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RESEARCH ARTICLE

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Neuropsychiatric symptoms and comorbidity: Associations with dementia progression rate in a memory clinic cohort

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Abstract

Objectives: Neuropsychiatric symptoms (NPS) are associated with dementia severity and progression rate. NPS clusters have different neurobiological underpinnings; therefore, their effect on dementia progression may differ. Furthermore, little is known about whether individual comorbidities affect progression rate. We investigated the effect of NPS clusters and individual comorbidities on dementia progression.

Methods: A memory clinic cohort with all-cause dementia ($N = 442$) was followed for up to 3 years from diagnosis. Previously, we found trajectory groups of dementia progression in this cohort: one with slow progression and two with rapid progression. In the present study, using principal component analysis, three symptom clusters of NPS were identified on the Neuropsychiatric Inventory Questionnaire (NPI-Q): agitation, affective and psychosis symptom clusters. Data regarding comorbidity were collected by linkage to the Norwegian Patient Registry. Multinomial logistic regression was applied to explore the association between NPS clusters and comorbidity with trajectory-group membership.

Results: Adjusted for demographics, dementia aetiology, comorbidity and cognition, we found that, at the time of dementia diagnosis, for every point within the psychosis symptom cluster of the NPI-Q, the risk of rapid progression increased by 53%; for every point within the affective symptom cluster, the risk of rapid progression increased by 29%. A previous diagnosis of mental and behavioural disorders (excluding dementia) decreased the risk of rapid dementia progression by 65%.

Conclusions: Psychosis and affective symptom clusters at the time of diagnosis were associated with rapid progression of dementia. Previous diagnoses of mental and behavioural disorders (excluding dementia) were associated with slow progression.

KEYWORDS

comorbidity, dementia, neuropsychiatric symptoms, progression

Key points

- Psychotic and affective symptom clusters at the time of diagnosis were associated with rapid progression of dementia
- Previous diagnoses of mental and behavioural disorders (excluding dementia) were associated with slow progression of dementia
- In dementia, individual assessments and follow-up protocols are essential

1 | INTRODUCTION

Dementia disorders are characterized by cognitive and functional decline, and many patients with dementia have neuropsychiatric symptoms (NPS)[1] and comorbidities[2] that may influence progression. Worldwide, approximately 50 million people suffer from dementia[3] and the global prevalence is increasing.[3] Understanding the factors associated with rapid progression is important not only for designing intervention studies but also for ensuring optimal follow-up protocols and quality of life for patients.

We lack robust methods for predicting the progression rate of dementia, preventing us from providing accurate prognoses to patients. Several risk factors have been associated with rapid dementia progression, but comparisons across studies are hampered by the differences in population, the statistical methods used, and the risk factors assessed.[4] Additionally, dementia is often multifactorial,[5] and the progression rate is likely to be affected by multiple components. However, studies typically evaluate risk factors separately, and few assess the effect of multiple determinants.

NPS are common in all dementia aetiologies and can be present at every stage of cognitive decline.[6,7] They have been associated with impairment in activities of daily living,[8] nursing home admission,[9] decreased quality of life,[10] greater caregiver burden [11] and increased informal care costs in dementia.[12] Previous progression studies link more-severe NPS with rapid progression of Alzheimer's disease (AD)[13,14] but also with more-advanced stages of dementia.[15,16] Notably, various NPS tend to cluster, indicating correlation and, possibly, shared pathology within symptom clusters.[15,17]

The number of comorbidities affecting an individual could affect the dementia progression,[18,19] at least at short-time follow-up. However, specific comorbid diseases might have distinct associations with the dementia syndrome and, thereby, may influence progression rates differently.[20] For instance, a history of hypertension or congestive heart failure has been associated with slower cognitive decline,[21] whereas a history of diabetes has been associated with slower functional and cognitive decline.[14,21] Additionally, a history of hypertension or psychiatric disorders has been associated with more NPS at the time of dementia diagnosis,[21] and the number of comorbidities might also be associated with more-severe NPS.[22] The effect of cerebrovascular comorbidities on dementia progression is not clear.[5,21,23]

We seek to increase the knowledge about distinct predictors of dementia progression by building on previous results where we found that more-severe overall NPS, but not the number of comorbidities, were associated with rapid progression of all-cause dementia in a memory clinic cohort.[24] Due to the clustering of NPS, together with differences seen in relation to neuropathology and dementia severity,[6], [7] we hypothesize that NPS clusters are valuable predictors of dementia progression rates. By including comorbidity data from the Norwegian Patient Registry,[25] we also evaluated the effect of specific comorbidities present before and at the time of the dementia diagnosis. We hypothesize that individual comorbidities will have different effects on the dementia progression rate. The findings may improve future planning for patients, and their caregivers, and may facilitate the selection of patients eligible for intervention studies.

2 | MATERIAL AND METHODS

2.1 | Subjects

The study population has been described in greater detail.[24] In brief, the patients were included in the Norwegian registry of persons assessed for cognitive symptoms (NorCog) between 12 January 2009, and 31 July 2016, at the Memory Clinic, Oslo University Hospital, were diagnosed with dementia and received at least one follow-up examination after the baseline period (6 months; number of patients [N] = 442). We restricted the follow-up period to 3 years to limit survival bias, and the participants were followed for an average of 2.2 years (standard deviations [SD] 1.5).

All participants signed an informed consent form; the project was approved by the Regional Ethics Committee (2015/1510 REK vest) and was conducted in accordance with the Helsinki Declaration.

2.2 | Assessments

Examinations were part of the standard practice at the clinic, and patients underwent an average of 3.5 (SD 1.7) consultations with varying time intervals. As a measure of cognitive and functional impairment, the Clinical Dementia Rating Scale (CDR)[26] was scored post hoc by the researchers, using all available information from the patients' records. Based on the severity of cognitive decline, a score of 0–3 was assigned within the following categories: memory, orientation, judgement and problem-solving, community affairs, home and hobbies and personal care.

2.3 | Diagnostic workup

At baseline, the NorCog research protocol[27] was used to assess the patients.[24] In summary, the NorCog protocol includes information on demographics, comorbidities, medication use, dementia symptoms, physical examination and blood sampling. The protocol also includes cognitive test results, for example, the MMSE[28] (0–30; lower values indicate greater cognitive impairment) and the Trail Making Test A (TMT-A)[29] and B (based on age-adjusted cut-off of −2 SD[30]); the Clock Drawing Test; the Consortium to Establish a Registry of Alzheimer's Disease 10-item word list and figure copying; the Controlled Oral Word Association Test; and the 15-item version of the Boston Naming Test. Magnetic resonance imaging brain scans were available for most of the cases, and positron emission tomography and single-photon emission computed tomography were available for selected cases. For 198 of the patients, the results of cerebrospinal fluid core biomarkers amyloid β42, total tau, and phosphorylated tau181 (P-tau) were used to aid the diagnoses.

All-cause dementia, AD and aetiologically mixed AD were diagnosed according to the National Institute on Aging and the Alzheimer's Association diagnostic criteria.[1] Further aetiological dementia diagnoses were made according to clinical diagnostic criteria for dementia associated with Parkinson's disease,[31] the revised criteria from the Fourth consensus report of the Dementia with Lewy Bodies Consortium,[32] the international consortium revised guidelines for the diagnosis of behavioural variant frontotemporal dementia[33] and the classification of primary progressive aphasia.[34] The cause of dementia was denoted as 'other' if none of the aetiological criteria were present. The diagnoses were made post hoc by one of the researchers (an experienced clinician) using all available information from the patients' records. In uncertain cases, two of the other researchers were consulted ($N = 61$).

At the baseline examination, the Neuropsychiatric Inventory Questionnaire (NPI-Q),[35] a brief questionnaire version of the Neuropsychiatric Inventory, was used to assess NPS.[36] The NPI-Q severity score (0–3; a higher score indicates a more-severe symptom) of the 12 NPS was included. These symptoms were as follows: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, night-time behaviour and appetite/eating disturbances. For participants with two or more missing items, the NPI-Q was set to missing ($N = 39$).

By regulation, the specialist health care service in Norway[25] must register diagnoses in the Norwegian Patient Registry according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes.[37] We selected the disease categories of interest based on the results of a systematic review[38] including those categories listed in the NorCog protocol.[27] For each patient, we searched both the NorCog and the Norwegian Patient Registry (from 1 January 2008 up until baseline) for comorbidities (present or absent) within the 12 selected disease categories (Table 2). If a comorbidity was registered in either of these registries, it was denoted as present. The comorbidities were registered up to 7 years prior to baseline, but because of the chronic nature of the conditions, they were assumed to have been present at the time of the dementia diagnosis.

2.4 | Outcome measures

We have previously described the scoring of the CDR scales and the selection of trajectory groups in this cohort.[24] In summary, the CDR scales were scored post hoc by a certified rater using all available information from standardized and comprehensive patient records. Using group-based trajectory modeling,[39] we identified three trajectory groups of dementia progression based on changes in CDR-sum of boxes (CDR-SB).[40] The selection of the number and shapes of trajectory groups was based on the Bayesian information criterion, the posterior probability of group membership, the odds of correct classification and class size. The findings were as follows: Group 1 progressed slowly and had the best global functioning at baseline; Group 2 progressed more rapidly and had poorer global functioning at baseline; and Group 3 progressed the fastest and had the worst global functioning at baseline (Table 1).

2.5 | Statistical analyses

Analyses were performed using Stata/IC 15.1 (StataCorp LLC2018, Stata Statistical Software, revision 17 December 2018, College Station, TX77845USA) and SPSS version 26. Summary statistics of the baseline characteristics were compared using one-way ANOVA, Kruskal–Wallis or Chi-square x^2 as appropriate. The annual changes in the CDR-SB were compared with a linear mixed model with interaction on time.

2.6 | Factor analysis

To identify NPS clusters, principal component analysis was applied to the 12 items of the NPI-Q scale, with a patient-symptom severity ranging from 0–3, using SPSS version 26. The correlation matrix revealed coefficients above 0.3.[41] The sampling adequacy, using Kaiser-Meyer-Olkin = 0.827 and Bartlett's Test of Sphericity at the significance level $p < 0.001$, supported the factorability of the correlation matrix. Due to somewhat weak correlations between some of the factors (range 0.459–0.855) and in order to facilitate interpretation, varimax rotation was chosen. The number of components was selected by combining Kaiser's criterion of eigenvalues, Cattell's scree test, and alpha factoring. Three factors explaining 51% of the variance were identified: Factor 1 (agitation symptom cluster) comprised the items elation/euphoria, disinhibition, agitation/aggression, irritability/lability and motor disturbance (32% of the variance explained, Cronbach's alpha 0.70); Factor 2 (affective symptom cluster) comprised the items anxiety, depression/

TABLE 1 Descriptive statistics of all the patients and by trajectory groups

Variables	All (N = 442)	Group 1 (N = 195)	Group 2 (N = 153)	Group 3 (N = 94)	Group comparison *p* value
Age in years, mean (SD)	70.5 (8.1)	69.7 (7.9)	71.3 (7.6)	70.7 (9.0)	0.182[a]
Female, N (%)	225 (50.9)	89 (45.6)	84 (54.9)	53 (55.3)	0.144[c]
Education in years, mean (SD)	12.8 (3.7)	13.2 (3.6)	12.8 (3.7)	12.0 (3.9)	0.612[a]
Aetiological diagnosis, *N* (%)					
AD	229 (51.8)	106 (54.4)	72 (47.1)	51 (54.3)	0.347[c]
AD mixed	93 (21.0)	33 (16.9)	36 (23.5)	24 (25.5)	0.157[c]
DLB/PDD	49 (11.1)	19 (9.7)	22 (14.4)	8 (8.5)	0.263[c]
FTD	29 (6.6)	12 (6.2)	9 (5.9)	8 (8.5)	0.687[c]
Other	42 (9.5)	25 (12.8)	14 (9.2)	34 (36.6)	0.032[c]
MMSE, mean (SD)	23.1 (4.1)	24.9 (2.8)	23.0 (3.4)	19.5 (5.0)	<0.001[b]
TMT-A (worse than −2SD), N (%)	206 (48.1)	63 (33.0)	88 (58.7)	55 (63.2)	<0.001[c]
NPI-Q severity, mean (SD)	5.8 (5.3)	4.5 (4.6)	5.9 (5.0)	8.3 (6.0)	<0.001[b]
NPS cluster severity, mean (SD)					
Agitation cluster (severity score 0–15)	1.7 (2.4)	1.3 (2.1)	1.8 (2.2)	2.5 (2.9)	<0.001[b]
Affective cluster (severity score 0–15)	3.6 (3.0)	2.9 (2.8)	3.6 (2.8)	4.9 (3.1)	<0.001[b]
Psychosis cluster (severity score 0–6)	0.5 (1.0)	0.2 (0.7)	0.5 (1.0)	0.9 (1.5)	<0.001[b]
CDR-SB, mean (SD)	5.1 (2.3)	3.5 (1.0)	5.3 (1.4)	8.2 (2.2)	<0.001[a]
CDR-SB yearly change, mean (SE)	1.0 (0.1)	0.7 (0.1)	2.4 (0.6)	2.9 (0.2)	<0.001[d]

Abbreviations: AD, Alzheimer's dementia; AD mixed, aetiologically mixed Alzheimer's dementia; CDR-SB, Clinical Dementia Rating Scale sum of boxes; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; MMSE, Mini Mental State Examination; N, number of patients; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptoms; PDD, Parkinson's disease dementia; SD, standard deviation; SE, standard error; TMT-A, Trail Making Test A.

[a]Means are compared using one-way ANOVA as appropriate.

[b]Means are compared by Kruskal Wallis as appropriate.

[c]Proportions are compared with Chi square x^2.

[d]Linear mixed model.

dysphoria, night-time behaviours, apathy/indifference and appetite/eating (10% of the variance explained, Cronbach's alpha 0.67); and Factor 3 (psychosis symptom cluster) comprised the items hallucinations and delusions (9% of the variance explained, Cronbach's alpha 0.49). The severity scores of the items within the symptom clusters were summed and included as predictors in the regression models.

2.7 | Multinomial logistic regression analyses

Multinomial logistic regression analyses with the three-level trajectory group membership as the outcome variable and using the slow-progression group (Group 1) as reference were performed using Stata/IC 15.1. In multinomial logistic regression, the outcome variable Y has more than two categories, and the coefficient is, therefore, a relative risk ratio (RRR) in contrast to the odds ratio of a standard logistic regression. Spearman intercorrelation ensured that the inter-correlation between the explanatory variables were ≤0.55. Based on previous results related to this cohort,[24] MMSE and TMT-A were used to adjust for cognitive function. In addition, all models were adjusted for age, sex, education and dementia aetiology. First, we ran preliminary models to consecutively test individual NPS clusters (continues severity score; Table S2) and comorbidity groups (present = 1 or absent = 0; Table S3). Covariates with $p \leq 0.2$ were retained for further analysis in the final multivariate model (Table 3). Patients without missing values were included in the multinomial logistic regression analyses (N = 380).

3 | RESULTS

Sample characteristics at the time of diagnosis are listed in Tables 1 and 2. The patients with frontotemporal dementia (FTD) showed more agitation and those with Lewy body dementia (LBD) showed more psychotic symptoms (Table S1).

TABLE 2 Comorbidity groups with ICD-10 codes in all patients and by trajectory groups

Comorbidities by diagnostic class, N (%)	All (N = 442)	Group 1 (N = 195)	Group 2 (N = 153)	Group 3 (N = 94)	Group comparison *p* value
Cardiovascular diseases (I00-I53 and I70-I99)	218 (49.3)	99 (50.8)	76 (49.7)	43 (45.7)	0.604
Cerebrovascular diseases[a] (I60–I69)	63 (14.7)	28 (14.8)	24 (16.3)	11 (11.8)	0.654
Diseases of the nervous system (G00-G99)	189 (42.8)	84 (43.1)	66 (43.1)	39 (41.5)	0.891
Diseases of the sense organs[a] (H15-H48, H53-H54 and H80-H95)	130 (30.3)	53 (28.0)	51 (34.7)	26 (28.0)	0.409
Mental and behavioural disorders[a] (F04-F99)	211 (49.2)	110 (58.2)	66 (44.9)	35 (37.6)	0.002
Diseases of the respiratory system[a] (J40-J84 and J95-J99)	21 (4.9)	13 (6.9)	5 (3.4)	3 (3.2)	0.232
Diseases of the musculoskeletal system and connective tissue[a] (M05-M19 and M30-M99)	109 (25.4)	54 (28.6)	37 (25.2)	18 (19.4)	0.248
Diseases of the digestive system[a] (K20-K31, K50-K52 and K70-K93)	47 (11.0)	21 (11.1)	18 (12.2)	8 (8.6)	0.695
Endocrine, nutritional and metabolic diseases[b] (E0-E90)	168 (39.0)	69 (36.3)	60 (40.5)	39 (41.9)	0.603
Diseases of the urinary system[a] (N00-N19)	14 (3.3)	5 (2.7)	5 (3.4)	4 (4.3)	0.759
Cancer[a] (C00-C97)	73 (17.0)	39 (20.6)	21 (14.3)	13 (14.0)	0.195
Haematological diseases[a] (D50-D89)	16 (3.7)	7 (3.7)	7 (4.8)	2 (2.2)	0.595
Comorbidity, mean (SD)	2.9 (1.8)	3.0 (1.8)	2.9 (1.9)	2.6 (1.8)	0.980

Note: Proportions are compared with Chi square and means are compared using one-way ANOVA.

Abbreviations: ICD-10, the 10th revision of the International Statistical Classification of Diseases and Related Health Problems; N, number of patients; SD, standard deviation.

[a]N = 429.

[b]N = 431.

From the preliminary models, all of the NPS clusters (Table S2) and six of the comorbidity groups (Table S3) were included in the final model.

3.1 | Predictors associated with rate clinical progression

Results from the final model are presented in Table 3. Adjusted for age, sex, education, dementia aetiology, comorbidity groups, MMSE and TMT-A, we found that, for every point within the affective symptom cluster, the relative risk of belonging to the most rapidly progressing group (Group 3) was 29% higher than that of Group 1 membership (RRR 1.29 [95% CI 1.11–1.50]). For every point within the psychotic symptom cluster, the relative risk of belonging to the most rapidly progressing group (Group 3) increased by 53% (RRR 1.53 [95% CI 1.03–2.28]). Adjusted for age, sex, education, dementia aetiology, NPS clusters, MMSE and TMT-A, the relative risk of belonging to the most rapidly progressing group (Group 3) was reduced with a previous diagnosis of mental and behavioural disorders (excluding dementia) (RRR 0.35 [95% CI 0.17–0.73]). A diagnosis of musculoskeletal system and connective tissue disorders (RRR 0.44 [95% CI 0.19–1.02]) seemed to decrease the relative risk of belonging to Group 3, while endocrine, nutritional and metabolic diseases (Group 3: RRR 2.03 [95% CI 0.99–4.15]) seemed to increase the relative risk of belonging to Group 3; however, these comorbidities were not statistically significant.

4 | DISCUSSION

In the present study, we found that psychotic and affective symptoms at the time of dementia diagnosis increased the risk for rapid clinical progression, even after adjusting for demographic information, dementia aetiology, cognitive function and comorbidities. Previous diagnoses of mental and behavioural disorders (excluding dementia) were associated with slow progression.

Psychotic symptoms at the time of diagnosis were associated with rapid progression in our cohort. Patients with LBD had more psychotic symptoms, but the overall association remained significant, even after adjusting for dementia aetiology. Likewise, Gerritsen and colleagues[42] found that psychotic symptoms were associated with cognitive decline in young-onset dementia (AD, vascular dementia [VaD] and FTD). Moreover, researchers also found psychotic symptoms to be associated with rapid cognitive decline[43,44] despite differences in the population (only AD and different age groups), according to the outcome measurements (change in MMSE or dementia severity vs. change in CDR-SB) and statistical methods used. In addition, a meta-analysis supported our results showing that psychotic symptoms in AD were associated with faster progression

TABLE 3 Multinomial logistic regression model assessing trajectory-group membership by retained comorbidity groups and neuropsychiatric symptoms

Fully adjusted model (N = 380)[a]	Group 2 versus Group 1		Group 3 versus Group 1	
Variables	**RRR**	**95% CI**	**RRR**	**95% CI**
Mental and behavioural disorders[b]	0.63	(0.37–1.06)	**0.35**	**(0.17–0.73)***
Disease of the respiratory system[b]	0.34	(0.08–1.45)	0.58	(0.10–3.28)
Disease of the musculoskeletal system and connective tissue[b]	0.78	(0.43–1.41)	0.44	(0.19–1.02)
Endocrine, nutritional and metabolic disease[b]	1.45	(0.84–2.49)	2.03	(0.99–4.15)
Disease of the urinary system[b]	1.87	(0.38–9.27)	4.18	(0.65–26.87)
Cancer[b]	0.57	(0.29–1.14)	0.60	(0.23–1.57)
Agitation symptom cluster (severity score)	1.03	(0.88–1.20)	0.96	(0.79–1.16)
Affective symptom cluster (severity score)	1.09	(0.97–1.22)	**1.29**	**(1.11–1.50)***
Psychosis symptom cluster (severity score)	1.20	(0.85–1.70)	**1.53**	**(1.03–2.28)***

Notes: This table shows the final multinomial logistic regression model assessing trajectory-group membership by comorbid diagnoses and neuropsychiatric symptoms. Variables are continuous unless otherwise specified.

Abbreviations: CI, confidence interval; N, number of patients; RRR, relative risk ratio.

*Significant level $p < 0.05$.

[a]Adjusted for age, sex, length of education, dementia aetiology, Mini Mental State Examination and Trail Making Test A.

[b]Variables are dichotomized and values for present are presented.

measured by change in MMSE.[14] Conversely, Haaksma et al. did not find that psychotic symptoms were associated with rapid progression in AD.[45] One explanation may be that their results were attenuated by adjusting for baseline dementia severity, even though changes in the same variables were their outcome measures.

Affective symptoms at the time of diagnosis were associated with the most rapidly progressing group in our cohort. Affective symptoms have been shown to increase the risk of AD,[46] but their effect on dementia progression rate has been less studied. A review[47] found that, in AD, depression was associated with rapid cognitive decline, greater functional decline, and higher rates of nursing home placement. Affective symptoms have also been associated with mortality.[43] However, other studies did not find any associations between affective symptoms and rapid progression of dementia[14,18] and one study indicated affective symptoms to be associated with slower cognitive decline in AD, VaD and FTD.[42] This discrepancy may be due to the overlap between symptoms of AD and depression and because depressive symptoms often occur with other NPS, making the diagnosis challenging and the comparison of studies difficult.[47] When exploring individual NPS in AD, researchers have found agitation/aggression,[14,16,43] aberrant motor behaviour,[14,16] and any clinically significant NPS[43] to be associated with rapid clinical progression. We did not find such associations.

Whether psychotic and affective symptoms reflect higher neurotoxicity in the brain remains unclear. Studies have, however, indicated several neuropathological changes linked to psychosis and to affective symptoms in dementia. For instance, AD patients with psychotic symptoms have been found to have more neurofibrillary tangles in neocortical areas independent of dementia severity,[48] as well as more intraneuronal P-tau.[49] Delusions have been associated with an upregulation of postsynaptic muscarinic receptors in dementia with Lewy bodies[50] and increased striatal dopamine receptor availability in AD.[51] Genetic variations could also have an impact on psychosis in AD,[52,53] but apolipoprotein E ε4 does not seem to increase the risk.[54] Regarding affective symptoms, a literature review found that depressive symptoms in AD were associated with more cerebral neurofibrillary tangles and senile plaques, hippocampus atrophy and changes in the serotonergic pathways.[55] Moreover, alterations in the monoaminergic network in the cortex[56] and the number of corticotropin-releasing hormone neurons[57] have been associated with depression in dementia. Furthermore, apathy has been linked to increased P-tau in cerebrospinal fluid and to neurofibrillary tangles in the anterior cingulated cortex in AD.[55] The neuropathological changes related to NPS in FTD and other dementias are much less understood, but psychotic symptoms have been found to correlate with grey matter atrophy in progranulin mutation carriers with FTD.[58]

The presence of previous mental and behavioural disorders was associated with slow progression, while psychotic and affective symptoms at baseline were associated with rapid progression in our cohort. This could indicate differences in underlying processes. Psychosis in AD and VaD differs from psychosis seen in schizophrenia, with the dementia syndromes being associated with mostly persecutory and misidentification delusions and visual hallucinations.[59] A study examining the interaction between psychosis in AD and schizophrenia found a possible genetic link, but the association was strongest for delusions.[53] Schizophrenia and other psychiatric conditions such as bipolar disorders have been linked to increased risk of dementia,[60] while our findings show that the same conditions are associated with slow dementia progression. One explanation

could be that these patients develop symptoms of dementia on the basis of less neuropathology because of reduced cognitive reserve.[61] Again, this may explain why the dementia progressed more slowly, as progression rate is known to increase with dementia severity.[14,24,62] To elaborate on this, we need further research, preferably combining clinical markers with biomarkers.

A trend was identified, although not reaching statistical significance, for the association of musculoskeletal system and connective tissue disorders with a slower progression rate of dementia (RRR 0.44 [95% CI 0.19–1.02], $p = 0.055$), and these conditions often result in the use of non-steroidal anti-inflammatory drugs (NSAIDs). An older longitudinal study found that NSAID usage was associated with slower progression of decreased verbal fluency, spatial recognition and orientation in AD.[63] Longitudinal studies have shown that the use of NSAIDs, especially long-term use,[64] could reduce the risk of AD development.[65] The mechanism of action is uncertain, but the attenuation of over-stimulated microglia has been suggested.[64] Clinical trials have, however, failed to prove any benefit of NSAIDs in the prevention of AD.[64,66] It is not clear why epidemiological studies find this association, while clinical trials do not. Possibly NSAID usage is a marker of some unknown residual confounding, or that the potential effect of NSAIDs is difficult to prove in prevention trials.[66] We do not have information on the use of medication in our cohort, and, therefore, we cannot know if these diagnoses reflect NSAID use. Perhaps, these diagnoses are proxies of another mechanism, thereby biasing the result.

The presence of endocrine, nutritional and metabolic diseases seemed to increase the risk of rapid progression, but again, this was a trend that was not statistically significant (Group 3: RRR 2.03 [95% CI 0.99–4.15], $p = 0.053$). Diabetes has been linked to decreased progression rate in AD.[14,21] Being overweight in mid-life increases the risk of dementia, while being underweight increases the risk during the preclinical phase.[67] Perhaps our results were weakened by the several conditions included in this group of diseases with potential opposite effects on dementia progression.

4.1 | Strengths and limitations

The patients included in the present study were from a specialized memory clinic, which may weaken the generalizability of the results. We did, however, include all-cause dementia reflecting numerous underlying pathologies, although nearly 73% of the patients had AD. Information on the use of medication and medical incidences during the follow-up period would have improved the knowledge of the general health of the patients. The ICD-10 categories encompass a wide range of disorders, which might affect the dementia progression rate differently, and therefore, the results should be interpreted with caution. Moreover, the various definitions and assessment tools applied to describe NPS in the literature—and the differences in study populations—hinders comparison. To enhance insight into the pathological mechanisms underlying NPS and comorbidities and their link to dementia progression, future studies should focus on a multidimensional approach with thorough clinical examinations and detailed biomarker profiles.

Using trajectory groups as measures of progression could be both a limitation and a strength. A study[62] comparing the development of cognitive and functional decline in two cohorts found different numbers of latent trajectories and class sizes, further emphasizing the need to assess multiple domains in progression studies. Our trajectory groups were based on the CDR, which provides a global score of functional and cognitive impairment.[26] Strengthening the results, our trajectory groups were similar to those of Haaksma et al.,[45] despite differences in study populations and statistical methods used. The course of dementia varies,[14,24,45,62] and future research should consider this heterogeneity in dementia progression rates. Nevertheless, the methods used to detect trajectories are exploratory, and this should be considered when comparing studies and interpreting the results.

A strength of the present study was its linkage to the Norwegian Patient Registry, which enabled us to assess comorbidities independent of patients and their caregivers' recall. Also, the patients were examined with an extensive research protocol and diagnosed according to validated research criteria. Information about demography, dementia aetiology and cognitive decline enabled us to adjust for important confounders. Another strength was the use of principal component analysis to determine the NPS clusters, taking the correlation of the symptoms in our cohort into consideration. Others have also found NPS grouped in similar symptom clusters,[15] indicating that they might be clinically meaningful.

5 | CONCLUSION

We have shown that psychotic and affective symptoms at the time of dementia diagnosis were associated with rapid progression in all-cause dementia. Previous diagnoses of mental and behavioural disorders were associated with slow progression. Our results contribute to the understanding of risk factors for dementia progression and show that multiple factors might affect the progression rate. This supports the need for individual assessments and follow-up protocols.

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CONFLICT OF INTEREST

Dr. Knapskog was the principal investigator and Dr. Edwin was a rater on the Roche BN29553 trial and the Boehringer-Ingelheim 1346.0023 trial at Oslo University Hospital, outside the submitted work. Dr. Persson was a rater on the Roche BN29553 trial at Oslo University Hospital, outside the submitted work.

AUTHOR CONTRIBUTION

Dr. Edwin and Dr. Knapskog reports work with Roche BN29553 and with Boehringer-Ingelheim 1346.0023, outside the submitted work. Dr. Persson reports work with Roche BN29553, outside the submitted work.

DATA AVAILABILITY STATEMENT

Data are available upon request to the corresponding authors. Approval from the Regional Ethics Committee for medical research in the west of Norway (contact: post@helseforsikring.etikkom.no) is necessary due to legal restrictions.

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