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Neuropsychiatric Symptoms and Caregiver Distress at Diagnostic Assessment for Suspected Memory Disorders: Evidence from the Oxford Brain Health Clinic

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Abstract

Background: Neuropsychiatric symptoms are common in later life, and can be as problematic as cognitive impairment for individuals with memory concerns, yet they are seldom assessed systematically in memory clinics. Early identification of NPS and caregiver distress may inform diagnosis, guide management, and improve outcomes. This study examines the prevalence and correlates of NPS and caregiver distress in a real-world memory clinic cohort at the time of diagnostic assessment.

Methods: Patients aged ⩾65 who underwent initial assessment at the Oxford Brain Health Clinic, subsequently attended the memory clinic for diagnosis, and completed the Neuropsychiatric Inventory Questionnaire (NPI-Q) were included. NPS prevalence, co-occurrence, and caregiver distress were described descriptively. Associated factors were analysed using Spearman's correlations and multivariable linear regression.

Results: A total of 242 met the inclusion criteria, with a mean age of 77.5± 6.3. Of them, 129 received a subsequent diagnosis of dementia, 59 were considered to have mild cognitive impairment (MCI), and 54 had no memory disorder diagnosis. NPS were prevalent (83.5%) in the cohort, generally of mild to moderate severity, with individuals exhibiting a mean of 2.8 symptoms. The no memory disorder and dementia groups showed higher NPS counts than the MCI group (means of 3.1 and 2.9 vs. 2.1). Co-occurrence patterns were complex and depression-centered in the no memory disorder group, limited in MCI, and apathy-centered in dementia. Caregiver distress was also higher in the dementia (mean 15.0) and no memory disorder groups (mean 13.3) than in MCI (mean 10.1). In multivariable analyses, cognitive decline ($\beta = 1.23$, $p < 0.001$) and caregiver distress ($\beta = 0.09$, $p < 0.001$) were independently associated with higher total NPS scores. Diagnostic group also remained significant, with the no memory disorder group exhibiting higher scores than the MCI group ($\beta = -0.98$, $p = 0.013$).

Conclusions: NPS and caregiver distress were already common when patients sought diagnostic assessments for memory concerns. Notably, individuals without memory disorders showed preserved cognition but more frequent and complex NPS. These findings highlight the importance of timely recognition of NPS and early caregiver support in diagnostic practice.

Keywords: Neuropsychiatric Symptoms; Early Stage; Dementia; Mild Cognitive Impairment; Caregivers; Distress; Memory Clinic; Real-World Data

Background

Neuropsychiatric symptoms (NPS) are highly prevalent across the trajectory of dementia and can emerge even in the prodromal stage.[1-3] These symptoms significantly impact patients' quality of life, increase caregiver burden, and can contribute to earlier institutionalisation and greater healthcare utilisation.[4-7] A variety of studies have reported the high prevalence of NPS in people with dementia. For instance, one Spanish study found a prevalence rate of 94.6% among individuals with mild to severe dementia[8]. Similarly, the Amsterdam Dementia Cohort revealed that NPS are highly prevalent across Alzheimer's Disease spectrum, including subjective cognitive decline (81.4%), mild cognitive decline (81.2%), and Alzheimer's dementia (88.7%).[1] And an Italian study showed that 85.2% of elderly participants with cognitive impairment experienced at least one NPS [9].

NPS in dementia frequently co-occur.[1, 10] Prior studies have explored NPS co-occurrence through clustering methods but have rarely quantified the prevalence of specific symptom combinations.[9, 11, 12] Co-occurrence analysis differs fundamentally from clustering. Two symptoms may frequently co-occur within an individual patient even if they belong to separate clusters at the group level. Descriptive co-occurrence analysis focuses on how often specific symptoms appear together, without assuming any fixed underlying syndromic structure. This approach may better reflect the complexity and variability of clinical presentations. To date, only one study has reported detailed co-occurrence frequencies of NPS pairs, highlighting the need for further investigation in this area.[13]

Regarding the early emergence of NPS, most prevalence studies do not distinguish dementia stages, and few have examined how NPS are presented at the diagnostic assessment. Emerging evidence indicates that NPS arise prior to a formal dementia diagnosis.[3, 14] This is further supported by evidence of increased psychotropic medication prescriptions in the six months preceding diagnosis, indicating the early clinical manifestation of NPS during the prodromal stage.[15] Some studies have shown that NPS are associated with cognitive and functional decline [16-19], as well as an increased risk of developing dementia.[20, 21] Early assessment of NPS at prodromal dementia may support diagnostic decision-making and resource allocation, inform management planning, and help prevent further deterioration.

The early occurrence of NPS not only affects individuals at risk but may also cause significant distress to caregivers.[5, 6, 22, 23] While caregiver distress is well recognised in established dementia [22-24], relatively little attention has been given to caregiver distress at the early diagnostic assessment. One study found that caregivers of individuals with mild dementia reported high levels of distress that increased over time.[25] Understanding caregiver distress during this early stage is important, as it may help clinicians identify when to provide appropriate support. Timely interventions could not only improve caregivers' well-being but also positively influence patient care and outcomes.

This study used the Oxford Brain Health Clinic (OBHC) dataset, a real-world memory clinic cohort of individuals aged 65 years or older.[26] The OBHC is an innovative joint clinical-research service that provides high-quality clinical and research assessments for individuals with suspected memory disorders, having been launched in August 2020.[26] All patients referred by their general practitioners to a memory clinic for further diagnostic assessment, and who are eligible for an MRI scan, are considered eligible to attend OBHC for their assessments. The OBHC dataset therefore provides a representative sample of real-world patients with cognitive concerns, making it particularly valuable for examining NPS and caregiver distress at the time of diagnostic assessment. This study aims to: (1) examine the prevalence and co-occurrence of NPS across clinical diagnostic groups, and explore their associations with other symptoms; and (2) characterise the level of caregiver distress across diagnostic groups and its relationship to the range of symptoms.

Methods

Data Source:

This study analysed data from the OBHC dataset collected between August 2020 and February 2024, including only patients who had provided consent for the use of their clinical data for research.

Inclusion criteria comprised subsequent attendance at the memory clinic for diagnosis and completion of the Neuropsychiatric Inventory Questionnaire (NPI-Q). No specific exclusion criteria were applied to maintain the representativeness of the OBHC cohort. Patients were categorised into three groups based on their subsequent diagnostic appointment at the memory clinic: dementia, MCI, or no memory disorders. The no memory disorder group included individuals without a formal memory-related diagnosis, including those with documented anxiety, depression, or bipolar disorder in the memory clinic records, as these conditions may reflect prodromal or comorbid neuropsychiatric symptoms.

Demographic data for patients included age, gender, and education level. Patients' clinical variables encompassed depression (assessed using the Patient Health Questionnaire-9, PHQ-9), physical activity (Short Active Lives Questionnaire), alcohol use (Single Alcohol Use Screening Questionnaire), sleep quality (selected items from the Pittsburgh Sleep Quality Index), frailty (Rockwood Clinical Frailty Scale), cognitive status (Addenbrooke's Cognitive Examination, ACE- III), changes in cognitive function (Informant Questionnaire on Cognitive Decline in the Elderly, IQCODE), neuropsychiatric symptoms (NPI-Q), long-term conditions (Long-Term Conditions Questionnaire-short form, LTCQ-8), health-related quality of life (EQ-5D-5L), and recorded diagnoses of memory disorder.

Caregiver related variables included age, gender, relationship to the patient, cohabitation status, caregiver distress (assessed using the Relative Stress Scale, RSS, and NPI-Q), long-term conditions (Long-Term Conditions Questionnaire-Carer version, LTCQ-Carer), and health-related quality of life (EQ-5D-5L). The term "caregiver" is used consistently in this manuscript because the NPI-Q includes the concept of "caregiver distress". To ensure terminological consistency with the NPI-Q, we refer to the relative or friend who accompanied the patient for diagnostic assessment as the caregiver.

The assessment battery was modified over time to meet evolving clinical and research needs. In July 2021, the LTCQ-8 was introduced. In November 2022, the LTCQ-Carer and EQ-5D-5L for both patients and caregivers were added. In December 2022, the RSS was removed.

Primary Outcome

The primary outcome was the presence and severity of NPS, assessed using the NPI-Q. The NPI-Q evaluates 12 symptom domains: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep and night-time behaviour disorders, and appetite and eating disorders.[27] Caregivers reported whether the patient had exhibited symptoms in the past month. If symptoms were present, severity was rated on a 3-point scale (1= mild, 2= moderate, 3= severe).

Secondary Outcome

The secondary outcome was caregiver distress, assessed using the NPI-Q and the RSS. In the NPI-Q, if a symptom was present, the associated caregiver distress was rated on a 6-point scale (0=not distressing at all, 1=minimal, 2=mild, 3=moderate, 4= severe, 5=extreme or very severe). The RSS is a 15-item questionnaire, with three domains: emotional distress (items 1-6), social distress (items 7-11), and negative feelings (items 12-15). Each item was rated on a 5-point scale measuring either frequency or severity (0= never, 1=rarely, 2=sometimes, 3=frequently, 4=always; or 0=not at all, 1=a little, 2=moderately, 3=quite a lot, 4=considerably).

Statistical Analysis:

Descriptive statistics summarised the characteristics of both patients and caregivers. Continuous variables were reported as either the mean and standard deviation (SD) or the median and interquartile range (IQR), depending on the distribution of the data. Categorical variables were presented as frequencies and percentages. Group differences were assessed using T-tests, one-way ANOVA, nonparametric tests, or Chi-square tests as appropriate.

The prevalence of NPS was calculated for the entire sample and for each diagnostic group, with between-group differences tested by Chi-square tests or Fisher's exact tests. Co-occurrence patterns were described by calculating raw frequencies of symptom dyads (two-symptom combinations) and triads (three-symptom combinations) within each diagnostic group. Spearman's correlation was conducted to examine associations between NPS (total count and severity) and demographics, lifestyle and risk factors, cognitive function, and health-related quality of life. Variables showing moderate to strong univariable correlations with NPS ($|\rho| \geqslant 0.35$) were considered candidate predictors for the multivariable model. Multivariable linear regression was then fitted to identify independent correlations with NPS while adjusting for caregiver distress, given that NPS was caregiver-reported.

Caregiver distress was summarised for the overall sample and across the diagnostic groups. Spearman's correlation was performed to explore the impact of patients' and caregivers' demographics, as well as patients' cognitive and clinical variables, on caregiver distress.

To evaluate the robustness of the results, we additionally repeated the analyses after excluding patients in the no memory disorder group who had documented anxiety, depression, or bipolar disorder.

All statistical analyses were performed using SPSS version 29.0.2.0, except for co-occurrence analysis, which was performed in R version 4.3.3. The data visualisation was plotted using R version 4.3.3.

Results

Patients' and Caregivers' characteristics

A total of 299 patients were identified, and 242 met the inclusion criteria, comprising 54 patients with no memory disorder, 59 patients with MCI, and 129 patients diagnosed with dementia. Among the 54 patients with no memory disorder, 37 were recorded as having no diagnosis or no formal diagnosis, 11 had depression, anxiety, or bipolar disorder, and 6 were noted as having no psychiatric diagnosis. Due to updates in the assessment battery, the number of caregivers with valid distress or quality of life data varied (RSS: n=150; LTCQ: n=81; EQ-5D-5L: n=87).

The demographics, lifestyle, and health-related characteristics of patients and caregivers are presented in Table 1 and Table 2. Patients with no memory disorder and MCI were younger than patients diagnosed with dementia ($p<0.01$). Depression scores assessed by PHQ-9 were highest in the no memory disorder group, followed by the MCI group and the dementia group. Frailty prevalence followed an inverse pattern, with the highest rate observed in dementia patients (38.3%) and the lowest in those with no memory disorder (9.3%). Cognitive function, as measured by the ACE-III, showed a progressive decline from no memory disorder to dementia. Meanwhile, IQCODE scores, which measure caregiver-reported cognitive change over time, indicated deterioration in cognition across all groups.

Caregiver characteristics did not differ significantly across diagnostic groups (all $p > 0.05$). The cohort predominantly comprised female (61.5%), spousal (69.1%), and cohabiting caregivers (71.3%), with a mean age of 68.4 years.

Prevalence and Co-occurrence of Neuropsychiatric Symptoms

NPS were highly prevalent in the overall OBHC cohort, with 83.5% of patients exhibiting at least one NPS in the past month at the time of their visit. The five most frequently reported symptoms: apathy, depression, irritability, sleep and night-time behaviour disturbance, and appetite changes, each affected more than 30% of patients (Table 3). When stratified by diagnostic groups, NPS prevalence was 85.3% in the dementia group, 76.3% in the MCI group and 87.0% in the no memory disorder group (Table 3). Symptom severity in the full sample was in the mild-to-moderate range (Figure 1), with detailed percentages provided in Supplementary Table 1.

Individuals commonly exhibited multiple NPS, with a mean of 2.8 symptoms (SD=2.2) per patient. Patients with no memory disorder (3.1 ± 2.3) and those with dementia (2.9 ± 2.2) showed significantly higher symptom counts than patients with MCI (2.1 ± 2.1; p=0.013). Due to the frequent presence of multiple concurrent symptoms, we examined the patterns of symptom co-occurrence across diagnostic groups. The no memory disorder group exhibited the greatest diversity, with 12 symptom dyads occurring at frequencies ⩾20% (Figure 2). Symptom dyads was predominantly depression-centred, with the most frequent combinations being depression-apathy (31.5%), depression-appetite changes (27.8%), depression-irritability (25.9%), and irritability-appetite changes (25.9%). The MCI group showed five frequent dyads: depression-irritability (18.6%), depression-apathy (17.0%), apathy-irritability (15.3%), irritability-nighttime behaviour (15.3%), and irritability-appetite changes (15.3%). In the dementia group, apathy-centred dyads were predominant, including depression-apathy (25.6%), apathy-nighttime behaviour (21.7%), and apathy-appetite changes (20.9%). Triplet co-occurrences were less common overall (prevalence <20%, Supplementary Table 2).

Neuropsychiatric Symptoms' associated factors

Spearman's correlation analysis (Figure 3; p-values are shown in Supplementary Table 3) revealed significant associations between NPS and several clinical and psychosocial factors. Higher NPS burden (counts or severity) was significantly correlated with lower weekly physical activity, greater frailty, more severe depressive symptoms (PHQ-9), caregiver-reported cognitive decline (IQCODE), and living less well with long-term conditions. In contrast, current cognitive status measured by the ACE-III was not associated with NPS. Additionally, caregiver-related factors, including reduced quality of life and increased caregiver distress, were also significantly associated with NPS (all $p < 0.05$). Among these variables, five showed moderate to strong correlations with NPS: caregiver-reported cognitive decline, caregiver health-related quality of life (EQ-5D-5L), caregiver ability to cope with providing care for someone with long-term conditions (LTCQ), caregiver distress measured using both NPI-distress and RSS scales.

We then examined independent correlations using multivariable linear regression after accounting for caregiver distress. Diagnostic group was included as a as a fixed variable to assess differences in NPS across diagnostic groups, with the no memory disorder group serving as the reference. To reduce same-source bias, RSS was preferred over NPI-distress. Because EQ-5D-5L and LTCQ were introduced after RSS was discontinued, resulting in only minimal overlap in the caregivers assessed, so these measures were not included in the regression. The final model included RSS-measured caregiver distress, cognitive decline (IQCODE), and diagnostic group, and explained $R^2 = 0.46$ of the variances. In this model, the MCI group exhibited significantly fewer NPS than the no memory disorder group (MCI: $\beta = -0.98$, $p = 0.01$; dementia: $\beta = -0.70$, $p = 0.058$). Caregiver-reported cognitive decline remained significantly associated with NPS ($\beta = 1.23$, $p < 0.001$) after controlling for diagnostic group and caregiver distress, indicating an independent association. Caregiver distress also showed a significant independent association with NPS ($\beta = 0.09$, $p < 0.001$). Detailed results of the regression analysis are presented in Supplementary Table 4.

A sensitivity analysis excluding individuals with recorded depression, anxiety, or bipolar disorder yielded consistent results. Overall associations and group differences remained unchanged; only the absolute frequencies of depression and anxiety decreased as expected, and co-occurrence patterns showed no material changes. As the sensitivity analysis yielded consistent findings, detailed results are not presented.

Prevalence and Correlates of Caregiver Distress

Caregiver distress assessed by RSS had a median of 12.0 (IQR: 6.0-19.0) and significantly differed across diagnostic groups (Kruskal-Wallis H=6.880, p=0.032). Caregiver distress levels were highest in the dementia group at 13.0 (7.0-20.0), followed by the no memory disorder group at 10.5 (4.8-19.3), and lowest in the MCI group at 7.5 (4.0-16.0]). At the subscale level, both emotional distress (p <

0.05) and social distress ($p < 0.05$) demonstrated statistically significant group differences (Table 2). In contrast, the negative feelings subscale showed no significant variation across groups. Caregiver distress ratings derived from the NPI-Q are reported separately in Supplementary Table 5.

Caregiver distress was significantly correlated with a range of caregiver- and patient- related factors (Figure 4; p-values in Supplementary Table 6). Among caregiver-related characteristics, female tends to experience more distress. Better caregiver ability to cope with providing care for someone with long-term conditions (LTCQ-Carer) and self-rated health status (assessed by EQ-5D-5L "health today" score) demonstrated moderate inverse associations with caregiver distress. Among patient-related variables, NPS and caregiver-reported cognitive decline (IQCODE) showed the moderate to strong correlations with caregiver distress. Patients' depressive symptoms (PHQ-9), frailty, and ability to live well with long-term conditions (LTCQ-8) were also significantly associated with caregiver distress, though to a lesser extent.

Table 1. Demographic, lifestyle, and health-related characteristics of patients

Patients' characteristics	Overall sample (N=242)	Diagnostic Group			P value
		No memory disorders (N=54)	MCI (N=59)	Dementia (N=129)	
Age, mean ± SD	77.5 ± 6.3	74.4 ± 5.4[a]	76.1 ± 5.3[a]	79.5 ± 6.3[b]	**<0.001**[§]
Gender, female, n (%)	117.0 (48.3%)	26.0 (48.1%)	27.0 (45.8%)	64.0 (49.6%)	0.886[¶]
Education years, mean ± SD	13.1 ± 3.4	14.0 ± 3.2	12.9 ± 3.6	12.9 ± 3.4	0.133[‡]
Physical active, yes, n (%)	93.0 (38.4%)	27.0 (50.0%)	25.0 (42.4%)	41.0 (31.8%)	0.054[¶]
Sleep duration, hours/per night, mean ± SD	7.3 ± 1.8	6.9 ± 1.6[a]	7.5 ± 1.3[a,b]	7.5 ± 2.0[b]	**0.022**[‡]
Sleep efficiency ↑ (0-100%), mean ± SD	78.3 ± 17.4	77.1 ± 13.5	81.7 ± 12.1	77.4 ± 20.6	0.296[‡]
Frailty, mean ± SD	3.1 ± 1.3	2.6 ± 0.9	2.8 ± 1.1	3.3 ± 1.5	-
Frailty ↓ (⩾4 means frail), n (%)	67.0 (27.8%)	5.0 (9.3%)[a]	13.0 (22.0%)[a,b]	49.0 (38.3%)[b]	**<0.001**[¶]
Alcohol, yes, n (%)	34.0 (14.3%)	12 (22.2%)	6 (10.3%)	16 (12.7%)	0.152[¶]
Change in cognition, IQCODE (1-5) ↓, mean ± SD	3.8 ± 0.5	3.5 ± 0.4[a]	3.5 ± 0.4[a]	4.1 ± 0.5[b]	**<0.001**[§]
LTCQ-8 ↑ (0-100), mean ± SD	75.5 ± 16.5	79.4 ± 14.0[a]	78.1 ± 17.0[a,b]	72.5 ± 17.0[b]	**0.030**[‡]
EQ-5D-5L, Health today ↑ (0-100), mean ± SD	79.9 ± 19.3	83.2 ± 14.0	85.0 ± 14.7	74.6 ± 23.5	0.161[‡]
PHQ-9 ↓ (0-27), mean ± SD	5.1 ± 5.0	6.7 ± 5.2[a]	5.0 ± 5.0[a,b]	4.5 ± 4.7[b]	**0.014**[‡]
Median [IQR]	3.0 [1.0-8.0]	6.0 [2.0-9.0]	3.0 [1.0-8.3]	3.0 [1.0-7.0]	
ACE-III ↑, Total (0-100), mean ± SD	73.9 ± 17.4	89.4 ± 6.7[a]	81.1 ± 9.0[b]	63.5 ± 17.0[c]	**<0.001**[‡]

One-way ANOVA[§], Chi-Square[¶], Nonparametric test[‡].
Superscript letters denote results of post-hoc pairwise comparisons. Groups sharing the same letter are not significantly different from each other, whereas groups with different letters differ significantly.
↑ Higher scores indicate better status. ↓ Higher scores indicate worse status.

Table 2. The characteristics and distress of the caregivers: overall and by patient diagnostic group

Caregivers'		Patient Diagnostic Group	P value

characteristics	Overall sample	No memory disorder	MCI	Dementia	
Age, mean ± SD	68.4 ± 12.4	67.7 ± 12.9	68.5 ± 12.2	68.7 ± 12.4	0.887‡
Gender, female, n (%)	147 (61.5%)	31 (57.4%)	36 (62.1%)	80 (63.0%)	0.775¶
Relationship, Spouse or Partner, n (%)	163 (69.1%)	40 (78.4%)	43 (72.9%)	80 (63.5%)	0.115¶
Live together, yes, n (%)	171 (71.3%)	42 (79.2%)	44 (74.6%)	85 (66.4%)	0.179¶
LTCQ-Carer ↑ (0-100), mean ± SD	82.4 ± 16.3	82.0 ± 19.5	88.9 ± 8.3	79.5 ± 16.9	0.174‡
EQ-5D-5L, Health today ↑ (0-100), mean ± SD	78.4 ± 19.1	75.4 ± 19.4	79.6 ± 19.0	79.4 ± 19.3	0.417‡
Caregiver Distress					
NPI, total **distress** ↓ (0-60), mean ± SD	7.2 ± 6.5	8.4 ± 7.6	5.7 ± 6.0	7.4 ± 6.2	0.159‡
Median [IQR]	5.0 [3.0-10.0]	5.0 [3.0-13.0]	5.0 [2.0-7.5]	5.0 [3.0-10.3]	
RSS ↓, (0-60), mean ± SD	13.5 ± 9.7	13.3 ± 10.1[a,b]	10.1 ± 7.8[a]	15.0 ± 9.9[b]	**0.032**‡
Median [IQR]	12.0 [6.0-19.0]	10.5 [4.8-19.3]	7.5 [4.0-16.0]	13.0 [7.0-20.0]	
Emotional Distress, mean ± SD	6.4 ± 4.7	6.1 ± 4.9[a,b]	4.8 ± 4.4[a]	7.1 ± 4.7[b]	**0.016**‡
Social Distress, mean ± SD	3.8 ± 3.8	3.6 ± 4.1[a,b]	2.3 ± 2.7[a]	4.4 ± 3.9[b]	**0.011**‡
Negative Feelings, mean ± SD	3.3 ± 2.4	3.5 ± 2.4	3.0 ± 1.8	3.4 ± 2.6	0.704‡

Nonparametric test‡, Chi-Square¶.
Superscript letters denote results of post-hoc pairwise comparisons. Groups sharing the same letter are not significantly different from each other, whereas groups with different letters differ significantly.
↑ Higher scores indicate better status. ↓ Higher scores indicate worse status.

Table 3. Prevalence and severity of neuropsychiatric symptoms

Neuropsychiatric symptoms	Overall sample (N=242)	Diagnostic Group			P value
		No memory disorders (N=54)	MCI (N=59)	Dementia (N=129)	
Total number of NPS (0-12), mean ± SD	2.8 ± 2.2	3.1 ± 2.3[a]	2.1 ± 2.1[b]	2.9 ± 2.2[a]	**0.013**‡
Median [IQR]	2.5 [1.0-4.0]	3.0 [1.8-4.0]	2.0 [1.0-3.0]	3.0 [1.0-4.0]	
Total Severity Score (0-36), mean ± SD	5.3 ± 4.4	6.2 ± 5.0[a]	4.0 ± 4.3[b]	5.5 ± 4.1[a]	**0.014**‡
Median [IQR]	4.0 [2.0-7.0]	4.0 [2.8-8.3]	3.0 [1.0-5.0]	4.0 [3.0-8.0]	
NPS, any symptom, n (%)	202 (83.5%)	47 (87.0%)	45 (76.3%)	110 (85.3%)	0.221¶
Apathy	101 (41.7%)	23 (42.6%) [a,b]	14 (23.7%)[a]	64 (49.6%)[b]	**0.004**¶
Depression	101 (41.7%)	29 (53.7%)	20 (33.9%)	52 (40.3%)	0.092¶
irritability	87 (36.0%)	25 (46.3%)	23 (39.0%)	39 (30.2%)	0.101¶
Sleep and Night-time Behaviour	83 (34.3%)	21 (38.9%)	14 (23.7%)	48 (37.2%)	0.141¶
Appetite	75 (31.0%)	22 (40.7%)	16 (27.1%)	37 (28.7%)	0.209¶
Agitation	58 (24.0%)	17 (31.5%)	10 (16.9%)	31 (24.0%)	0.195¶
Anxiety	53 (21.9%)	11 (20.4%)	10 (16.9%)	32 (24.8%)	0.459¶
Aberrant Motor Behaviour	36 (14.9%)	5 (9.3%)	7 (11.9%)	24 (18.6%)	0.203¶
Disinhibition	33 (13.6%)	8 (14.8%)	5 (8.5%)	20 (15.5%)	0.411¶
Hallucinations	18 (7.4%)	3 (5.6%)	1 (1.7%)	14 (10.9%)	0.072¶
Delusions	15 (6.2%)	1 (1.9%)	2 (3.4%)	12 (9.3%)	0.104¶
Euphoria	9 (3.7%)	1 (1.9%)	1 (1.7%)	7 (5.4%)	0.359¶

Chi-Square¶, Nonparametric test‡.
Superscript letters denote results of post-hoc pairwise comparisons. Groups sharing the same letter are not significantly different from each other, whereas groups with different letters differ significantly.

Figure 1. Prevalence and Severity Distribution of Neuropsychiatric Symptoms Among the Total Sample

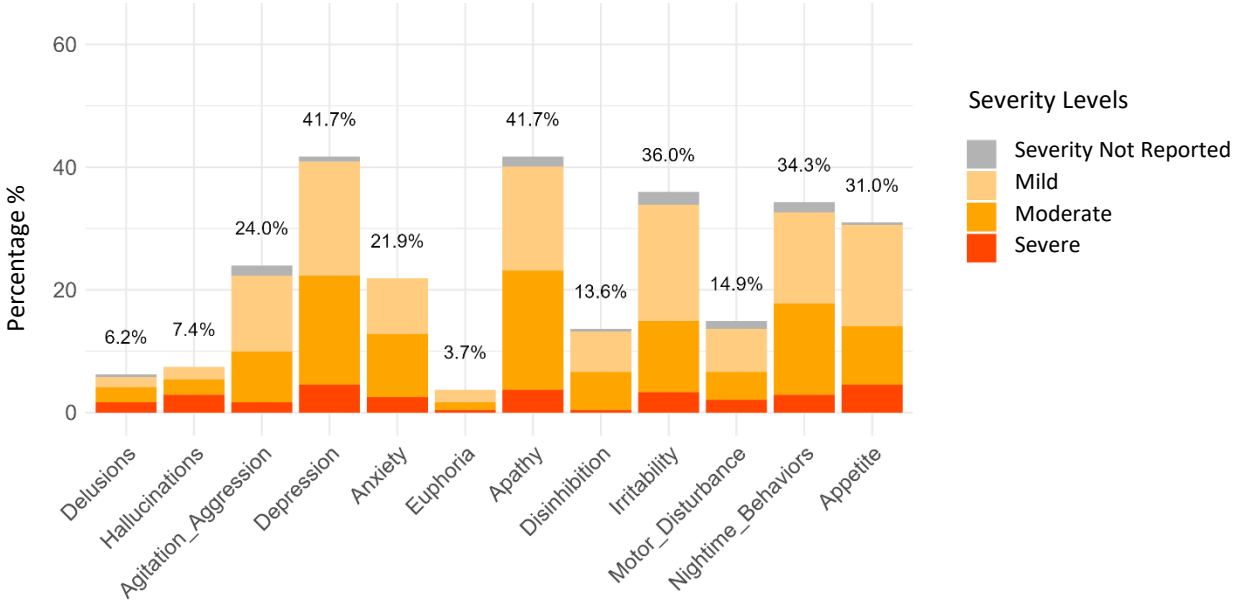


Figure 2. Prevalence of NPS Dyads Across Diagnostic Groups (a, b, c). Values in each cell represent the prevalence of NPS dyads, calculated as the proportion of patients exhibiting each dyad relative to the total number of patients in the corresponding diagnostic group. The color gradient indicates the prevalence level, with darker shades representing higher prevalence.

Figure 2(a). No Memory Disorder Group

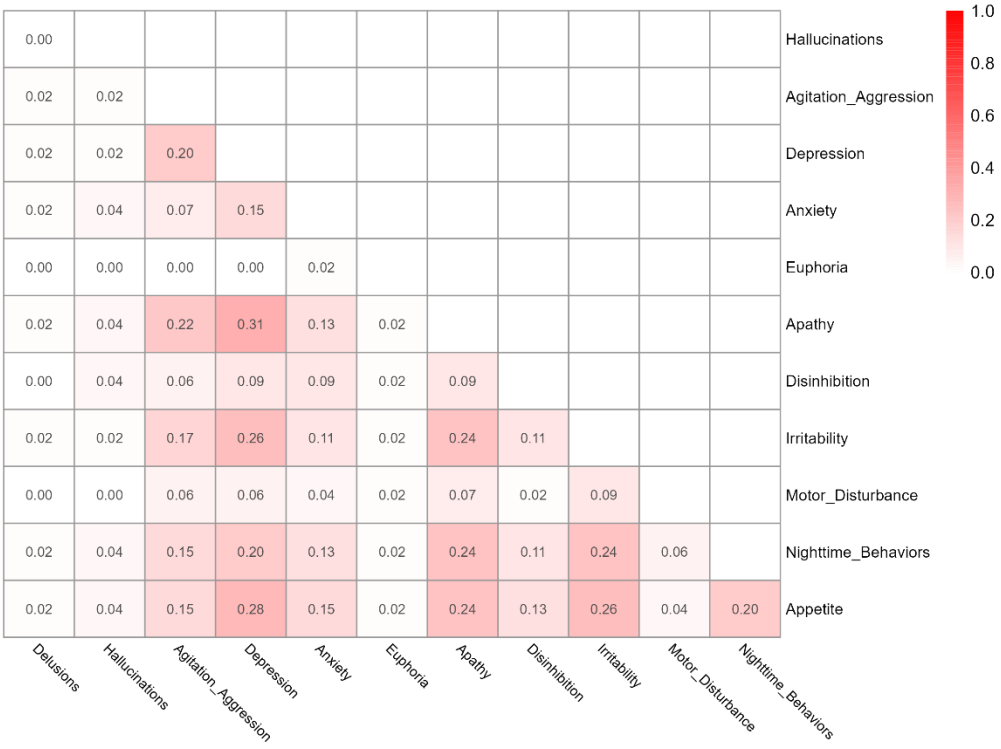


Figure 2(b). MCI Group

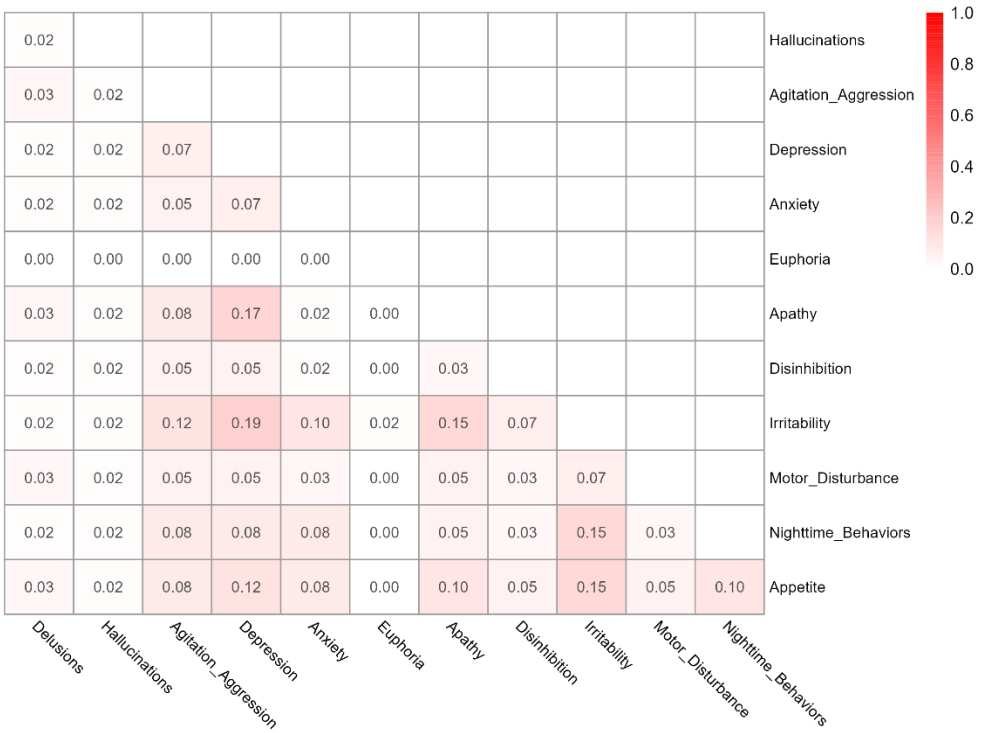


Figure 2(c). Dementia Group

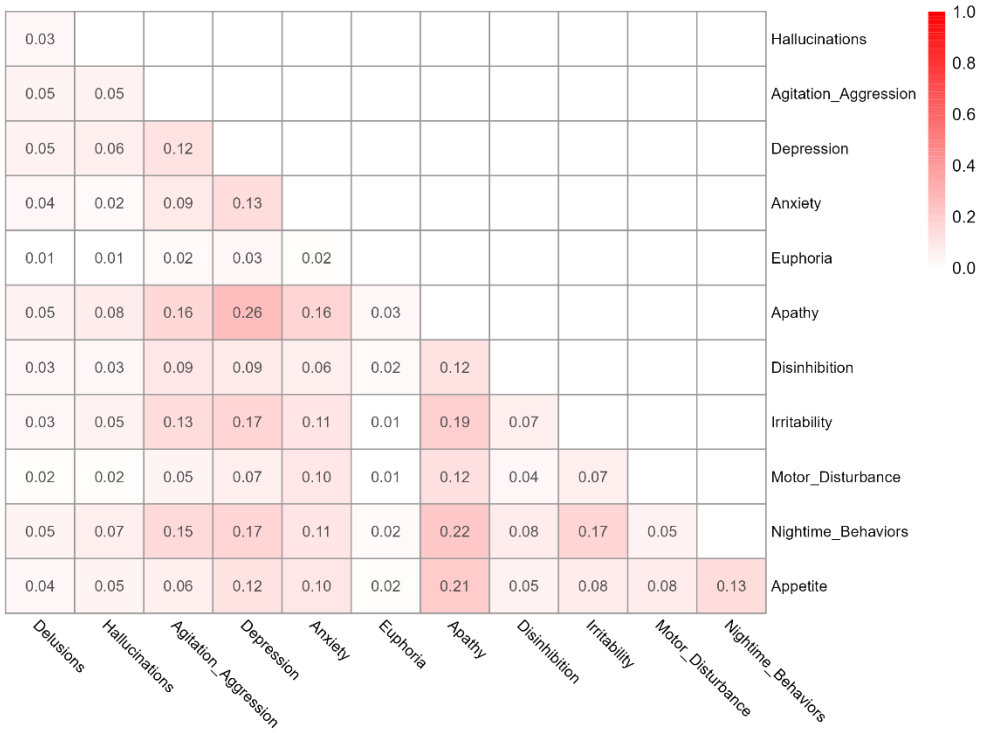


Figure 3. Spearman Correlations Between Total Number and Severity Score of NPS and Associated Factors

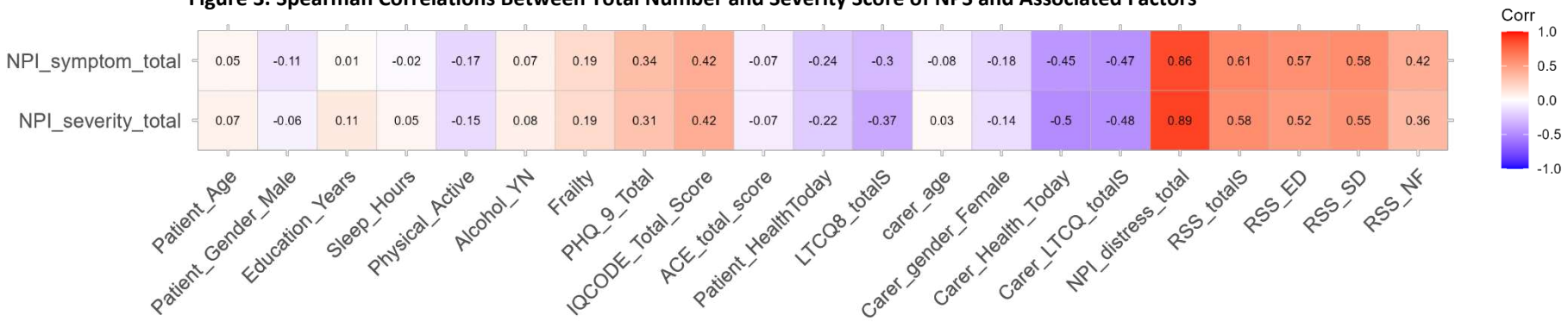
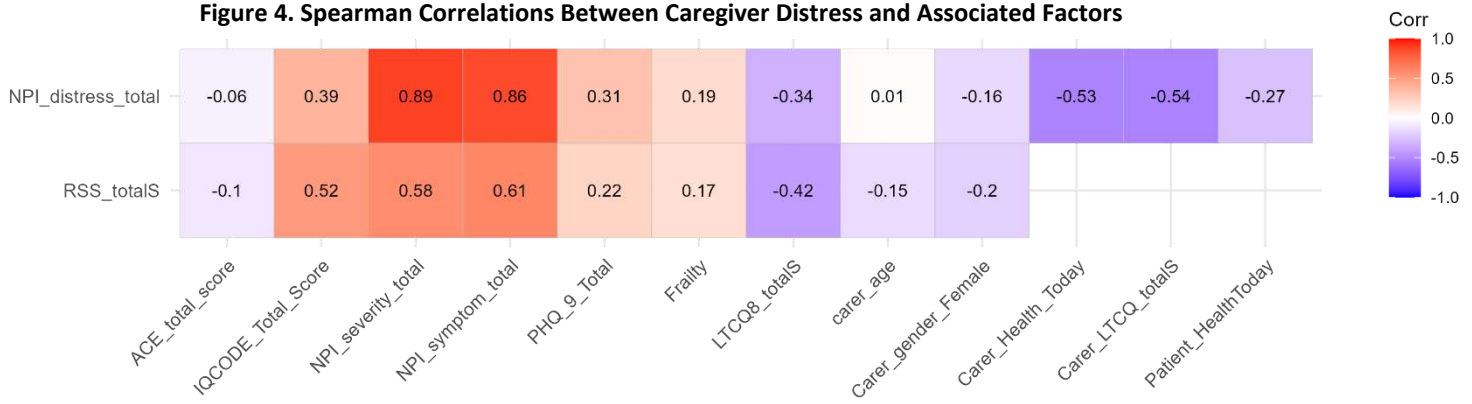


Figure 4. Spearman Correlations Between Caregiver Distress and Associated Factors



Discussion

Using real-world data from the OBHC, this study found that NPS were common across all diagnostic groups, with dementia and no memory disorder groups showing similar NPS frequency and symptom counts, both of which were higher than in the MCI group. NPS also tended to co-occur more frequently in these two groups compared with MCI. In the multivariable regression, NPS were independently associated with caregiver-reported cognitive decline after accounting for caregiver distress. Caregiver distress followed a similar pattern, with higher levels reported in the dementia and no memory disorder groups than in MCI. Together, these findings highlight the importance of early recognition of NPS and timely support for both patients and caregivers, and suggest that NPS may have potential value as an early screening signal.

Early-Emerging Neuropsychiatric Symptoms: Prevalence, Co-Occurrence, and Associated Factors

NPS are prevalent among patients undergoing diagnostic assessment, with mild to moderate severity levels commonly observed. Over 84% of the patients reported that they have experienced one or more NPS. This aligns with prior studies showing high NPS prevalence in early stages.[1, 9, 10, 28] Moreover, patients experienced multiple NPS. Patterns of symptom co-occurrence showed greater diversity in those with no memory disorders, with depression-centred dyads predominating, while apathy-centred dyads were more common in dementia. Depression-centred co-occurrence patterns have been reported previously in cognitively healthy individuals.[13] While dyad-level evidence is scarce, Zhao et al. found that apathy was more prevalent in dementia than in subjective cognitive decline and MCI, consistent with the pattern observed in our study.[29] The high prevalence and frequent co-occurrence of NPS underscore the complexity of symptom presentations in individuals undergoing diagnostic assessment for memory problems.

Although cognitively intact, individuals in the no memory disorder group showed more prevalent and complex NPS than those with MCI. This suggests that NPS may play a critical role in prompting individuals to seek clinical assessment, independent of cognitive concerns. Our data support the view that early neurodegenerative changes may initially present as behavioural or affective symptoms before cognitive deficits become detectable.[30, 31] The mild behavioural impairment framework, introduced in 2016 to capture early behavioural changes[30], is less recognised than MCI. These results highlight the importance of considering NPS as early, clinically meaningful indicators warranting attention during diagnostic assessments.

Following this, our findings showed that NPS were associated with caregiver-reported cognitive decline, but not with current cognitive function. This dissociation suggests that NPS may arise independently of current cognitive status and potentially serve as early markers of neurodegenerative progression. This is consistent with studies identifying NPS as prodromal features of cognitive decline[32], though some research has reported no such association[1]. Given that both NPS and cognitive decline were caregiver-reported, potential reporting bias cannot be excluded, and findings should be interpreted with caution.

Early Emergence and Correlates of Caregiver Distress

Caregiver distress was already evident when individuals sought diagnostic assessment for memory problems, suggesting that burden can arise at an early stage of help-seeking. Caregiver distress levels were higher in both the dementia and no memory disorder groups compared with the MCI group. This pattern parallels the distribution of NPS and suggests that behavioural changes may impose greater challenges for caregivers than cognitive performance alone. In the no memory disorder group, elevated caregiver distress may reflect challenges of managing NPS, despite relatively preserved cognition. Individuals in this group experienced more NPS, such as apathy, agitation, and nighttime behaviours, which combined with lack of access to services typically available for diagnosed dementia, could lead to high caregiver distress.[5, 22, 23] In the dementia

group, high caregiver distress is consistent with previous findings and is likely driven by a combination of NPS, poor cognitive function, and increasing care demands.[5, 25]

Caregiver distress correlated with NPS and caregiver-reported cognitive decline, but not with current cognitive function. This aligns with previous research, suggesting objective cognitive function has little effect on caregiver burden.[24] Since NPS and cognitive decline were caregiver-reported whereas cognitive function was objectively measured, distressed supporters may overreport symptoms, potentially inflating these associations. The strong association between NPS and distress highlights the significant challenges behavioural symptoms pose for caregivers [5, 22, 24]. These findings underscore the need to broaden early caregiver support to include those caring for individuals with NPS but no cognitive deficits, whose needs are often overlooked.

Limitations:

This study has several limitations. NPS and cognitive decline were both reported by caregivers, which may have introduced reporting bias and inflated associations with caregiver distress. To address this limitation, future research could consider incorporating multi-informant approaches (e.g., patient self-reports) and objective measures (e.g., clinician-rated scales or behavioural observations) to enhance the validity of the findings.

One extreme outlier in the MCI group was excluded from the linear regression analysis due to an unusually high number of reported NPS (11 out of 12). All other patients with MCI reported four or fewer symptoms, suggesting that this case may not be representative of the group. While the exclusion improved the normality of residuals and model fit, it may limit the generalisability of findings within the MCI group, especially if such extreme cases do exist in the broader population. This decision was made after careful consideration of the model's statistical requirements and was deemed necessary to ensure the robustness of the analysis.

Additionally, a descriptive co-occurrence analysis was conducted to explore symptom dyads. Due to the modest sample size and reliance on unadjusted frequency counts, these results should be considered exploratory. Apparent co-occurrence of symptoms may largely reflect their individual prevalence, as more frequent symptoms are more likely to appear together by chance. Future studies should apply adjusted statistical methods to identify symptom pairs with clinically meaningful associations beyond raw frequencies.

Conclusions

In this real-world memory clinic sample, NPS were prevalent and often co-occurred across diagnostic groups. The co-occurrence patterns showed more complex and depression-centred dyads in the no memory disorder group, a smaller number of dyads in MCI, and predominantly apathy-centred dyads in dementia. Notably, patients with no memory disorder showed relatively preserved cognitive function but exhibited more frequent and complex NPS, underscoring the potential clinical relevance of these symptoms even in the absence of cognitive impairment. Caregiver distress also emerged early and was closely associated with NPS, and not with cognitive performance. These findings suggest that greater attention to NPS during diagnostic assessments, along with early support for caregivers, may aid in timely identification and management of dementia-related challenges.

List of abbreviations

OBHC: Oxford Brain Health Clinic

MC: Memory Clinic

MCI: Mild Cognitive Impairment

NPS: Neuropsychiatric Symptoms

NPI-Q: Neuropsychiatric Inventory Questionnaire

PHQ-9: Patient Health Questionnaire-9

ACE-III: Addenbrooke's Cognitive Examination

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

LTCQ-8: Long-Term Conditions Questionnaire-short form

RSS: Relative Stress Scale

LTCQ-Carer: Long-Term Conditions Questionnaire-Carer version

Declarations

Ethics approval and consent to participate

The Oxford Brain Health Clinic Research Database was reviewed and approved by the South Central—Oxford C research ethics committee (SC/19/0404).

All patients attending the Oxford Brain Health Clinic are provided with full study information and the opportunity to ask questions. Informed written consent is obtained prior to participation. Patients may consent to the use of their clinical data for research, additional research assessments, and/or recontact for future studies. Capacity to consent is assessed, and if lacking, a consultee may provide agreement. Accompanying individuals are also offered the opportunity to participate and provide consent.

Clinical trial number: not applicable.

Consent for publication

Only participants who provided consent for the use of their clinical data in research were included in the OBHC dataset. All data were anonymised, and no additional consent for publication was required.

Availability of data and materials

The Oxford Brain Health Clinic dataset will be available through the Dementias Platform UK, with access granted via an application reviewed by the OBHC Data Access Group.

Competing interests

No potential conflict of interest was reported by the authors.

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Authors' contributions

VR, CM, CP supervised the project. **JD** conceptualised the study, conducted the formal analysis, developed the methodology, created the visualisations, and wrote the original draft of the

manuscript. **CM, LM, JB, GG and VR** designed the Oxford Brain Health Clinic assessment protocol and database, and **JB and GG** additionally contributed to data collection**.** All authors participated in the critical review and editing of the manuscript.

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