Neuropsychiatric symptoms in dementia: long-term course and neuropathology

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1. Abbreviations

AD, Alzheimer's disease

CAA, cerebral amyloid angiopathy

CDR, clinical dementia rating scale

CSF, cerebrospinal fluid

DLB, Dementia with Lewy-bodies

LBD, Lewy-body dementia (DLB and PDD)

MMSE, Mini Mental Status Examination

MRI, magnetic resonance imaging

NPI, Neuropsychiatric Inventory

NPS, neuropsychiatric symptoms

PDD, Parkinson's disease dementia

PET, positron emission tomography

2. Scientific environment

The funding, administrative, and official part of this work was supported by University of Bergen, Faculty of Medicine, Department of Clinical Sciences. My formal research education was part of Norwegian Centre for Mental Disorders Research (NORMENT).

The scientific work was co-ordinated at the Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, and the participants were from the local geriatric and psychiatric sections at Helse Stavanger, Helse Fonna, and Helse Bergen, which are all part of Helse Vest Trust.

I have been part of a larger scientific environment with both local PhD students in psychiatry and community health services, but also international collaborations through SESAM, King's College London, and Exeter Medical School. I have been working part-time at the Department of Old Age psychiatry, Stavanger University Hospital, which allows stability and grounding of this work.

3. Acknowledgements

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4. Abstract

Aim: Neuropsychiatric symptoms (NPS) such as anxiety, apathy, and psychosis are important manifestations of dementia that have a major impact on the patient's quality of life, carer burden, and risk of institutionalisation. There are few treatment options, the clinical course is not understood, and the mechanism behind the symptoms is unknown. This thesis analyses the frequency, long-term course, and pathological underpinnings of NPS.

Methods: The Demvest study is a 12-year prospective longitudinal multicentre cohort study in the western part of Norway. Among the 667 patients with suspected mild dementia who were screened, 223 fulfilled the inclusion criteria were included and followed with annual assessments using the Neuropsychiatric Inventory (NPI). The attrition rate was very low, and data from 56 patients who underwent autopsy after death confirmed that the clinical diagnoses were highly accurate. The diagnostic distribution was 113 patients with Alzheimer's disease (AD), 86 patients with Lewy-body dementia (LBD), and 24 patients with other types of dementia.

Results: NPS were common at baseline and only a moderate increase in NPS was observed during the first 5 years. There was also no increase in the proportion of patients with high NPI total scores. LBD was associated with a higher NPI total score and higher psychotic symptom scores. Most patients had a relapsing course or single symptomatic episodes rather than persistent symptoms, and 57% of AD and 84% of DLB patients had reoccurring psychotic symptoms. We found a significant association between cerebral amyloid angiopathy and psychosis in AD.

Discussion: Severe NPS are already common at time of dementia diagnosis, and their increase with disease progression is moderate. We observed a highly individual course of NPS with unstable symptomatology. Cerebrovascular disease may increase the risk of psychosis in AD. The individual variations in NPS over time underline the need for personalised medicine in dementia care. NPS, including psychotic symptoms, should be highlighted as a natural part of the dementia syndrome.

5. List of publications

Article 1 [1]

Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study

International Journal Geriatric Psychiatry, 2018

Article *2* [2]

The individual course of neuropsychiatric symptoms in people with Alzheimer's and Lewy body dementia: a 12-year longitudinal cohort study

Submitted

Article 3 [3]

Advanced cerebral amyloid angiopathy and small vessel disease are associated with psychosis in Alzheimer's disease.

Journal of Neurology, Neurosurgery and Psychiatry, 2018

6. Contents

7. Introduction

Dementia is a leading health burden worldwide. It is estimated that one-third of elderly people will develop dementia, and up to half of all people aged 85 or older will have some form of dementia. The number of people with dementia in Norway is expected to increase from 77,000 in 2017 to more than 140,000 in 2040, and this represents a great challenge [4]. Most other countries have lower societal resources and higher increases in life expectancy. There are neither economic resources nor health carers to accommodate the future increase in dementia patients' needs using the current practice. The World Health Organisation (WHO) raised dementia care as a global challenge and included it in the United Nations goals for sustainable development because the search for better and more precise treatment is imminent [5].

During the last decade, the awareness of non-cognitive dementia symptoms has increased. The reason for this is probably multifaceted, including stronger individual focus, awareness of the costs and burden associated with neuropsychiatric symptoms (NPS), and more research in nursing home settings. Additionally, there have been important discoveries about the high risk of stroke and death combined with a minimal effect of commonly used antipsychotic drugs.

The frequency and clinical course of NPS are of great importance for clinical management and scientific studies. Few studies have explicitly investigated NPS in different dementia disorders from a long-term longitudinal perspective. Psychotic symptoms are of special interest because of their burden, associated stigma, and association with a more severe subgroup.

This introduction is focused on the NPS frequency and course in two of the most common dementia diseases: Alzheimer's disease (AD) and dementia with Lewy bodies (DLB). The psychotic symptoms and their suggested pathogenesis are highlighted, with additional information on cerebral amyloid angiopathy.

7.1 Dementia

Originally deduced from Latin meaning *mad* or *out of one's mind*, —and for many years it was coined with the prefix *senile* meaning old—it has been a descriptor for a wide range of diseases affecting mental function in the elderly. Unfortunately, the term 'dementia' often carries unintended cruel lay language connotations and it is also medically imprecise, and for this it has been criticised [6]. The revised American Psychiatric Association's DSM-5 has moved away from a diagnosis using the word dementia. They, instead, introduced the term 'neurocognitive disorder' in an attempt to help reduce the stigma and presume that a neurocognitive disorder improves focus on the decline rather than on the deficiencies [7].

Dementia is a syndrome that does not have a specific cause, and it is diagnosed according to the criteria of the International Classification of Diseases, version 10 (ICD-10), which was published by the World Health Organisation (WHO) in 1993 [8]. This work is based on ICD-10 (see below) and DSM-IV definitions. Because the term 'dementia' is still in widespread use in clinical practice and research, this term will be used throughout the thesis, although I am aware of the variety of different definitions.

ICD-10 Dementia:

Dementia (F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in Alzheimer's disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain.

7.2 Causes of dementia

In the scientific literature, all-cause dementia includes several different diseases, but with a majority of AD, and varying numbers of patients with Lewy-body dementia (LBD), vascular dementia, and frontotemporal lobe dementia (FTLD; Figure 1). Ninety-five percent of dementia is caused by those four diseases [9-11]. Depending on the cohort recruitment procedures, age, and cardiovascular risk profile, either vascular dementia or DLB is the second most common dementia type, and Figure 1 illustrates the difference in sample recruiting and age. AD and DLB are the focus of this thesis and will be described in detail below.

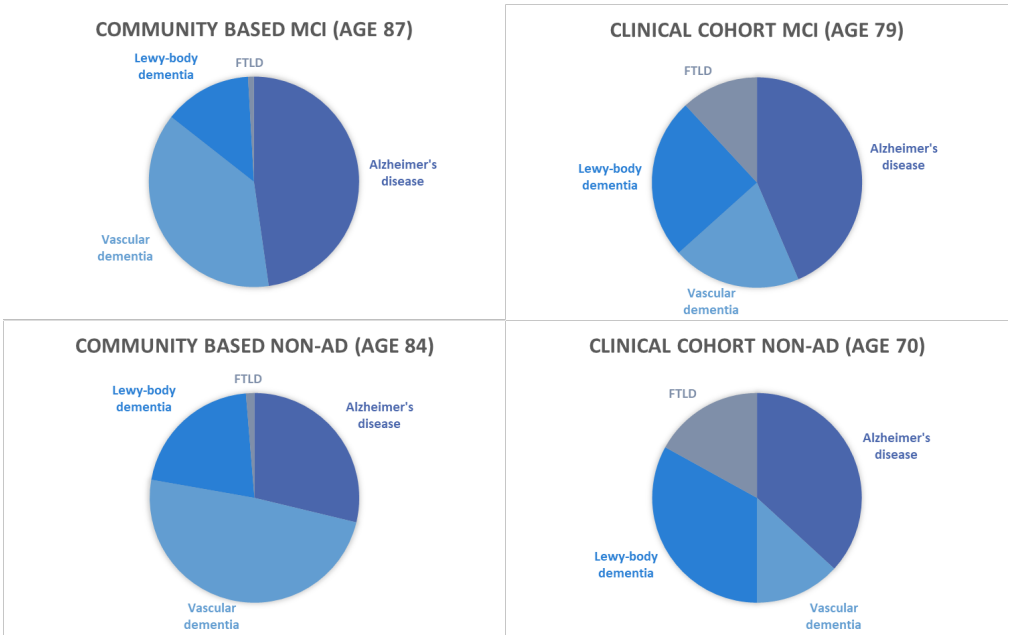


Figure 1. The load of neuropathology in all-cause Mild Cognitive Inhibition (MCI, n=150) and not clinically diagnosed as Alzheimer's disease (NON-AD, n=59) in a community and clinical cohort from Chicago [12]. FTLD; Frontotemporal lobe dementia

7.2.1 Alzheimer's disease

Epidemiology

AD is the most common single cause of dementia, accounting for 50%–75% of all dementia cases [11]. AD was first formally described by Alois Alzheimer in 1906. The incidence is strongly affected by age, roughly doubling in prevalence every 5 years after age 65. One in 20 Europeans aged ≥65 have Alzheimer's dementia, and this number is expected to double in Western Europe and triple in Eastern Europe by 2040 [10].

Pathology

The most striking diagnostic features of AD pathology is the visible loss of cortical brain tissue and inflated ventricles inside the brain. The two major microscopic hallmarks are amyloid plaques and neurofibrillary tangles, which are assessed post-mortem according to staging.

The first hallmark, neurofibrillary tangles, are aggregates of hyperphosphorylated tau protein, which is a naturally occurring protein that is important in microtubules inside the cell. Their presence is also found in numerous other diseases, which are known as tauopathies and include several types of frontotemporal dementia. Little is known about their exact relationship with the different pathologies. The degree and localisation of neurofibrillary tangles are described according to the Braak stages. Braak stages I and II are used when neurofibrillary tangle involvement is confined mainly in the transentorhinal region of the brain, stages III and IV are used with involvement of the limbic regions such as the hippocampus, and stages V and VI are used when there is extensive neocortical involvement [13]. This should not be confused with the degree of senile plaque involvement, which progresses differently.

Amyloid plaques, or senile plaques, are the second hallmark of AD. The plaques are protein aggregates of many different proteins including the amyloid precursor protein, which is suggested to have a 'seed effect' on development [14]. There are

many different species of amyloid with different propensities to aggregate into oligomeric and fibrillary forms. The different species also have differentiated effect synaptotoxic effects when evaluated *in vitro*, *in situ*, and *in vivo* using experimental models of learning and behaviour. Modifying clearance of synaptotoxic elements, including amyloid species, from the brain is a promising drug development track [15]. The natural function of amyloid is unknown, but it is preserved in evolution and produces similar plaques in animals. There are three kinds of amyloid aggregations: diffuse plaques, neuritic plaques, and deposited amyloid fibrils in the vessel walls. The latter is called cerebral amyloid angiopathy is presented later in the Introduction [16].

The topographical development of amyloid plaques is less ordered and several different scoring systems are used. The National Institute of Health and Alzheimer's Association (NIHAA) diagnostic guidelines support categorisation (Thal phase 0–5) based on progressive amyloid deposition [17, 18]. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) developed an amyloid plaque (neuritic and diffuse) scoring system, which ranks the density and type of amyloid plaques in the hippocampus and amygdala as well as in the frontal, temporal, parietal, and occipital neocortex. The CERAD amyloid pathology score is reported as 0-A-B-C, with 0 meaning no pathology and C meaning severe pathology [19]. The different scales are highly correlated, but they also describe important differences [14, 17, 19].

Pathogenesis

The causes of AD are complex and have not been fully identified. The most common late-onset AD is driven by a complex interplay between genetic and environmental factors, although the risk that is attributable to genetic factors may be as high as 70%. The effect is polygenic with over 29 risk loci that have been identified, and 215 potential causative genes that implicate inflammation, cholesterol metabolism, microglial activation, and other factors [20]. The APOE gene, which has three variants, ε2, ε3, and ε4, is the single greatest risk factor for sporadic AD. The clinical value of analysing for these variants in individual patients is modest, with an odds

ratio (OR) for AD of 3 and 12 in ε4 heterozygotes and homozygotes, respectively. Genetic testing for APOE ε4 is not recommended outside of a research setting. However, when assessing the effects in cohorts, APOE is an important factor for determining disease progression [21].

There are also rare types of familial AD that are caused by mutations in the amyloid precursor protein, presenilin 1, or presenilin 2 genes. People who inherit any of these mutations will usually develop Alzheimer's dementia before 65 years of age. Genetic testing and guidance are available for these families [22].

Vascular risk factors, loss of hearing, social isolation, and depression are important modifiable risk factors. There are many studies with single risk factors that show strong associations, such as repeated traumatic head injures (e.g. athletic boxers and repeated concussions), sleep disorders, or high levels of air-pollutants from roads. The degree to which they influence the risk of AD on a population level or may be relevant for a smaller part of the total number is unknown [22, 23].

Clinical features

A gradual onset of cognitive decline in elderly individuals often begins with typical features such as short-term memory loss, word-finding difficulties, or personality changes. More complex tasks such as orientation outside the familiar milieu, episodic memory, and executive function are often affected. As the condition progress, the degree of dependence on others also increases dramatically. Insight into ones' symptoms is often occluded or associated with shame, leaving patients in need of being referred to medical help by others.

The clinical diagnosis of Alzheimer's disease is based on clinical history, physical examination, and cognitive screening tests such as the Montreal Cognitive Assessment (MOCA) or Mini Mental Status Examination (MMSE), which are complimented by more advanced neuropsychological tests as required. There are also more structured interviews with carers regarding activities of daily life. A

comprehensive assessment to rule out other somatic or psychiatric causes is imperative [17].

Biomarkers

Biomarkers are increasingly being used in clinical and research diagnostics. Suggested research criteria categorised patients as either normal or abnormal based on amyloidosis (A+/−) and neurodegeneration (N+/−) biomarkers [22]. Biomarkers of amyloidosis are amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) Aβ42, and established biomarkers of neurodegeneration are CSF tau, FDG-PET, and structural MRI. Structural MRI with an assessment of cortical thickness and hippocampal atrophy are most frequently used and are included under caution in the national guidelines for dementia care [4, 24]. The CSF biomarkers Aβ42 (amyloid) and tau (including p-tau and total tau) are used in most large diagnostic centres in Norway, as well as in the current study. Internationally, CSF biomarkers are gradually becoming more recognised in the research guidelines for their diagnostic utility and are being considered for qualification for subject selection in clinical trials.

Definitive and clinical diagnosis

The definitive diagnosis of AD is made via pathological examination of brain tissue, which it is ranked using the three parameters Amyloid, Braak, and CERAD, to obtain an 'ABC score.' Because of the high incidence of Alzheimer's pathology in healthy elderly people, the clinical data is important. The pathological diagnosis suggested by National Institute of Health – Alzheimer's Association (NIA-AA) is that in individuals with cognitive impairment at the time tissue was obtained, only intermediate or high levels of AD neuropathological changes should be considered as an adequate explanation. When low levels of AD neuropathologic changes are observed in the setting of cognitive impairment, it is likely that other diseases are present [17].

In all patients with cognitive impairment, it is essential to determine the presence or absence of other disease(s) that might have contributed to the clinical deficits. For patients with incomplete clinical history, large clinicopathologic studies indicate that higher levels of AD neuropathologic changes are typically correlated with a greater likelihood of cognitive impairment.

Patients diagnosed with AD without post-mortem assessments are implicitly cases with high, intermediate, or low likelihood of underlying Alzheimer's pathology. The degree to which the clinical diagnosis truly represents AD is often unclear and AD is, in most clinical cases, a diagnosis of exclusion. Therefore, the sensitivity and specificity of clinical diagnosis is important when assessing study validity [9, 17].

Prodromal stages

Traditionally, there were no effective treatment options following a diagnosis of AD, and therefore it was often made late in the disease course. Recent advances in both imaging and CSF analyses have increased the weight of the biomarkers, leaving a difference between clinical practice, guidelines, and research and allowing an early diagnosis to be made. A prodromal state called mild cognitive impairment (MCI) includes patients who are at high risk of developing dementia. The best identifiers of a prodromal state are under constant revision with several sub-forms that have been reported and suggested. Patients with only subjective cognitive impairment (often referred to as SCI) or with established biological markers such as amyloid-PET may be included. Recently, patients reporting behavioural symptoms (mild behavioural impairment, MBI) has been suggested as a prognostic and important prodromal form, which is closely related to our current work [25]. Changes in diagnostic classifications based on new methodology with prospective information in patients without clinical dementia, have significant ethical and practical consequences because disease-modifying treatment is still unavailable. However, this thesis is focused on patients who have already been diagnosed with dementia.

7.2.2 Dementia with Lewy-bodies

Epidemiology and terms

DLB was first described in 1961 by Okazaki et al. and was primarily believed to be a curiosity [26]. DLB was first proposed as a disease in 1976 and the first diagnostic criteria were established in 1996 and updated in 1999, 2005, and 2017 [27, 28]. Today, DLB is considered one of the most common causes of dementia and Lewy-body pathology is also very common (10–60%) in those with 'mixed dementia' [13]. The exact prevalence and incidence of DLB is unknown, but it is believed to occur in 1–1.5% of elderly people and clinically constitutes 5% of dementia cases [29]. There have been several revisions of the clinical criteria to increase their sensitivity, and improved imaging techniques have increased the estimates and allowed physicians to make earlier diagnoses. The comparative incidence of diagnosed DLB to other neurodegenerative diseases may be higher in wealthy parts of the world but the suggested geographical differences may also be associated with other factors [27].

Parkinson's disease dementia (PDD) is closely related and is pathologically not differentiable from DLB, and only clinically separated by the relative order of motor symptoms (occur first in PDD) or memory symptoms (which occur first in DLB). PDD and DLB are suggested to represent aspects of a disease continuum and share important common underlying molecular pathogenesis. However, they differ in the pathological spreading patterns and scientists argue that there remains a pressing need to differentiate between the mechanisms of the two syndromes [30]. The current thesis uses both the terms Lewy-body dementia (LBD, including DLB and PDD) and dementia with Lewy-bodies (DLB, not including PDD).

Pathology

Lewy bodies are named after Dr. Friederich Lewy, a German neurologist. In 1912, he discovered abnormal protein deposits that disrupt the brain's normal function in people with Parkinson's disease, and these deposits were later called Lewy bodies.

The characteristic alpha-synuclein lesions form into aggregates inside neurons, becoming immunopositive with anti-alpha-synuclein antibodies [31]. Such lesions are increasingly common with age, and they are also present in healthy elderly people. The neuropathology is staged according to several different staging systems that are used in parallel in diagnostic practice. One staging scale that is used to describe co-morbid synuclein pathology in AD is the CERAD scale, which has the following stages: no to scarce, moderate, and frequent. The most widely accepted and used scale that is used to diagnose DLB is the McKeith criteria. These criteria differentiate brainstem, limbic, and diffuse neocortical stages, which are consistent with the neuroanatomical spread concept proposed by Braak et al. for alpha-synuclein pathology [19, 27].

Pathogenesis

The underlying cause of DLB is unknown. The genetic component of DLB is less described than in AD and Parkinson's disease, but shows overlap with both. Both DLB and Parkinson's disease have abnormal alpha-synuclein deposits in the brain, but at different locations. In the healthy brain, alpha-synuclein plays several important roles in neurons, especially at the synapses. Abnormal alpha-synuclein processing causes synapses and neurons to work less effectively, and eventually leads to synapse loss and neuronal death. The result is widespread damage to the function of specific brain regions and a decline in abilities that are controlled by those brain regions. Escalation of alpha-synuclein pathology distribution was suggested to result from a prion-like effect with propagation of pathology between the cells [32].

Clinical features

The first description of DLB in 1961 reported the concurrent development of progressive cognitive decline with fluctuating attention, motor symptoms (parkinsonism), and visual hallucinations, which are part of the core clinical syndrome. Rapid eye movement (REM) sleep behaviour disorder, which is recurrent dream enactment behaviour that includes movements mimicking the dream content, was later included as core symptom. All the major symptoms place a considerable

burden on carers. These symptoms combined with a more rapid disease progression create a large clinical challenge.

Biomarkers

The most frequently used marker for distinguishing DLB from AD is well-established dopamine transport imaging (DaT-Scan) with a sensitivity of 78% and a specificity of 90%. This method was primarily developed for Parkinson's disease and focused on the loss of dopaminergic neurons in the substantia nigra. Normal DAT uptake may be reported in autopsy-confirmed DLB either because of minimal brainstem involvement and limited nigral neuron loss or a balanced loss of dopamine across the whole striatum, rather than predominantly in the putamen. Other strong biomarkers are reduced uptake on metaiodobenzylguanidine myocardial scintigraphy and polysomnographic confirmed REM sleep disturbance without atonia. More supportive biomarkers are relative preservation of the medial temporal lobe structures on CT and MRI, hypoperfusion/metabolism in the occipital cortex on FDG-PET, and characteristic EEG changes. Reduced CSF alpha-synuclein has been reported but is not yet available as a biomarker in clinical practice. The most recent DLB criteria revisions supported the importance of using biological markers to increase the accuracy of the DLB diagnosis [27].

Possible, probable, and definitive diagnosis

Clinically, DLB is diagnosed as probable or possible based on the certainty of the diagnosis. Probable DLB has two of four core clinical symptoms, or one of four symptoms with abnormal indicative markers (i.e. DaT-Scan, myocardial IBG-scintigraphy, or polysomnography). Possible DLB can be diagnosed with one core symptom (but no indicative markers), or one or more indicative markers (without a core symptom).

The definitive DLB diagnosis is neuropathological and is based on the localisation of alpha-synuclein pathology in neocortical and limbic regions, as well as the brainstem,

amygdala, and olfactory bulb. With the high comorbidity risk of AD pathology, these findings are cross-examined with the likelihood of the presence of AD [27].

Prodromal stage

Current efforts are focused on developing criteria for prodromal DLB stages, using both clinical features such as loss of olfactory function, restless legs, RBD, autonomic dysfunction, frequent delirium episodes, and more specific neuropsychological tests of executive and visuospatial functions. Alpha-synuclein PET ligands are in development, and artificial intelligence and machine learning have been successfully used in the EEG analyses [33, 34].

7.2.3 Other dementias

Vascular dementia

Vascular dementia is responsible for approximately 10–20% of dementia cases, but because of the life-style risk factors in vascular disease and large differences in sensitivity in the diagnostic methods, the incidence is highly variable. Vascular dementia may arise as a sequel to any form of cerebrovascular disease, including both large haemorrhagic events and chronic ischaemia. The most common vascular contributor to dementia is cerebral small vessel disease. Small vessel disease is most often diagnosed using radiological methods but refers to several different changes in brain microvessels in the cortical and subcortical matter.

The diagnosis is based on a temporal relationship between the presence of focal signs on a neurologic examination and evidence of vascular damage on brain imaging in accordance with the National Institute of Neurological Disorders and Stroke (NINDS) criteria [35]. Three clinical features are necessary to diagnose probable vascular dementia, which are: (1) acute onset of dementia, demonstrated by impairment of memory and two other cognitive domains, such as orientation, praxis, or executive dysfunction; (2) relevant neuroimaging evidence of cerebrovascular lesions; and (3) evidence of a temporal relationship between stroke and cognitive loss [35, 36]. A

definitive diagnosis of vascular dementia requires neuropathological examination with the absence of neurofibrillary tangles and neuritic plaques, exceeding those expected for age, and an absence of other conditions that are associated with dementia [37].

Many patients with vascular dementia will not have episodic memory deficits, particularly in the early stages. They predominantly develop frontal dysexecutive syndrome [36].

Frontotemporal dementia

Frontotemporal dementia or frontotemporal lobar degeneration (FTLD) is a heterogeneous group of disorders with distinct psychiatric and psychological symptomology.

There are three clinical syndromes with different symptoms, progression, and underlying pathology, although there is overlap. The most common clinical syndrome that accounts for more than half of the cases is the behavioural variant frontotemporal dementia, which is characterised by social disinhibition, apathy, and emotional blunting, and it is associated with atrophy of the frontal and anterior temporal lobes. A second, less common, clinical syndrome is semantic dementia, which is characterised by an impaired understanding of the meaning of words, faces, objects, and other sensory stimuli. The patients with predominantly left-sided atrophy have particular difficulty understanding words whereas right-predominant patients show difficulties in face recognition. The third clinical syndrome, termed progressive non-fluent aphasia, is typically characterised by effortful speech and impaired use of grammar [38].

These patients show neuropathological similarities to other degenerative diseases such as amyotrophic lateral sclerosis with nuclear factor (TDP-43) that presents with non-physiologically fibrils and granules. Because of differences in age, clinical progression, and symptoms, these patients are often studied separately.

Frontotemporal-like pathology and TDP-43 aggregation are also found to some degree in many AD and DLB patients [17, 38].

Mixed dementia

Many different pathologies are associated with increasing age, and thus, there is a naturally increasing co-morbidity with age. A mixed cause of dementia is common, and AD pathology, especially, is often combined with some degree of vascular and Lewy-body pathology [12].

Several dementia disease pathologies are also more often associated with each other, when the shared risk factors of time and somatic co-morbidity are taken into consideration. Vascular damage is very common in elderly people and some degree of cerebrovascular disease is seen in most patients with dementia. As a comorbid condition, cerebrovascular disease may worsen the dementia because of other causes such as AD and DLB. This is consistent with the cognitive reserve model, suggesting that the combined pressure of neurodegenerative and vascular pathologies increases the risk of mixed dementia in an aging population. The prevalence of mixed dementia is, therefore, often discussed as a continuum of causes, which is also supported by genetic results [23]. However, there are pathological data showing a different disease trajectory based on the type of dementia rather than the overall pathology load, suggesting a threshold of importance. Differentiation between AD and vascular dementia has received the most attention [39].

Dementia caused by excessive use of alcohol is also a prevalent cause, and it is highly co-morbid with other risks of dementia and poor physical health. Additionally, drugs such as benzodiazepines, morphine, and central stimulants such as amphetamine will probably become a more common part of the dementia pathogenesis process with increased illicit use. There are also more uncommon causes of dementia, ranging from individual gene mutations to individual environmental factors [40].

7.3 Neuropsychiatric symptoms

The psychological and behavioural changes in dementia covers a wide range of symptoms. Some symptoms are mood-like, such depression, euphoria, apathy and anxiety. Other symptoms are more hyperactivity-like, such as irritability, disinhibition, wandering, and aggression, which are often separated from psychotic symptoms such as hallucination and delusions. However, there is a large clinical overlap between symptoms.

However, the importance in diagnostics and management has been relatively neglected for decades, with a focus on the cognitive decline and especially amnestic memory [41]. The clinical optimism that is based on imaging and biomarkers reinforces this effect because the cognitive decline is more persuasively associated with the test results. However, the burden of NPS in dementia on the quality of life for both patients and carers is as least as high as the burden that results from loss of daily activity (e.g. washing, dressing, ability to be alone) and cognitive disabilities [42].

Awareness is increasing about the important role that NPS play in the dementia disease burden. NPS are highly associated with time of admission to institutionalised care [43], and are associated with excess morbidity and mortality, longer hospital stays, and higher overall cost of dementia care [44, 45]. Carers are important, and they are also severely affected by stress, depression, and reduced carer income [46]. Eventually, the carers' own health and quality of life is at risk [47]. Clinically significant NPS are associated with more rapid disease progression [48]. Therefore, improved management of NPS may have the potential to modify the disease course, lower costs, and improve the quality of life for patients and carers [43, 49].

Definition

The definition of NPS has suffered from imprecise nomenclature. Different designations such as non-cognitive symptoms, behavioural and psychological

symptoms (often abbreviated BPSD), and neuropsychiatric symptoms (NPS) are commonly used. The current work uses NPS to highlight the combined psychiatric and presumed neurological aspects. NPS is also the most frequently used term in research, with 1611 (NPS in full) references compared to 438 (BPSD in full) references when cross-searched with 'dementia' in PubMed, among 110118 total references.

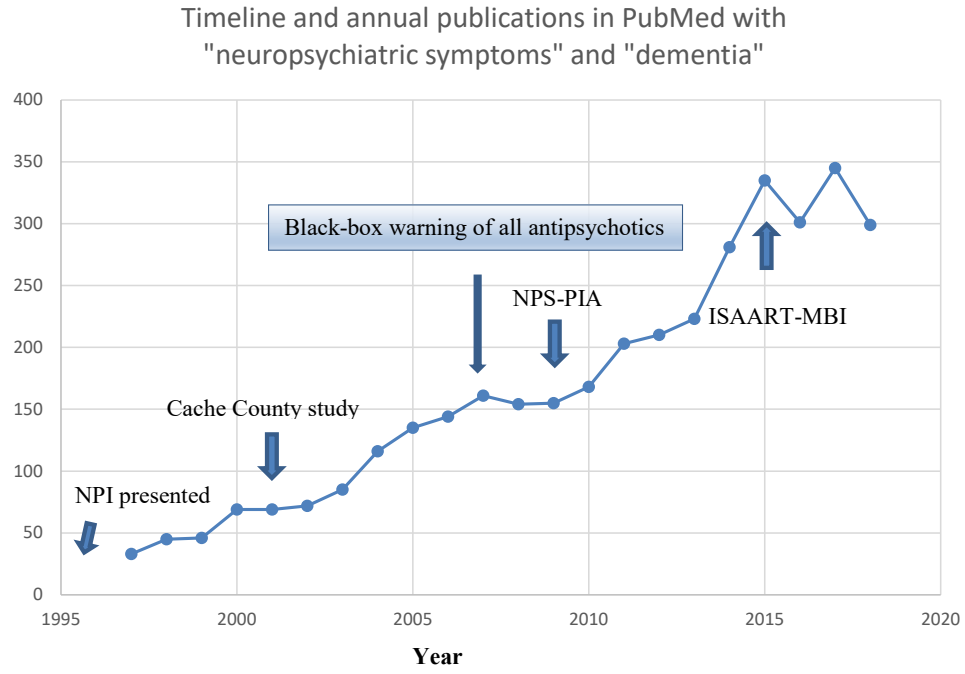


Figure 2. NPI (Neuropsychiatric Inventory), Cache County study (presented later); NPS-PIA (Neuropsychiatric Syndromes of AD Professional Interest Area [NPS-PIA]) from the International Society to Advance Alzheimer's Research and Treatment (ISTAART), which presented the Mild Behavioural Impairment (MBI) criteria [50]. In 2008, based on studies from 2007, the FDA issued a black-box warning on the use of all antipsychotics in elderly people.

Neuropsychiatric symptom rating-scales

The Neuropsychiatric Inventory (NPI) has increased in scientific popularity since it was first introduced by Cummings in 1994. The NPI includes an interview with a carer (either family or professional) about 12 symptoms, and it scores the severity and frequency of all symptoms. It provides a symptom item score (0–12) and an NPI total score (0–144). NPI is popular in dementia research and several other diseases that are associated with psychiatric symptoms [51]. The wide range of symptoms, and ease of administration has made it a commonly used clinical instrument. The NPS interest group (NPS-PIA) at the Alzheimer's Association has designated the NPI the gold standard [52]. Many reviews and meta-analyses that only include studies using NPI also consolidate the role of NPI in research. Additionally, many spin-off versions have been introduced, such as the NPI-questionnaire (NPI-Q) and the nursing home edition. The symptoms are described in Table 1.

With an increasing focus on NPS, several different scales have been developed such as the Behaviour Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease (BEHAVE-AD), the Cambridge Examination for Mental Disorders of the Elderly (CAMCOG), the Brief Psychiatric Rating Scale (BPRS), the Psychogeriatric Dependency Rating Scale (PDRS), and the Present Behavioural Examination (PBE). None of these scales have shown better validity in describing symptoms or have been introduced in clinical practice to the same extent as the NPI [25, 52-54]. The NPI covers a wide range of symptoms and may not have the strength of more specific scales such as the Cohen-Mansfield Agitation Inventory (CMAI) or instruments that selectively measure apathy or depression. The strengths and limitations of the NPI are further discussed in the Methods.

7.3.2 Frequency of neuropsychiatric symptoms

Although not obligatory in dementia, most studies report that NPS are present in nearly all patients when they are assessed repeatedly. The frequency reports vary considerably between studies, but there are also large differences in methodology, case selection, and assessment procedures. Apathy is the most common symptom, while other symptoms vary in frequency but are rarely reported in fewer than 10% of patients (with exception of elation/euphoria) [55, 56].

There are several reviews and meta-analyses that are dedicated to the frequency and persistency of NPS, with the most recent comprehensive work by van der Linde et al. (2016), which is the sixth revision of their meta-data (Table 1 also shown in the Discussion in Figure 5) [55]. They analysed data from 59 prospective longitudinal studies (3 months long or more) to determine the incidence and persistence of NPS, which are called behavioural and psychological symptoms, although most studies used the NPI. The studies were mostly from population-based or general practice with only eight studies from nursing homes. Using the baseline prevalence scores, they found that NPS were more frequent in younger patients, moderate to moderate-severe dementia patients, and those recruited from psychiatric settings. The meta-analysis points out the high variability between studies and emphasises the need for more long-term studies, primarily in home-care settings [55].

Nursing home studies focusing on NPS were systematically reviewed by Selbæk et al. [56]. Selbæk et al. also conducted meta-analysis using a weighted mean score of a wide range of NPS from 28 articles including 8486 nursing home residents, with seven studies and 1458 residents having longitudinal assessment (Table 1 and Figure 5). The residents had all-cause dementia, the mean age was 83 years, and 73% were women. Their analysis included an NPI item score ≥4, and their prevalence rate for any NPS was 82%. This longitudinal review shows that NPS are stable or decrease after admission to nursing homes, which is contrary to the results obtained from cross-sectional studies that report a greater prevalence of most NPS in moderate or

severe stages of dementia than in mild dementia. They also pinpoint the diversity of the study population and the need for studies with a duration longer than 2 years [56].

Item #	Item Name	Description		Prevalence (%) Linde et al	Prevalence (%) Selbeak et al	Persistency (%) Linde et al	Persistency (%) Selbaek et al
1	Delusions	False beliefs, stealing or harm		Moderate (9-40)	22	Low (0-52)	13-66
2	Hallucinations	Visions, voices or other things not present		Low (0-18)	14	Low (0-82)	25-100
3	Agitation/ Aggression	Resistive to help from others at times, or hard to handle		High (18-87)	30	Moderate (21-77)	53-75
4	Depression	Seem sad or say that their depressed		High (8-57)	20	Moderate (16-70)	0-85
5	Anxiety	Upset when separated, nervousness, sighing, unable to relax, excessively tense		High (17-52)	21	Moderate (17-52)	
6	Euphoria	Act excessively happy or feel to good		Low (3-9)		Low (0)	
7	Apathy	Less interested in usual activities or in others		High (19-51)	32	High (20-55)	36-70
8	Disinhibition	Act impulsively, talks to strangers or saying hurtfull things			18		10-79
9	Irritability	Impatient, cranky, difficulty coping with delays or waiting		High 6-57)	31	Moderate (12-80)	
10	Aberrant motor behaviour	Repetitive activties, pacing, restless hands, other things repeatedly			25	High (60)	42-68
11	Sleep	Night awakening, too early mornings or take excessive naps		Moderate (6-11)		Low (10-57)	
12	Eating	Lost or gained weight, change in food preferances					
	Total NPI	Sum of item scores			79		

Table 1. The description is based on key features from the NPI (Cummings) and the prevalence and persistency scores are presented from Van der Linde et al. and Selbæk et al. [55, 56].

7.3.3 Persistency of neuropsychiatric symptoms

The course of a symptom is most often reported as persistency over a given time period (i.e. risk of having the symptom at a second assessment if it is present at the first assessment). A recent meta-analysis concluded that many NPS are persistent, but with large differences between the symptoms (Table 1) [55]. Several other reviews on general NPS management and treatment describe the longitudinal course of NPS broadly as fluctuating or persistent [50, 52, 53, 56, 57].

Consistent with meta-analysis and systematic reviews, apathy is the most persistent symptom, while other affective symptoms (anxiety, depression) are less persistent. Even a high frequency symptom like apathy shows large variability between studies (10–55%). The two studies showing high symptom persistency have different designs, cohort selection, and time between assessments, but both use the NPI as a rating scale. Van der Linde et al. rate wandering (similar to aberrant motor behaviour) as also highly persistent, while Selbæk et al. rate agitation/aggression as persistent.

The studies that are included in the reviews are very different. The duration of observation varies; most studies lasted for 3–6 months, and few had more than four follow-up visits. Because patients with dementia have high mortality and co-morbidity rates, attrition rates in the studies are also high (up to 90%).

7.3.4 Individual patient's course

Studies on the long-term course of NPS are often reduced to the discussed persistency levels as mean scores or proportions at two different observation points. Thus, they do not provide information about an individual patient's long-term course.

One of the few studies describing an individual patient's long-term course is a 9-year study with assessments every 4 months by Hope el al., who reported that most patients had persistent symptoms until death or single symptom episodes [58]. A relapsing-remitting pattern was less common. Fewer than 14% of people who rated positively had more than a single episode. They also argued that the data did support the view that behavioural and psychiatric changes occur predominantly in a late stage of the dementing illness.

However, other studies report a low persistency over 18 months and four assessments, and except for apathy (13%), no symptom on the NPI had greater than 10% persistency, but there was a higher incidence of new symptoms [59]. Additional selected studies on single symptoms report that wandering or agitation occurs most frequently in three of four consecutive visits over 2 years, while paranoid delusions and hallucinations occurred intermediately, and depressed mood with vegetative signs were rarely persistent [60]. A recent study reported an equal distribution between absent/minimal, fluctuating, and persistent total NPS scores over 6 months [61].

7.3.5 NPS according to dementia type

There are relatively few longitudinal studies of NPS besides all-cause dementia or AD, and the existing studies have small study populations. The degree of diagnostic accuracy is different in the studies, but some studies report non-AD as a comparison. The European Alzheimer Disease Consortium's meta-analysis of 2,808 patients reported no significant difference between dementia diagnoses in a cross-sectional study [62].

Few studies have especially aimed at describing the differences between NPS in DLB and AD, and very few had a longer follow-up. A Japanese multicentre-study of 1091 AD and 249 DLB patients based on admission assessments showed a higher prevalence and more severe NPS in DLB than in AD patients [63]. This is consistent with data from our Demvest study, which also shows a higher baseline frequency of symptoms and more severe hallucinations and apathy in DLB compared to AD patients [64]. A large Taiwanese study reported more frequent and more severe depression in DLB compared to AD patients using the DSM-IV diagnosis, with the largest difference in symptoms such as anhedonia and fatigue in a mild dementia population [65].

NPS in vascular dementia is also less studied. Single studies found few differences, except for more sleep disturbances, in vascular dementia compared to AD patients [66]. Similarly, others found that vascular dementia patients had significantly more agitation and sleep disturbances than AD patients [67].

Patients with frontotemporal dementia diseases show personality and behavioural changes that are important diagnostic features. The many different underlying pathological mechanisms that produce diverse behavioural variants. Aggression is often reported, and management is an important clinical issue because of the combination of disinhibition and aggression. Although previously thought to be rare, it is now recognised that some behavioural variants in frontotemporal dementia

patients include psychotic symptoms, which are common (20–40%) but there is a large difference between sub-types [68].

Alcohol-related dementia is understudied, especially the NPS. Apathy is reported to be more prevalent in this group. These patients are also prone to high co-morbidity of somatic or psychiatric symptoms, which increases the frequency and persistency of NPS [69].

7.3.6 Pathogenesis

The underlying mechanism of psychiatric symptoms has been hard to determine, even with advances in genetic analysis. The relevance of biological findings from primary psychiatric disorders such as depression has also failed to be reproduced in elderly people.

Pathological studies report more severe pathology in those parts of the brain with corresponding importance to the normal behavioural and emotional regulation functions, such as limbic structures and the prefrontal cortices [53, 61]. Patients with agitation have more pronounced pathology in cortex-thalamic circuitry that is involved in emotional regulation [52]. Depression is associated with higher total pathology scores and with lower serotonin receptor and transporter binding levels. Apathy has been associated with more temporal cortex atrophy, as well as hypoperfusion and hypometabolism in these areas. These findings highlight the biological nature of NPS and the possibility of developing treatment options [53]. The high degree of plasticity even in old age also raises the questions whether some of these pathological changes may be secondary rather than causal [70].

7.3.7 Management

NPS management has received much attention because many approaches have been found to be ineffective or have a high risk of adverse side effects. The clinical guidelines and scientific reviews agree that the best treatment option for NPS is structured individualised dementia care with psychological, social, and environmental interventions [43, 71, 72]. Therapeutic methods based on capturing the patient's engagement is important [73]. A wide variety of different approaches exist, supported by evidence suggesting that variation exists in the effect size between the various strategies. Many non-pharmacological interventions are costly in long-term care but some of these interventions have been shown to be cost-effective [49, 72].

International scientific and government guidelines are restrictive in the use of psychopharmacological interventions and especially antipsychotics because the risk of side effects often outweighs the benefits. For depression and anxiety, antidepressants can be routinely prescribed. The use of anti-depressants for depression and anxiety is primarily recommend for those with previous depression and especially those who experienced previous effects of medication [23]. Citalopram has shown some effect on aggression, especially in frontotemporal dementia [74]. The use of melatonin and benzodiazepines for sleep problems is also discouraged [75].

The effectiveness of antipsychotics is under scrutiny because of serious adverse effects and for ethical reasons related to a lack of consent and therapeutic sedation. Antipsychotics are still frequently used for both aggression and psychotic symptoms because there are no other effective medications. Therefore, the pharmacological treatment of agitation/aggression and psychotic symptoms are secondary to non-pharmacological interventions. The suggested indication for antipsychotics is consistently the risk of harm to patients or carers. There are differences in guidelines whether there is severe distress including symptoms of agitation, hallucinations, or delusions (NICE, UK), while in the Norwegian guidelines, only severe distress with

symptoms of aggression should be considered an indication for antipsychotic drug treatment [75]. A small dose of risperidone (0.5–1 mg) to treat severe psychosis in dementia is the only approved treatment, and it is only approved for up to 6 weeks. The Norwegian national guidelines suggest olanzapine and aripiprazole as secondary choices, but consistent with the UK guidelines, they emphasise the need for structured assessments and thorough discussion with the patient and family. The gap between theory and practice of prescribing antipsychotics is heavily debated, and their use has decreased in elderly patients. Risperidone is not approved for dementia by the US Food and Drug Administration (FDA). Other nonapproved treatments are sometimes suggested but there is no sufficient evidence to use these in clinical settings unless there are other intervention points, such as diabetic neuropathy or epilepsy.

Treatment of DLB is also more difficult because of the patients' sensitivity to anti-psychotic drugs. Donepezil and rivastigmine, which are acetylcholinesterase inhibitors, may be effective in treating hallucinations in DLB patients, while other similar drugs and anti-depressants have shown no effect [76].

Both the symptoms and treatments are costly to society and a great burden to patients, carers, and health professionals. The limited understanding of the underlying mechanism is one of the reasons that no major advances in pharmacotherapy have been made in the last decade.

7.4 Psychotic symptoms

Psychotic symptoms in dementia include hallucinations or delusions, although more complex symptomology such as thought disorganisation, misidentification, and conflicted self-identity also occur. The latter symptoms may be harder to identify in patients with dementia. Previously assumed to be uncommon or present late in dementia, psychotic symptoms are now recognised earlier in dementia and in non-demented/healthy elderly [77, 78]. Several studies have shown an overlap between late onset schizophrenia and early psychotic symptoms in dementia. This thesis includes hallucination and delusions as psychotic symptoms, which is consistent with most reviews on NPS and focuses on people diagnosed with dementia.

Patients are typically able to report these experiences when specifically asked, as are observant caregivers. Patient responses to their hallucinations vary both in their degree of insight and emotional reaction to them. Psychotic symptoms are often frightening and stigmatising. Patients and carers are afraid to tell others because there are legal consequences and patients worry about being institutionalised. Psychotic symptoms are often associated with agitation/aggression, and together they represent a large part of the burden of dementia disease, both emotionally and economically.

Hallucinations

Hallucinations are any form of false sensory experiences and can be from any of our senses: vision, hearing, touch, taste, or smell. Visual hallucinations are the most common form of hallucinations, and they are especially common in DLB patients. These hallucinations are typically well-formed and can feature people, children, or animals. Auditory hallucinations (speech or sounds of music) are usually less organised than those observed in schizophrenia. Olfactory hallucinations are uncommon and are often associated with other diseases such as stroke or brain tumour. Tactile hallucination with feeling of things crawling inside or outside one's body or the touch of others are often similar to delusions.

Delusions

Delusions are beliefs or impression that are maintained despite being contradicted by reality or rational argument. Symptoms may also be more complex with false memories of events or false or bizarre beliefs. The nature of such symptoms is subjective, and thus, clinical assessment is essential. Patients are blind to their symptoms, and thus, they do not seek help directly because of the symptoms, but rather they experience the consequences of the delusions. Information from next-of-kin is essential. This is especially important for elderly people because these symptoms are often less invasive.

7.4.2 Frequency

Reviews estimate that 18% of dementia patients experience psychotic symptoms, but studies with a longer follow-up time have reported higher estimates. In the cohort from Hope et al., 45% reported persecutory ideas and 25% reported hallucination (co-occurrence was not reported). Recurrent, complex visual hallucinations occur in up to 80% of patients with DLB and are a core symptom of that diagnosis [27]. The prevalence of hallucination in AD is more uncertain, with studies reporting a prevalence rate as low as 1% and others reporting a rate of more than 50%. Delusions are reported more commonly than hallucination in AD, but there is no clear difference between AD and DLB. One study reported subclass *delusional misidentification* to be common in DLB whereas *paranoid delusions* were associated with AD [79].

7.4.3 Course

For all dementia patients, psychotic symptoms were reported with a low persistency (below 30%) by van der Linde et al. [55]. However, there are large differences between the studies. Ballard et al. (1997) reported psychotic symptoms as brief or persistent, with few having an intermediary course [80]. Hallucinations are reported with a higher stability compared to delusions [55, 58, 81]. Hallucination seem to be

more persistent in DLB than in AD [80]. The differences in both frequency and course between studies are likely related to differences in the cohorts such as type and stage of dementia and the care settings, as well as use of different rating scales.

7.4.4 Pathological mechanisms

Several cohorts demonstrate familial aggregation of psychosis in AD, and studies also indicate association with psychotic diseases within families, indicating a genetic contribution [82, 83]. Patients with previous psychotic episodes or with first degree relatives with psychosis have a higher risk of severe NPS [84]. Using a polygenic risk score, which is a method to analyse the combined effects of many genes on the increased risk, Creese et al. showed a link between AD psychosis and primary schizophrenia [85]. Although care should be taken regarding the validity of negative results, there are is no evidence that genetic variants that increase the risk of AD also predict psychotic symptoms, which suggests that psychotic symptoms are secondary to a more severe dementia disease.

While no single specific brain area has been identified as responsible for psychosis symptoms, both imaging and post-mortem neuropathological studies suggest that tau levels are increased in the dorsolateral prefrontal cortex of AD patients with psychosis compared to AD patients without psychosis, rather than in the entorhinal cortex or hippocampus [86]. The severity of pathological changes does not seem to be of major importance, but these studies are difficult to interpret because of the risk of selection bias, differences in the time from psychotic symptoms to death, and the varying degree of psychotic symptomology.

Having mixed dementia with two or more pathological changes has been suggested as a risk factor for psychosis as a variant of the total load hypothesis. Studies have reported higher levels of delusion, hallucinations, and aberrant motor behaviour in patients with both LBD and AD pathologies [87, 88], but other contradictory findings exist [79, 89]. Other studies report differences between AD and LBD, such as

reduced occipital metabolism in DLB patients was found to be associated with the frequency and severity of visual hallucinations but not in AD [90].

Psychotic symptoms were found to be associated with cerebrovascular disease such as small vessel disease and subcortical arteriosclerotic leukoencephalopathy [91]. Small vessel disease has been associated with depression in elderly patients, but few studies have addressed its associations with psychotic symptoms.

A small MRI study showed increased vascular disease in eight patients with late onset schizophrenia, and a recent study in young psychotic patients shows microvascular abnormality changes on MRI, which supports vascular dysfunction as a contributing factor to psychosis [92, 93]. The vascular components in psychosis in the elderly need to be further validated, and especially in those with severe psychotic symptoms in early dementia.

7.4.5 Cerebral amyloid angiopathy

A specific form of vascular pathology, cerebral amyloid angiopathy (CAA), is defined as deposits of amyloid in the vessel walls, which may lead to necrotic lesions with an increased risk of haemorrhage and a smaller lumen with reduced perfusion. Age is the largest known risk factor for CAA, and it is very common in most elderly people (80–90 years), with 20–40% occurring in non-demented and 50–60% occurring in demented patients who showed post-mortem CAA [16, 94].

The neuropsychological profile of both CAA and small vessel disease in patients without clinical dementia shows decreased processing speed [94]. Dementia is not directly associated with processing speed, but psychotic diseases are associated with processing speed [95]. Vascular pathology and reduced information processing speed may be modifiable risk factors of psychosis in dementia, and thus, to some extent, it is potentially preventable through improved cardiovascular health and brain training exercises.

With improved radiological techniques, the focus on CAA is increasing, and the risk of spontaneous lobar haemorrhage and transient focal neurological episodes (‘amyloid spells’) are important [96]. CAA contributes to neurodegeneration, but its relationship to clinical symptoms and the course of dementia is not fully understood [16].

The mechanisms underlying accumulation of β-amyloid in arterioles is unclear. It is unknown whether the deposition of β-amyloid in the vessel wall originates from the central nervous system and accumulates because of reduced perivascular drainage or if it is produced and deposited locally by vascular smooth muscle cells. Circulating amyloid beta peptide may also bind to the receptor for advanced glycation end-products in endothelial cells and then be transported through the blood-brain barrier into brain [16].

Studies have shown an association between MRI-diagnosed microbleeds that may represent CAA and neuropsychiatric symptoms, but not psychosis, in non-demented elderly patients [97]. CAA, either as a post-mortem finding or identified using more precise radiological markers of CAA, has rarely been studied and an associated between neuropsychiatric symptoms in dementia has not been found.

8. Aims

Overarching aim

Describe the frequency, course, and neuropathology of NPS in people with mild dementia in a long-term longitudinal perspective.

Specific aims

1) Profile the frequency and associated variables of each NPS over 5 years in patients with mild dementia, and report NPS in patients with AD and LBD separately.

2) Describe the longitudinal course of NPS in individual patients with AD and LDB from diagnosis to death.

3) Investigate the post-mortem pathological correlates of severe psychotic symptoms in AD and LBD patients who were followed annually from the time of diagnosis until death.

9. Methodological considerations

9.1 Validity of the Demvest study

All three articles are based on data collected from participants in the Demvest study. The study started enrolling people with mild dementia in 2005 and it is a prospective longitudinal cohort multicentre study of patients with a clinicopathological diagnosis. A more detailed technical methodological description is enclosed as supplementary information.

Demvest researchers have published baseline (cross-sectional), short-term, and long-term longitudinal data. The Demvest cohort has been investigated in several projects and articles, both as independent and aggregated data materials. It is ongoing after 15 years, during which time there have been changes in the diagnostic criteria, the use of supplementary diagnostics, and the use of biomarkers in clinical practice to diagnose dementia. A thorough discussion of strengths and limitations of the Demvest study is therefore imperative.

9.1.1 Strengths

Follow-up time

Compared to most other studies, the Demvest study has a very long follow-up time. Annual assessments are conducted using structured instruments, and the high level of data completeness (except for attrition because of death) are additional strengths because the bias introduced by selective attrition is likely small. Repeated measurements with a high follow-up rate allow for persistency and reoccurrence analyses of mild to severe dementia.

Low attrition

The Norwegian health care system has a common electronic data system, few specialised clinics working with dementia, and a public with a high participation rate in similar studies [98]. Study participation was integrated into clinical management. With 98% data completeness for the possible assessments, this study is unique. This also means that many patients with vascular events, hip fractures, and cancer (diagnosed after inclusion) are included. Although this creates the risk of camouflaging the true effect of dementia, our evaluation is that these are integral parts of dementia diseases and they are, thus, relevant to the aim of this thesis, which is to study NPS in dementia.

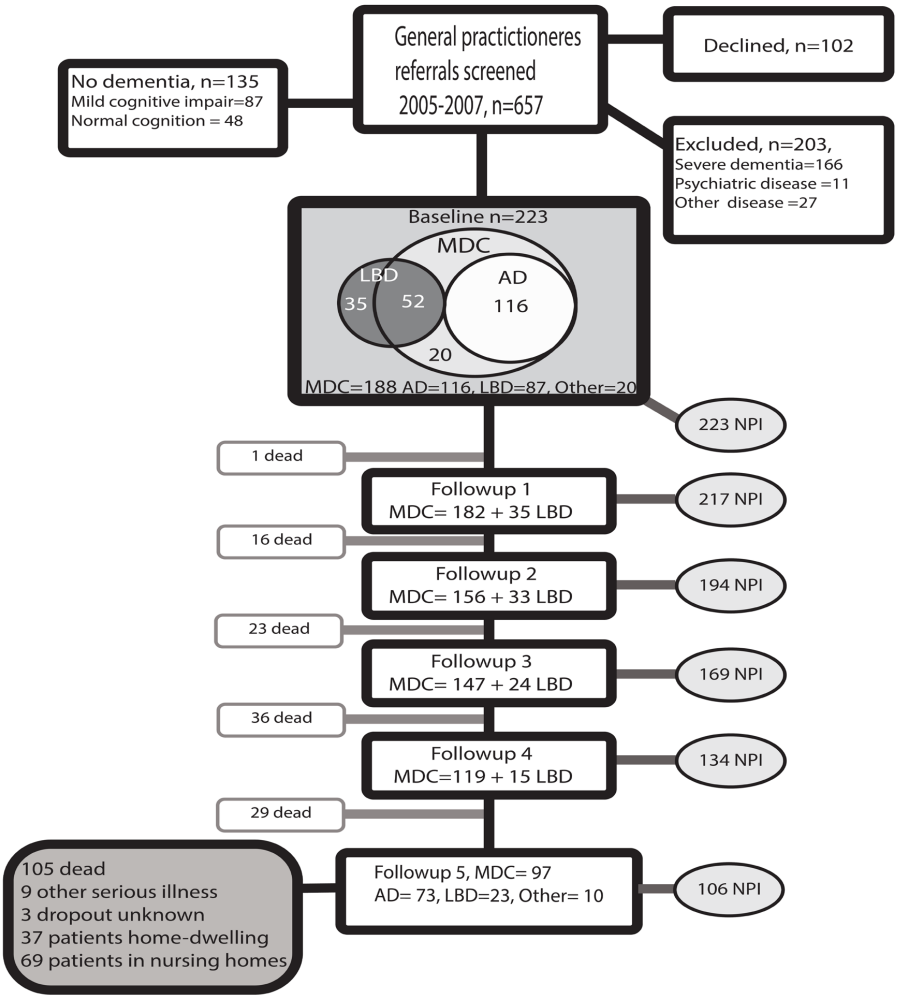


Figure 1: Flowchart of study design and data retrieval

MDC: Mild dementia cohort

AD; Alzheimer's disease

LBD; Lewy-body dementia

Other; 9 vascular dementia, 5 mixed AD/vascular, 5 frontotemporal dementia, and 3 alcoholic dementia

NPI; Neuropsychiatric inventorys present (including MDC and prolonged inclusion LBD)

Figure 3. Flowchart of the study design and data retrieval from Vik-Mo et al. [1].

Diagnostic accuracy

A high diagnostic accuracy was demonstrated in the 56 patients with a neuropathological diagnosis. In the current cohort, we were able to correctly identify and diagnose 16 of 20 patients with neuropathologically verified DLB, resulting in a sensitivity and a specificity for probable DLB alone of 73% and 93%, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value for a clinical diagnosis of probable AD, including the two mixed diagnoses, were 81%, 88%, 89%, and 79%, respectively [99].

With improving clinical diagnostics and changes in clinical diagnostic criteria, we have, therefore, chosen to use the final diagnoses based on all known information, including post-mortem findings now up to 65 patients.

Hope et al. reported data from pathologically diagnosed patients separately, but no other long-term prospective studies reporting on a wide range of NPS have pathologically confirmed diagnoses [58]. The use of a pathological diagnosis and accurate diagnostic tests ensures that results are valid even with changing clinical diagnostic criteria. Repeated diagnostic assessments in patients with diagnostic uncertainty is part of ordinary clinical management.

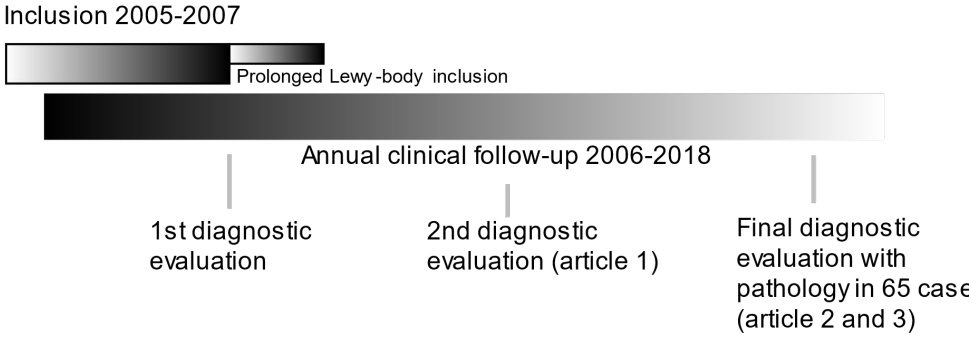


Figure 4: Timeline of inclusion, follow-up, and diagnostics in the Demvest study

DLB prevalence

This is one of the largest long-term studies of LBD including the 38 patients from the extended inclusion period. In article 1, we used the originally recruited all-cause dementia patients as the *mild dementia cohort*. There is a high percentage of patients with DLB who are also in the initially recruited patient group. Our DLB prevalence in this sub-cohort is comparable to epidemiological studies by applying stringent methodology to detect DLB, according to the original criteria [27, 100]. Most patients with suspected DLB had a DaT-Scan, which might have yielded more patients with DLB than in other comparable cohorts. Finally, we did not have access to cardiac scintigraphy, which has demonstrated high sensitivity for diagnosing DLB [27], or polysomngraphy to secure the RBD diagnosis, both of which were recently included as 'indicative biomarkers for DLB' together with a DaT-Scan.

Comprehensive diagnostic procedures are costly and time-consuming, other studies like Brodaty et al. [84] with 3% DLB did not use such diagnostic strategies, and thus, DLB may be underdiagnosed or have a negative selection bias resulting from DLB patients with a shorter duration of mild-to-moderate dementia before being institutionalised or passing away. Studies that included neuropathological diagnostics include more similar DLB percentages in the clinical cohorts (21%) [12, 91]. DLB is also highly associated with age, and the inclusion of people with mild dementia (as defined) may have increased the selection bias because the MMSE is less sensitive to the cognitive decline that is associated with DLB than that in AD.

9.1.2 Limitations

Recruitment bias

Our data may have potential recruitment bias because of referrals from primary care physicians, which may have led to an increased number of patients with complicated dementia or NPS in this clinical cohort [12]. Inclusion based on psychiatric services have shown a higher frequency and severity of NPS. However, primary care physicians were invited to refer any patients with suspected dementia, and patients

were included from psychiatric, neurologic, and geriatric clinics. We had a low number of alcohol-related dementia patients and a low number of fronto-temporal dementia patients. The exclusion criterion of no severe somatic or neurological illnesses may have excluded some of these patients. Most inclusion and clinical assessments were performed by geriatricians and geriatrics nurses, and not psychiatric personnel. There were bi-annual meetings of study personnel who were involved in the study during the first 10 years to ensure similar evaluation of symptoms.

The high life expectancy and low rate of poverty in adults have probably affected the recruitment base towards more patients with DLB and less with vascular dementia but with cerebrovascular disease. Because most dementia patients are unable to travel by themselves, there are also some patients with involved family carers. The national focus of a self-reliant and important primary care health service may have led to the recruitment of more complicated cases.

The current cohort represents to a very high degree a generation of ethnic Norwegians, with a large proportion of patients born, living, and dying in a geographically small area. Mono-ethnicity may not be a limitation, but it must be addressed when assessing the wider clinical application of the findings and may strengthen internal stability. We have very high stability of adherence to the hospital to which the patients are geographically assigned, and this increases the opportunity for systematic and longitudinal data collection. The national death registry showed that all participants (up to January 1,2017) died in the western part of Norway (our catchment area).

Dementia definition at inclusion

Mild dementia was defined as a clinical dementia rating scale (CDR) score of 1 or a MMSE score of 20 or more. The MMSE is language and memory dominant, and thus, it is less sensitive to the earliest changes in the LBD patients, which included both PDD and DLB patients, although the sensitivity of MMSE is comparable to

other screening instruments when approaching moderate dementia levels. Our definition may, therefore, have selected more progressed DLB patients compared to AD patients. Although the term mild dementia is imprecise, this definition is used in many studies and represents a group of patients who are often in contact with health services because they have a definite disability but are still living at home.

Non-pharmacological treatments

Because of the naturalistic design, patients were treated according to the recommendations for pharmacological and non-pharmacological treatment, which may influence the course of NPS. However, because treatment was not standardised, individual treatment differences may have influenced the course of NPS. The patients included were followed as out-patients in hospitals and clinics; they received up-to-date management, and they were also followed after admission to nursing homes. Patients may have been provided a more extensive follow-up because they were part of the study protocol.

Pharmacological treatments

The psychopharmacological interventions received by the participants were likely in accordance with national guidelines, which are restrictive regarding use of psychopharmacological interventions, particularly antipsychotics. Compared to other studies, the prescription levels of antipsychotics were low. At the first follow-up (not baseline), 61% used antidementia drugs, 9% used antipsychotics, and 40% used antidepressants. Included in these figures were occasional and minor doses that were used for sleep difficulties and prochlorperazine that was used as an occasional antiemetic (n=6) exclusively accounted for 2.6% of the 9% using antipsychotics.

In the population-based Cache County study, only 9% of patients used antidementia drugs, while 26% used psychotropics. In other comparable studies such as the PRIME study, 21% used antipsychotics and in the LASER-AD study, 41% used psychotropic drugs [84, 101, 102]. In the Selbæk et al. review, the mean drug use was 69% for psychotropics, 32% for antipsychotics, and 31% antidepressants in nursing homes

[56]. The restrictive use of psychotropics in the Demvest study is consistent with the most recent guidelines. This was probably because of increasing awareness of detrimental effects in the elderly, and it was also a caution about the high rate of diagnosed DLB patients in our population, who are particularly sensitive to the side effects of psychotropic drugs.

The overall prescription of drugs in the Demvest cohort at inclusion was analysed thoroughly. Few patients had potentially inappropriate medications (14%) or potentially severe drug–drug interactions (4%), indicating that the prescribing quality was acceptable [103]. Thus, the observed poor prognosis in the DLB group is unlikely related to the side effects of psychotropics or other drugs.

Mortality and disease progression

The cohort had a high mortality rate, particularly the LBD patients, who may have confounded the observed course of NPS. The results may be skewed in the direction of more DLB patients being assessed closer to the time of death or those with a high rate of NPS might have a higher mortality rate, and thus, there is a risk for selective drop-out. There is consistent evidence for higher and earlier mortality in DLB compared to AD patients [104]. Patients diagnosed with DLB also had nearly 2 years less time to nursing home admission than those diagnosed with AD [105]. Differences between AD and DLB related to mortality and cognitive decline seen in the Demvest study are consistent with meta-analyses [106]. The difference between AD and DLB was adjusted using statistical methods described in article 1, which included a model where diagnosis of AD/DLB, time, and cognitive decline were included. We tried to eliminate the last NPS assessment to adjust for peri-mortem worsening of symptoms, and this did not significantly change the results.

9.2 Measurement of NPS

Extent of use in the thesis
Assessment of NPS is the key outcome variable in articles 1 and 2, and the key defining variable in article 3, all of which were assessed using the NPI.

9.2.1 Neuropsychiatric Inventory (NPI)

The validated Norwegian 12-question NPI was used to interview a family member or carer [54]. The 12 items are registered as present, and if present, they are scored according to their frequency (1–4) and severity (1–3). NPI reports the frequency × severity score for individual items that occurred within the last 4 weeks. The NPI item score is a product term of two ordinal scales with many of the NPI items scored as 0 (reflecting 'not present').

Articles 1 and 2 report if the symptom is present (item score ≥1) and the established cut-off item score of ≥4 was a point to determine the clinical significance, which includes moderately severe symptoms at a frequency rating of 'often' or more frequently, and 'mild symptoms' that are present at a frequency rating of 'very frequent,' as previously reported [16, 26]. NPI has a multiplicative scoring system of items with a frequency (1–4) and severity (1–3), providing a score of 1, 3, 4, 6, 8, 9, or 12. Both the item scores and NPI total score are non-continuous and non-normally distributed variables that generate problems when using parametric methods [107]. Especially when using advanced statistical analysis with an underlying assumption of normal distribution, the large skewed effect with a high number of zeros and lack of the numbers 5, 7, and 11 provide challenges.

9.2.2 Psychometric properties

Content validity

The NPS categories dysphoria, aggression, aberrant motor behaviour, anxiety, delusions, and hallucinations were compared with the affective disturbance, aggressiveness, activity disturbances, anxiety and phobia, delusion, and hallucinations items from the Behavioral Pathology of Alzheimer's Disease Rating Scale (BEHAVE-AD) and other scales in the primary publication [108]. The NPI domain of dysphoria was significantly correlated with the Hamilton Rating Scale for Depression (HAM-D). The psychometric properties of the Norwegian version were also examined directly compared to the clinicians who rated a patient's behaviour using the same BEHAVE-AD, with equally satisfactory results. The weakest correlations were between items assessing affective and anxiety symptoms [54]. The NPI has been used as a concurrent validity measure against the revised Cambridge Behavioural Inventory to establish its validity in behavioural symptoms in persons with dementia in general practice settings [109].

Internal consistency

The original study presenting NPI also provided between-rater, test-retest, and internal consistency reliabilities, all of which showed high reliability. Cummings et al. reported a high level of internal consistency for the overall score as measured by Cronbach's alpha, α=0.88, and that 78% of the scale's items showed no significant relationship with each other, indicating that these items were assessing different behaviours [108]. Reviews of NPI reported an α-range of 0.67–0.8 in terms of the NPI's internal consistency, and concluded that overall, the NPI can be said to have reasonable to good internal consistency [107].

The Norwegian version has reported a similar internal consistency α=0.80. Inter-rater reliability was, except for one item, between 0.85 and 1.0 across assessors with different levels of health education. The Norwegian version of the NPI is a reliable

and valid instrument for assessing psychiatric symptoms and behavioural disturbances in the residents of nursing homes [54].

Spin-off versions

The content of NPI and NPI-Nursing Home (NPI-NH) are identical but have been rephrased appropriately. The caregiver distress scale on the NPI has been changed to an occupational disruptiveness scale for the NPI-NH to allow an assessment of the impact of behavioural disturbances on professional caregivers. Ten- and 12-question versions are also available, and the latter includes night time disturbances and appetite as the two last items. NPI and NPI-NH scales are therefore assumed to be similar and comparable. The use of a subscale is also commonly endorsed by the neuropsychiatric domain hypothesis, but its clinical validity is questioned [110, 111]. It has also been discouraged by Cummings [107]. Several spin-off tests have also been tested, such as the quicker NPI-Questionnaire, the more elaborative NPI-Clinicians, and the NPI-diary version that is focused on detecting temporal changes in nursing homes. NPI-Questionnaire is the most frequently used spin-off version.

Criticism of the NPI

Some psychiatric symptoms described in dementia are not included in the NPI or are assumed to be covered to some extent by existing items. Symptoms such as ruminative behaviour, repetitive and compulsive behaviour, and somatoform behaviour are not reported, but they are included in the NPI-Clinicians [53]. NPI is currently the most comprehensive tool, but hypersexuality is left out and spousal violence is not explicitly mentioned.

The ease-of-use weighted against the questionnaire being too short or superficial will always emerge, especially for patients with excessive and severe symptoms. More specific and pinpointed tests such as the Cohen–Mansfield Aggression Scale and the Geriatric Depression Scale are often used in addition to the NPI. Cummings et al.

argue that they never intended the NPI to be fully comprehensive but that it was intended to minimise administration time [108].

However, criticism has also been raised as to whether the NPI in combination with a clinical cohort may exaggerate the frequency of clinically significant NPS [112]. The primary validity testing was performed in the spouses of 40 non-demented elderly patients who showed a mean depression item score of 0.25 (range, 0–6), disinhibition score of 0.13 (range, 0–4), and irritability score of 0.05 (range, 0–2). Cummings et al. (1995) concluded that 'NPI scale scores should be regarded as important evidence for the presence of psychopathology.' No larger study on healthy elderly using the NPI or NPI-Questionnaire was found, but one study showed a mean NPI-Questionnaire total score of 0.67 (SD 1.54, n=3644) in participants who did not convert to dementia [113].

The NPI is a structured interview for carers, rather than for the patients. Investigators continue to be concerned about the limitation of collecting data only from the informants because the patient's own experience may be disregarded and there is a risk of reporting bias. This concern was made explicit by a consensus paper published by an expert panel that was convened by the Alzheimer's Association in collaboration with leaders in academia and industry [114]. Although patients with mild dementia may have good insight into their symptoms, describing the frequency and severity is often difficult and requires a high degree of self-awareness and episodic memory. The inability to acknowledge symptoms is a key part of dementia. The NPI does not necessarily reflect the emotional state of patients, but rather their objective states and behaviour.

The increased use of NPI and the lack of proven effective pharmacological treatments have raised concerns regarding the validity of NPI [52]. However, studies about tapering of drugs and non-pharmacological interventions have shown an effect, and many studies using more specific scales have shown equally poor effects of pharmacological interventions. Other scales include the Behavior Rating Scale for

Dementia of the Consortium to Establish a Registry for Alzheimer's Disease (BEHAVE-AD), Brief Psychiatric Rating Scale (BPRS), and Present Behavioural Examination (PBE), but these scales have not shown better dynamic validity in describing symptoms [25, 52-54].

9.3 Neuropathology

Extent of use in the thesis

Diagnosis of patients in article 2 is based on a definitive diagnosis in a subgroup and article 3 quantifies pathology related to psychotic symptoms. The neuropathological methods were not fully described in article 3, and they are, therefore, included as supplements to article 3 in the thesis.

The final diagnostic assessment included the Braak stage of tau pathology (0–6), amyloid plaques CERAD (Consortium to Establish a Registry for Alzheimer Disease assessment) probability of AD (0-C), Braak stage of alpha synuclein pathology (0–6), and vascular pathologies including cerebral amyloid angiopathy (none, mild, moderate, severe) and small vessel disease (none, mild, moderate, severe). Vascular pathologies, such as amyloid angiopathy and small vessel disease were scored according to the Vascular Cognitive Impairment Neuropathology Guidelines [13, 27, 37, 115].

9.3.2 Neuropathological diagnosis

Each case was assessed by an experienced neuropathologist who was blinded to clinical data. Pathological diagnosis was made thereafter according to an international consensus with reference to the diagnostic criteria for AD, DLB, and PDD. Patients were classified as having DLB if the likelihood of a DLB syndrome was 'intermediate' or 'high,' according to McKeith et al. [27]. The presence of possible co-existing TDP-43 proteinopathy was assessed according to the guidelines, and microscopic vascular lesions were considered and recorded.

Patients with borderline DLB/PDD pathology at autopsy were classified as PDD or DLB if they had a clinical diagnosis of PDD or DLB, respectively. The few patients who were misidentified as AD or DLB all had significant NPS. The pathological evaluation suggests that although both parkinsonism and visual hallucinations are common in AD, even when they occur several years after the dementia diagnosis, they may indicate Lewy body pathology [99].

9.3.3 Consideration regarding neuropathology

The importance of post-mortem diagnostics cannot be overestimated when comparing the differences between diseases. Even with full clinical information and a long follow-up, there is a risk of misdiagnosis. Methodological strengths include that patients were diagnosed prospectively and consecutively underwent autopsy, and only age and duration differed between autopsied and non-autopsied patients [99].

Categorisation

Most patients were present in a few of the many possible pathological categories and, therefore, for statistical analyses used to investigate the pathological load, the scores were collapsed into binary categories, as follows: none/mild and moderate/severe according to stages 0–4 compared to stages 5–6 (Braak-tau and alpha-synuclein), CERAD class 0–B compared to class C, and cerebral amyloid angiopathy and small vessel disease scored as none/mild compared to moderate/severe. None of the collapsed categories were originally continuous scales, but ordinal categories defined by pathologists. Currently, efforts are being made to quantify the pathological data from the Demvest study, but the quantification of these data is not yet complete. The approach of collapsing categories reduced the risk of a type 1 error as the outlier contribution is reduced. Both the low number of patients and categorisation of data increase the risk of type 2 error and dismissing an actual association. With the small sample size in the current study, little importance was therefore given to the lack of association that was found for the severity of Lewy-body pathology or amyloid pathology with psychosis or the rate of cognitive decline.

Comorbidity

The presence and interactions of multiple pathologies in the brain of patients with dementia, as observed in this cohort, is well known [116]. Nine AD patients had some degree of TDP-43 pathology: two had mild pathology in the amygdala only, and two had mild, four had moderate, and one had severe pathology in the amygdala and hippocampus; one of these patients also had mild TDP-43 proteinopathy in the neocortex. Six DLB/PDD patients had TDP-43 pathology, five had moderate changes in the amygdala and hippocampus, and one had severe pathology in the amygdala and moderate pathology in the hippocampus and neocortex. Vascular pathology, such as amyloid angiopathy and small vessel disease was common in both AD and DLB/PDD patients, and some patients also had infarctions. Regarding vascular pathology and evaluating its contribution to dementia, we applied the concepts outlined in our recent consensus papers for neuropathological correlates of vascular dementia [115].

9.4 Ethics and legality

The Demvest study was approved by the Regional Committee for Medical and Health Research Ethics, Western Norway (167.04) and the Norwegian Authorities for Collection of Medical Data. The patients provided written informed consent to participate after the study procedures had been explained in detail to the patient and a caregiver, who was usually the spouse or son/daughter.

All data from the Demvest study are kept in accordance to Norwegian recommendations on data privacy, and they were anonymised to as high a degree as possible. At certain points, such as obtaining data from the National Death Registry, the data must be re-personalised.

With the long-term course presented in article 2, carers may assume that a certain course is their family member. Describing individual patients will always include a risk, but we tried to disguise any specific information and only provide very general descriptions. Thus, the risk of identifying a participant is regarded as extremely low.

Patients received the usual treatment, or standard-of-care, or the treatment may have been better than usual because of the annual study assessments, compared to off-study patients who would normally be followed by nursing home staff only. CSF analysis and radiological techniques may have been used to a larger extent in the study than in common clinical practice, but all procedures were in accordance with standard clinical recommendations.

Lumbar puncture may sometimes be painful and carry a risk of adverse effects, which in most cases, are mild and transient. DaT-Scan imaging has some radiation risks, although this is minimal, and this test was only performed once. Repeated contact with specialised health care may cause over-diagnosis and secondary overtreatment. The cognitive threshold for inclusion into the study is rather high, meaning that all patients had only mild everyday functional deficits. Specialised health care in the last decade has requested restrictive use of psychopharmacology, and thus the participants

likely had a lower risk than non-participants of receiving a dangerous drug treatment. Additionally, a secondary positive effect of more focus on these patient's care cannot be ruled out.

10. Results

Article 1

The first article's aim was to profile the frequency and associated variables of NPS over 5 years in patients with mild dementia.

Neuropsychiatric symptoms were common at baseline, and we observed only a moderate increase in the average NPI total score, from 15 to 17, with no increase in the proportion of patients with high NPI total scores. Ninety seven percent scored ≥16, and 49% scored ≥36 on the NPI total score at least once during follow-up. The most common symptoms reported were apathy (83%), depression (63%), appetite (63%), and aberrant motor behaviour (60%). Cognitive decline was associated with higher NPI total and several NPI item scores. Only the frequency of apathy increased significantly over time. LBD was associated with a higher NPI total score and psychotic symptoms compared to AD.

Article 2

The second article's aim was to describe the individual course for up to 12 years from the diagnosis of dementia to death in people with AD and LBD.

Nearly all patients had NPS while 50% had a stable modest NPI total score ≥12 and 25% had a stable NPI total score ≥24. Very severe NPS (≥48) were mostly single episodes, but 8% of AD patients had stable severe NPS. The AD patients with the highest 20% of NPI total scores had a more stable or a relapsing course for the four key symptoms: aberrant motor behaviour, aggression/agitation, delusions, and irritability. This was not seen in LBD. There were wide variations between patients, diagnoses, and specific NPS. Single episodes represented the most common course, followed by a relapsing course, while a stable course was less common. Additionally, 57% of AD and 84% of LBD patients had reoccurring psychotic symptoms. Hallucinations were more frequent and stable in LBD, while aggression in more stable in AD.

Article 3

We investigated the post-mortem pathological correlates of severe psychotic symptoms.

Neuropathologic assessments were available in 31 AD and 16 LBD patients who had been followed from mild dementia to death. AD patients with early and severe hallucinations and delusions had more severe cerebral amyloid angiopathy than those without psychotic symptoms. No significant associations between pathological scores and psychotic symptoms were found in DLB.

11. Discussion

About the discussion

The objective of this discussion is to present and discuss the complete thesis as a whole, whereas discussion of the specific papers is provided in the respective articles. I have concentrated the findings based on both scientific and clinical perspective into six key points. These key points are critically discussed after an interpretation of the findings from the most important and similar published studies.

Key points for discussion

Part 1: Longitudinal course of NPS

1. Neuropsychiatric symptoms are common in mild dementia and their increase is only moderate. NPS in mild dementia may therefore be under-recognised if it is not explicitly assessed.
2. Over the long-term, NPS are mostly relapsing or single episodes. There are large individual variations that support the need for personalised medicine.
3. Because most patients exhibit repeated psychotic symptoms, these symptoms should be emphasised in communications with patients and carers.

Part 2: Differences between AD and DLB

4. LBD patients have more NPS in mild dementia and there are more delusions and apathy, but NPS are also more often single episodes compared to AD..
5. NPS are more stable in AD than LBD patients, and there is a subgroup of AD patients with a severe course of wandering, aggression, delusions, and irritability.

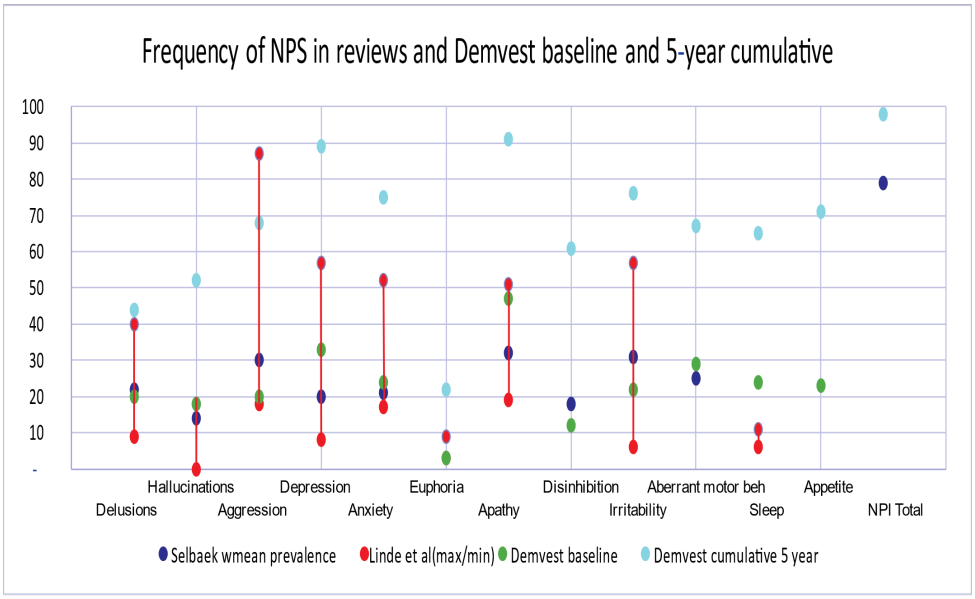
Part 3: Neuropathological correlates of NPS

6. Advanced cerebral amyloid angiopathy was associated with persistent and severe psychotic symptoms in AD.

11.1 Findings in context

Meta-analyses and reviews have shown large differences in the frequency and persistency of NPS. The results from the Demvest study (baseline and 5-year cumulative results) are presented together with both of the key reviews by Selbæk et al. and van der Linde et al. in Figure 5. The Demvest study fits well within the large variation described in these studies. The 5-year cumulative frequency (six assessments) of NPS is higher in the Demvest study than in the reviews, but very few studies have more than 3–4 assessments.

The frequency and persistency of key studies with a similar prospective longitudinal design and inclusion criteria are presented in Figure 6. Because of the variation in methodology, these studies are described and discussed in detail.



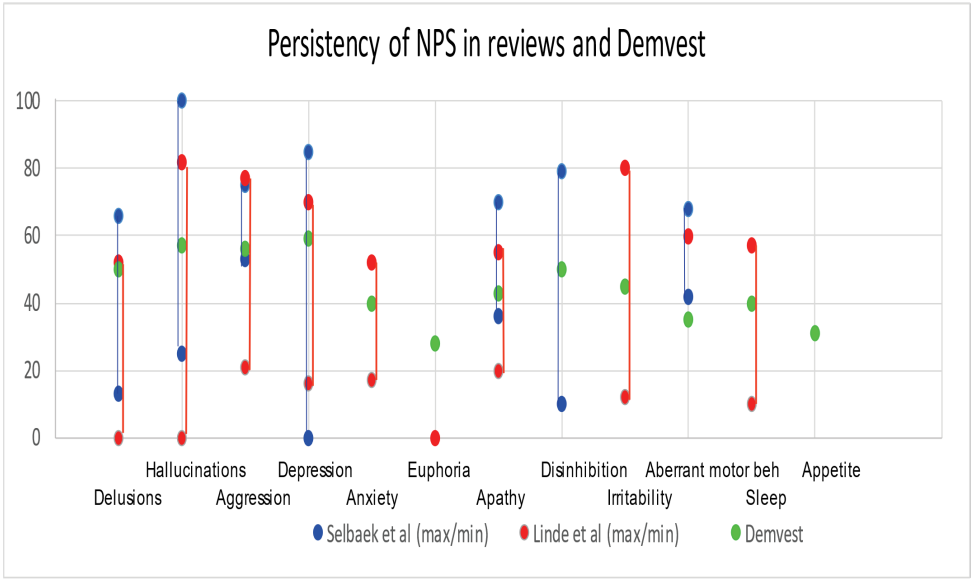


Figure 5. The frequency (top, in %) and persistency (below, in %) of different NPS in the reviews and in the Demvest study. Not all studies provided information on all NPS and not all provided the information defined by NPI [55, 56].

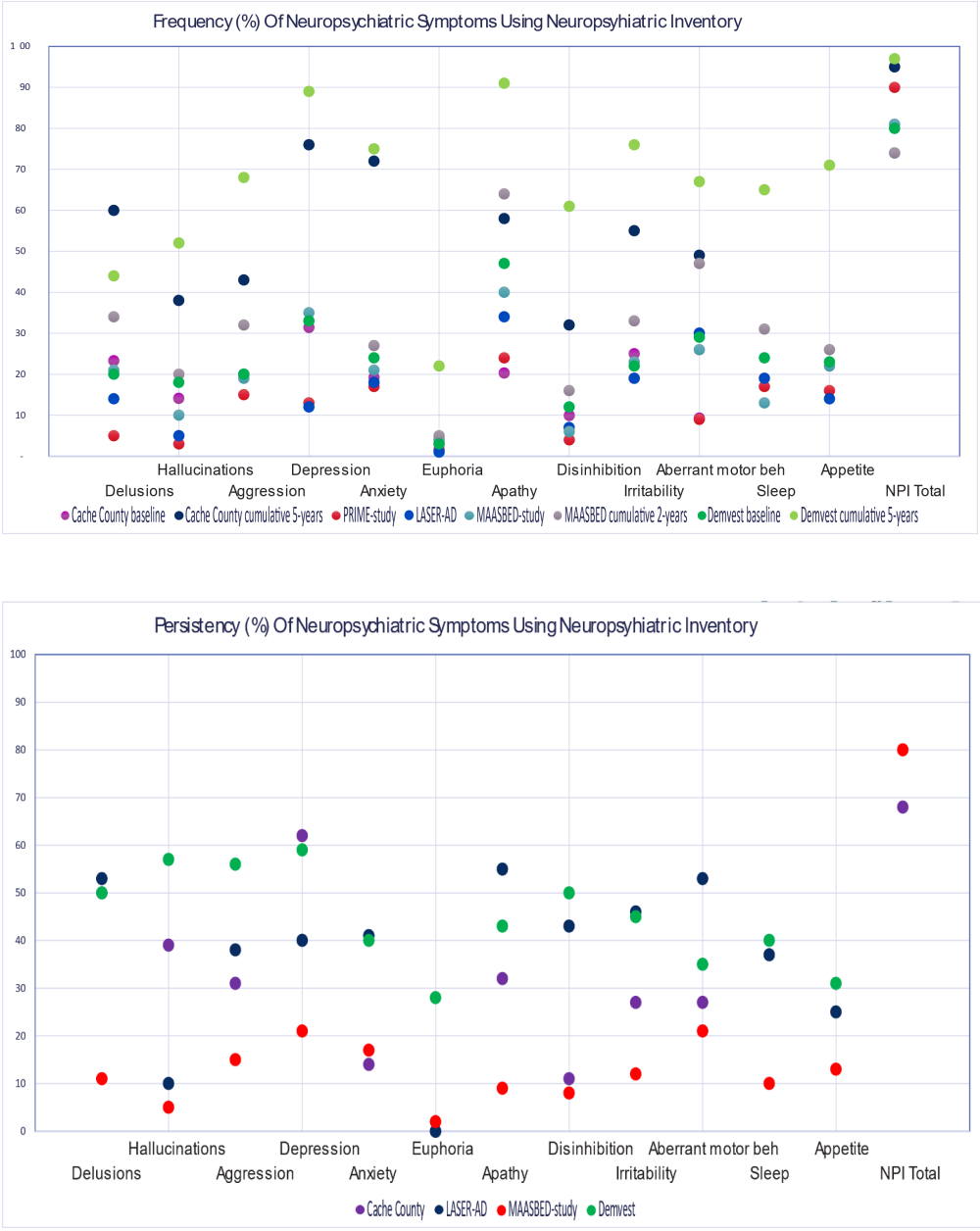


Figure 6. The frequency (top, in %) and persistency (below, in %) of different NPS in key studies presented in text and the Demvest study using NPI. Not all studies reported the persistency [1, 59, 84, 102, 117].

11.1.1 Key studies compared to the Demvest study

Cache County study

The large prospective population-based 'Cache County study' was a dementia progression study that followed patients for 5 years and reported the prevalence, persistency, and trajectory of NPS [48, 70, 101, 117-119]. With initial screening of 5677 patients, 437 dementia patients were identified, among whom 236 had at least one follow-up. This is one of the largest longitudinal studies of NPS in dementia. However, because of a high drop-out rate, only 36 patients had four follow-ups (5.3 years). With the number of patients, the long-term follow-up and the wide range of NPS assessed, this is the closest study compared to the Demvest study. The Cache County study showed that the risk of any NPS was 56% at baseline and the cumulative incidence was 95% [117]. The same symptoms were most frequent (depression, apathy, and anxiety), and thus, the findings were comparable to the Demvest study. The Demvest study had a higher 5-year cumulative prevalence probably because of a higher number of repeated assessments. More extroverted symptoms such as hallucination, aggression, disinhibition, and aberrant motor symptoms were more frequent and more severe in the Demvest cohort. The higher rate of these symptoms may be because of the more progressed dementia stage in the Cache County study. A mean MMSE of 14 was reported in a persistency analysis (n=117) [120], while the 5-year prevalence analysis did not provide MMSE, but 15% had a CDR core of >2 already at baseline (n=236) [117]. This is an important difference compared to the Demvest study, which had a mean MMSE of 24 and excluded patients with CDR ≥1. The Cache County study also had a higher attrition rate in patients with hallucinations, aggression, disinhibition, irritability, or aberrant motor behaviour than in those without these symptoms [117]. As will be discussed later, the patients with severe NPS are often difficult to retain in study protocols.

LASER-AD

The LASER-AD study from England followed only AD patients (n=198) and reported the frequency of all 12 NPI items at baseline and after 6 months of follow-up [102, 121]. Although shorter than the Demvest study, the LASER-AD study provides good diagnostics and an epidemiologically representative sample of mild, moderate, and severe AD patients. Thirty-three percent of the patients were in nursing homes and the remainder were home-dwelling. LASER-AD found that patients with *any* NPS were very common (75%) and highly persistent over 6 months (96%), and the NPI total score was not associated with living at home or in a nursing home. They reported a similarly high frequency and persistency similar to the Demvest study, although the LASER-AD study reported a lower frequency and persistency of hallucinations in their AD patients than in the overall Demvest group. This was probably because of the DLB patients in the Demvest study. In our AD subgroup, we report a 5-year frequency of hallucination of 40% compared to a 19% baseline frequency in the LASER-AD study (NPI ≥1). A lower persistency of NPI was present (item score >0) compared to clinically significant NPS (score >3), which was similar to the Demvest study. LASER-AD found no association between psychotropic drug use, use of services, cost of care, and improvements in NPS, while the MMSE decline was the only significant predictor of increased NPI score. Their focus is the low effect of proposed treatment measures. The authors propose that a shorter follow-up and selectively including AD distinguishes their study from other studies. Compared to Demvest, the structured inclusion of dementia stages could also induce bias because several NPS are associated with a lower MMSE score that is intermittent or stable [102]. Both LASER-AD and Demvest are clinical cohorts that were recruited through health care worker referrals, and they have a risk of selection bias. LASER-AD also showed that aggression accounted for 12% of the health and social care costs of AD [45].

MAASBED

The MAASBED study from The Netherlands reported data from 99 patients (among the 199 patients who were included) for 2 years, with 6-month assessment intervals [59]. Patients were recruited from specialised health care but living at home. Among those who were initially included, 75% were diagnosed with AD, 16% with vascular dementia, and only 4% with DLB. Diagnoses were not included in the analysis but were reported as all-cause dementia. The mean MMSE was 18 with a decline of 1.7 points per year, which is consistent with the Demvest study (mean, 2.1), considering both the higher frequency of DLB and the floor-effect of MMSE. The frequency of NPS was similar, except for more hallucinations and night time behaviour symptoms in the Demvest group, and both of these symptoms are frequent in DLB.

The persistency reported for 6, 12, 18, and 24 months in the MAASBED study was lower than in the Demvest and LASER-AD studies (Figure 6). Apathy was still the most persistent but there were large differences. For example, there may be a difference in the clinical management of delusion if the persistency is 11% (MAASBED) or 53% (LASER-AD) compared to 50% (Demvest). The reason for lower persistency of symptoms in MAASBED is not clear, but the persistency on any NPS (defined by NPI total >3) was 65%. These data are consistent with the Demvest results, in which 78% had a stable course with NPI total ≥1, and 46% had a stable course with NPI total ≥12 (Article [2]). The MAASBED authors suggest that the risk of selective attrition biased the results, and they also argue the importance of using sub-syndromes (see the data reduction below).

In the MAASBED study there was no increase of the NPI total score over 2 years, but there was an increase in apathy and aberrant motor behaviour analysed and a decrease in depression assessed by the mean item score. A statistical model without cognitive decline showed that time was significantly associated with this increase. The Demvest study showed no change in depression, but there was an increase in the frequency of clinically significant symptoms of apathy and aberrant motor behaviour, which were associated with the MMSE decline, but not with time.

PRIME

In a 3-year follow-up study from Australia (Prospective Research in Memory clinics, the PRIME study), Brodaty et al. enrolled 511 patients, with 331 patients completing the study, and these patients were assessed on six occasions using the NPI [84]. Patients were recruited from specialised memory clinics. Only patients living at home were included in the results. With a MMSE of 22% and 85% and a CDR score of 0.5 or 1, this is the closest cohort to the Demvest study in terms of dementia stage. Patients were diagnosed based on clinical criteria, and 67% of patients had AD, 15% of patients had vascular, and only 3% of patients had DLB. Baseline severity of dementia was associated with a higher NPI total score. The severity of symptoms including delusions, hallucinations agitation, anxiety, apathy, and aberrant motor symptoms was associated with time, while the cognitive decline was not modelled in this study. Demvest study showed similar effects of time, but this effect was not significant when the MMSE decline was introduced into the model in article 1. A similar sex difference as in the Demvest study was reported with higher risk for apathy in men and anxiety in women, and Demvest study found that women were also more likely to have delusions. Besides the differences in LBD frequency, the key outcome variable was analysed quite differently. Both the MAASBED study and the PRIME study used mean the NPI score, which required transformation of the data before analyses because of the skewness. Although statistically handled, this introduces the question of whether the NPI scores should be treated as a continuous or ordinal (non-continuous) scale. The Demvest study is presented and analysed using the clinical cut off NPI ≥4 [1].

The main conclusion of the PRIME study is that NPS worsens over time, and that symptoms have different trajectories associated with sex, diagnosis, and the use of medications when dementia severity is controlled.

OPTIMA

The Hope et al. study is unique because it is an up to 10-year follow-up study with 4-month assessment intervals as part of the Oxford Project to Investigate Memory and Ageing (OPTIMA) [58, 122, 123]. OPTIMA was a collaboration between post-mortem examinations and computed tomography scans. The study sample was initially 100 patients, of whom 48 had pathologically confirmed AD and most results were based on this group. There was low attrition for causes other than death. The mean follow-up time was 3.3 years and the focus of the study was also the course of behavioural symptoms.

OPTIMA did not use NPI, but Present Behavioural Examination (PBE) and thus, comparing results directly is difficult. The PBE rates most items on a seven-point frequency scale (0–6), depending on the proportion of days on which the behaviour occurred. PBE also took into account carer-reported behaviour within the last 4 weeks. Hope et al. rated an episode if it was 'persistent and severe' which does not include an isolated episode (PBE score 1). This is similar or more restrictive compared to NPI and our clinically significant cut off (NPI ≥4) because we did not include any symptom that occurred less than once per week. Although key symptoms are likely to be similar, delusions were compared to persecutory ideas (46%) and hallucinations were considered to be auditory hallucinations (26%), while in the Demvest study, the 5-year cumulative frequency was 41% and 24%, respectively. With a mean follow-up time of 3.3 years in Hope et al., the frequencies are best compared to the Demvest study 5-year frequency, and not to the full course cohort that has a mean follow-up time of 6.4 (SD 2.9) years. A 4-month assessment interval in the OPTIMA study did not seem to increase the cumulative frequency compared to the 1-year assessment interval in the Demvest study, although the differences described should be interpreted with caution.

The OPTIMA study reported that all patients with dementia had NPS to some degree during a long-term follow-up, and the course of the symptoms was different. Most

patients had persistent symptoms until death or single episodes. A relapsing–remitting pattern was less common. Fewer than 14% of people who were rated positively for a symptom had more than a single episode. They also argued that the data supported the view that behavioural and psychiatric changes occur predominantly at a late stage of the dementing illness. It is difficult to compare the OPTIMA and Demvest studies because of the differences in design and instruments used, but many AD patients with persistent severe NPS is a common finding in both studies. Hope et al. conclude by stating the importance of NPS instability in trial and management evaluation, which is the similar to the conclusion raised by the Demvest study [58].

ADNI

A more recent study presented the course of NPI total scores in an AD cohort (n=181) that was initially designed to evaluate if positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment and early AD [61]. The mean MMSE score was 23, and patients were assessed using the NPI-Questionnaire at baseline and at 6 months, and they were grouped into persistent (both assessments), fluctuating (one assessment), and no NPS based on the NPI total score ≥4. AD subjects with persistent and fluctuating NPS showed more atrophy of the right and left prefrontal cortex compared to those with minimal/absent NPS. AD subjects with persistent or fluctuating NPS showed worse cognitive and functional outcomes compared to AD subjects with minimal/absent NPS. Although only including a 6-month time-span, this study showed a biological difference in patients with more stable NPS either as cause or consequence of NPS. The cohort with mild dementia is similar to that of the Demvest study and the proportion of patients with a persistent compared to a fluctuating (relapsing) course is also similar.

EADC and data reduction

Several large cross-sectional studies argue that NPS are clustered together in sub-syndromes such as psychotic and affective syndromes. The NPI was not originally designed for this [108]. However, several studies show the data in domains that were acquired statistically or logically. One such key study is the meta-analysis from the multicentre European Alzheimer's Disease consortium (EADC) collection of 2,354 patients with 'any dementia' [62, 124]. The EADC data showed convincingly that NPI in cross-sectional data can be reduced to domains such as psychosis, hyperactivity, and affective using principal component analysis. They also reported that the diagnosis was a less important predictor of NPS (see the discussion below). Longitudinal data have challenged the usefulness of such domains [110, 111], and the theoretical background regarding both the assumption of the NPI item scores as continuous and the data inflation of scores equal to 0. The data from the PRIME study on NPS were analysed according to NPS domains hypothesis, showing a lack of stability in the domains at the group level [111]. This thesis has therefore explicitly avoided data reduction methods.

11.2 Longitudinal course of NPS

1. Neuropsychiatric symptoms are common in mild dementia and their increase is only moderate. NPS in mild dementia may therefore be under-recognised if it is not explicitly assessed.

Key reviews and text books report an increase in NPS over time and increasing dementia severity based on cross-sectional data that is transformed into a longitudinal course that shows an increase in NPS according to severity or a crescendo-decrescendo effect, with the highest NPS scores in the moderate-to-severe group [23, 52, 55-57, 62, 125]. These cross-sectional studies have more selection bias, with the risk of patients being recruited into studies and more recall bias as patients and carers are seeking help. Most longer-term studies are nursing home studies that often have multi-morbid and severely demented patients [57, 62]. Therefore, truly long-term cohorts with low attrition rates and proper diagnostics that are relevant to current clinical practice are a priority [52, 55]. The Demvest study provides such a cohort. The observed small increase in the mean NPI total from 15 to 17 over 5 years is unlikely to be clinically significant. Other studies such as PRIME, LASER-AD, and Cache County show the same statistically significant increases, but also the same very modest increase with no increase in mean NPI item score more than 1 point and no NPI total score more than 3 points. The NPS in mild cognitive impairment (MCI are under investigation in many studies after the minimal behavioural impairment initiative, and NPS are reported to be common at the MCI stage [25, 50]. The Cache County study also found a high risk for NPI in patients with cognitive impairment and no dementia, and a higher risk of conversion to dementia in people with NPS [119].

There is an important distinction between time and cognitive decline, although dementia progression is assumed to be inevitable. The association between NPS and the cognitive decline is probably not causative, and they may affect each other and other unknown factors may affect both these factors. NPS may impact the cognitive

decline in several ways, but the most discussed is the permanent negative effects on elderly brain plasticity.

The large differences between studies do not seem to have any geographical or sociological causes [56], but are most likely a result of the recruitment and assessment differences. Because many symptoms are both phenomenologically hard to describe and stigmatising, and they place patients at high risk of unwanted consequences (e.g. patient–carer disputes or institutionalisation), a structured interview is appropriate.

2. Over the long-term, NPS are mostly relapsing or single episodes. There are large individual variations that support the need for personalised medicine.

Longitudinal studies with high follow-up rates and structured assessments such as LASER-AD, MAASBED, and PRIME are all in agreement with the van der Linde et al. meta-analysis but the description is limited to group levels and there is a high degree of variability. Using these data for clinical management is difficult and further studies are required. In article 1, we show a high rate of symptom reoccurrence (57–86%), and in article 2, there are large variations between patients. Most patients have an intermediate overall score with many single episodes or relapsing individual symptoms. Some patients had complete symptom resolution late in the disease course, even those patients with severe symptom scores. The pattern of relapsing or a single episode course was more pronounced among patients with higher item scores. Apathy was the most stable symptom in both AD and LBD, with 34% and 27% of patients having stable apathy, respectively.

Hope et al. argue the difficulty of assessing the intervention effects and this issue is raised by several others [52, 58]. The lack of intervention efficacy is often suspected based on mostly negative clinical trials, but the design of such studies must take into

account the unstable symptom course. Non-pharmacological interventions could be less sensitive to these variations because they are unblinded and person-specific. A large generalised clinical effect of any of our current medications are less likely.

A diagram of AD patient movements between NPI total severity levels from baseline to the fourth follow-up is provided to illustrate the complex longitudinal course (Figure 7). Except for a small group of patients with very significant NPS, there was a high degree of instability.

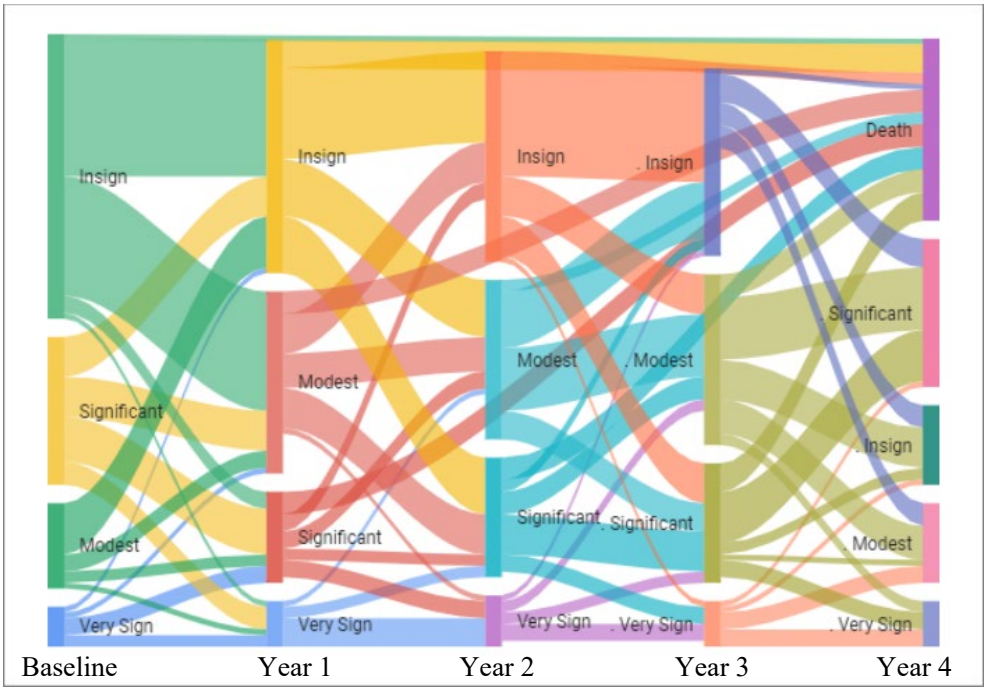


Figure 7: A Sankey diagram of the NPI total scores according to severity level, showing the stability from baseline to the fourth follow-up (4 years). Insign, Insignificant NPI total 0–11 (including both Present (<11) and None); Modest, NPI total 12–23; Significant, NPI total 24–47; and Very Significant, NPI total 48 or more. The order of categories within each follow-up is based on the closest relationship.

3. Because most patients exhibit repeated psychotic symptoms, these symptoms should be emphasised in communications with patients and carers.

Psychotic symptoms carry with them direct consequences of agony, burden, and loss of self-preservation, but also many indirect consequences such as institutionalisation and isolation. The current management assumes that psychotic symptoms are common and most often are permanent. We show that 94% of LBD and 77% of AD patients experienced at least one psychotic symptom (NPI ≥1 for delusions or hallucinations). In LBD, 83% had reoccurring psychotic symptoms, compared to 57% of AD patients, while clinically significant hallucinations (NPI≥4) had a stable course in 24% of LBD and only 4% of AD patients [2]. The findings in the Cache County study are the closest to our findings, while other shorter studies with fewer follow-up assessments found lower frequencies (Figure 6). The Demvest study 5-year psychosis frequency was similar to the OPTIMA study that also followed a long-term course.

Even with potential bias of more psychiatric recruitment in the Demvest cohort, the data are consistent with the common occurrence of psychotic symptoms in dementia, and the unstable course in most of these patients. These changes in clinical understanding are important because they can improve management through an increasing effort to identify and understand psychosis as an integral part of dementia. A shift in the focus from permanent to episodic symptoms may increase efforts from carers to stimulate and continue their activities of daily life. For scientific studies, these data show the need for longitudinal assessment of NPS when identifying a subgroup for a study.

11.3 Differences between AD and LBD

4. LBD patients have more NPS in mild dementia and there are more delusions and apathy, but NPS are also more often single episodes compared to AD.

All three articles reveal significant differences in NPS between AD and LBD, which is in contrast to studies, meta-analyses, and a review that conclude that NPS are similar between these diagnoses, which justifies reporting of all-cause dementia. The largest meta-analysis study from European Alzheimer's Disease consortium (the EADC) found no differences in NPS between different diagnoses [62]. The Cache study reported that there were no differences in the prevalence of neuropsychiatric symptoms between participants with Alzheimer-type dementia and those with other dementias combined, with the exception of aberrant motor behaviour, which was more frequent in Alzheimer-type dementia [126]. However, we found differences in both hallucination and night time disturbances, both of which are core symptoms of LBD [27, 64, 84]. The Demvest study provides findings that are complementary with other studies that describe differences in core clinical symptoms of DLB and AD, but this study also showed that these differences in symptoms decrease with increasing dementia severity. This observation is consistent with the total load pathology hypothesis and the consequence is a risk of misdiagnosis in patients with late onset core DLB symptoms [99].

The Demvest study shows a higher frequency of both apathy and delusions in LBD. Depressive symptoms were higher on the Montgomery and Åsbergs Depression Rating Scale (MADRS) score at baseline, and a higher apathy score was shown on the NPI in LBD patients in the early phase of the disease [1, 127]. In the Demvest study, apathy was more extensively studied and found to be associated with a faster global cognitive decline and early nursing home admission in DLB [128]. These findings are consistent with studies with a high diagnostic accuracy and that focus on mild dementia using the DSM-IV diagnosis showing the largest difference in

symptoms such as anhedonia and fatigue compared to AD [65]. Other studies may have missed this effect if it was most evident in mild-to-moderate dementia patients and it has never been shown in previous long-term longitudinal studies.

Although much focus is on hallucinations, delusions were also reported as a common symptom in LBD and also recently in prodromal LBD [129]. The Demvest study reports both a higher frequency of delusions that are associated with a cognitive decline, and a more unstable course of delusions compared to AD. Delusions are associated with an overall severe NPS trajectory in all-cause dementia. It has previously been shown that DLB patients who presented with delusions had poorer cognitive function, but few studies have followed patients longitudinally. Ballard et al. reported no difference between AD and DLB in the frequency or severity of delusions over 6 months in mild dementia patients living at home [130]. None of the other large studies reported differences in delusions [84, 117].

The lower sensitivity of MMSE to detect DLB (because it was designed for AD) and the shorter survival time may indicate that the Demvest study had biased recruitment of more severe LBD patients compared to AD patients. However, there was no difference in the CDR score at baseline, but there was a significantly more rapid decline in DLB patients [105]. In contrast to MMSE, the CDR captures the full range of functional deficits resulting from cognition, as judged by a trained clinician after interviewing the patients and caregivers, and it is likely a more accurate and comprehensive measure of severity. However, the CDR was also developed for use in AD and has not been adequately tested in DLB. In the articles from this thesis, LBD includes Parkinson's disease dementia (PDD). A recent study with a focus on PDD compared to DLB showed that PDD patients had fewer delusions and had an NPS profile that was similar to AD [131].

Differences in NPS between AD and LBD are important because they could describe a different biological underpinning. If LBD apathy and depression are closer to Parkinson's disease, there might be better intervention strategies related to

hypodopaminergic states such as piribedil for apathy and pivamanserin for psychosis [132, 133].

5. NPS are more stable in AD than LBD patients, and there is a subgroup of AD patients with a severe course of wandering, aggression, delusions, and irritability

A long-term assessed subgroup with severe and psychotic symptoms in articles 2 and 3 is novel, although AD is associated with more severe NPS. The Demvest study provides a large number of patients, long-term follow-up, and, importantly, a definitive diagnosis in a high percentage of patients. Our analysis of diagnostic accuracy also describes that patients with severe NPS are especially complex and difficult to accurately diagnose clinically [99]. The ADNI study identified a group of subjects with persistent NPS over only 6 months, with atrophy of the right and left prefrontal cortex in AD compared to others. The ADNI study also provided rigorous diagnostics.

We did a sub-analysis in our data in article 3, which showed a loss of difference between groups when using the last assessment and ever present psychotic symptoms compared to severe and persistent symptoms. The last assessment and ever present symptoms are two common ways of analysing psychosis data [83, 86]. However, our negative finding cannot be strongly weighted because of the lack of power with a small sample size and the risk of type II error.

An increased effort to identify AD patients with persistent and severe NPS may improve ordinary treatment and treatment in a clinical trial. This group may represent the outliers and an important clinical and biological subgroup [86]. Although aggression has been targeted in studies, no novel treatment has emerged. It can be speculated that they represent a group with inconsistent treatment plans based on an emergency, a high degree of polypharmacy, and re-occurring hospital admissions. This group of patients may be especially hard to study, because they are only a small

group, they do not fit standardised trial inclusion criteria, and they can seldom provide consent. Early identification through NPS and imaging may have the potential to improve clinical trials.

11.4 Neuropathological correlates of NPS

6. Advanced cerebral amyloid angiopathy was associated with persistent and severe psychotic symptoms in AD

Cerebrovascular pathology such as small vessel disease has been associated with depression in elderly people, but few studies have addressed psychotic symptoms. In a large neuropathological AD study (n=1618), vascular pathology was not found to be associated with psychosis ever present, but subcortical arteriosclerotic leukoencephalopathy and vascular risk factors were associated with this symptom [91]. Vascular risk factors did not predict a change in NPS in the Cache County study, but the use of antihypertensive medications was associated with a higher NPI total score and affective symptoms, but not psychosis [101].

Our sample had considerable co-morbid vascular pathology, but the patients were diagnosed clinically and pathologically with AD, and our findings are consistent with others regarding the high CAA presence [16, 134]. It is not likely that misdiagnosis of primary vascular pathology biased the results because prevalence of post-stroke psychosis is also much lower than in AD and DLB [135]. As one of a few prospective longitudinal studies, OPTIMA also assessed neuropathology, but NPS associations with neuropathology have not been published. OPTIMA found a relationship between CAA and subcortical tissue damage, and they concluded that vascular disease had a modest contribution to cognitive impairment in AD [136]. These results were consistent with more recent publications showing the low impact of vascular damage on the progression of AD [39].

Causative conclusions cannot be drawn from post-mortem studies because of the cross-sectional and end-stage pathological data. Cerebrovascular pathology may take many years to develop and is associated with the duration of life and genetic risk factors [35, 115].

Both genetic, clinical and pathological studies show how immune reactions and vascular pathology are important in psychosis development [16, 137]. Systemic inflammation is also known to play a key role in small vessel disease and to induce CAA through the blood-brain barrier pathway [138-141]. Inflammation may be a possible link between vascular pathology and psychosis in dementia. Monitoring and modifying inflammation are hot topics in psychosis research.

12. Conclusions

Patient level

NPS should be highlighted as an important part of the dementia syndrome even in mild dementia. Although apathy and affective symptoms are most common, aggression, irritability, and wandering should be emphasised to the general public as integral aspects of the disease. Psychotic symptoms, which carry strong prejudice and stigmata, should be screened for and integrated as a part of dementia patient treatment and management.

Health care level

Focus on the high frequency and relapsing remitting course of severe NPS can improve patient care and management. If patients are provided with strengthened home-based support or short-term nursing home placement with a focus on maintaining daily life-function, the consequences of single NPS episodes could be reduced. Identification of those patients a with good prognosis may be just as important as identifying those with a poor prognosis. A proper diagnosis is essential in managing NPS.

Research

An unstable course of NPS when assessing all-cause and all-level dementia must be taken into account when designing and interpreting trials. The importance of a correct diagnosis, especially in patients with psychotic symptoms, should also be noted.

13. Future perspective

The rigorous diagnostic procedures and long-term follow-up period of NPS in the Demvest study reveal more information about the relationship of NPS with the within-patient variation of cognitive decline and with key mechanisms such as vascular and inflammation and their risk factors. Identification of a high-risk AD group for severe NPS and a better description of the pathological mechanisms are the basis for a proposed future clinical trial in collaboration with King's College, London.

Identifying the role of NPS in the prodromal phase of dementia is another consequence stemming from the current work, highlighting that NPS are already prominent at the time of diagnosis. This research is being continued in a prospective new long-term follow-up study (Dementia Disease Initiation), focusing on people at pre-dementia stages, which is also underway in a multi-centre Norwegian collaboration.

This work highlights the complex task of translating the knowledge about NPS into clinically relevant and comprehensible information. Dissemination of facts about NPS is of the greatest importance; enabling those with the best knowledge about the patients to make the best decisions, for the patients and their carers.

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15. Appendex

15.1 Article I

Supplements article 1

15.2 Article II

Supplements article 2

15.3 Article III

Methological supplements article 3

I

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RESEARCH ARTICLE

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Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study

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Objective: Neuropsychiatric symptoms (NPS) in dementia are frequent and challenging for patients, carers, and the health care system, but few long-term studies exist. We analyse the longitudinal course of NPS in patients with mild dementia.

Methods: A longitudinal cohort study of 223 patients with mild dementia and annual assessments using the Neuropsychiatric Inventory (NPI) for 5 years.

Results: A total 1043 NPI assessments, representing 97% of all possible measurements of living cohort members, were analysed. Neuropsychiatric symptoms were common at baseline, and only a moderate increase in total NPS score from 15 to 17 with no increase in the proportion with high NPI total scores. Ninety seven percent scored ≥16, and 49% scored ≥36 on NPI total score at least once during follow-up. Individual NPS fluctuated and often reappeared. The most common symptoms ever reported was apathy (83%), depression (63%), appetite (63%), and aberrant motor behavior (60%). Cognitive decline was associated with higher NPI total score and several NPI items, but only the frequency of apathy increased significantly with time. Lewy body dementia was associated with higher NPI total score and psychotic symptoms. Alzheimer's disease was associated with increase in apathy.

Conclusions: Severe NPS are already common at time of dementia diagnosis, and the increase in overall severity over 5 years was moderate. Individual symptoms tend to fluctuate over time within patients and correspond to states rather than traits. These findings highlight the need to focus on, and plan for, NPS as part of dementia pathway, and are relevant for clinical trial design.

KEYWORDS

Alzheimer's disease, behavioral disturbances, dementia, depression: apathy, Lewy body dementia, longitudinal, Neuropsychiatric Inventory, neuropsychiatric symptoms, psychosis

1 | INTRODUCTION

Neuropsychiatric symptoms (NPS) are common and impactful features of dementia with key implications for patients' quality of life, carer burden, and societal costs.[1,2] Most studies of NPS (or behavioral and psychological disturbances in dementia) are cross-sectional, and the few longitudinal studies have mostly been performed in nursing home patients. Very few studies have explored the longitudinal course of NPS in patients with dementia from the time of diagnosis. Understanding the full course of NPS is important to inform patients and relatives about prognosis, to inform treatment decisions, and to optimize clinical trial designs and for health care planners. The Cache County study showed increase of NPS over 5 years but was limited by high attrition rate with less than 10% of patients participating after 5 years.[3] Another recent study[4] reported increased NPS during 36 months of follow-up; however, patients were excluded when institutionalized. Importantly, although the frequency and profile of NPS differ between dementia subtypes, most studies report NPS frequencies in all-cause dementia rather than in specific diagnoses.[3,5] Previously, we have published baseline frequency of NPS in Dementia

Study of Western Norway (Demvest), a cohort study of patients with mild dementia.[6] We here present the first reports of the NPS profile and frequency during 5 years in patients with mild dementia from time of diagnosis, reporting NPS in patients with Alzheimer's disease (AD) and Lewy body dementia (LBD) separately.

Key points

- Severe NPS were common already early in dementia.
- NPS were present in all patients with dementia, and severe NPS occurred in half of them.
- NPS were fluctuant, suggesting that NPS represent states rather than traits.
- Alzheimer's disease and Lewy body dementia differed in frequency and progression of NPS.

2 | METHODS

2.1 | Study design

The Dementia Study of Western Norway (Demvest) is a longitudinal cohort study with annual assessments of patients referred to dementia clinics in Hordaland and Rogaland counties. There are no other hospitals and none, or little, private health care for these patients. As previously described,[7] to reduce referral bias, the GPs in the area were contacted by letter prior to study start and invited to refer all patients with suspect dementia. All dementia diagnostic units (geriatric, neurology, and psychiatric) in the region recruited to the study and all residents are covered by the same National Insurance Scheme with restricted copayments allowing the representation of a general dementia population. After the main inclusion period between 2005 and 2007 ("mild dementia cohort" (MDC)), we continued to selectively recruit patients with LBD, ie, dementia with Lewy bodies and Parkinson's disease dementia to enhance the number of patients in this group. After screening 657 patients (Figure 1), 223 were included in the baseline consisting of 116 ADs, 87 LBDs, and 20 other dementia diagnosis (9 vascular dementia, 3 mixed AD and vascular, 5 frontotemporal dementia, and 3 alcohol-related dementia). We describe NPS in the MDC (n = 188), which represents a nonbiased reference cohort not including the additional LBD patients. The LBD cohort consisted of 69 probable and 2 possible dementia with Lewy bodies; we also included 16 Parkinson's disease dementia as there are no major differences between these diseases in long-term follow-up.[8] Alzheimer's disease cohort consisted of 102 probable and 14 possible AD patients.

2.2 | Inclusion criteria and follow-up assessments

Physical, neurological, and psychiatric examinations were performed, including a detailed neuropsychological test battery, Montgomery-Aasberg depression rating scale (MADRS) routine blood and CSF analyses, and brain MRI. Dopamine transporter SPECT scans were available for most patients with suspected dementia with Lewy bodies. Caregivers completed the Informant Questionnaire on Cognitive Decline in the Elderly (the IQCODE), a questionnaire shown to be a reliable and valid instrument to detect dementia, and the clinician completed the Clinician Dementia Rating (CDR) scale and the Hachinski Ischemia Scale.[9-11] Patients were defined as with dementia according to ICD 10,[12] and patients with Mini Mental Status Examination (MMSE) score of at least 20 or a CDR global score = 1 were included to represent a MDC. Exclusion criteria were no dementia or moderate or severe dementia, acute delirium, previous bipolar disorder or psychotic disorder, terminal illness, or recently diagnosed major somatic illness which according to the clinician would significantly impact on cognition, function, or study participation. The final clinical diagnosis was made according to the consensus criteria for dementia with LBD, PDD, and AD (NINDS-ADRDA) after a consensus meeting with 3 specialists including both geriatric psychiatry and geriatric medicine.[13-15] A pathological diagnosis was available for 56 patients in the Demvest cohort, showing diagnostic accuracy above 80% for both AD and LBD.[16] Patients were followed as outpatients with annual structured assessments including Neuropsychiatric Inventory (NPI) and MMSE. Pharmacological and nonpharmacological interventions followed national guidelines. Data are included only for the first 5 years of the study period because of reduced survival beyond 5 years. Complete medication data were only available at first follow-up. The diagnostic assessment is described in detail elsewhere.[7]

The vast majority of dropout was because of death (Figure 1), and only 12 patients were not examined during the year prior to death; of these, 9 reported other serious somatic illness (heart failure, cancer), 2 long travel time, and 1 for unknown reason. The number of patients who missed a single follow-up assessment was 3, 4, 3, 1, and 1 for each of the 5 follow-up assessments, respectively, leaving a highly representative sample with a total of 1043 NPI assessments (97% of all possible measurements).

2.3 | Assessment of neuropsychiatric symptoms

The validated Norwegian 12-question Neuropsychiatric Inventory was used to interview the family or caregivers.[17,18] The 12 items were registered as present and, if present, scored according to their frequency (1-4) and severity (1-3), and we report the *frequency* × *severity* score for the individual items representing the last 4 weeks. Neuropsychiatric Inventory items score is a product term of 2 ordinal scales with many of the NPI item scored as 0 (reflecting "not present"), along with a non-Gaussian distribution of the item score with an absence of the numbers 5, 7, 10, and 11. This resulting scale follows a nonparametric distribution. We used established cut-off item score of ≥4 as a point of determination of clinical significance, which includes a moderately severe symptoms at frequency rating of "often" or more frequently and "mild symptoms" present "very frequent," as previously reported.[4,19] Neuropsychiatric Inventory *total score* is summed to a maximum possible of 144, and we used NPI total score >36 as cut-off as suggested by others.[20,21]

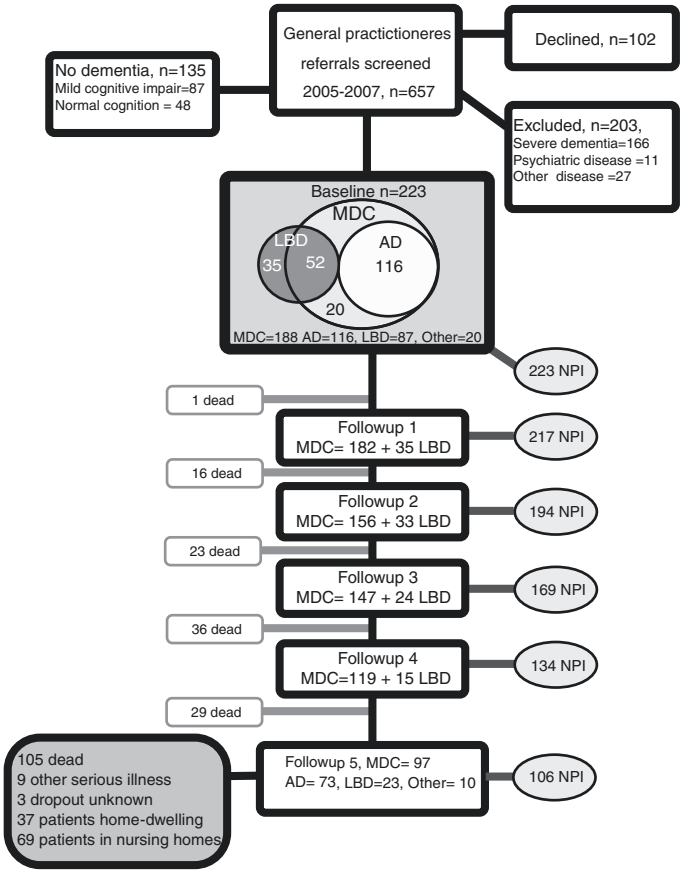

FIGURE 1 Flow chart of study design and data retrieval

2.4 | Statistics

Baseline characteristics of the cohort are presented as proportions, mean, or median values. Univariate comparisons of groups were made with Mann-Whitney *U* tests, Pearson chi-square tests, and Student's *t*-test, the latter in accordance with the results of the Welch test for variance. Because of the highly non-normal distributions of the NPI item scores with both considerable skew and zero inflation, the descriptive statistics are presented as present (item score ≥1), clinically significant (item score ≥4) and medians.

For each NPI item, we present the percentage of patients with score ≥1 (Digital supplement, DS 2 (found in the Supporting Information)) and ≥4 (Figure 2 and DS 2), as *NPI item frequency*. Item descriptive values from MDC are shown in Table 3 with risk of patient *ever* reporting symptom (item score *1* or *4* at any assessment). As an indicator of the stability of each item on an individual patient level, we calculated 12-month *persistency* (percentage of patients with items also present at next follow-up[5]) and *reoccurrence* (percentage of patients with reoccurring items, ie, item present at ≥2 follow-ups). These data are presented crude as recommended,[5,22] not adjusted for missingness or mortality.

For multivariate analysis, the NPI items were collapsed to binary (NPI items ≥4, details DS 1 (found in the Supporting Information)) or ordered categories (NPI-total, details in Table 2) prior to being entered as dependent variables for analysis in mixed effects models. A random intercept or random intercept-random slope model was fitted, in accordance with the Bayesian information criterion, which was also used to select the optimal covariance matrix. Age, gender, time, and diagnosis (AD versus LBD) were included as fixed covariates, while MMSE, transformed to normality by the square roots of its errors (30 − MMSE), was included as a time-changing covariate, measured at each occasion allowing for odds ratio (OR) estimation. All statistical analyses were performed using SPSS version 23 (IBM SPSS Statistics for Windows, version 23.0, Armonk, NY: IBM Corp.) and Stata 15 (StataCorp. 2017, Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC).

2.5 | Ethical issues

The study was approved by the regional ethics committee (2010/633) and the Norwegian authorities for collection of medical data and received financial support from the regional health authorities of western Norway, Helse Vest. All data were handled and kept in accordance with national health and data privacy protocol.

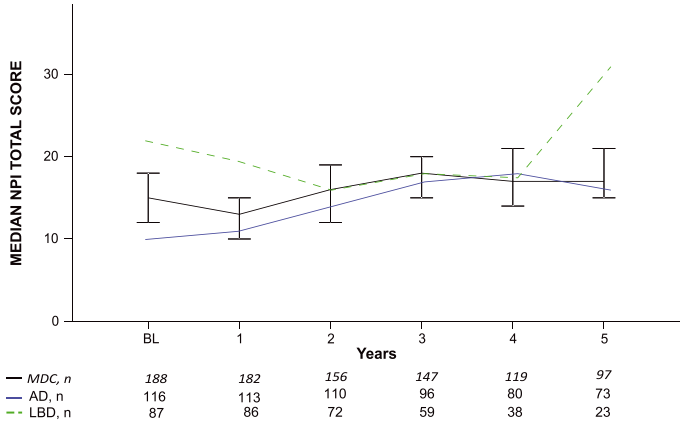

FIGURE 2 Course of Neuropsychiatric Inventory total scores in mild dementia cohort, Alzheimer's disease, and Lewy body dementia for 5 years. NPI, Neuropsychiatric inventory; MDC, Mild dementia cohort (black); AD, Alzheimer's disease (blue); LBD, Lewy-body dementia (green); n, number of patient at assessments. Error bars show 95% confidence interval [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

Cohort characteristics are shown in Table 1. The LBD and AD groups did not differ regarding age and baseline MMSE score, but there were more females in the AD group, while LBD had longer disease duration. As previously described,[23] the mean decline on MMSE was 2.1 points/year, from 23.8 at baseline to 13.3 at year 5, and at the fifth follow-up 105 of the 223 patients had died (Figure 1). At baseline, only 1 patient (with frontotemporal dementia) resided in a nursing home, while 65% of the participants resided in nursing homes at year 5. At first follow-up, 61% used antidementia drugs, 9% used antipsychotic, and 40% used antidepressants.

3.1 | Mild dementia cohort

3.1.1 | NPI total

The median NPI total score overall increased marginally from 15 at baseline to 17 at year 5 (Figure 2). Using a mixed effects model proportional odds model, we found that time had a significant effect on NPI total (OR 1.70, $P < .001$, Table 2). When adjusted cognitive decline (OR 1.47, $P < .001$) in model 2, the effect of time disappeared. The frequency NPI total score ≥36 was stable at 20% during the 5 years. The proportion of patients with ≥12 increased with time from 55% to 68%, and there was a decline in patients with <4 NPI total score from 37% to 25% (Figure 3). Nearly all (97%) patients had a NPI total score ≥16 *ever*, and half of the patients (49%) had a NPI total score ≥36 *ever* during the study period.

3.1.2 | NPI items

The percentage of patients with item score ≥4 at each assessment is presented in Figure 4 (numerical in DS 2). Apathy was the most common item (83%) at each assessment with high stable annual frequency (37%-48%), while 9 of the 12 items had stable crude frequency around 25% (Figure 4, DS 2). Cognitive decline was associated with a higher probability of delusions, hallucinations, agitation, apathy, and aberrant motor behavior, all with small effect sizes (ORs of 1.5-2, $P = .009$-<.001, DS 1). Females were more at risk for delusions (OR 2.4, $P = .008$) and anxiety (OR 2.3, $P = .006$), but less at risk for apathy (OR 0.46, $P = .002$). Time in itself, when adjusted for cognitive decline, showed no significant effect on items, with the exception euphoria/elation which was infrequent (Figure 4, DS 2).

Apathy was also the symptom most often *ever* reported (83%) in follow-up; other common items were depression (63%), appetite (63%), and aberrant motor behavior (60%, Table 3). The item profile was similar in using ≥1 and ≥4 as the cut-off. Persistency of a symptom (present at next follow-up) ranged from 53% to 74%, but declined when cut-off was raised to ≥4 (35%-59%). Reoccurrence of a symptom (present at any 2 follow-ups) increased from 34% to 84% to 57% to 86% when cut-off was raised from ≥1 to ≥4, respectively.

TABLE 1 Baseline characteristics

	Alzheimer's disease (n = 106)		Lewy body dementia (n = 97)					
							t/z	*P*
Age (mean, SD)[a]	75.3	7.8	75.3	7.8	75.2	7.2	0.05	.957
Female percentage[b]	71%		46%		45%		−3.97	<.001
Years of education (mean, SD)[a]	9.6	2.9	9.8	2.9	9.7	2.8	−0.22	.826
Years of symptoms (mean, SD)[a]	2.2	2.2	1.9	1.8	2.7	2.1	−2.73	.007
MMSE score (mean, SD)[a]	23.7	2.4	23.7	2.2	23.7	3.1	−0.28	.774

AD; Alzheimer's disease; LBD; Lewy body dementia; MMSE; Mini Mental State Examination; SD; standard deviation.

[a]Student's *t*-test showing *t*-score for AD and LBD.

[b]Mann-Whitney *U* test, showing *z*-score for AD and LBD.

TABLE 2 Neuropsychiatric symptom total score, Lewy body dementia, and cognitive decline[a]

	Model 1					Model 2				
	LBD and Covariates[a]					LBD, Covariates, and MMSE Decline[b]				
Fixed eff.	OR	SE	*P*	LLCI	ULCI	OR	SE	*P*	LLCI	ULCI
Age	1.04	0.02	.238	1.01	1.07	1.01	0.02	.352	0.98	1.04
Female	0.93	0.23	.750	0.57	1.49	0.93	0.22	.754	0.58	1.48
Time	1.70	0.09	<.001	1.53	1.89	1.01	0.06	.908	0.89	1.14
LBD	2.58	0.62	<.001	1.61	4.11	1.79	0.43	.015	1.12	2.86
MMSE[c]						1.47	0.14	<.001	1.22	1.77

Proportional odds model with random slope and intercept. NPI-total collapsed into 4 categories (0 = no symptoms, 0-16 = mild, 17-30 = moderate, >30 = severe, based on frequencies, even membership). Random effects not shown.

OR, odds ratio; SE, standard error; *P*, *P* value; LLCI, lower level confidence interval; ULCI, upper level confidence interval; eff, effects; LBD, Lewy body dementia; MMSE, Mini Mental State Examination.

[a]NPI total as ordinal with age, gender, time (linear), and LBD.

[b]Same model as above, but with MMSE decline as a time-varying covariate.

[c]Transformation with √(30 − MMSE).

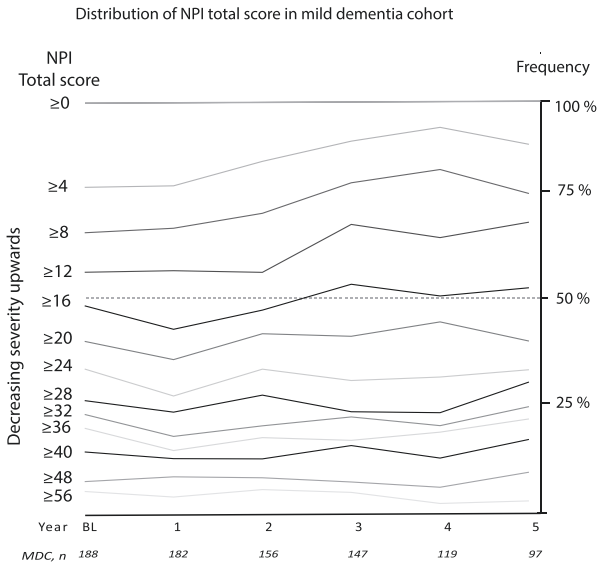

FIGURE 3 Frequency of different Neuropsychiatric Inventory total scores in mild dementia cohort

3.2 | Comparison between AD and LBD

3.2.1 | Total NPI score

Lewy body dementia patients had a higher NPI-total score (OR 2.58, *P* < .001) over 5 years; this association was reduced when adjusted for cognitive decline (OR 1.79, *P* = .015), which is steeper in LBD patients in this cohort[23] (Table 2). The difference between LBD and AD was most pronounced during the first years, but there were only 23 LBD patients alive in the study at year 5 (Figure 2).

3.2.2 | NPI item frequency

The frequency of NPI item scores ≥4 for LBD and AD is presented in Figure 2 and Table DS5. Lewy body dementia had stable and significant higher frequency of hallucinations with a large effect size (OR 6.8, *P* < .001, DS 1). The association between LBD and increased frequency of delusions and apathy was similar, with moderate effect sizes (OR 2.9, *P* < .001 and 2.6, *P* = .006), although the association between LBD and apathy decreased with time (OR 0.65, *P* < .001) with concurrent increase in AD. The likelihood of *ever* experiencing apathy was similar between AD and LBD, while the likelihood of hallucinations (AD 24%, LBD 66%) and delusions (AD 41%, LBD 53%) were higher in LBD than AD (Table 3).

4 | DISCUSSION

4.1 | Summation of findings

This is one of the first studies following a cohort of both AD and LBD from the diagnosis of mild dementia and 5 years onward with

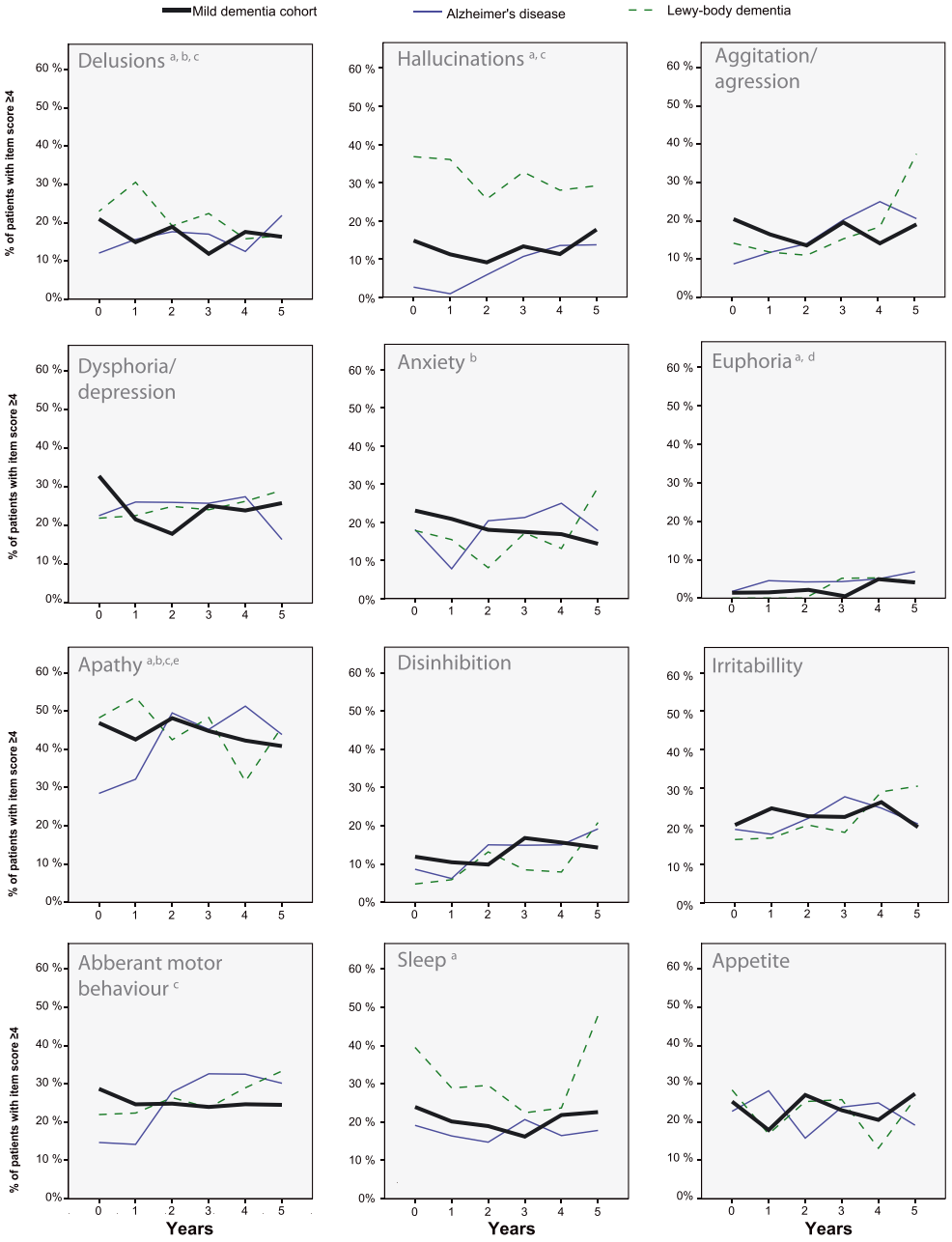

FIGURE 4 Frequency Neuropsychiatric Inventory items ≥4 for 5-year follow-up. NPI, Neuropsychiatric inventory; MDC, Mild dementia cohort (n = 188, black); AD, Alzheimer's disease (n = 116, blue); LBD, Lewy-body dementia (n = 87, green). Note: MDC includes 116 AD, 52 LBD and 20 other dementia patients [a-e]denotes *p*-value < 0.05 for probability of symptoms in multivariate analysis in [a]DLB, [b]female, [c]cognitive decline, [d]time, [e]LBD with time [Colour figure can be viewed at wileyonlinelibrary.com]

annual assessments of NPS and low attrition rate. There was only a moderate increase in NPI total score from 15 to 17 during the study period and no increase in the proportion with high NPI total scores. Neuropsychiatric symptoms are present in all patients with dementia and severe NPS occurred in nearly half of them. Cognitive decline was associated higher NPI total score and several NPI items, but only the frequency of apathy increased significantly with time, and only for AD. Patients with LBD had higher NPI

TABLE 3 Full Neuropsychiatric Inventory item descriptive from all years

	Mild Dementia Cohort (n = 188)							AD	LBD	AD	LBD	AD	LBD
	Ever		Persistency		Reoccurrence		Median	Ever >1		Ever >4		Median	
NPI item	>1	>4	>1	>4	>1	>4							
Delusions	64%	44%	53%	50%	59%	72%	4	59%	75%	41%	53%	4	6
Hallucinations	52%	35%	69%	57%	63%	71%	4	40%	89%	24%	66%	4	4
Agitation/aggression	68%	44%	53%	56%	66%	78%	4	68%	60%	40%	43%	3	4
Dysphoria/depression	89%	63%	64%	59%	83%	86%	3	88%	94%	66%	61%	3	3
Anxiety	75%	49%	51%	40%	65%	78%	3	74%	74%	51%	41%	3	3
Euphoria	22%	11%	59%	28%	34%	57%	3	25%	14%	14%	7%	4	3
Apathy	91%	83%	64%	43%	82%	85%	6	91%	93%	82%	84%	6	6
Disinhibition	61%	37%	55%	50%	66%	80%	3	59%	55%	36%	23%	3	2
Irritability	76%	53%	55%	45%	71%	86%	4	76%	72%	50%	46%	4	4
Aberrant motor behavior	67%	60%	74%	35%	59%	66%	6	69%	66%	60%	59%	6	6
Sleep	65%	53%	48%	40%	61%	70%	6	58%	80%	47%	66%	6	6
Appetite	71%	63%	42%	31%	59%	62%	6	70%	67%	62%	57%	6	6

Ever is frequency of patients to have 1 or more item score (≥1 or ≥4) throughout study. Persistency is the frequency item score (≥1 or ≥4) present next follow-up (12 months). Reoccurrence is the frequency of patients having the same symptom at several assessments if present once. Median is calculated from those with positive screening question at assessments.

NPI, Neuropsychiatric Inventory; MDC, mild dementia cohort (n = 188); AD; Alzheimer's disease (n = 116); LBD, Lewy body dementia (n = 87).

total score and more hallucinations than AD patients throughout the study.

4.2 | Strengths and limitations

Our data may have potential recruitment bias because of referrals of primary care patients, which may have led to an increased number of patients with complicated dementia or NPS. However, GPs were invited to refer any patients with suspected dementia, and patients were included from psychiatric, neurologic, and geriatric clinics. Mild dementia was defined as CDR = 1 or MMSE of 20 or more. Mini Mental Status Examination is language and memory dominant and thus less sensitive to the earliest changes in the LBD patients, which included both PDD and DLB, although the sensitivity of MMSE is comparable to other screening instruments when approaching moderate dementia levels.[24] Because of the naturalistic design, patients were treated according to recommendations for pharmacological and nonpharmacological treatment which likely influence the course of NPS, but because treatment was not standardized in the study, individual treatment differences may have influenced the course of NPS. We used the NPI to assess NPS, which does not capture the full spectrum of NPS and is entirely based on carer report and thus not subjective experience of the patients. Finally, because of high mortality, only half of the patients completed the 5-year follow-up. There was an expected high mortality, particularly in LBD,[25] which may have confounded the observed course of NPS.

Strengths of the study include the long follow-up time, annual assessments with structured instruments, and the very high completeness of data except attrition because of death, which allowed for persistency and reoccurrence analysis from mild to severe dementia. This is also 1 of the largest long-term studies of NPS in LBD. The diagnostic procedures were rigorous, and high accuracy was demonstrated in the 56 cases with neuropathological diagnosis.[16]

4.3 | High NPS scores are common also in early dementia

Neuropsychiatric symptoms are generally assumed to increase with severity,[26] and the observed stable frequency of high NPI total scores early in disease is therefore important. Neuropsychiatric symptoms are strongly associated with key outcome variables such as caregiver distress, quality of life,[27] and hospitalization.[28] A quarter of the patients at any time had NPI total score >36, which is above the score considered in need of antipsychotic drug treatment in trials.[20,21] Previous longitudinal studies have reported that NPS increase over time,[5,29] and are associated with duration of disease[22] and time.[30] Our finding that NPS are associated with cognitive decline is also consistent with other studies.[30-32] However, this increase is small, and likely of minor clinical relevance. Recently, Brodaty et al[4] showed an increase in NPS with dementia progression, but in a cohort with only 1.9% LBD, and where atypical antipsychotics were used by 21%, suggesting difference compared our study in both selection and treatment.

The high follow-up rate and attempts to include all patients with newly diagnosed dementia in the defined geographical area lend support to our findings that NPS is prevalent already early in dementia. The heterogeneity of the studies of NPS makes meta-analysis difficult and introduces referral bias also in reviews.[5] All patients in this study received standard treatment to the best of current practice, including reassessment and interventions if needed, and participants with severe NPS have likely received pharmacological and nonpharmacological intervention which could affect NPS. The presence of severe NPS early in dementia is thus an important finding with clinical and health economic consequences.

4.4 | NPS are highly frequent throughout dementia

Our observations that NPS are very common in dementia through the 5-year course after diagnosis extend previous reports. Half of

dementia patient experienced severe NPS (NPI total ≥ 36). Our reported *ever* scores are consistently higher than 5-year prevalence score reported in the Cache County study,[3] and with higher completeness of data. There were few deaths during the first years of the study, allowing for quite complete dataset of early dementia. Apathy is the most frequent item overall, which is different from other studies showing depression as most frequent.[3,5,31,33] The clinical distinction between apathy and depression, especially in more severe dementia is challenging,[34] and our ≥4 cut-off may also favor a consistent symptom as apathy in the NPI item score.

Stable factors such as diagnosis and gender were more important risk factors for NPI than further cognitive decline after the diagnosis of dementia and study inclusion, indicating that NPS do not solely arise secondary to cognitive decline.

4.5 | Symptoms fluctuate and relapse

The frequency of each item is in line with a comparable longitudinal study,[4] showing stable frequency of many NPI items. The persistency of items reported in our study is higher than reported in most studies,[5] but consistent with studies of longer duration.[35] Patients had ongoing follow-up all year at demand as hospital outpatients, while the 12-month persistency reflect assessments assumed to be in clinical stable condition with minimal referral bias and representative of current clinical practice.[26] To describe the dynamics of NPS, we report a reoccurrence rate, and with the narrow time span of NPI (4 weeks out of 52), the actual relapse of symptoms is probably higher. The persistency and reoccurrence still demonstrate fluctuant symptoms, suggesting that NPI items represent states rather than traits. The lower risk of not being present at next assessment (lower persistency) and the higher risk of symptom relapse (*reoccurrence*) for item scores ≥4 rather than ≥1 suggest better precision when assessing need for clinical intervention when using the ≥4 cut-off.

4.6 | Difference between AD and LBD

Diagnosis has considerable effect on NPS frequency. Few longitudinal comparative studies exist, and our findings show that these differences tend to decrease with increasing severity of disease. For example, apathy tended to increase in AD but not LBD. This may explain why other studies have not reported NPS differences between AD and LBD.[29] On the other hand, hallucinations had consistently higher frequency in LBD than AD, in line with data from previous longitudinal studies with shorter duration.[36] Hallucinations are associated with more severe cognitive decline and early institutionalization, and thus is a key NPS. Unfortunately, there is no systematic evidence regarding how to treat hallucinations in dementia with Lewy bodies,[26] although pimavanserin, a 5HT2a inverse agonist, has demonstrated positive effects on psychosis in Parkinson's disease and may represent a potential candidate also in LBD.[37] A large Taiwanese study reported more frequent and more severe depression in dementia with Lewy bodies compared to AD using DSM-4 diagnosis, with largest difference in symptoms such as anhedonia and fatigue.[38] We report more depressive symptom with higher MADRS score at baseline, higher apathy in LBD early in course, and overall more sleep disturbances in LBD, but NPI item depression did not show any difference between groups. Difference in severity of early NPS and profile of depressive symptoms may indicate need for different diagnostic and treatment strategies for NPS in AD and LBD.

4.7 | Implications

The high frequency of severe NPS throughout the 5-year period highlights the need for health service planning to address NPS from time of dementia diagnosis. Disease-related differences in NPS profile and course underline the importance of careful diagnosis in studies. The high reoccurrence rate suggests that clinical intervention at first time occurrence of symptoms may be appropriate and the fluctuations of symptoms suggest vigilance in effect evaluation and clinical trial design. Neuropsychiatric symptoms are an integrated part of dementia and need tailored and dynamic nonpharmacological management[26] throughout disease course. Clinical trials on NPS in dementia with Lewy bodies are a priority. Informing health care providers and raising public awareness on the early occurrence of NPS and its management are crucial.

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CONFLICT OF INTEREST

Audun Vik-Mo and Lasse Giil declare that they have no conflict of interest. Clive Ballard has received grants and personal fees from Acadia and Lundbeck and personal fees from Heptares, Roche, Lilly, Otsuka, Orion, GSK, and Pfizer. Dag Aarsland has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, and GE Health and serves as paid consultant for H. Lundbeck, Eisai, and Axovant.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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DS1. Neuropsychiatric symptom items: Alzheimer's disease versus Lewy-body dementia[a]

	Delusions[b]		Hallucinations[b]		Agitation[c]		Depression[b]		Anxiety[c]		Euphoria[d]	
	OR	p	OR	P	OR	P	OR	p	OR	p	OR	P
Age	1.04	0.097	1.01	0.644	1.06	0.010	0.98	0.106	0.97	0.126	1.28	0.030
Female	**2.44**	0.008	0.99	0.980	0.65	0.203	1.33	0.189	**2.28**	0.006	1.48	0.035
Time	0.87	0.114	1.05	0.524	1.10	0.276	0.95	0.398	1.03	0.761	**1.29**	<0.001
MMSE	**1.70**	<0.001	**1.47**	<0.001	1.41	0.019	1.19	0.089	1.14	0.321	1.17	0.080
LBD	**2.88**	0.001	**6.86**	<0.001	1.08	0.837	1.17	0.467	1.08	0.799	**1.80**	0.001
	Apathy[c]		Disinhibition[c]		Irritability[c]		Motor[c]		Sleep[c]		Appetite[c]	
	OR	p	OR	P	OR	P	OR	p	OR	p	OR	P
Age	1.01	0.568	1.05	0.075	1.03	0.174	0.99	0.369	1.03	0.231	1.01	0.933
Female	**0.46**	0.002	0.85	0.698	0.92	0.823	1.83	0.032	0.63	0.171	1.26	0.321
Time	1.19	0.024	1.37	0.051	1.05	0.680	1.08	0.416	0.92	0.459	0.89	0.141
MMSE	**1.31**	0.009	1.30	0.146	1.24	0.148	**1.75**	<0.001	1.12	0.411	1.13	0.268
LBD	**2.64**	0.006	0.70	0.401	0.84	0.623	1.53	0.119	**2.25**	0.012	1.04	0.862
LBD*T	**0.65**	<0.001										

Abbreviations: OR; odds ratio, p; p-value, MMSE; transformed to $\sqrt{(30 - MMSE)}$, LBD; Lewy-body dementia T; Time.

[a] Mixed effects logistic regression, NPI items ≥ 4.

[b] Random intercept model

[c] Random intercept, random slopes model

[d] Fixed effects model

DS2: NPI Item frequency of both ≥1 and ≥4 at each assessment in mild dementia cohort

Year	BL		1		2		3		4		5	
NPI-item	≥1	≥4	≥1	≥4	≥1	≥4	≥1	>4	≥1	≥4	≥1	≥4
Delusions	27 %	16 %	29 %	19 %	33 %	20 %	34 %	18 %	30 %	13 %	31 %	21 %
Hallucinations	21 %	12 %	21 %	11 %	26 %	12 %	31 %	17 %	23 %	12 %	28 %	15 %
Agitation/aggression	29 %	14 %	27 %	13 %	34 %	16 %	38 %	19 %	43 %	26 %	44 %	24 %
Dysphoria/depression	58 %	24 %	54 %	25 %	52 %	25 %	56 %	25 %	57 %	26 %	51 %	20 %
Anxiety	41 %	19 %	30 %	12 %	37 %	16 %	37 %	20 %	39 %	21 %	39 %	21 %
Euphoria	4 %	1 %	4 %	3 %	8 %	3 %	9 %	4 %	8 %	4 %	12 %	8 %
Apathy	53 %	37 %	61 %	41 %	58 %	46 %	57 %	44 %	56 %	48 %	56 %	43 %
Disinhibition	24 %	10 %	27 %	7 %	29 %	17 %	30 %	14 %	33 %	17 %	39 %	23 %
Irritability	41 %	24 %	37 %	18 %	38 %	24 %	46 %	25 %	41 %	26 %	42 %	25 %
Abb motor behavior	26 %	16 %	22 %	17 %	31 %	26 %	39 %	30 %	37 %	30 %	42 %	32 %
Sleep	36 %	26 %	28 %	19 %	30 %	19 %	29 %	22 %	30 %	19 %	27 %	21 %
Appetite	36 %	26 %	32 %	21 %	28 %	22 %	33 %	28 %	30 %	24 %	27 %	21 %

Each item's frequency at each assessment for both present (≥1) and ≥4 presented in Figure 3. Number of patients (*n*) shown in Figure 1.

II

III

Methodological supplements article 3

Sampling and characterisation of post-mortem brain samples

Brain dissection, macroscopic description, regional sampling, tissue processing and staining were done following standard protocols including BrainNet Europe and Brains for Dementia Research UK [1-6]. Block taking for histological and immunohistochemical studies and neuropathological assessment of neurodegenerative and control cases was performed in accordance with published guidelines [1-4, 7-9]. For histology, 7µm thick sections were cut and stained with hematoxylin and eosin (H&E) and selected blocks also with Luxol fast blue/Nissl (LFB/Nissl) for first stage neuropathological assessment of cytoarchitecture and basic cytopathology (for example the presence of Lewy bodies), extent and neuroanatomical distribution of neuronal and myelin loss, and selection of tissue blocks for detailed immunohistochemical analysis.

Immunohistochemistry

Briefly, 7 µm-thick paraffin sections were routinely de-waxed, blocked for endogenic peroxidase activities in ethanol containing 1.5% (v/v) H2O2, and heat-treated in appropriate antigen retrieval buffer solutions using a household electronic pressure cooker. After protein blocking in 50 mM TRIS-buffered saline (TBS pH 7.4) containing 5% (w/v) low fat milk powder, the sections were incubated with the primary antibodies at room temperature for 70 min. Detection was performed using Novolink polymer kit (Leica Biosystems/Novocastra), and nuclear staining was carried out with Mayer's hematoxylin. For primary goat antibody, rabbit anti-goat linker IgG (GenWay Biotech), for primary rat antibody, rabbit anti-rat linker IgG (Vector Laboratories) were used.

Immunostaining (location and intensity) was examined by a consultant neuropathologist and the intensity and frequency of respective nuclear and of

cytoplasmic staining assessed scored using the following standard semiquantitative scale: 0 - no staining, 1 - mild staining, 2 - moderate staining and 3 - intense staining.

Antibodies

Primary antibodies dilutions used in this study are as follows: mouse monoclonal anti-amyloid-β (Agilent/DAKO)(1:100), rat monoclonal anti-phospho-TDP-43 (Ser 409/410)(Merck/Millipore)(1:100), rabbit polyoclonal anti-phospho TDP-43 (pSer409/410-1)(Cosmo-Bio)(1:1000), mouse monoclonal anti-phospho-tau (Ser 202/Thr205) (ThermoFisher/Invitrogen) (1:100), goat polyclonal anti-α-synuclein (R&D Systems)(1:1.000), mouse monoclonal anti α-synuclein (clone 5G4)(Roboscreen)(1:2.000), mouse monoclonal anti-p62 (lck ligand)(1:200)(BD Biosciences), rabbit polyclonal anti-ubiquitin (DAKO)(1:1.000). Fixation time varied considerably in our cohort which may have affected immunoreactivity, especially regarding α-synuclein. Therefore, we applied two α-synuclein antibodies when immunoreactivity was unequivocal or inconsistent with findings on, HE and p62 (which was applied when primary immunohistochemical work-up was negative or immunoreactivity questionable).

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