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Symptom clusters of neuropsychiatric symptoms in mild cognitive impairment and their comparative risks of dementia: a cohort study of 8,530 older persons

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Abstract

Objectives: Neuropsychiatric symptoms (NPS) have been recognized to increase the risk of dementia among individuals with mild cognitive impairment (MCI). However, it is unclear whether the risk is shared across the various NPS or driven primarily by selected few symptoms. This study sought to provide confirmatory evidence on the comparative risk of dementia across the various NPS in MCI.

Design: Cohort study (median follow-up 4.0 years; interquartile range 2.1–6.4 years).

Setting: Alzheimer's Disease Centers across the United States.

Participants: Participants who were ≥60 years and diagnosed with MCI at baseline (n=8,530).

Measures: Participants completed the Neuropsychiatric Inventory–Questionnaire at baseline and were followed-up almost annually for incident dementia. Symptom-clusters of NPS – as identified from confirmatory factor analyses – were included in cox regression to investigate their comparative risks of dementia.

Results: Three symptom-clusters of NPS were identified among participants with MCI, namely Hyperactivity, Affective and Psychotic symptoms. The risk of dementia was present among participants with Affective symptoms (HR 1.6, 95% CI 1.4–1.9) and Psychotic symptoms (HR 1.6, 95% CI 1.2–2.2), but not among those with Hyperactivity symptoms (HR 1.1, 95% CI 0.9–1.3). The risk was higher when Affective symptoms and Psychotic symptoms co-occurred (HR 2.5, 95% CI 2.0–3.2), with half of the participants in this group developing dementia within 2.7 years of follow-up.

Conclusions and Implications: The findings illustrate the potential usefulness of NPS as a convenient prognostic tool in the clinical management of MCI. They also suggest the need for

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CONFLICT OF INTEREST

None declared

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future research to focus on Affective/Psychotic symptoms in MCI when studying the neurobiological links between NPS and neurodegenerative processes.

Brief summary:

Affective and Psychotic symptoms (but not Hyperactivity symptoms) increase the risk of dementia, and may be useful as a convenient prognostic tool in the clinical management of mild cognitive impairment.

Keywords

mild cognitive impairment; neuropsychiatric symptoms; cox regression; cohort study; comparative risk; dementia

INTRODUCTION

Neuropsychiatric symptoms (NPS) have been hypothesized as early manifestations of neurocognitive disorders and may potentially be useful in identifying those at high risk of developing dementia.[1,2] Despite being well-evidenced, a critical gap remains in the literature on NPS in mild cognitive impairment (MCI). NPS comprise a heterogeneous range of symptoms, such as those related to affective regulation, motivation, and abnormal perception or thought content.[2] Previous studies on NPS in MCI have mostly investigated specific NPS in isolation without adjusting for the effects of the other NPS in the same statistical models.[1] They have not provided definite conclusions on whether the risk related to NPS are shared across the various NPS or driven primarily by selected few symptoms.

Several studies[3–5] attempted to address this gap but generated conflicting results – for example, after adjusting for the mutual effects of various NPS, one study[4] reported that both depression and anxiety were significant predictors of dementia, while another[5] reported that both were not significant and yet another[3] reported that only anxiety was significant. These conflicting results are understandable – many of the NPS tend to co-occur and are highly correlated with each other, such as among the symptoms of depression, anxiety, sleep and appetite; or between the symptoms of delusions and hallucinations. The inclusion of correlated NPS within the usual statistical models may introduce collinearity and render the results erratic.

Ideally, the correlated NPS should be grouped together as “symptom-clusters” – using factor analysis – before being included in statistical models to evaluate their comparative risks of dementia. The use of symptom-clusters also has an additional benefit, where we can group the co-occurring NPS in a clinically meaningful way to facilitate interpretations on the findings of NPS. Notwithstanding these benefits, the findings on the symptom-clusters of NPS have been inconsistent, with different studies reporting different symptom-clusters of NPS.[6–11]

To address the gaps in the literature, this study sought to provide confirmatory evidence – using a large sample – on:

1. the symptom-clusters of NPS among individuals with MCI; and

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2. the comparative risks of dementia among the various symptom-clusters of NPS in MCI.

METHOD

Participants and procedures

The participants of this cohort study were from the National Alzheimer's Coordinating Center (NACC)[12] database which included individuals from the Alzheimer's Disease Centers across the United States between September 2005 and May 2018. At baseline and on an approximately annual basis, the participants took part in standardized assessments to evaluate for the presence of MCI and dementia.

The current study included participants with the following criteria: (1) aged ≥60 years; (2) diagnosed as having mild cognitive impairment at baseline; and (3) completed the Neuropsychiatric Inventory-Questionnaire (NPI-Q) at baseline. Research using the NACC database was approved by the University of Washington Institutional Review Board.

Measures

NPI-Q is a 12-item clinical measure that assesses NPS in 12 domains (*agitation, irritability, disinhibition, elation, motor disturbance, depression, anxiety, apathy, sleep, appetite, delusions*, and *hallucinations*). It was administered by trained healthcare professionals, based on informant-reports on whether each symptom was present in the past month (yes/no). The Mini-Mental State Examination (MMSE)[13] is a widely-used cognitive assessment tool. It consists of 11 items across cognitive domains such as orientation, memory, concentration, language and constructional praxis.

The diagnoses of MCI or dementia were made based on all available data, with majority of the diagnoses made via consensus conference (in 84.9% of the participants) and the remainder made by single clinicians. MCI was diagnosed using the modified Petersen criteria,[14] with further classification into the subtypes of Amnestic Single-domain, Amnesic Multiple-domains, Non-amnesic Single-domain, and Non-amnesic Multiple-domains. Dementia was diagnosed using either the McKhann (1984) criteria[15] or the McKhann (2011) criteria,[16] with further classification into the primary aetiologies of Alzheimer's dementia,[15,16] vascular dementia,[17] dementia with Lewy Bodies,[18–20] frontotemporal lobar degeneration,[19,21–26] and other aetiologies.

Statistical analyses

Confirmatory factor analysis (CFA) was first conducted – based on items in NPI-Q – to identify the symptom-clusters of NPS in MCI at baseline. CFA was conducted in structural equation modelling using a probit link (which models the binary responses of yes/no for the NPS). All the previously-reported factor structures of NPI-Q (ranging from two-[6,7] to three-[8,9] and four-factor models)[9–11] were compared in CFA. The model that fulfilled the criteria of excellent fit (that is, fulfilling all of the following four criteria: Root-Mean-Square-Error-of-Approximation≤0.05, Standardized-Root-Mean-Square-Residual≤0.05,

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Comparative-Fit-Index≥0.95 and Tucker-Lewis-Index≥0.95)[27] were used to constitute the symptom-clusters of NPS in the subsequent analyses.

Cox proportional-hazard regression was conducted to evaluate the comparative risks of dementia among the symptom-clusters of NPS, with time-to-event defined as the duration from baseline to the diagnosis of dementia. All the symptom-clusters were concurrently included in the cox regression to evaluate the independent risks that were attributable to each of them (after adjusting for the effects of each other). They were included as binary variables based on whether the participants endorsed the presence of each symptom-cluster (yes/no) at baseline. The cox regression also adjusted for baseline covariates which can be potential confounders between NPS and dementia, including age, sex, ethnicity, years of education, first-degree family member with cognitive impairment, MMSE scores, MCI subtypes, recruitment sites, year of recruitment, and whether the diagnosis was made via consensus conference. The proportional-hazard assumption of cox regression was tested statistically based on whether the Schoenfeld residuals were associated with time – variables that violated the proportional-hazard assumption ($p<0.05$) were included in the cox regression as stratified variable.

Inverse probability weighting (IPW)[28] was used in cox regression to account for participants who did not have follow-up data. IPW is a well-accepted strategy which gives more weight to participants who resemble those who did not have follow-up data and ensures that the results are less biased towards participants who provided follow-up data.[28] As such, this method minimizes any potential bias in the results due to differential risks between those with and without follow-up data. Details on IPW are further described in Supplementary Material 1.

Five sensitivity analyses were conducted to evaluate the consistency of the results when some parts of the cox regression were modified, with further details available in Supplementary Material 2. Additionally, a stratified analysis was conducted to evaluate the risk of dementia across different combinations of the symptom-clusters. CFA was performed in R (version 3.5.1). The other analyses were conducted in Stata (version 14).

RESULTS

Supplementary Material 3 presents the flow diagram related to participant selection, while Supplementary Material 4 shows the participant characteristics. The included participants (n=8,530) had a median age of 76 (inter-quartile range, IQR 70–81), a median education of 16 years (IQR 12–18), and a median MMSE score of 28 (IQR 26–29). At baseline, 61.5% of the participants reported at least one NPS, with the most common symptoms being depression (29.4%) and irritability (27.4%). Among the included participants, 30.2% only had baseline data and did not have any follow-up data, while the rest of the participants had a median duration of follow-up of 4.0 years (IQR 2.1–6.5 years). During follow-up, 2,477 participants progressed to dementia (of which 79.0% were Alzheimer's dementia, 2.7% vascular dementia, 3.6% mixed Alzheimer's/vascular dementia, 6.7% dementia with Lewy Bodies, 4.9% frontotemporal lobar degeneration, and 3.2% dementia due other or unknown etiologies).

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The results of CFA are presented in Table 1. Two models fulfilling the criteria of excellent fit – namely the three-factor model and the four-factor model by Sayegh (2013).[9] In such circumstance of similar model-fit, the more parsimonious model (three-factor model) is generally preferred, considering that the more complex model (four-factor model) did not further improve the model-fit. Hence, the three-factor model by Sayegh (2013)[9] was chosen for all the subsequent analyses.

The three-factor model by Sayegh (2013)[9] groups the items in NPI-Q into 3 symptom-clusters of NPS: (1) **Hyperactivity symptoms** (comprising *agitation, irritability* and *disinhibition*); (2) **Affective symptoms** (comprising *depression, anxiety, apathy, sleep* and *appetite*); and (3) **Psychotic symptoms** (comprising *delusions* and *hallucinations*). The Hyperactivity symptoms were endorsed by 34.3% of the participants at baseline, while Affective symptoms by 54.1% and Psychotic symptoms by 4.8%.

The results of cox regression are presented in Table 2. The three symptom-clusters were *individually* associated with the risk of dementia (that is, when each symptom-cluster was *separately* investigated in the cox regression). However, only Affective and Psychotic symptoms remained significant (HR 1.6) when the three symptom-clusters were *concurrently included* in the cox regression, indicating that only Affective and Psychotic symptoms (but not Hyperactivity symptoms) had independent contributions to the risk of dementia. The findings remained consistent in the five sensitivity analyses (Supplementary Material 5).

The risk of dementia was further evaluated by stratifying the two significant symptom-clusters, based on the presence of *Affective symptoms only*, *Psychotic symptoms only*, or *both Affective and Psychotic symptoms*. As shown in Table 3, individuals with *Affective symptoms only* or *Psychotic symptoms only* had similar risk of dementia (HR1.6–1.8), while individuals reporting *both Affective and Psychotic symptoms* had relatively higher risk (HR 2.5). Among individuals with *no Affective or Psychotic symptoms*, half of them developed dementia by 6.1 years. This duration became as short as 2.7 years in the presence of *both Affective and Psychotic symptoms*.

DISCUSSION

Using a large sample, this study provided more conclusive evidence on the presence of three symptom-clusters of NPS among individuals with MCI, namely Hyperactivity, Affective and Psychotic symptoms. Of which, only Affective symptoms and Psychotic symptoms (but not Hyperactivity symptoms) were significantly associated with the risk of dementia (HR 1.6). The risk was higher when Affective symptoms and Psychotic symptoms co-occurred (HR 2.5), with half of the participants in this group developing dementia within 2.7 years of follow-up.

While prior studies have reported the association between NPS and incident dementia among older persons with MCI,[1–5] the current study further demonstrated that the risk of dementia is specific to Affective and Psychotic symptoms but not Hyperactivity symptoms. The findings provided an illustration on the need to adjust for the mutual effects of the

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various NPS, before we can draw more definitive conclusion on the risk of dementia associated with each neuropsychiatric symptom. As shown in Table 2, all the three symptom-clusters appeared to be associated with the risk of dementia when they were *individually evaluated* without accounting for the mutual effects of each other. However, when the three symptom-clusters were *concurrently included* in the same statistical model, only the Affective and Psychotic symptoms truly demonstrated their independent risks of dementia, indicating that the association between Hyperactivity symptoms and dementia is likely due to the confounding effects of the other two symptom-clusters. In other words, the Hyperactivity symptoms are possibly the consequences of Affective or Psychotic symptoms (that is, a person becomes agitated due to the underlying Affective or Psychotic symptoms), and the apparent risk associated with Hyperactivity symptoms may possibly be traced back to those of Affective and Psychotic symptoms. Notwithstanding these findings, it may be pertinent to note that the negative result on Hyperactivity symptoms is only specific to the context of incident dementia and does not preclude the general relevance of Hyperactivity symptoms in dementia care, especially considering that Hyperactivity symptoms can be increasingly common in later stages of dementia[29] and may be associated with poorer outcomes such as caregiver burden[30] and increased cost of care.[31]

The findings can have research implications. In the literature, there has been increasing recognition on the need to improve our understanding of the neurobiological links between NPS and neurodegenerative processes, with the hope of discovering potential drug targets for the prevention of dementia.[32] Considering the findings from this study, it may be relevant for future research in this area to focus on the neurobiological underpinnings related to Affective and Psychotic symptoms in MCI (instead of Hyperactivity symptoms) to understand how these neurobiological underpinnings may be related to the risk of dementia. Future research should also further delineate the neurobiological distinctions between Affective symptoms and Psychotic symptoms, considering the independent risks of dementia associated with the two symptom-clusters and the compounding risk when they co-occur (all of which are evidence to suggest the separate neurobiological underpinnings of the two symptom-clusters).

The findings also have clinical implications. They demonstrated the potential usefulness of NPS as a convenient prognostic tool in the clinical management of MCI.[1,2] For example, one may expect that MCI patients without Affective or Psychotic symptoms would have approximately 6.1 years before they progress to dementia, while those reporting Affective or Psychotic symptoms would have significantly shorter time (2.7–3.5 years) to dementia. This information can be relevant to clinicians when providing patient counselling on disease process and risk factor modification, as well as when selecting participants for preventive trials in dementia.

Several limitations should be considered. First, the participants in the study involved those who volunteered at the Alzheimer’s Disease Centers. They may be more representative of patients who voluntarily present to healthcare settings than those in the community. Second, the participants were mostly White and highly educated. Hence, the risk estimates from this study may not necessarily be the same in another population with a different composition of ethnicity and educational attainment. Third, among participants who progressed to dementia,

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79.0% had the primary etiology of Alzheimer's dementia. Although such large proportion of Alzheimer's dementia is consistent with what is expected of the older population with dementia, the findings may not necessarily apply to the other etiologies of dementia.

CONCLUSIONS AND IMPLICATIONS

Among older persons with MCI, the risk of dementia is higher in the presence of Affective and Psychotic symptoms (but not Hyperactivity symptoms), with the risk further compounded when Affective and Psychotic symptoms co-occur. The findings illustrate the potential usefulness of NPS as a convenient prognostic tool in the clinical management of MCI. They also suggest the need for future research to focus on Affective/Psychotic symptoms in MCI when studying the neurobiological links between NPS and neurodegenerative processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Fit indices of previously-known models for Neuropsychiatric Inventory-Questionnaire (NPI-Q) in confirmatory factor analysis (CFA). The models which fulfilled the criteria of excellent fit are highlighted in bold.[a]

CFA model	RMSEA	SRMR	CFI	TLI
One-factor model (Unidimentional)[b]	0.042	0.071	0.95	0.94
Two-factor model by Travis Seidl 2016 (*Negative/Oppositional behavior, Anxiety/Restlessness*)[c]	0.050	0.069	0.95	0.93
Two-factor model by Donovan 2014 (*Affective factor, Psychotic factor*)[d]	0.044	0.062	0.95	0.94
Three-factor model by Johnson 2011 (*Frontal, Mood, Psychosis*)[e]	0.030	0.053	0.98	0.97
Three-factor model by Sayegh 2013 (*Hyperactivity, Affect, Psychosis*)[f]	**0.029**	**0.044**	**0.98**	**0.98**
Four-factor model by Sayegh 2013 (*Hyperactivity, Affect, Apathy/vegetative, Psychosis*)[g]	**0.023**	**0.038**	**0.99**	**0.99**
Four-factor model by Aalten 2007 (*Hyperactivity, Affective, Apathy, Psychosis*)[h]	0.030	0.051	0.98	0.97
Four-factor model by Aalten 2008 (*Hyperactivity, Affective, Apathy, Psychosis*)[i]	0.029	0.056	0.98	0.97

NPI-Q, Neuropsychiatric Inventory-Questionnaire; CFA, confirmatory factor analysis; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; CFI, comparative fit index; TLI, Tucker-Lewis index.

[a] A model is considered to have excellent fit if it fulfils all of the following four criteria: RMSEA<0.05, SRMR<0.05, CFI>0.95, TLI>0.95.[27]

[b] This one-factor model indicates NPI-Q as a unidimensional scale.

[c] This two-factor model consisted of *Negative/Oppositional behavior* (agitation, irritability, apathy, depression disinhibition, delusions) and *Anxiety/Restlessness* (sleep, anxiety, hallucinations, appetite).[7]

[d] This two-factor model consisted of *Affective factor* (depression, irritability, agitation, disinhibition, anxiety, apathy) and *Psychotic factor* (hallucinations, motor disturbnce, sleep, appetite, delusions).[6]

[e] This three-factor model consisted of *Frontal* (elation, disinhibition), *Mood* (anxiety, apathy, depression) and *Psychosis* (irritability, delusions, hallucinations, agitation).[8]

[f] This three-factor model consisted of *Hyperactivity* (agitation, disinhibition, irritability), *Affect* (depression, anxiety, apathy, sleep, appetite) and *Psychosis* (delusions, hallucinations).[9]

[g] This four-factor model consisted of *Hyperactivity* (agitation, disinhibition, irritability), *Affect* (depression, anxiety), *Apathy/vegetative* (apathy, sleep, appetite) and *Psychosis* (delusions, hallucinations).[9]

[h] This four-factor model consisted of *Hyperactivity* (agitation, disinhibition, irritability, motor disturbance), *Affective* (depression, anxiety), *Apathy* (apathy, appetite) and *Psychosis* (delusions, hallucinations, sleep).[10]

[i] This four-factor model consisted of *Hyperactivity* (agitation, elation, disinhibition, irritability, motor disturbance), *Affective* (depression, anxiety), *Apathy* (apathy, appetite) and *Psychosis* (delusions, hallucinations, sleep).[11]

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Table 2.

The risk of dementia based on the presence of Affective, Hyperactivity, and Psychotic symptoms (n=8,530).

Symptom-cluster at baseline	Individually-evaluated effect[a]		Mutually-adjusted effect[b]	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Presence of Hyperactivity symptoms	**1.3 (1.1–1.5)**	**<0.001**	1.1 (0.9–1.3)	0.364
Presence of Affective symptoms	**1.7 (1.5–2.0)**	**<0.001**	**1.6 (1.4–1.9)**	**<0.001**
Presence of Psychotic symptoms	**1.8 (1.3–2.5)**	**<0.001**	**1.6 (1.2–2.2)**	**0.004**

HR, hazard ratio; CI, confidence interval.

[a]Only one symptom-cluster was included in the model at a time. In other words, three separate models of cox regression were evaluated, each including only one of the symptom-clusters (either Hyperactivity, Affective or Psychotic symptoms). The models also adjusted for baseline covariates of age, sex, ethnicity, years of education, first-degree family member with cognitive impairment, Mini-Mental State Examination score, subtypes of mild cognitive impairment, recruitment sites, year of recruitment, and whether the diagnosis was made via consensus conference.

[b]The three symptom-clusters were concurrently included in the model to evaluate their mutually-adjusted effects. In other words, a cox regression was conducted by including the three symptom-clusters, as well as adjusting for the baseline confounders (age, sex, ethnicity, years of education, first-degree family member with cognitive impairment, Mini-Mental State Examination score, subtypes of mild cognitive impairment, recruitment sites, year of recruitment, and whether the diagnosis was made via consensus conference).

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Table 3.

Stratified analysis on the risk of dementia across the different combinations of neuropsychiatric symptoms, based on the presence of Affective or Psychotic symptoms at baseline (n=8,530).

Combination of symptom-clusters	Sample size, n (%)	HR (95% CI)[a]	Median time to dementia, year (95% CI)[b]
No Affective or Psychotic symptoms	3,864 (45.3)	Ref	6.1 (6.2–7.6)
Affective symptoms only	4,253 (49.9)	1.6 (1.4–1.7)	3.4 (3.4–4.5)
Psychotic symptoms only	55 (0.6)	1.8 (1.2–2.8)	3.5 (3.1–4.0)
Both Affective and Psychotic symptoms	358 (4.2)	2.5 (2.0–3.2)	2.7 (2.1–3.5)
TOTAL	8,530 (100%)		

HR, hazard ratio; CI, confidence interval; ref, reference group.

[a]Model adjusted for baseline covariates of age, sex, ethnicity, years of education, first-degree family member with cognitive impairment, Mini-Mental State Examination score, subtypes of mild cognitive impairment, recruitment sites, year of recruitment, and whether the diagnosis was made via consensus conference.

[b]The 95% CI was computed with 1000 bootstrap sampling.