-mortem brains: a multi-centre study. Acta Neuropathol. 2021;141(2):159–72.
57. Kantarci K, et al. β-Amyloid PET and neuropathology in dementia with Lewy bodies. Neurology. 2020;94(3):e282–91.
58. Irwin DJ, et al. Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. Lancet Neurol. 2017;16(1):55–65.
59. Armstrong MJ, et al. Biomarker use for dementia with Lewy body diagnosis: survey of US experts. Alzheimer Dis Assoc Disord. 2021;35(1):55–61.
60. Ferman TJ, et al. Subtypes of dementia with Lewy bodies are associated with α-synuclein and tau distribution. Neurology. 2020;95(2):e155–65.
61. Merdes AR, et al. Influence of Alzheimer pathology on clinical diagnostic accuracy in dementia with Lewy bodies. Neurology. 2003;60(10):1586–90.
62. Tiraboschi P, et al. Clinicians' ability to diagnose dementia with Lewy bodies is not affected by β-amyloid load. Neurology. 2015;84(5):496–9.
63. Group F-NBW. BEST (Biomarkers, EndpointS, and other Tools) Resource. 2016; Food and Drug Administration (US) National Institutes of Health (US): Silver Spring, Bethesda.
64. Dubois B, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol. 2021;20(6):484–96.
65. Jack CR Jr, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement. 2018;14(4):535–62.
66. Simuni T, et al. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol. 2024;23(2):178–90.
67. Dubois B, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. Alzheimers Dement. 2016;12(3):292–323.
68. Karas GB, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. Neuroimage. 2004;23(2):708–16.
69. Braak H, Braak E. Evolution of neuronal changes in the course of Alzheimer's disease. J Neural Transm Suppl. 1998;53:127–40.
70. Bayram E, Caldwell JZK, Banks SJ. Current understanding of magnetic resonance imaging biomarkers and memory in Alzheimer's disease. Alzheimers Dement (N Y). 2018;4:395–413.
71. Kantarci K, et al. Hippocampal volumes predict risk of dementia with Lewy bodies in mild cognitive impairment. Neurology. 2016;87(22):2317–23.
72. Donaghy PC, et al. Research diagnostic criteria for mild cognitive impairment with Lewy bodies: a systematic review and meta-analysis. Alzheimers Dement. 2023;19(7):3186–202.
73. Chételat G, et al. Atrophy, hypometabolism and clinical trajectories in patients with amyloid-negative Alzheimer's disease. Brain. 2016;139(Pt 9):2528–39.
74. Levin F, et al. Data-driven FDG-PET subtypes of Alzheimer's disease-related neurodegeneration. Alzheimers Res Ther. 2021;13(1):49.
75. Watson R, Colloby SJ. Imaging in dementia with Lewy bodies: an overview. J Geriatr Psychiatry Neurol. 2016;29(5):254–60.
76. Kantarci K, et al. FDG PET metabolic signatures distinguishing prodromal DLB and prodromal AD. Neuroimage Clin. 2021;31: 102754.
77. Chiba Y, et al. Early differential diagnosis between Alzheimer's disease and dementia with Lewy bodies: comparison between (18)F-FDG PET and (123)I-IMP SPECT. Psychiatry Res Neuroimaging. 2016;249:105–12.
78. Massa F, et al. Neuroimaging findings and clinical trajectories of Lewy body disease in patients with MCI. Neurobiol Aging. 2019;76:9–17.
79. Massa F, et al. Added value of semiquantitative analysis of brain FDG-PET for the differentiation between MCI-Lewy bodies and MCI due to Alzheimer's disease. Eur J Nucl Med Mol Imaging. 2022;49(4):1263–74.
80. Mattioli P, et al. Cognitive and brain metabolism profiles of mild cognitive impairment in prodromal alpha-synucleinopathy. J Alzheimers Dis. 2022;90(1):433–44.
81. Fujishiro H, et al. A follow up study of non-demented patients with primary visual cortical hypometabolism: prodromal dementia with Lewy bodies. J Neurol Sci. 2013;334(1–2):48–54.
82. McKeith I, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol. 2007;6(4):305–13.
83. Walker RW, Walker Z. Dopamine transporter single photon emission computerized tomography in the diagnosis of dementia with Lewy bodies. Mov Disord. 2009;24(Suppl 2):S754–9.
84. Thomas AJ, et al. Autopsy validation of 123I-FP-CIT dopaminergic neuroimaging for the diagnosis of DLB. Neurology. 2017;88(3):276–83.
85. Roberts G, et al. Accuracy of dopaminergic imaging as a biomarker for mild cognitive impairment with Lewy bodies. Br J Psychiatry. 2021;218(5):276–82.
86. Thomas AJ, et al. Diagnostic accuracy of dopaminergic imaging in prodromal dementia with Lewy bodies. Psychol Med. 2019;49(3):396–402.
87. Chen Q, et al. β-Amyloid PET and (123)I-FP-CIT SPECT in mild cognitive impairment at risk for Lewy body dementia. Neurology. 2021;96(8):e1180–9.
88. Iranzo A, et al. Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol. 2017;82(3):419–28.
89. Saeed U, Lang AE, Masellis M. Neuroimaging advances in Parkinson's disease and atypical Parkinsonian syndromes. Front Neurol. 2020;11:572976.

90. Donaghy P, Thomas AJ, O'Brien JT. Amyloid PET imaging in Lewy body disorders. Am J Geriatr Psychiatry. 2015;23(1):23–37.
91. Surendranathan A, O'Brien JT. Clinical imaging in dementia with Lewy bodies. Evid Based Ment Health. 2018;21(2):61–5.
92. Yousaf T, et al. Neuroimaging in Lewy body dementia. J Neurol. 2019;266(1):1–26.
93. Gomperts SN, et al. Tau positron emission tomographic imaging in the Lewy body diseases. JAMA Neurol. 2016;73(11):1334–41.
94. Kantarci K. Toward imaging of alpha-synuclein with PET. Cell. 2023;186(16):3327–9.
95. Smith R, et al. (18)F-AV-1451 in Parkinson's disease with and without dementia and in dementia with Lewy bodies. Sci Rep. 2018;8(1):4717.
96. Kantarci K, et al. Longitudinal atrophy in prodromal dementia with Lewy bodies points to cholinergic degeneration. Brain Commun. 2022;4(2):fcac013.
97. Kantarci K, et al. AV-1451 tau and β-amyloid positron emission tomography imaging in dementia with Lewy bodies. Ann Neurol. 2017;81(1):58–67.
98. Nedelska Z, et al. Association of longitudinal β-amyloid accumulation determined by positron emission tomography with clinical and cognitive decline in adults with probable Lewy body dementia. JAMA Netw Open. 2019;2(12):e1916439.
99. Donaghy PC, et al. Amyloid imaging and longitudinal clinical progression in dementia with Lewy bodies. Am J Geriatr Psychiatry. 2020;28(5):573–7.
100. Komatsu J, et al. (123)I-MIBG myocardial scintigraphy for the diagnosis of DLB: a multicentre 3-year follow-up study. J Neurol Neurosurg Psychiatry. 2018;89(11):1167–73.
101. Roberts G, et al. Accuracy of cardiac innervation scintigraphy for mild cognitive impairment with Lewy bodies. Neurology. 2021;96(23):e2801–11.
102. Beach TG, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol. 2010;119(6):689–702.
103. Braak H, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.
104. Sakakibara R, et al. MIBG myocardial scintigraphy identifies premotor PD/DLB during a negative DAT scan period: second report. Mov Disord Clin Pract. 2019;6(1):46–50.
105. Kanel P, et al. Molecular imaging of the cholinergic system in Alzheimer and Lewy body dementias: expanding views. Curr Neurol Neurosci Rep. 2021;21(10):52.
106. Surendranathan A, et al. Early microglial activation and peripheral inflammation in dementia with Lewy bodies. Brain. 2018;141(12):3415–27.
107. Andersen KB, et al. Reduced synaptic density in patients with Lewy body dementia: an [(11) C]UCB-J PET imaging study. Mov Disord. 2021;36(9):2057–65.
108. Mecca AP, et al. Synaptic density and cognitive performance in Alzheimer's disease: a PET imaging study with [11C]UCB-J. Alzheimers Dement. 2022;18(12):2527–36.
109. Schuitemaker A, et al. Microglial activation in Alzheimer's disease: an (R)-[11C] PK11195 positron emission tomography study. Neurobiol Aging. 2013;34(1):128–36.
110. Montplaisir J, et al. Polysomnographic diagnosis of idiopathic REM sleep behavior disorder. Mov Disord. 2010;25(13):2044–51.
111. Cesari M, et al. Video-polysomnography procedures for diagnosis of rapid eye movement sleep behavior disorder (RBD) and the identification of its prodromal stages: guidelines from the International RBD Study Group. Sleep. 2022;45(3):zsab257.
112. Skorvanek M, et al. Accuracy of rating scales and clinical measures for screening of rapid eye movement sleep behavior disorder and for predicting conversion to parkinson's disease and other synucleinopathies. Front Neurol. 2018;9:376.
113. Bonanni L, et al. EEG markers of dementia with Lewy bodies: a multicenter cohort study. J Alzheimers Dis. 2016;54(4):1649–57.
114. Bonanni L, et al. EEG comparisons in early Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease with dementia patients with a 2-year follow-up. Brain. 2008;131(Pt 3):690–705.
115. Kai T, et al. Quantitative electroencephalogram analysis in dementia with Lewy bodies and Alzheimer's disease. J Neurol Sci. 2005;237(1–2):89–95.
116. Lee H, Brekelmans GJ, Roks G. The EEG as a diagnostic tool in distinguishing between dementia with Lewy bodies and Alzheimer's disease. Clin Neurophysiol. 2015;126(9):1735–9.
117. Roks G, et al. The use of EEG in the diagnosis of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2008;79(4):377–80.
118. Bonanni L, et al. Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies. Neurobiol Aging. 2015;36(1):434–45.
119. Law ZK, et al. The role of EEG in the diagnosis, prognosis and clinical correlations of dementia with Lewy bodies—a systematic review. Diagnostics (Basel). 2020;10(9):616.
120. Garn H, et al. Quantitative EEG markers relate to Alzheimer's disease severity in the Prospective Dementia Registry Austria (PRODEM). Clin Neurophysiol. 2015;126(3):505–13.
121. Moretti DV, et al. Increase of theta/gamma ratio is associated with memory impairment. Clin Neurophysiol. 2009;120(2):295–303.
122. Rossini PM, et al. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience. 2006;143(3):793–803.
123. Poil SS, et al. Integrative EEG biomarkers predict progression to Alzheimer's disease at the MCI stage. Front Aging Neurosci. 2013;5:58.
124. Lejko N, et al. Alpha power and functional connectivity in cognitive decline: a systematic

review and meta-analysis. J Alzheimers Dis. 2020;78(3):1047–88.
125. Zhang Y, et al. Sleep in Alzheimer's disease: a systematic review and meta-analysis of polysomnographic findings. Transl Psychiatry. 2022;12(1):136.
126. Massa F, et al. Utility of quantitative EEG in early Lewy body disease. Parkinsonism Relat Disord. 2020;75:70–5.
127. Schumacher J, et al. Quantitative EEG as a biomarker in mild cognitive impairment with Lewy bodies. Alzheimers Res Ther. 2020;12(1):82.
128. Cromarty RA, et al. Neurophysiological biomarkers for Lewy body dementias. Clin Neurophysiol. 2016;127(1):349–59.
129. van der Zande JJ, et al. Diagnostic and prognostic value of EEG in prodromal dementia with Lewy bodies. Neurology. 2020;95(6):e662–70.
130. Franciotti R, et al. Anterior EEG slowing in dementia with Lewy bodies: a multicenter European cohort study. Neurobiol Aging. 2020;93:55–60.
131. Schumacher J, et al. EEG alpha reactivity and cholinergic system integrity in Lewy body dementia and Alzheimer's disease. Alzheimers Res Ther. 2020;12(1):46.
132. Mollenhauer B, et al. Follow-up investigations in cerebrospinal fluid of patients with dementia with Lewy bodies and Alzheimer's disease. J Neural Transm (Vienna). 2005;112(7):933–48.
133. Bousiges O, et al. Cerebrospinal fluid Alzheimer biomarkers can be useful for discriminating dementia with Lewy bodies from Alzheimer's disease at the prodromal stage. J Neurol Neurosurg Psychiatry. 2018;89(5):467–75.
134. Spies PE, et al. Cerebrospinal fluid tau and amyloid beta proteins do not correlate with cognitive functioning in cognitively impaired memory clinic patients. CNS Spectr. 2010;15(9):588–93.
135. Zhong XM, et al. Alterations of CSF cystatin C levels and their correlations with CSF Aβ40 and Aβ42 levels in patients with Alzheimer's disease, dementia with Lewy bodies and the atrophic form of general paresis. PLoS ONE. 2013;8(1): e55328.
136. Bousiges O, et al. Diagnostic value of cerebrospinal fluid biomarkers (Phospho-Tau181, total-Tau, Aβ42, and Aβ40) in prodromal stage of Alzheimer's disease and dementia with Lewy bodies. J Alzheimers Dis. 2016;51(4):1069–83.
137. Howell JC, et al. Race modifies the relationship between cognition and Alzheimer's disease cerebrospinal fluid biomarkers. Alzheimers Res Ther. 2017;9(1):88.
138. Mollenhauer B, et al. Total tau protein, phosphorylated tau (181p) protein, beta-amyloid(1–42), and beta-amyloid(1–40) in cerebrospinal fluid of patients with dementia with Lewy bodies. Clin Chem Lab Med. 2006;44(2):192–5.
139. Abdelnour C, et al. Alzheimer's disease cerebrospinal fluid biomarkers predict cognitive decline in Lewy body dementia. Mov Disord. 2016;31(8):1203–8.
140. Bongianni M, et al. α-Synuclein RT-QuIC assay in cerebrospinal fluid of patients with dementia with Lewy bodies. Ann Clin Transl Neurol. 2019;6(10):2120–6.
141. Bargar C, et al. Streamlined alpha-synuclein RT-QuIC assay for various biospecimens in Parkinson's disease and dementia with Lewy bodies. Acta Neuropathol Commun. 2021;9(1):62.
142. Palmqvist S, et al. Discriminative accuracy of plasma phospho-tau217 for Alzheimer disease vs other neurodegenerative disorders. JAMA. 2020;324(8):772–81.
143. Risacher SL, et al. Plasma amyloid beta levels are associated with cerebral amyloid and tau deposition. Alzheimers Dement (Amst). 2019;11:510–9.
144. Sugarman MA, et al. A longitudinal examination of plasma neurofilament light and total tau for the clinical detection and monitoring of Alzheimer's disease. Neurobiol Aging. 2020;94:60–70.
145. Preische O, et al. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. Nat Med. 2019;25(2):277–83.
146. Pawlik P, Błochowiak K. The role of salivary biomarkers in the early diagnosis of Alzheimer's disease and Parkinson's disease. Diagnostics (Basel). 2021;11(2):371.
147. Laske C, et al. Decreased α-synuclein serum levels in patients with Lewy body dementia compared to Alzheimer's disease patients and control subjects. Dement Geriatr Cogn Disord. 2011;31(6):413–6.
148. Al-Qassabi A, et al. Immunohistochemical detection of synuclein pathology in skin in idiopathic rapid eye movement sleep behavior disorder and parkinsonism. Mov Disord. 2021;36(4):895–904.
149. Antelmi E, et al. Skin nerve phosphorylated α-synuclein deposits in idiopathic REM sleep behavior disorder. Neurology. 2017;88(22):2128–31.
150. Kurapova R, Chouliaras L, O'Brien JT. The promise of amplification assays for accurate early detection of α-synucleinopathies: a review. Exp Gerontol. 2022;165: 111842.
151. Mammana A, et al. RT-QuIC detection of pathological α-synuclein in skin punches of patients with Lewy body disease. Mov Disord. 2021;36(9):2173–7.
152. Chirila FV, Khan TK, Alkon DL. Spatiotemporal complexity of fibroblast networks screens for Alzheimer's disease. J Alzheimers Dis. 2013;33(1):165–76.
153. Wen GY, et al. Presence of non-fibrillar amyloid beta protein in skin biopsies of Alzheimer's disease (AD), Down's syndrome and non-AD normal persons. Acta Neuropathol. 1994;88(3):201–6.
154. Chirila FV, Khan TK, Alkon DL. Fibroblast aggregation rate converges with validated peripheral biomarkers for Alzheimer's disease. J Alzheimers Dis. 2014;42(4):1279–94.
155. Bougea A, Koros C, Stefanis L. Salivary alpha-synuclein as a biomarker for Parkinson's disease: a systematic review. J Neural Transm. 2019;126(11):1373–82.
156. Chahine LM, et al. Central and peripheral α-synuclein in Parkinson disease detected by

seed amplification assay. Ann Clin Transl Neurol. 2023;10(5):696–705.
157. Lee M, et al. A method for diagnosing Alzheimer's disease based on salivary amyloid-β protein 42 levels. J Alzheimers Dis. 2017;55(3):1175–82.
158. McGeer PL, et al. Saliva diagnosis as a disease predictor. J Clin Med. 2020;9(2):377.
159. Pekeles H, et al. Development and validation of a salivary tau biomarker in Alzheimer's disease. Alzheimers Dement (Amst). 2019;11:53–60.
160. Marksteiner J, Defrancesco M, Humpel C. Saliva tau and phospho-tau-181 measured by Lumipulse in patients with Alzheimer's disease. Front Aging Neurosci. 2022;14:1014305.
161. Weigand AJ, et al. Association of anticholinergic medications and AD biomarkers with incidence of MCI among cognitively normal older adults. Neurology. 2020;95(16):e2295–304.
162. Gray SL, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015;175(3):401–7.
163. de Crom TOE, et al. MIND diet and the risk of dementia: a population-based study. Alzheimers Res Ther. 2022;14(1):8.
164. Akbaraly TN, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009;73(11):854–61.
165. Kuiper JS, et al. Social relationships and risk of dementia: a systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev. 2015;22:39–57.
166. Inskip M, et al. Interrupting the trajectory of frailty in dementia with Lewy bodies with anabolic exercise, dietary intervention and deprescribing of hazardous medications. BMJ Case Rep. 2020;13(4):e231336.
167. Rostamzadeh A, et al. Psychotherapeutic interventions in individuals at risk for Alzheimer's dementia: a systematic review. Alzheimers Res Ther. 2022;14(1):18.
168. Huh TJ, et al. The effectiveness of an environmental and behavioral approach to treat behavior problems in a patient with dementia with Lewy bodies: a case study. Ann Longterm Care. 2008;16(11):17–21.
169. Takahashi S, et al. Ventilatory response to hypercapnia predicts dementia with Lewy bodies in late-onset major depressive disorder. J Alzheimers Dis. 2016;50(3):751–8.
170. Armstrong MJ, Weintraub D. The case for antipsychotics in dementia with Lewy bodies. Mov Disord Clin Pract. 2017;4(1):32–5.
171. Sezgin M, et al. Parkinson's disease dementia and Lewy body disease. Semin Neurol. 2019;39(2):274–82.
172. Gilat M, et al. A critical review of the pharmacological treatment of REM sleep behavior disorder in adults: time for more and larger randomized placebo-controlled trials. J Neurol. 2022;269(1):125–48.
173. Chouinard G. Issues in the clinical use of benzodiazepines: potency, withdrawal, and rebound. J Clin Psychiatry. 2004;65(Suppl 5):7–12.
174. Elder GJ, Lazar AS, Alfonso-Miller P, Taylor JP. Sleep disturbances in Lewy body dementia: a systematic review. Int J Geriatr Psychiatry. 2022;37(10):10.1002/gps.5814.
175. Liguori C, et al. Sleep-disordered breathing and the risk of Alzheimer's disease. Sleep Med Rev. 2021;55:101375.
176. Udow SJ, et al. "Under pressure": is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies? J Neurol Neurosurg Psychiatry. 2016;87(12):1311–21.
177. Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020;396(10248):413–46.
178. Marucci G, et al. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. Neuropharmacology. 2021;190:108352.
179. Ikeda M, et al. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial. Alzheimers Res Ther. 2015;7(1):4.
180. Edmonds EC, et al. Unmasking the benefits of donepezil via psychometrically precise identification of mild cognitive impairment: a secondary analysis of the ADCS vitamin E and donepezil in MCI study. Alzheimers Dement (N Y). 2018;4:11–8.
181. Birks J, Flicker L. Donepezil for mild cognitive impairment. Cochrane Database Syst Rev. 2006;(3):CD006104.
182. Fink HA, et al. Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia: a systematic review. Ann Intern Med. 2018;168(1):39–51.
183. Wang HF, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry. 2015;86(2):135–43.
184. Bayram E, et al. Sex differences for phenotype in pathologically defined dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2021;92(7):745–50.
185. Babulal GM, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: update and areas of immediate need. Alzheimers Dement. 2019;15(2):292–312.
186. Mooldijk SS, Licher S, Wolters FJ. Characterizing demographic, racial, and geographic diversity in dementia research: a systematic review. JAMA Neurol. 2021;78(10):1255–61.
187. Chen C, Zissimopoulos JM. Racial and ethnic differences in trends in dementia prevalence and risk factors in the United States. Alzheimers Dement (N Y). 2018;4:510–20.
188. Balls-Berry JJE, Babulal GM. Health disparities in dementia. Continuum (Minneap Minn). 2022;28(3):872–84.
189. Franzen S, et al. Diversity in Alzheimer's disease drug trials: the importance of eligibility criteria. Alzheimers Dement. 2022;18(4):810–23.
190. Bayram E, Coughlin DG, Litvan I. Sex differences for clinical correlates of Alzheimer's pathology in

people with Lewy body pathology. Mov Disord. 2022;37(7):1505–15.
191. D'Antonio F, et al. Dementia with Lewy bodies research consortia: a global perspective from the ISTAART Lewy Body Dementias Professional Interest Area working group. Alzheimers Dement (Amst). 2021;13(1):e12235.
192. Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. J Neural Transm (Vienna). 2018;125(4):615–50.
193. Eissman JM, et al. Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. Brain. 2022;145(7):2541–54.
194. Dumitrescu L, et al. Sex differences in the genetic predictors of Alzheimer's pathology. Brain. 2019;142(9):2581–9.
195. Chiu SY, et al. Sex differences in dementia with Lewy bodies: focused review of available evidence and future directions. Parkinsonism Relat Disord. 2023;107: 105285.
196. Hogan DB, et al. The prevalence and incidence of dementia with Lewy bodies: a systematic review. Can J Neurol Sci. 2016;43(Suppl 1):S83-95.
197. Mouton A, et al. Sex ratio in dementia with Lewy bodies balanced between Alzheimer's disease and Parkinson's disease dementia: a cross-sectional study. Alzheimers Res Ther. 2018;10(1):92.
198. Nebel RA, et al. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimers Dement. 2018;14(9):1171–83.
199. Oltra J, et al. Sex differences in brain atrophy in dementia with Lewy bodies. Alzheimers Dement. 2023;20(3):1815–22.